

RAD 2018-00012-00(012-12) / ENTREGA DICTAMEN PERICIAL CASO IDANNA SOFIA MITCHELL MENA

C&C Corporacion <contacto@cyccorporacion.com>

Mié 26/07/2023 3:45 PM

Para:Juzgado 02 Civil Circuito - Valle Del Cauca - Buenaventura <j02ccbuenaventura@cendoj.ramajudicial.gov.co>

 1 archivos adjuntos (13 MB)

DICTAMEN_FINAL_IDANNA SOFIA.pdf;

HONORABLE:

LUIS ANTONIO BALCERO ESCOBAR

Juez de Juzgado Segundo Civil Del Circuito De Buenaventura (Valle Del Cauca)

E...S...D...

RADICADO: 2018-00012-00

DEMANDANTES: BERNARD EUGENE MITCHEL Y OTRA

DEMANDANDOS: COMFENALCO VALLE DE LA GENTE; CLÍNICA SANTA SOFÍA DEL PACÍFICO. Llamados en garantía: ALLIANZ SEGUROS S.A.; LA PREVISORA S.A.; GRUPO OPERADOR CLÍNICO HOSPITALARIO POR OUTSOURCING S.A.S. (GRUP OCHOS S.A.S); SEGUROS DEL ESTADO

Cordial saludo,

Dando alcance al asunto nos permitimos hacer entrega del dictamen pericial rendido por especialista en Pediatría, para su conocimiento y fines pertinentes.

De antemano agradecemos al despacho y a las partes, instarnos para colocar a la administración de justicia el recurso humano especializado y privado que tiene C&C Corporación para coadyuvar en la resolución de conflictos.

Sin otro particular,

Edacsil Narváez

Asistente Administrativo

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C&C Corporación

(+57) (2) 4050160 – 3153745039
Calle 1C #61-05, Pampa Linda
Santiago de Cali,
Valle del Cauca – Colombia



(+57) (2) 4050160 - 3153745039

Santiago de Cali, Valle del Cauca - Colombia

WWW.CYCCORPORACION.COM

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DICTAMEN PERICIAL

JUZGADO:	JUZGADO SEGUNDO CIVIL DEL CIRCUITO DE BUENAVENTURA
RADICADO:	2018-00012-00
RADICADO INTERNO DE C&C:	2023-06-26-0148
DEMANDANTES:	BERNARD EUGENE MITCHEL Y OTRA
DEMANDANDOS:	COMFENALCO VALLE DE LA GENTE; CLÍNICA SANTA SOFÍA DEL PACÍFICO. Llamados en garantía: ALLIANZ SEGUROS S.A.; LA PREVISORA S.A.; GRUPO OPERADOR CLÍNICO HOSPITALARIO POR OUTSOURCING S.A.S. (GRUPO OCHOS S.A.S); SEGUROS DEL ESTADO



NIT 900.973.844-9

ESPECIALIDAD PEDIATRIA

Santiago de Cali, 13 de julio 2023

JUZGADO SEGUNDO CIVIL DEL CIRCUITO DE BUENAVENTURA

ASUNTO:

ENTREGA DE DICTAMEN MÉDICO PERICIAL

RADICADO:

2018-00012-00

PROCESO:

ORDINARIO DE RESPONSABILIDAD CIVIL
EXTRA CONTRACTUAL

RADICADO INTERNO DE C&C:

2023-06-26-0148

DEMANDANTES:

BERNARD EUGENE MITCHEL Y OTRA

DEMANDANDOS:

COMFENALCO VALLE DE LA GENTE; CLÍNICA SANTA
SOFÍA DEL PACÍFICO.

Llamados en garantía: ALLIANZ SEGUROS S.A.; LA
PREVISORA S.A.; GRUPO OPERADOR CLÍNICO
HOSPITALARIO POR OUTSOURCING S.A.S. (GRUPO
OCHOS S.A.S); SEGUROS DEL ESTADO

NOMBRE DEL PACIENTE:

IDANNA SOFIA MITCHELL MENA (Q.E.P.D.)

EDAD DEL PACIENTE:

4 meses (Según historia clínica)

ESPECIALIDAD:

PEDIATRIA

Respetado Señor Juez

De manera atenta hacemos entrega del Dictamen Médico Pericial en el proceso en referencia. Dicho Dictamen es rendido por la Doctora MARLEN ORTIZ BURGOS, Médico Especialista en **PEDIATRIA E INFECTOLOGIA**, a través **C&C CORPORACIÓN**. Para lo cual me permito allegar la siguiente documentación:

1. Copia del dictamen pericial 120 folios
2. Copia de la historia clínica aportada para la investigación (27 folios)
3. Oficio con la relación adjunta de los peritajes rendidos por la doctora MARLEN ORTIZ (01 folio)
4. Hoja de vida en 16 folios

Atentamente,



MARIA CERÓN
DIRECT. JURIDICA

Santiago de Cali, 13 de julio 2023

JUZGADO SEGUNDO CIVIL DEL CIRCUITO DE BUENAVENTURA

ASUNTO: ENTREGA DE DICTAMEN MÉDICO PERICIAL

RADICADO: 2018-00012-00
PROCESO: ORDINARIO DE RESPONSABILIDAD CIVIL
EXTRA CONTRACTUAL

RADICADO INTERNO DE C&C: 2023-06-26-0148
DEMANDANTES: BERNARD EUGENE MITCHEL Y OTRA
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HOSPITALARIO POR OUTSOURCING S.A.S. (GRUPO
OCHOS S.A.S); SEGUROS DEL ESTADO

NOMBRE DEL PACIENTE: IDANNA SOFIA MITCHELL MENA (Q.E.P.D.)
EDAD DEL PACIENTE: 4 meses (Según historia clínica)
ESPECIALIDAD: PEDIATRIA

Respetado Señor Juez:

De manera atenta rindo informe de los peritajes realizados a través de **C&C CORPORACIÓN**.
PERFIL PROFESIONAL DEL PERITO

- MÉDICO CIRUJANO, Egresado de la Universidad Del Valle en el año 2009.
- ESPECIALISTA EN PEDIATRIA, egresado de la Universidad ICESI en el año 2015.
- ESPECIALISTA EN INFECTOLOGIA PEDIATRICA, Egresado de la Universidad Del Valle en el año 2020.

De acuerdo con el Código General del Proceso en su Artículo 226:

- Expreso que cuento con los conocimientos necesarios, soy imparcial y no tengo impedimento alguno en la peritación que elabora.
- Anexo Hoja de Vida y los certificados de formación académica que me acreditan como idóneo para la presente evaluación pericial.
- La lista de proceso en los que he participado como perito se anexa a este oficio
- Declaro que los métodos, experimentos e investigaciones efectuados son los mismos que se emplean para la rendición de dictámenes periciales a través de C&C CORPORACIÓN.

- Declaro que los métodos, experimentos e investigaciones efectuados son los mismos respecto de aquellos que utilizo en el ejercicio regular de mi profesión, indicando que una cosa es la prestación de los servicios de salud y otra, muy diferente es la elaboración de dictámenes periciales.
- Manifiesto que el dictamen fue elaborado con la Historia Clínica suministrada por la parte interesada correspondiente a la Paciente: IDANNA SOFIA MITCHELL MENA (Q.E.P.D.)

Atentamente,



MARLEN ANABEL ORTIZ BURGOS
ESPECIALISTA EN INFECTOLOGÍA PEDIÁTRICA
TP / RM: 521445

Santiago de Cali, 13 de julio 2023

JUZGADO SEGUNDO CIVIL DEL CIRCUITO DE BUENAVENTURA

ASUNTO: DICTAMEN MÉDICO PERICIAL EN LA ESPECIALIDAD DE PEDIATRIA

RADICADO:	2018-00012-00
PROCESO:	ORDINARIO DE RESPONSABILIDAD CIVIL EXTRA CONTRACTUAL
RADICADO INTERNO DE C&C:	2023-06-26-0148
DEMANDANTES:	BERNARD EUGENE MITCHEL Y OTRA
DEMANDANDOS:	COMFENALCO VALLE DE LA GENTE; CLÍNICA SANTA SOFÍA DEL PACÍFICO. Llamados en garantía: ALLIANZ SEGUROS S.A.; LA PREVISORA S.A.; GRUPO OPERADOR CLÍNICO HOSPITALARIO POR OUTSOURCING S.A.S. (GRUPO OCHOS S.A.S); SEGUROS DEL ESTADO
NOMBRE DEL PACIENTE:	IDANNA SOFIA MITCHELL MENA (Q.E.P.D.)
EDAD DEL PACIENTE:	4 meses (Según historia clínica)

IDENTIFICACIÓN DE QUIEN RINDE EL PERITAJE (de conformidad al numeral 1 del artículo 226 CGP)

MARLEN ANABEL ORTIZ BURGOS identificado con cedula de ciudadanía 38601255, Tarjeta profesional de médico número 521445.

Soy medico egresado de la Universidad Del Valle en el año 2009, especialista EN PEDIATRIA egresado de Universidad ICESI en el año 2015, especialista en INFECTOLOGÍA PEDIATRICA egresado de Universidad Del Valle en el año 2020, actualmente tengo 13 años de experiencia profesional como Médico, 7 años como Pediatra y 2 años como Infectóloga Pediatra.

De conformidad con lo dispuesto por el Código General del Proceso en su artículo 226, me permito hacer las siguientes declaraciones:

1. Actúo con completa autonomía e independencia profesional, de manera tal que mi opinión es independiente y corresponde a mi real convicción profesional sobre la materia de la experticia.
2. El dictamen fue elaborado directamente por este servidor.

3. Los exámenes, métodos, y parámetros de análisis utilizados para evaluar el caso y soportar mi opinión profesional para el dictamen, corresponden a los que utilizo de manera sistemática y usual para el ejercicio de mi profesión.
4. He sido designado como perito para la Corporación C&C.
5. No estoy incurso en ninguna de las causales del artículo 50 del CGP.
6. Acompaño a la presente, copia de los documentos que acreditan mi idoneidad sobre la materia objeto del dictamen
7. Lo descrito entre comillas son las anotaciones de forma literal a como aparecen en la historia clínica

FUNDAMENTO: Efectúo el presente concepto médico especializado con base en la copia de la historia clínica del paciente **IDANNA SOFIA MITCHELL MENA**

ANALISIS DE REGISTROS

Se realiza una revisión y estudio de la información de los registros remitidos de la historia clínica del Paciente **IDANNA SOFIA MITCHELL MENA**

1. ESTADO DE SALUD ANTERIOR

Se trata de una paciente de 4 meses de edad. El peso aportado en la historia clínica es de riesgo de sobrepeso, no contamos con talla para otros marcadores antropométricos. Adicionalmente en las historias clínicas presentadas no se mencionan alteraciones en el desarrollo de la menor previo a la enfermedad actual tanto en la primera atención prestada en la Clínica Comfenalco de Buenaventura como en la Clínica Santa Sofía de Buenaventura. Sin embargo, en la atención prestada por Clínica Comfenalco de Buenaventura el día 01/04/16 por el Dr. WILMAR DALEY PEREA SINISTERRA se menciona cuadro de un mes de evolución de síntomas respiratorios *“un mes de evolución consistente en síndrome gripal, con rinorrea hialina, acompañado de tos no productiva con dificultad respiratoria”*. Se infiere que en el último mes la paciente había tenido síntomas respiratorios. Al parecer tratados de forma particular con antihistamínico (loratadina).

En la atención del 02/04/16 prestada por Dr. IVAN ALEXANDER PINTO MARTINEZ (PEDIATRA) no se encuentran antecedentes de enfermedad o infección durante el embarazo (de la paciente), ni antecedentes patológicos, quirúrgicos, transfusionales, hospitalizaciones. Según la madre tiene

vacunas completas para la edad, no aporta carnet de vacunas. Alimentada con leche formula etapa 1.

2. DESCRIPCION DEL EVENTO O ATENCION EN CUESTION

Atención en Clínica Comfenalco de Buenaventura.

- **Consultas iniciales en Triage:**

01/04/16 a las 08:31 horas, Enfermera DIANA ROCIO CAICEDO RODRÍGUEZ: *"Paciente manifiesta que la menor presenta, fiebre, diarrea en 2 ocasiones e intolerancia a la vía oral"* lo clasifica como TRIAGE Prioridad III. Los signos vitales de la paciente al ingreso a Triage: frecuencia cardíaca 228 x min, frecuencia respiratoria 22 x min, temperatura axilar 38.8 grados centígrados, SaO2 100%, peso 7.5 kg, estado de hidratación hidratado, no se aportan más datos.

- **Historia clínica de Ingreso a urgencias:**

- 01/04/16 a las 08:41 horas, atención prestada por el Dr. WILMAR DALEY PEREA SINISTERRA (MEDICO GENERAL) *"Lactante menor con cuadro clínico de 1 mes de evolución consistente en síndrome gripal, con rinorrea hialina, acompañado de tos no productiva con dificultad respiratoria. Hoy la trae a consulta la abuela por deposiciones líquidas verdosa, moderada cantidad, con moco, sin sangre desde hace 1 día en múltiples ocasiones, concomitante a esto fiebre de 38.5 grado."* Al examen físico sin dificultad respiratoria, sin presencia de ruidos sobreagregados en campos pulmonares. El único antecedente positivo anotado es que se encuentra tomando loratadina. Diagnóstico: Diarrea y gastroenteritis de presunto origen infeccioso. Solicita exámenes y ordena dipirone 50 mg endovenoso y 2 nebulizaciones con terbutolol.
- 01/04/16 a las 10:07 horas, atención prestada por Auxiliar de enfermería ELECCENIA BLANATA AMU. *"Se cumple orden médica a pte sin complicación"*. No describe el estado de la paciente.
- 01/04/16 a las 11:41 horas, atención prestada por el Dr. WILMAR DALEY PEREA SINISTERRA (MEDICO GENERAL) *"Llega reporte de hemograma: leucos 25.060, N 67% L 20% HGB: 12 PLQ: 457.000. Pendiente uroanálisis, coprológico y Rx Tórax. Paciente mejora dificultad respiratoria con nebulizaciones, persiste febril se ordena dosis oral de acetaminofen"*
- 01/04/16 a las 12:48 horas, atención prestada por el Dr. WILMAR DALEY PEREA SINISTERRA (MEDICO GENERAL) *"Rx tórax: no evidencio infiltrados, no atrapamiento de aire. Se observa colección de materia fecal en intestino. Abdomen doloroso a la palpación. Pendiente uroanálisis y coprológico para definir conducta"*

- 01/04/16 a las 17:40 horas, atención prestada por el Dra. TATIANA ODETH MOSQUERA STOMER (MEDICO GENERAL) *"Se revalora paciente estable, con mejoría de su cuadro clínico de ingreso, no fiebre, tolera vía oral. Se decide dar egreso con signos de alarma para reconsultar: intolerancia a la vía oral, fiebre persistente, no respira bien, dolor abdominal, si se pone morado, etc, el familiar refiere entender"*

Atención en Clínica Santa Sofía de Buenaventura.

- 01/04/16 a las 23:45 horas, atención prestada por el Dr. GERMAN JOSE SANJUELO CONRADO (MEDICO GENERAL) *"CC de +- 12 horas de evolución, consistene en fiebre no cuantificada asociado a tos húmeda y dificultad respiratoria, acude a COMFAMAR donde realizan laboratorios encontrando leucocitosis, dan egreso, con formula medica, ingresa en malas condiciones generales, polipneica, con agregados pulmonares. Se decide ingresar para cubrimiento, con corticoides, inhaladores, y toma de nuevos laboratorios, paciente febril"* Al examen físico encuentra hipoactiva.
- 02/04/16 a las 01:01 horas, atención prestada por el Dr. GERMAN JOSE SANJUELO CONRADO (MEDICO GENERAL) *"CC de +- 12 horas de evolución, consistente, en tos húmeda asociada a dificultad respiratoria, paciente ingresa en malas condiciones generales polipneica con tirajes intercostales agregados puloanres, se revisa rx torax encontrando infiltrados para hiliares, sin consolidados aereos, paciente con leve mejoría pero persiste con agregados pulmonares, se decide dejar en observación para valoración por pediatría, se inicia antibioticoterapia, teniendo en cuenta lecucitgos iniciales de 25 mil reportados en 2do nivel".* Diagnóstico: Bronquiolitis sobre infectada. Inicia líquidos endovenosos, antibiótico, terapia respiratoria, inhaladores.
- 02/04/16 a las 01:57 horas, atención prestada por TERAPIA RESPIRATORIA. *"Ingresa al servicio en brazos de su madre, dormida, con signos de dificultad respiratoria severa, aleteo nasal, tirajes infracostales, supracostales, disbalance toracoabdominal. SV FC 257 ppm, SATO2 0.98"* suministran oxígeno por venturi.
- 02/04/16 a las 04:04 horas, atención prestada por el Dra. MILDRED LUCIA FERNANDEZ QUIRAMA (MEDICO GENERAL) *"Insuficiencia respiratoria 2ria a bronquiolitis sobreinfectada, sospecha de sepsis de origen pulmonar, riesgo inminente de falla ventilatoria". "Paciente ingresa a observación en malas condiciones generales, taquicárdica, con distres respiratorio marcado a pesar de soporte de oxígeno por ventury" "recibió a su ingreso dosis de antipiretico endovenoso pero persiste con alza termica de 39 grados". "Paciente con marcada distensión abdominal se indica paso de SOG observando drenaje de debito sanguinolento" "reactante de fase aguda significativamente aumentada con rx de torax con horizontalización de los arcos costales, silueta cardiotímica normal, con infiltrados parahiliares, sin consolidaciones ni*

atelectasias, a nivel abdominal se observa marcada distensión de asas". Considera traslado a Unidad de Cuidado Intensivo Pediátrico.

- 02/04/16 Nota retrospectiva 4:50 a.m atención prestada por Dr. IVAN ALEXANDER PINTO MARTINEZ (PEDIATRA) quien reinterroga a la madre *"cuadro clínico de inicio 23/03/2016 dado por rinorrea hialina y tos, manejado por pediatra particular con terapia respiratoria la cual inició el 28/03/2016 con posterior inicio de alteración características de deposiciones pastosas y fétidas, el día 31/03/16 inicia cuadro febril cuantificado en 38 grados con tirajes intercostales, tos e hipoactiva"* *"paciente quien primeramente fue llevada a comfamar en la mañana del 1ero de abril donde realizan laboratorios que muestran leucocitosis con neutrofilia leve trombocitosis...sin embargo dan salida con manejo con sulanp"*
- 02/04/16 a las 5:22 a.m nota auxiliar enfermería AURA PAOLA SANCHEZ. *"por orden médica se intuba con TOT conectado a ventilación mecánica"*
- 02/04/16 a las 06:19 horas, atención prestada por el Dr. IVAN ALEXANDER PINTO MARTINEZ (PEDIATRA): Ingresa a UCI en malas condiciones generales, con diagnósticos de insuficiencia respiratoria, hemorragia alveolar difusa, sepsis de origen pulmonar, neutropenia febril, coagulación intravascular diseminada descompensada. Requiere intubación orotraqueal, tratamiento inotrópico y vasoactivo, manejo de hemorragia alveolar, tratamiento antibiótico de amplio espectro con cefepime amikacina, transfusión de globulos rojos, toma de exámenes complementarios, rx torax muestra infiltrados algodonosos multilobar radiopacidad en hemitorax izquierdo.
- 02/04/16 Nota retrospectiva de las 6:00 horas atención prestada por el Dr. IVAN ALEXANDER PINTO MARTINEZ (PEDIATRA). Realizan maniobras de reanimación avanzada por 2 paros cardiorrespiratorios por más de 30 minutos y la paciente fallece.

Exámenes aportados:

- 02.04.16 Leucocitos 2650 Neutrófilos 380 Linfocitos 2060 Monocitos 20 Hb 8.9 Plt 396.000 PT 35.9 PTT 51 INR 3.75

3. RELACION CAUSA EFECTO O ANEXO DE CAUSALIDAD

Las infecciones virales respiratorias tienen un curso aproximado de duración entre 7 a 10 días, sin embargo, en una minoría de pacientes y por diferentes motivos estas pueden prolongarse o complicarse incluyendo una sobre infección respiratoria por bacterias. La infección bacteriana puede localizarse a nivel de los bronquiolos, bronquios o pulmonar y/o extenderse de forma

sistémica a la sangre o a otros órganos con alteraciones gastrointestinales (por ejemplo), posteriormente causando sepsis y falla ventilatoria que llevan al fallecimiento de la paciente.

CUESTIONARIO PRESENTADO

1. **¿Hubo un adecuado enfoque diagnóstico en la primera atención en urgencias en la Clínica Comfenalco de Buenaventura?**

En la primera atención en Clínica Comfenalco de Buenaventura se contempló la presencia de infección respiratoria por lo cual dan salida con antibiótico ampicilina/sulbactam. Sin embargo la paciente en ese momento presenta signos de respuesta inflamatoria sistémica dada por taquicardia, leucocitosis, neutrofilia, fiebre, y dada la edad de la paciente (lactante menor) requería manejo intrahospitalario o remisión a un nivel mayor de atención que cuente con servicio de pediatría para manejo de soporte, antibiótico endovenoso y vigilar evolución.

2. **¿Hubo un inicio oportuno de antibióticos al sospechar infección respiratoria?**

Al sospechar infección respiratoria si hubo un inicio del tratamiento antibiótico oportuno. Sin embargo, dado que la paciente ya presenta signos de infección sistémica, el antibiótico oral y los cuidados en casa no son suficientes para controlar esta infección. **Requería manejo y soporte intrahospitalario por especialista en pediatría.**

3. **¿La atención en el segundo lugar de atención de la paciente Clínica Santa Sofía de Buenaventura fue adecuada?**

En la Clínica Santa Sofía de Buenaventura hubo un manejo oportuno de la paciente con tratamiento antibiótico y tratamiento de soporte con líquidos endovenosos, terapia respiratoria con soporte con venturi y posteriormente intubación orotraqueal; sin embargo, ya se encontraba en un punto de no retorno en cuanto su cuadro clínico dado por la gravedad de la infección que estaba presentando, clínicamente una falla ventilatoria y sepsis.

4. **¿La institución hospitalaria contaba con los elementos necesarios para realizar el tratamiento? ¿contaba con los laboratorios en el lugar? ¿contaba con unidad de cuidados intensivos o estaba sujeta a la red de prestadores?**

En la Clínica Santa Sofía de Buenaventura si contaba con todos los elementos requeridos para la atención del paciente incluidos unidad de cuidados intensivos con buena oportunidad, terapia respiratoria, ventilación mecánica, medicamentos disponibles y personal disponible.

5. ¿Cuáles son las recomendaciones a seguir cuando existe un cuadro clínico de los que presentaba la menor?

Cuando un niño presenta signos de respuesta inflamatoria sistémica y especialmente si se trata de un lactante menor se debe tratar, si la Institución de salud a la que consulta tiene los medios para hacerlo, de lo contrario se debe remitir a un nivel de mayor complejidad que cuente con especialista en Pediatría. **Un niño con signos de respuesta inflamatoria sistémica no se le debe tratar ambulatoriamente.**

ANALISIS CIENTIFICO

Paciente lactante menor de 4 meses de edad quien consulta en Clínica Comfenalco de Buenaventura con cuadro respiratorio donde no es clara la duración. Según historias clínicas puede corresponder a 7 días hasta un mes de evolución. El cuadro clínico consiste en rinorrea hialina, tos, incremento progresivo de dificultad respiratoria. En esta primera atención se enfoca como bronquiolitis con sobre infección bacteriana e inician tratamiento antibiótico con ampicilina sulbactam. Sin embargo los datos del examen físico, signos vitales y laboratorios dan cuenta de la presencia de signos de respuesta inflamatoria sistémica en la paciente. Al presentar este tipo de cuadro clínico se infiere que la infección se ha extendido de forma sistémica y requiere manejo intrahospitalario, **en este punto no se puede dejar la responsabilidad de cuidado a los familiares en casa debido a que en adelante hay alta probabilidad de complicaciones, el paciente requiere atención por personal de salud especializado.**

En la nota médica de salida de esta institución se describe a la paciente como estable, con mejoría de su cuadro clínico después del tratamiento administrado (antipiréticos y terapia respiratoria), sin embargo, no hay datos de signos vitales que confirmen esta información.

En adelante, lo más probable es que el cuadro infeccioso continuara su curso mientras estaba en casa y aproximadamente 6 horas después de la salida se presenta en muy regulares condiciones a otra clínica (Clínica Santa Sofía Buenaventura) donde se inicia nuevamente el proceso de atención pero la paciente se encuentra en un punto de no retorno de la infección y sepsis en la cual toda maniobra de resucitación es inefectiva.

Las infecciones respiratorias en pediatría son muy frecuentes, según datos del Instituto Nacional de Salud en Colombia un niño consulta en promedio tres veces por año por infección respiratoria aguda (IRA). Se encuentra entre las principales causas de hospitalización en menores de 2 años. Siete de cada 10 niños que mueren por IRA son menores de un año de edad.

En IRA se encuentra la bronquiolitis que ocurre en los menores de un año de edad con un pico entre los 3 a 6 meses de edad, el principal virus implicado en bronquiolitis es el Virus Sincitial Respiratorio

(VSR) que causa entre el 70 a 80% de los casos de bronquiolitis, entre otros virus se encuentra Influenza, Parainfluenza, Rhinovirus, Adenovirus, Metapneumovirus, Mycoplasma pneumoniae y SARS COV2 entre otros. La fisiopatología de esta infección es principalmente un acúmulo de detritus en las vías respiratorias terminales como son los bronquiolos, obstruyendo parcialmente el paso del aire por acumulación de células inflamatorias y moco principalmente, ocurre una destrucción de la arquitectura del epitelio respiratorio dificultando su función de limpieza del aparato respiratorio. En algunos pacientes (20-30%) adicionalmente se presenta cierre de los bronquiolos por acción del músculo respiratorio localizado alrededor de los mismos lo cual dificulta aún más el paso del aire por estas vías. A medida que la infección evoluciona el epitelio se va recuperando y vuelve a funcionar normalmente, momento en el cual el paciente presenta mejoría de síntomas alrededor del día 7 a 10 del inicio de la infección.

El cuadro clínico de bronquiolitis se caracteriza por un inicio de síntomas respiratorios altos como rinorrea y tos, fiebre, posteriormente presenta sibilancias y en algunas ocasiones progresa a dificultad respiratoria. Sin embargo la mayoría de los niños resuelven este cuadro con medidas como aseo nasal, tratamiento de la fiebre, hidratación y solo el 2% requiere hospitalización. Los pacientes con bronquiolitis que se complican progresan a sobreinfección y/o insuficiencia respiratoria, presentando signos clínicos como dificultad respiratoria, intolerancia a la vía oral, fiebre prolongada más allá de lo esperado para el cuadro clínico, somnolencia, irritabilidad, desaturación entre otros. La sobre infección puede presentarse por bacterias como *S. pneumoniae*, *H. influenzae*, *S. aureus* entre otras causando leucocitosis, incremento de reactantes de fase aguda, hallazgos anormales en radiografía de tórax, signos de respuesta inflamatoria sistémica, signos de dificultad respiratoria. Cuando ocurren estas complicaciones los lactantes menores deben ser hospitalizados y prestarles manejo de soporte como hidratación endovenosa, terapia respiratoria, tratamiento antibiótico (si es necesario), observación y manejo por personal especializado en pediatría y si es necesario traslado a Unidad de Cuidado Intensivo Pediátrico.

El cuadro clínico de la paciente es compatible con bronquiolitis con sobreinfección bacteriana dado por edad de la paciente, cuadro clínico, tratamiento inicial con beta 2 agonista, signos de respuesta inflamatoria sistémica e insuficiencia respiratoria que progresa y finalmente presenta deceso.

SOPORTE BIBLIOGRAFICO:

1. Something Is Changing in Viral Infant Bronchiolitis Approach. Frontiers in Pediatrics 2022
Link: <https://www.frontiersin.org/articles/10.3389/fped.2022.865977/full>
2. Activity of Oral ALS-008176 in a Respiratory Syncytial Virus Challenge Study. NEJM.,
Link: <https://www.nejm.org/doi/10.1056/NEJMoa1413275>

3. Factors Associated With Pneumonia Severity in Children: A Systematic Review • JPIDS 2018:7
Link: <https://pubmed.ncbi.nlm.nih.gov/29850828/>
4. Is Higher Viral Load in the Upper Respiratory Tract Associated With Severe Pneumonia? Findings From the PERCH Study. CID, 2018.
Link:
https://www.researchgate.net/publication/317245470_Is_Higher_Viral_Load_in_the_Upper_Respiratory_Tract_Associated_With_Severe_Pneumonia_Findings_From_the_PERCH_Study
5. Guia de la práctica clínica para evaluación del riesgo y manejo inicial de la neumonía en niños y niñas menores de 5 años y bronquiolitis en niños y niñas menores de 2 años. Sistema General de Seguridad Social en Salud – Colombia. 2014 - Guia No. 42.
Link: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/CA/gpc-completa-neumonia-bronquiolitis.pdf
6. World Health Organization. Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Evidence Summaries. Geneva: World Health Organization; 2014
Link: <https://www.ncbi.nlm.nih.gov/books/NBK264162/>
7. Application of a Prognostic Scale to Estimate the Mortality of Children Hospitalized with Community-acquired Pneumonia. PIDJ, 2015.
Link:
https://www.researchgate.net/publication/285573866_Application_of_a_Prognostic_Scale_to_Estimate_the_Mortality_of_Children_Hospitalized_with_Community-Acquired_Pneumonia
8. Human Rhinoviruses. Clinical Microbiology Reviews. 2013.
Link: <https://journals.asm.org/doi/10.1128/CMR.00077-12>

Atentamente,



MARLEN ANABEL ORTIZ BURGOS

C.C.: 38601255

ESPECIALISTA EN INFECTOLOGÍA PEDIÁTRICA

TP / RM: 521445

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ANEXOS

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| 1. Something Is Changing in Viral Infant Bronchiolitis Approach. Frontiers in Pediatrics 2022 | (6 FOLIOS) |
| 2. Activity of Oral ALS-008176 in a Respiratory Syncytial Virus Challenge Study. NEJM,. | (11 FOLIOS) |
| 3. Factors Associated With Pneumonia Severity in Children: A Systematic Review • JPIDS 2018:7 | (12 FOLIOS) |
| 4. Is Higher Viral Load in the Upper Respiratory Tract Associated With Severe Pneumonia? Findings From the PERCH Study. CID, 2018. | (10 FOLIOS) |
| 5. World Health Organization. Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Evidence Summaries. Geneva: World Health Organization; 2014 | (34 FOLIOS) |
| 6. Application of a Prognostic Scale to Estimate the Mortality of Children Hospitalized with Community-acquired Pneumonia. PIDJ,2015.
Link: | (06 FOLIOS) |
| 7. Human Rhinoviruses. Clinical Microbiology Reviews. 2013. | (28 FOLIOS) |
| 8. COPIA DE LA HISTORIA CLINICA APORTADA PARA ESTUDIO | (27 FOLIOS) |
| 9. OFICIO CON LA RELACION DE PERITAJES EMITIDOS | (01 FOLIOS) |
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Something Is Changing in Viral Infant Bronchiolitis Approach

Paolo Bottau^{1†}, Lucia Liotti^{2†}, Eleonora Laderchi^{3†}, Alessandra Palpacelli^{2†}, Elisabetta Calamelli^{1†}, Carlotta Colombo³, Laura Serra^{1‡} and Salvatore Cazzato^{2‡}

¹ Pediatric and Neonatology Unit, Imola Hospital, Imola, Italy, ² Pediatric Unit, Department of Mother and Child Health, Salesi Children's Hospital, Ancona, Italy, ³ Postgraduate School of Pediatrics, University of Bologna, Bologna, Italy

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Renato Cutrera,
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United Kingdom
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Pontificia Universidad Católica de
Chile, Chile

*Correspondence:

Paolo Bottau
paolo.bottau@gmail.com

[†]These authors have contributed
equally to this work and share first
authorship

[‡]These authors share
senior authorship

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Acute Viral Bronchiolitis is one of the leading causes of hospitalization in the first 12–24 months of life. International guidelines on the management of bronchiolitis broadly agree in recommending a minimal therapeutic approach, not recommending the use of bronchodilators. Guidelines, generally, consider bronchiolitis as a “unique disease” and this runs the risk of not administering therapy in some patients who could benefit from the use of bronchodilators, for instance, in those who will develop asthma later in their life and face first episode in the age of bronchiolitis. Today, there is growing evidence that bronchiolitis is not a single illness but can have different “endotypes” and “phenotypes,” based on age, personal or family history of atopy, etiology, and pathophysiological mechanism. There is evidence that some phenotypes of bronchiolitis are more strongly associated with asthma features and are linked to higher risk for asthma development. In these populations, possible use of bronchodilators might have a better impact. Age seems to be the main feature to suggest a good response to a bronchodilator-trial, because, among children > 6 months old with bronchiolitis, the presence of a subset of patients with virus-induced wheezing or the first episode of asthma is more likely. While waiting for new research to define the relationship between therapeutic options and different phenotypes, a bronchodilator-trial (using short-acting β_2 agonists with metered-dose inhalers and valved holding chambers) seems appropriate in every child with bronchiolitis and age > 6 months.

Keywords: bronchiolitis, guideline, viral bronchiolitis phenotype, bronchodilator, valved holding chambers

INTRODUCTION

Acute Viral Bronchiolitis is one of the leading causes of lower respiratory tract infection and hospitalization in the first 12–24 months of life (1, 2). Several guidelines have been published on the diagnosis and management of bronchiolitis; these guidelines have different reference ages in the diagnosis (<24 months in United States and <12 months in Europe), but basically agree in recommending a minimal therapeutic approach without the use of bronchodilators (3–6).

Accumulating evidence has revealed that bronchiolitis is not a single disease but can have different “endotypes” and “phenotypes” based on age of presentation, personal or family history of atopy, etiology, pathophysiological mechanism and clinical presentation (7–10). Therefore, today something seems changing in the viral infant bronchiolitis approach: in some phenotypes, drug treatment may be effective.

In this review, we try to address these topics, evaluating the different etiopathogenetic, clinical and therapeutic aspects of acute viral bronchiolitis.

PATHOGENETIC MECHANISMS

Bronchiolitis is more often described as inflammation and oedema of the bronchioles caused by respiratory viruses that invade the epithelial cells of the small airways. Although the exact mechanism is unknown, epithelial cells become necrotic and are sloughed off with an excessive amount of mucus. This condition leads to obstruction of the bronchioles and varying degrees of bronchospasm and air trapping (11).

Bronchiolitis is mostly associated with respiratory syncytial virus (RSV), that is detected in 50–80% of the hospitalized bronchiolitis cases (1, 12, 13). Other viruses can also be associated with bronchiolitis: rhinovirus (RV), human bocavirus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, coronavirus. Viral co-infections (usually with RSV and RV) are detected in 10–40% of severe cases (12). RSV is an RNA virus with two antigenically different subtypes (A with 11 genotypes and B with 23 genotypes) (14). RSV infection can be transmitted through direct inoculation of contaminated secretions in the nasal and conjunctival mucosa or by inhalation of large respiratory droplets (2, 15). Reinfections in young children are possible and are usually mild, although severe cases have been reported (16).

RSV binds to epithelial cells and replicates, causing epithelial necrosis and ciliary destruction. After being infected by RSV, the epithelial cells are sloughed to lower respiratory tract, where the virus infects the ciliated epithelial cells of the bronchioles mucosa and pneumocytes in the alveoli. Viral attachment to the target cell is mediated by F and G RSV surface glycoproteins. Epithelial cells necrosis results in the inflammatory response, by increasing the production of cytokines, including alarmins, chemokines, and growth factors. This inflammatory milieu attracts innate lymphoid cells, dendritic cells, and granulocytes to the site of infection (17, 18).

A strong induction of antiviral type I and type III interferons and interferon-induced genes is the primary response of the RSV infected mucosa, but RSV has developed the capacity to evade this innate interferon (INF) response through RSV-NS1/2 proteins, which are able to reduce both IFN-I and INF-III responses (19, 20). The disease state following RSV infection is associated with an increase in IL-17 production. This cytokine is more prominent in neonates, thus contributing to more severe clinical aspects (21, 22).

Intraluminal airway obstruction is caused by cellular infiltration of the peribronchiolar tissue, mucus overproduction, sloughing of infected epithelial cells and inefficient ciliary beating (15). Air trapping and varying degrees of lobar collapse can be caused by plugs composed of cellular debris and mucus in the bronchiole lumens (1). Viral clearance is permitted by innate and adaptive immune responses and the bronchiolar epithelium begins to regenerate within 3–4 days after the symptoms resolution. Currently, many studies indicate an association between RSV bronchiolitis and subsequent development of asthma (8).

Three RSV genotypes have been identified: NA1, ON1, and BA, respectively. The NA1 genotype infects young infants and is related to a more severe clinical course; the BA genotype

is associated with eosinophilia and family history of asthma, while, in general, the ON1 genotype is associated with less severe symptoms (23). Interestingly, Harford et al. found that RSV infection resulted in dysregulation of β 2-adrenergic receptor (β 2AR) function, position and number. This dysregulation can explain the ineffectiveness of β 2 agonists in treating obstruction in RSV infected patients (24).

The second most common virus causing bronchiolitis during infancy is RV. Its detection frequently occurs in children over 12 months of age. RV is an RNA Enterovirus belonging to the Picornaviridae family.

Lower respiratory tract infections are typically due to a RSV infection, particularly in very young children; on the contrary, RV infections are more common in slightly older children, in those with atopic predisposition in particular, and can cause severe wheezing (17). Lower respiratory tract infection is usually caused by RV type A, while severe wheezing is more commonly linked to RV type C infection (13, 25).

A partial defect in mucosal antiviral innate interferon responses may be related to a higher risk of severe RV infection and wheezing in young children with a family history of allergy and asthma. Cadherin-related family member 3 (CDHR3) has recently been identified as a unique receptor for RV-C (26), thus explaining the high pathogenic potential of RV-C. It is important to underline that an increased risk of childhood asthma has been associated with a polymorphism in the CDHR3 gene (27). RV infections seem to induce a milder epithelial inflammation than RSV, but in RV infections the expression of IFN type I decreases, with a predominant Th2 immune response (28).

Recently, a group of Italian researchers has demonstrated the presence of differing Th1/Th2 balance in patient hospitalized during the peak epidemic months or out of this period. The latter group was found to have a higher Th2 polarization in the immune response with a greater production of IL-4 and lower levels of IFN γ ; therefore, they hypothesize the presence of two phenotypes of bronchiolitis: the first with RSV infection during the peak period and the second with a possible genetic predisposition to atopy and hospitalized during the non-peak season (29).

In conclusion, bronchiolitis is due to direct viral cytotoxic injury in conjunction with a robust host inflammatory response, but the relative contribution remains uncertain and is probably related to the type of virus involved and to the variability of the individual immune response. The role of the underlying genetic mechanisms is not yet clearly understood.

CLINICAL PRESENTATION

Diagnosis of acute bronchiolitis is clinical, supported by epidemiological and virological data. The term is generally applied to the first episode of wheezing in infants younger than 12–24 months of age (2, 5, 8). Peak incidence occurs between 3 and 6 months of age (1). After an incubation period of 4–6 days, infants show signs of upper respiratory tract infection (2): cough, runny nose, and fever are followed by lower respiratory distress characterized by nasal flaring, tachypnea, increased work of breathing with intercostal, subcostal or supraclavicular

retractions, use of abdominal muscles and grunting in the next 1–3 days (1, 8). Multiple respiratory sounds can be heard: respiratory crackles and bilateral wheezing are typical (1). Acute viral bronchiolitis is a quite dynamic disease: clinical severity usually peaks around 3–5 days from the symptoms onset, and the minute-to-minute variation in clinical findings is characteristic, as mucus and debris are cleared from the airways by coughing or as the child becomes asleep or agitated; thus, several examinations are recommended (1). Clinical assessment is also possibly confounded by nasal congestion, the resolution of which, with nasal discharge, can help ascertain whether respiratory sounds come from lower respiratory tract (2). Fever can be present in almost 30% of infants and usually occurs early in the course of disease (30).

Most infants have a mild clinical form that resolves in 10–14 days and can be managed at home; cough usually resolves within 2–3 weeks (31). Infant aged <3 months, born pre-term or with cardiopulmonary (e.g., chronic lung disease or congenital heart disease), immunodeficiency or neuromuscular disorders are at greater risk of severe disease, with complications including apnoea or bacterial infection (32). In particular, preterm infants are at a higher risk of apnoea (with a reported rate from 1 to 24%) (2), especially if with a corrected age of <2 weeks, birth weight <2.3 kg, respiratory rate <30 or >70 at presentation, and SpO₂ of 90% or less at presentation (33).

RSV infection is typically associated with an increased severity of presentation, while other viruses cause milder phenotypes (26, 34). In a retrospective cohort of previously healthy RSV-infected patients, respiratory failure was associated with lethargy, grunting, and a PaCO₂ ≥ 65 mmHg at initial emergency department presentation (35, 36).

Hospitalization is usually recommended when children present with poor feeding, severe retractions, oxygen saturation of 92% or less, a respiratory rate higher than 60/min and in the presence of significant social risk factors (e.g., poor parental reliability or inadequate home environment) (35). Severity Scoring tools have been developed and validated to be used in clinical settings and can be useful for an objective measure. In general, these scores should be integrated with other measures and repeated to obtain clinical assessment to guide practical decisions (1, 7).

Finally, attempts have recently been made to characterize the clinical phenotype of bronchiolitis. Dumas et al. identified several clinical profiles from a multicenter study on children admitted to hospital with bronchiolitis: Profile A with high probability of RV etiology, history of wheezing and wheezing at presentation, eczema, and older age of the patient; profile B: wheezing at presentation, but no history of wheezing or eczema and high probability of RSV infection; profile C: the most severely ill group, with a longer hospital stay, and a high probability of RSV infection; profile D: the less severe illness, including non-wheezing children with a shorter length of hospitalization (26). A clinical respiratory assessment of the first bronchiolitis episode based on lung-X-rays, respiratory outcomes (hypoxemia, wheezing, and/or sub-costal retractions), nasal protein levels of antiviral and type 2 cytokines (IFN γ , IL-10, IL-4, IL-13, IL-1 β ,

and TNF α) was conducted also by Arroyo et al. (37) in 2020 to define mild, hypoxemia or wheezing phenotypes.

These studies provide informations about outcomes, disease patterns and underlying airway immunobiology and, above all, they may be the evidence of the need of a tailored clinical and therapeutic approach (8, 27).

THERAPEUTIC OPTIONS

Among international guidelines, there is broad agreement on the role of support therapy; it is well-established that bronchiolitis management should be focused on guarantying proper hydration and oxygenation of the child. Intravenous or nasogastric fluid administration is recommended to ensure hydration whenever oral route is non-viable. Moreover, the enteral route should be preferred to the intravenous route (1). Oxygen therapy is recommended in children with peripheral oxygen saturation below 92% (1, 38) and should be performed through standard oxygen therapy (SOT) or *via* high flow nasal cannula (HFNC), providing heated and humidified air (39, 40).

Drug administration is ground for controversy, as corticosteroids, nebulized hypertonic saline, and nebulized epinephrine are mostly not recommended, while β 2 agonist bronchodilators are contemplated in some guidelines and object of a long-lasting debate (1, 41–43). Although several guidelines advise against bronchodilators administration (4–6), in some countries, such as in Italy (3), the β 2 agonist trial is considered as a possibility in selected cases as well. The recommendation of some guidelines on minimal handling of bronchiolitis (3–6) may result in several concerns of pediatric care providers and in the lack of adherence to the guidelines themselves (7, 44).

The indication on the utility of bronchodilators is mainly based on Gadomski and Scribani Chochrane systematic review, which states that albuterol administration does not result in a significant reduction in hospitalization or disease duration in non-hospitalized children. However, these same authors point out that some children may benefit from the administration of bronchodilators (45). As Wall suggests (42), it may be possible that some children, who will develop asthma later in their life, may experience their first episode in the age range of bronchiolitis and, thus, be indistinguishable from children with “pure” bronchiolitis (4, 42). This could be the reason why older patients (>6–12 months) with history of personal or familial atopy, moderate to severe respiratory distress and wheeze as predominant auscultatory feature (i.e., no crackles) may improve with an asthma type therapy (42). Common practice as well suggests that clinical features of bronchiolitis in infants under 3 months of age are quite different from infants 8–12 months old. These data have been confirmed by two Italian studies, that noted how bronchiolitis in infants under 6 months of age is different from that in infants older than 6 months (46, 47).

Recent evidence noted that several pathogenetic clusters based on age, viral agents, immune phenotype, presence of wheeze and crackles, disease severity and risk of recurrent wheezing and asthma may underlie bronchiolitis (7–10). One group may be formed by very young infants (<6 months of age) with

RSV infection and increased risk of recurrent wheezing; instead, another group may comprise older children (>6 months of age) with RV infection, atopic predisposition, high risk of developing asthma (8) and, probably, a better response to bronchodilators. Although much more evidence is required, proposals were put forward for a more personalized treatment, based on the hypothesis of different entities of bronchiolitis (8, 48). An interesting recent study by Rodríguez-Martínez et al. (49) found out that therapeutic options based on a phenotypic-guided strategy are also more cost-effective than a guideline-guided strategy.

Considering all these data, there is evidence that some phenotypes of bronchiolitis are more strongly associated with asthma features and are linked to higher risk for asthma development. In these populations, use of bronchodilators might have a better impact. More specifically, we propose that an inhaled bronchodilator trial could be considered particularly in children older than 6 months of age, but two specific conditions must be advised. The first is that in these infants, that we can consider as “viral wheezers,” bronchodilators should be administered by metered-dose inhalers and valved holding chambers, as recommended by current guidelines, since this method is more effective and with less side effects than nebulized therapy (50, 51). The second is the indication to observe a clinical improvement with clinical scores after the bronchodilator trial (52). The dose and the time when to re-evaluate the clinical picture are still debated, perhaps the treatment scheme of worsening asthma in children younger than 5 years proposed by the GINA 2021 guidelines (short-acting β_2 agonist: 2–4 puff every 20' for three times in the first hour and review) can be applied (51).

Similarly to bronchodilators, the use of corticosteroid is not recommended in the management of infant bronchiolitis (1), but is part of the treatment of viral wheezing or asthma, so we agree that a course of corticosteroid could be indicated in moderate to severe clinical pictures, when the bronchodilators trial gave a positive result (42, 53–56).

These several data and considerations stress the necessity of subtype-specific studies, in order to evaluate the clinical response to different treatments and meet the need for a more personalized precision therapy.

DISCUSSION AND CONCLUSION

Bronchiolitis is one of the major health problems in infants around the world, but unfortunately, to date, no therapy has been validated for the management of this disease. Many guidelines have been published by various scientific societies, which agree on minimal handling (i.e., hydration and the administration of oxygen as the only treatment options) (3–6). Unfortunately, this approach risks excluding some patients who might benefit from the bronchodilator treatment (48). However, as pointed out by the American Academy of Pediatrics, guidelines are intended

to assist clinicians in decision making and are not intended to “replace clinical judgment or establish a protocol for the care of all children with bronchiolitis” (5). In light of the data emerging from the scientific literature, acute bronchiolitis should no longer be considered as a single disease but rather as characterized by different phenotypes and endotypes (7–10, 26). In particular, it seems that the phenotype characterized by older age, type 2 immune response, personal or family (first-degree) history of atopy, RSV genotypes (ON1 and BA) or RV etiology and infection during non-RSV-predominant or non-peak viral months may have a good response to a trial with bronchodilators (48).

Evaluating all the evidence, age seems to be the main feature that may suggest a good response to the bronchodilator-trial. For instance, in the research by Dumas et al., the “profile A” (patient with personal or family history of wheezing and eczema, wheezing at clinical presentation, and RV infection) is often >6 months, probably have initial sign of asthma and may respond to a short-acting β_2 agonist-trial (26, 57). Probably, the “true” bronchiolitis (in which therapy is useless) affects the child <6 months. This hypothesis may be supported by epidemiological data (1, 4), showing that bronchiolitis reaches its peak of incidence between 3 and 6 months, and by other studies suggesting that bronchiolitis in infants under 3–6 months of age is quite different from that in infants >6 months old (46, 47).

In a recent multicenter study with the objective of identifying factors associated with the use of albuterol among infants hospitalized for bronchiolitis, Condella et al. found that there is a subgroup of patients to whom clinicians preferentially administer albuterol. Characteristics of these infants mainly include presentation with wheeze and older age (>6 months), and these children may be similar to those affected by viral wheezing or their first episode of asthma (58).

This knowledge suggests that among infants >6 months with bronchiolitis, there could be a subset of patients who may have a virus-induced wheezing or their first episode of asthma and may respond to the bronchodilator-trial (4, 42).

To conclude, there is evidence that some phenotypes of bronchiolitis are more strongly associated with asthma features and are also linked to higher risk for asthma development. In these populations, use of bronchodilators might have a better impact.

Looking forward to future RCTs targeted to assess the utility of short-acting β_2 agonists in different bronchiolitis phenotypes, a bronchodilator-trial (using short-acting β_2 agonists with metered-dose inhalers and valved holding chambers) could be performed in infants with bronchiolitis and age > 6 months.

AUTHOR CONTRIBUTIONS

PB and LL designed the review. PB, LL, EL, AP, and CC performed literature search and draft the manuscript. PB, LL, and EC review and editing. LS and SC supervision the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

- Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. *Lancet*. (2017) 389:211–24. doi: 10.1016/S0140-6736(16)30951-5
- Meissner HC. Viral bronchiolitis in children. *N Engl J Med*. (2016) 374:62–72. doi: 10.1056/NEJMra1413456
- Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, Rimini A, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. *Italian J Pediatr*. (2014) 40:65. doi: 10.1186/1824-7288-40-65
- Bronchiolitis in Children: Diagnosis and Management. *National Institute for Health and Care Excellence: Guidelines*. London: National Institute for Health and Care Excellence (NICE) (2021). Available online at: <http://www.ncbi.nlm.nih.gov/books/NBK573086/> (accessed August 4, 2021).
- Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. (2014) 134:e1474–e502. doi: 10.1542/peds.2014-2742
- O'Brien S, Borland ML, Cotterell E, Armstrong D, Babl F, Bauert P, et al. Australasian bronchiolitis guideline. *J Paediatr Child Health*. (2019) 55:42–53. doi: 10.1111/jpc.14104
- Rodríguez-Martínez CE, Castro-Rodríguez JA, Nino G, Midulla F. The impact of viral bronchiolitis phenotyping: Is it time to consider phenotype-specific responses to individualize pharmacological management? *Paediatr Respir Rev*. (2020) 34:53–8. doi: 10.1016/j.prrv.2019.04.003
- Jartti T, Smits HH, Bønnelykke K, Bircan O, Elenius V, Konradsen JR, et al. Bronchiolitis needs a revisit: distinguishing between virus entities and their treatments. *Allergy*. (2019) 74:40–52. doi: 10.1111/all.13624
- Polack FP, Stein RT, Custovic A. The syndrome we agreed to call bronchiolitis. *J Infect Dis*. (2019) 220:184–6. doi: 10.1093/infdis/jiz082
- Petrarca L, Nenna R, Di Mattia G, Frassanito A, Castro-Rodríguez JA, Rodríguez Martínez CE, et al. Bronchiolitis phenotypes identified by latent class analysis may influence the occurrence of respiratory sequelae. *Pediatr Pulmonol*. (2022) 57:616–22. doi: 10.1002/ppul.25799
- Smith DK, Seales S, Budzik C. Respiratory syncytial virus bronchiolitis in children. *Am Fam Physician*. (2017) 95:94–9.
- Mansbach JM, Piedra PA, Teach SJ, Sullivan AF, Forgey T, Clark S, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med*. (2012) 166:700–6. doi: 10.1001/archpediatrics.2011.1669
- Miller EK, Gebretsadik T, Carroll KN, Dupont WD, Mohamed YA, Morin L-L, et al. Viral etiologies of infant bronchiolitis, croup and upper respiratory illness during 4 consecutive years. *Pediatr Infect Dis J*. (2013) 32:950–5. doi: 10.1097/INF.0b013e31829b7e43
- Vandini S, Biagi C, Lanari M. Respiratory syncytial virus: the influence of serotype and genotype variability on clinical course of infection. *Int J Mol Sci*. (2017) 18:E1717. doi: 10.3390/ijms18081717
- Silver AH, Nazif JM. Bronchiolitis. *Pediatr Rev*. (2019) 40:568–76. doi: 10.1542/pir.2018-0260
- Lambert L, Sagfors AM, Openshaw PJ, Culley FJ. Immunity to RSV in early-life. *Front Immunol*. (2014) 5:466. doi: 10.3389/fimmu.2014.00466
- Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol*. (2017) 140:895–906. doi: 10.1016/j.jaci.2017.08.003
- Rossi GA, Colin AA. Infantile respiratory syncytial virus and human rhinovirus infections: respective role in inception and persistence of wheezing. *Eur Respir J*. (2015) 45:774–89. doi: 10.1183/09031936.00062714
- Kalinowski A, Galen B, Ueki I, Sun Y, Mullen A, Osafo-Addo A, et al. Respiratory syncytial virus activates epidermal growth factor receptor to suppress interferon regulatory factor 1-dependent interferon-lambda and antiviral defence in airway epithelium. *Mucosal Immunol*. (2018) 11:958–67. doi: 10.1038/s41385-017-120
- Thwaites RS, Coates M, Ito K, Ghazaly M, Feather C, Abdulla F, et al. Reduced nasal viral load and IFN responses in infants with RSV bronchiolitis and respiratory failure. *Am J Respir Crit Care Med*. (2018) 198:1074–84. doi: 10.1164/rccm.201712-2567OC
- Mukherjee S, Lindell DM, Berlin AA, Morris SB, Shanley TP, Hershenson MB, et al. IL-17-induced pulmonary pathogenesis during respiratory viral infection and exacerbation of allergic disease. *Am J Pathol*. (2011) 179:248–58. doi: 10.1016/j.ajpath.2011.03.003
- de Almeida Nagata DE, Demoor T, Ptaschinski C, Ting H-A, Jang S, Reed M, et al. IL-27R-mediated regulation of IL-17 controls the development of respiratory syncytial virus-associated pathogenesis. *Am J Pathol*. (2014) 184:1807–18. doi: 10.1016/j.ajpath.2014.02.004
- Midulla F, Nenna R, Scagnolari C, Petrarca L, Frassanito A, Viscido A, et al. How respiratory syncytial virus genotypes influence the clinical course in infants hospitalized for bronchiolitis. *J Infect Dis*. (2019) 219:526–34. doi: 10.1093/infdis/jiy496
- Harford TJ, Rezaee F, Gupta MK, Bokun V, Naga Prasad SV, Piedimonte G. Respiratory syncytial virus induces b2-adrenergic receptor dysfunction in human airway smooth muscle cells. *Sci Signal*. (2021) 14:eabc1983. doi: 10.1126/scisignal.abc1983
- Turunen R, Koistinen A, Vuorinen T, Arku B, Söderlund-Venermo M, Ruuskanen O, et al. The first wheezing episode: respiratory virus etiology, atopic characteristics, and illness severity. *Pediatr Allergy Immunol*. (2014) 25:796–803. doi: 10.1111/pai.12318
- Dumas O, Mansbach JM, Jartti T, Hasegawa K, Sullivan AF, Piedra PA, et al. A clustering approach to identify severe bronchiolitis profiles in children. *Thorax*. (2016) 71:712–8. doi: 10.1136/thoraxjnl-2016-208535
- Bønnelykke K, Sleiman P, Nielsen K, Kreiner-Møller E, Mercader JM, Belgrave D, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. *Nat Genet*. (2014) 46:51–5. doi: 10.1038/ng.2830
- Spann KM, Tran KC, Collins PL. Effects of nonstructural proteins NS1 and NS2 of human respiratory syncytial virus on interferon regulatory factor 3, NF- κ B, and proinflammatory cytokines. *J Virol*. (2005) 79:5353–62. doi: 10.1128/JVI.79.9.5353-5362.2005
- Nenna R, Frassanito A, Petrarca L, Di Mattia G, Pierangeli A, Scagnolari C, et al. RSV bronchiolitis in infants hospitalized during the epidemic peak and non-peak months: different Th1/Th2 response. *Am J Respir Crit Care Med*. (2018) 197:A2865.
- McCulloh R, Koster M, Ralston S, Johnson M, Hill V, Koehn K, et al. Use of intermittent vs continuous pulse oximetry for nonhypoxemic infants and young children hospitalized for bronchiolitis: a randomized clinical trial. *JAMA Pediatr*. (2015) 169:898–904. doi: 10.1001/jamapediatrics.2015.1746
- Thompson M, Vodicka TA, Blair PS, Buckley DI, Heneghan C, Hay AD, et al. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ*. (2013) 347:f7027. doi: 10.1136/bmj.f7027
- Karampatsas K, Kong J, Cohen J. Bronchiolitis: an update on management and prophylaxis. *Br J Hosp Med (Lond)*. (2019) 80:278–84. doi: 10.12968/hmed.2019.80.5.278
- Paluch L. Identifying and managing bronchiolitis. *J Am Acad Phys Assist*. (2020) 33:12–5. doi: 10.1097/01.JAA.0000694944.22382.39
- Ramagopal G, Brow E, Mannu A. Demographic, clinical and hematological profile of children with bronchiolitis: a comparative study between respiratory syncytial virus [RSV] and [Non RSV] groups. *J Clin Diagn Res*. (2016) 10:SC05–S8. doi: 10.7860/JCDR/2016/20331.8262
- Kou M, Hwang V, Ramkellawan N. Bronchiolitis: from practice guideline to clinical practice. *Emerg Med Clin North Am*. (2018) 36:275–86. doi: 10.1016/j.emc.2017.12.006
- Prodhan P, Sharoor-Karni S, Lin J, Noviski N. Predictors of respiratory failure among previously healthy children with respiratory syncytial virus infection. *Am J Emerg Med*. (2011) 29:168–73. doi: 10.1016/j.ajem.2009.08.020
- Arroyo M, Salka K, Perez GF, Rodríguez-Martínez CE, Castro-Rodríguez JA, Gutierrez MJ, Nino G. Phenotypical sub-setting of the first episode of severe viral respiratory infection based on clinical assessment and underlying airway disease: a pilot study. *Front Pediatr*. (2020) 8:121. doi: 10.3389/fped.2020.00121
- Cunningham S, Rodríguez A, Adams T, Boyd KA, Butcher I, Enderby B, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet*. (2015) 386:1041–8. doi: 10.1016/S0140-6736(15)00163-4
- Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. A Randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med*. (2018) 378:1121–31. doi: 10.1056/NEJMoa1714855

40. Lin J, Zhang Y, Xiong L, Liu S, Gong C, Dai J. High-flow nasal cannula therapy for children with bronchiolitis: a systematic review and meta-analysis. *Arch Dis Child*. (2019) 104:564–76. doi: 10.1136/archdischild-2018-315846
41. Elliott SA, Gaudet LA, Fernandes RM, Vandermeer B, Freedman SB, Johnson DW, et al. Comparative efficacy of bronchiolitis interventions in acute care: a network meta-analysis. *Pediatrics*. (2021) 147:e2020040816. doi: 10.1542/peds.2020-040816
42. Wall MA. Bronchodilators and steroids should not be given in viral bronchiolitis - CON. *Paediatr Respir Rev*. (2019) 32:20–2. doi: 10.1016/j.prrv.2019.09.001
43. Brown MA. Bronchodilators and steroids should not be given in viral bronchiolitis - PRO. *Paediatr Respir Rev*. (2019) 32:18–9. doi: 10.1016/j.prrv.2019.09.002
44. Wolf ER, Richards A, Lavalley M, Sabo RT, Schroeder AR, Scheffl M, et al. Patient, provider, and health care system characteristics associated with overuse in bronchiolitis. *Pediatrics*. (2021) 148:e2021051345. doi: 10.1542/peds.2021-051345
45. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev*. (2014) 2014:CD001266. doi: 10.1002/14651858.CD001266.pub4
46. Nenna R, Frassanito A, Petrarca L, Di Mattia G, Midulla F. Age limit in bronchiolitis diagnosis: 6 or 12 months? *Front. Pediatr*. (2020) 8:144. doi: 10.3389/fped.2020.00144
47. Ferrante G, Fondacaro C, Cilluffo G, Dones P, Cardella F, Corsello G. Identification of bronchiolitis profiles in Italian children through the application of latent class analysis. *Italian J Pediatr*. (2020) 46:147. doi: 10.1186/s13052-020-00914-4
48. Rodríguez-Martínez CE, Nino G, Castro-Rodríguez JA, Acuña-Cordero R, Sossa-Briceño MP, Midulla F. For which infants with viral bronchiolitis could it be deemed appropriate to use albuterol, at least on a therapeutic trial basis? *Allergol Immunopathol (Madr)*. (2021) 49:153–8. doi: 10.15586/aei.v49i1.12
49. Rodríguez-Martínez CE, Nino G, Castro-Rodríguez JA, Perez GF, Sossa-Briceño MP, Buendia JA. Cost-effectiveness analysis of phenotypic-guided versus guidelines-guided bronchodilator therapy in viral bronchiolitis. *Pediatr Pulmonol*. (2021) 56:187–95. doi: 10.1002/ppul.25114
50. Csonka P, Tapiainen T, Mäkelä MJ, Lehtimäki L. Optimal administration of bronchodilators with valved holding chambers in preschool children: a review of literature. *Eur J Pediatr*. (2021) 180:3101–9. doi: 10.1007/s00431-021-04074-3
51. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. (2021). Available online at: <http://www.ginasthma.org>
52. Rodríguez-Martínez CE, Sossa-Briceño MP, Nino G. Systematic review of instruments aimed at evaluating the severity of bronchiolitis. *Paediatr Respir Rev*. (2018) 25:43–57. doi: 10.1016/j.prrv.2016.12.006
53. Alansari K, Sakran M, Davidson BL, Ibrahim K, Alrefai M, Zakaria I. Oral dexamethasone for bronchiolitis: a randomized trial. *Pediatrics*. (2013) 132:e810–6. doi: 10.1542/peds.2012-3746
54. Koistinen A, Lukkarinen M, Turunen R, Vuorinen T, Vahlberg T, Camargo CA, et al. Prednisolone for the first rhinovirus-induced wheezing and 4-year asthma risk: a randomized trial. *Pediatr Allergy Immunol*. (2017) 28:557–63. doi: 10.1111/pai.12749
55. Jartti T, Nieminen R, Vuorinen T, Lehtinen P, Vahlberg T, Gern J, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. *J Allergy Clin Immunol*. (2015) 135:691–8.e9. doi: 10.1016/j.jaci.2014.07.001
56. Hurme P, Homil K, Lehtinen P, Turunen R, Vahlberg T, Vuorinen T, et al. Efficacy of inhaled salbutamol with and without prednisolone for first acute rhinovirus-induced wheezing episode. *Clin Exp Allergy*. (2021) 51:1121–32. doi: 10.1111/cea.13960
57. Dumas O, Erkkola R, Bergroth E, Hasegawa K, Mansbach JM, Piedra PA, et al. Severe bronchiolitis profiles and risk of asthma development in Finnish children. *J Allergy Clin Immunol*. (2021). doi: 10.1016/j.jaci.2021.08.035. [Epub ahead of print].
58. Condella A, Mansbach JM, Hasegawa K, Dayan PS, Sullivan AF, Espinola JA, et al. Multicenter study of albuterol use among infants hospitalized with bronchiolitis. *West J Emerg Med*. (2018) 19:475–83. doi: 10.5811/westjem.2018.3.35837

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ORIGINAL ARTICLE

Activity of Oral ALS-008176 in a Respiratory Syncytial Virus Challenge Study

John P. DeVincenzo, M.D., Matthew W. McClure, M.D., Julian A. Symons, D.Phil., Hosnieh Fathi, M.D., Christopher Westland, B.A., Sushmita Chanda, Ph.D., Rob Lambkin-Williams, Ph.D., Patrick Smith, Pharm.D., Qingling Zhang, Ph.D., Leo Beigelman, Ph.D., Lawrence M. Blatt, Ph.D., and John Fry, B.S., R.G.N.

ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) infection is a cause of substantial morbidity and mortality. There is no known effective therapy.

METHODS

We conducted a randomized, double-blind, clinical trial in healthy adults inoculated with RSV. Participants received the oral nucleoside analogue ALS-008176 or placebo 12 hours after confirmation of RSV infection or 6 days after inoculation. Treatment was administered every 12 hours for 5 days. Viral load, disease severity, resistance, and safety were measured throughout the 28-day study period, with measurement beginning before inoculation. The primary end point was the area under the curve (AUC) for viral load, which was assessed immediately before administration of the first dose through the 12th day after inoculation in participants infected with RSV.

RESULTS

A total of 62 participants received placebo or one of three ALS-008176 dosing regimens: 1 loading dose of 750 mg followed by 9 maintenance doses of 500 mg (group 1), 1 loading dose of 750 mg followed by 9 maintenance doses of 150 mg (group 2), or 10 doses of 375 mg (group 3). In the 35 infected participants (23 of whom were treated with ALS-008176), the AUCs for viral load for groups 1, 2, and 3 and the placebo group were 59.9, 73.7, 133.4, and 500.9 log₁₀ plaque-forming-unit equivalents × hours per milliliter, respectively ($P \leq 0.001$). The time to nondetectability on polymerase-chain-reaction assay ($P < 0.001$), the peak viral load ($P \leq 0.001$), the AUC for symptom score ($P < 0.05$), and the AUC for mucus weight were lower in all groups receiving ALS-008176 than in the placebo group. Antiviral activity was greatest in the two groups that received a loading dose — viral clearance was accelerated ($P \leq 0.05$), and the AUC for viral load decreased by 85 to 88% as compared with the placebo group. Within this small trial, no viral rebound or resistance was identified. There were no serious adverse events, and there was no need for premature discontinuation of the study drug.

CONCLUSIONS

In this RSV challenge study, more rapid RSV clearance and a greater reduction of viral load, with accompanying improvements in the severity of clinical disease, were observed in the groups treated with ALS-008176 than in the placebo group. (Funded by Alios BioPharma; ClinicalTrials.gov number, NCT02094365.)

From the Departments of Pediatrics, Microbiology, Immunology, and Biochemistry, University of Tennessee College of Medicine, and the Children's Foundation Research Institute at Le Bonheur Children's Hospital — both in Memphis (J.P.D.); Alios BioPharma, South San Francisco (M.W.M., J.A.S., C.W., S.C., Q.Z., L.B., L.M.B., J.F.); RetroScreen Virology, London (H.F., R.L.-W.); d3 Medicine, Parsippany, NJ (P.S.); and the University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, NY (P.S.). Address reprint requests to Dr. DeVincenzo at the Children's Foundation Research Institute, Le Bonheur Children's Hospital, Rm. 400R, 50 N. Dunlap St., Memphis, TN 38103, or at jdevincenzo@uthsc.edu.

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RESPIRATORY SYNCYTIAL VIRUS (RSV) INfections are a cause of substantial morbidity and mortality in various patient populations worldwide, including children. Globally, RSV infections were estimated to cause 3.4 million hospitalizations and 66,000 to 199,000 deaths in 2005 in children younger than 5 years of age, primarily in the developing world.¹ In U.S. infants, RSV infection causes substantial outpatient disease² and is a common cause of hospitalization.³ The risk of death from respiratory causes is nine times as high among U.S. infants with RSV infection as the risk among infants with influenza.⁴ Immunocompromised patients and elderly patients, especially those with coexisting conditions, are also at a higher risk for severe RSV infections.⁵⁻⁷

Currently, the standard of care for the management of RSV infection is limited to supportive care.⁸ There are no licensed RSV vaccines, and palivizumab, an RSV-specific monoclonal antibody, is recommended only for the prevention of RSV infection in the small percentage of infants who are born prematurely or who have serious underlying conditions.^{9,10}

Viral load appears to drive the clinical manifestations of RSV disease. Higher viral loads have been associated with more severe disease in infants and children,^{11,12} faster rates of RSV clearance are associated with more rapid improvements in hospitalized children,¹³ and the onset, peak, and resolution of disease parallel the viral dynamics in adults.¹⁴

ALS-008176 is an orally bioavailable prodrug of the novel RSV replication inhibitor ALS-008112, a cytidine nucleoside analogue (the molecular structure of ALS-008176 is shown in Fig. S4 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In non-clinical studies, ALS-008112 enters various types of epithelial cells in the respiratory tract and is subsequently phosphorylated to form an intracellular nucleoside triphosphate with a half-life of approximately 29 hours. The nucleoside triphosphate analogue inhibits RSV replication by means of chain termination.

A phase 1 study of oral ALS-008176 identified no safety signals in a group of 76 healthy adults who received dosing regimens containing up to 2 loading doses of 750 mg followed by up to 26 maintenance doses of 500 mg that were administered every 12 hours over 14 days (see the de-

scription of safety data in Section 3.0 in the Supplementary Appendix). The current study, which used an established experimental viral challenge model, was conducted to evaluate proof of concept for the antiviral activity of ALS-008176 in healthy adults infected with a clinical strain of RSV.

METHODS

STUDY PARTICIPANTS

Participants were 18 to 45 years of age and had a median serum neutralizing antibody titer for the Memphis-37b challenge virus of 973 Mu (range, 187 to 2023 Mu), which represented the lowest quartile of the screened population.^{14,15} The selection criteria are available in the Supplementary Appendix and in the protocol, which is available at NEJM.org.

STUDY DESIGN

We conducted this randomized, double-blind, placebo-controlled study over three separate study periods. Up to 22 eligible participants per period were confined to a specialized quarantine unit for 14 days (starting 2 days before inoculation and ending 12 days after inoculation [study days -2 to 12]), and outpatient assessments were conducted on study days 16 and 28 (Fig. S1 in the Supplementary Appendix). On study day 0, participants were inoculated intranasally with 4 log₁₀ plaque-forming-units (PFUs) of the RSV-A Memphis 37b challenge virus.¹⁶ From study day 2 until randomization, we monitored participants twice daily for RSV infection, using a Simplexa (Focus Diagnostics) qualitative reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay. The samples tested were fresh, nonfrozen, nasal washings. Participants underwent randomization and received the first dose of ALS-008176 or placebo approximately 12 hours after the qualitative detection of RSV or on the morning of day 6, whichever occurred first.

The number of participants receiving each dose and the dosing regimens for the first study period were predefined. The protocol allowed for the modification of these specifications in subsequent study periods, by a monitoring group whose members were aware of the study-group assignments, on the basis of emerging data on the numbers of participants who became infected after inoculation, the timing of that infection

relative to randomization, safety, and pharmacokinetic and viral kinetic data (see Section 4.0 and Fig. S1 in the Supplementary Appendix, and the protocol).

In each of the three study periods, ALS-008176 or matching placebo was administered orally every 12 hours over 5 days (10 total doses). Three ALS-008176 dosing regimens were evaluated over the three study periods: a single loading dose of 750 mg followed by 9 maintenance doses of 500 mg (group 1), a single loading dose of 750 mg followed by 9 maintenance doses of 150 mg (group 2), and 10 doses of 375 mg (group 3). The study medication was prepared by a pharmacist who was aware of the treatment assignments. The placebo consisted of methylcellulose and water, which was also used to administer ALS-008176. The investigators and all other members of the study team were unaware of the treatment assignments.

STUDY OVERSIGHT

The study was conducted in accordance with the Declaration of Helsinki (1996 version), the International Conference on Harmonisation Good Clinical Practice guidelines, applicable regional and local regulations, and the study protocol. The protocol was approved by the Medicines and Healthcare Products Regulatory Agency and the Cambridge East Regional Ethics Committee of the National Research Ethics Service, all in the United Kingdom. All participants provided written informed consent. The study was sponsored by Alios BioPharma and was designed and managed by the sponsor and the first author; the sponsor and the first author were also responsible for the data analysis. All authors were involved in the collection, analysis, or interpretation of the data. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

END POINTS AND ASSESSMENTS

The prespecified primary end point was the area under the curve (AUC) for viral load in nasal washes, as determined by the measurement of RSV RNA with the use of a quantitative RT-PCR assay.^{14,15,17,18} Measurements were obtained immediately before administration of the first dose of the study drug or placebo through day 12. Secondary end points included time to nondetectability of the virus, the slope of the curve for

viral load during the first 24 to 48 hours after the start of dosing, peak viral load, scores for symptoms related to RSV, and the AUC for mucus weight. All efficacy data were collected and analyzed by study team members and technicians who were unaware of the treatment assignments.

After the inoculation of participants on study day 0, the RSV load in nasal-wash samples was measured twice daily from study days 2 through 12 and once on study days 16 and 28.¹⁸ Specimens were stored at a temperature of -80°C from the time of sample collection until the time of analysis. Results were reported as $\log_{10}$ PFU equivalents (PFUe) per milliliter. In aliquots of nasal washes, we also amplified and sequenced the RSV L gene region that encodes the polymerase domain (amino acids 550 to 1100) to evaluate for mutations developing during treatment that conferred resistance to the study drug. This region includes the sites of all amino acid substitutions previously shown to confer *in vitro* resistance to ALS-008112 (M628L, A789V, L795I, I796V). There are no other known sites of ALS-008112 resistance. Amino acid sequences were compared with a participant's first available RSV-positive sample and with the reference RSV Memphis 37b sequence.¹⁶ The criteria for selecting participants for the evaluation of resistance are defined in Section 5.0 in the Supplementary Appendix. Although none of the participants met the prespecified criteria for the evaluation of resistance, 29 participants (17 receiving ALS-008176 and 12 receiving placebo) were selected for evaluation on the basis of less stringent, post hoc criteria (defined in Section 5.0 of the Supplementary Appendix).

Symptoms of RSV infection were assessed three times daily during confinement and once on study day 16 with the use of an established participant-reported symptom score.¹⁵ Mucus weight was determined every 24 hours by measuring the net weight of secretions within facial tissues.

Safety data were collected through study day 28 (± 3 days). The principal investigator, who was unaware of the treatment assignments, regularly assessed adverse events for the possibility of a relationship between an event and the study medication. Symptoms recorded on diary cards by participants were documented as adverse events only if the investigator considered them to be substantial. Plasma samples were collected

and analyzed with the use of high-performance liquid chromatography and tandem mass spectrometry to characterize the pharmacokinetic assessments of ALS-008176, ALS-008112, and other metabolites after each dose of ALS-008176.

STATISTICAL ANALYSIS

All participants who were inoculated with the challenge virus and received at least one dose of study drug were included in the safety (intention-to-treat [ITT]) population (Fig. S2 in the Supplementary Appendix). Participants who were RSV-positive according to the results of quantitative RT-PCR assay immediately before dosing (baseline) or who subsequently became positive on at least two occasions after baseline were defined as infected and were included in the primary analysis population for efficacy evaluation (ITT-infected population). Pharmacokinetic analysis was performed on all participants in the ITT population from whom at least one blood specimen had been obtained for the purpose of pharmacokinetic measurement.

On the basis of an enrollment of 20 participants per study period and three study periods, the study had a power of approximately 80% to detect a 50% reduction in the AUC for viral load for the comparison of active, drug-containing regimens with placebo, assuming a 45% coefficient of variation in the AUC for viral load. Up to 22 participants per study period were enrolled to allow for dropouts. Randomization was performed with the use of a permuted-block algorithm.

The primary end point was assessed for each of the three regimens for ALS-008176 as compared with placebo with the use of a mixed-effects model that included a repeated-measures approach to allow for unequal variances, with baseline viral load as a covariate. The errors were assumed to be normally distributed, and a standard covariance structure was assumed. The null hypothesis was that there was no difference between each of the three active treatment regimens and placebo. This same model was used to assess the following secondary end points: the slope of the viral load during the 24-hour and 48-hour periods after first dose, peak viral load, and total RSV symptom score for the AUC (from the time just before administration of the first dose to study day 16).

Between-group differences were evaluated with the use of an analysis-of-variance model,

with treatment as the dependent variable for the following secondary end points: time to the point at which RSV was not detectable, time to symptom resolution, and the AUC for mucus weight (from the time just before administration of the first dose to study day 12). ALS-008176 dosing regimens were individually compared with the pooled placebo group, and all comparisons were two-sided, with the level of significance set at 0.05. The results for participants receiving the same dosing regimen in different study periods were pooled and analyzed as a single treatment regimen.

RESULTS

PARTICIPANT DISPOSITION AND PRETREATMENT CHARACTERISTICS

Among 302 persons screened for participation in the study (Fig. S2 in the Supplementary Appendix), 64 met the criteria for eligibility and were inoculated during one of the three study periods. Two participants did not receive a dose; 1 withdrew consent because of a family emergency, and the other had an elevated baseline level of serum alanine aminotransferase that was cause for exclusion. Of the remaining 62 participants (ITT population), 35 (56%) met the definition for RSV infection and were included in the ITT-infected population.

The pretreatment characteristics of the participants were similar across treatment regimens in both the ITT and ITT-infected populations (Table 1). The mean baseline viral load was higher in ITT-infected participants assigned to receive ALS-008176 than in the placebo group.

EFFICACY

A statistically significant reduction ($P \leq 0.001$) in the primary end point, the AUC for viral load, was observed in the ITT-infected population for each ALS-008176 dosing regimen as compared with placebo, with values of 59.9, 73.7, 133.4, and 500.9 $\log_{10}$ PFUe $\times$ hours per milliliter in group 1, group 2, group 3, and the placebo group, respectively (Table 2). These values represented respective reductions of 88.0%, 85.3%, and 73.4% of the AUC for viral load relative to placebo.

Viral load increased logarithmically in the placebo group, peaking approximately 3.5 days after randomization. As compared with placebo, the absolute reductions in viral load in the ALS-

Table 1. Baseline Characteristics of the ITT and ITT Infected Populations.*

Table 1. Baseline Characteristics of the ITT and ITT Infected Populations.*										
Characteristic	ITT Population				ITT Infected Population					
	Group 1 ALS-008176 750 mg LD + 500 mg MD (N = 14)	Group 2 ALS-008176 750 mg LD + 150 mg MD (N = 19)	Group 3 ALS-008176 375 mg (N = 11)	All ALS-008176 Groups (N = 44)	Placebo (N = 18)	Group 1 ALS-008176 750 mg LD + 500 mg MD (N = 8)	Group 2 ALS-008176 750 mg LD + 150 mg MD (N = 7)	Group 3 ALS-008176 375 mg (N = 8)	All ALS-008176 Groups (N = 23)	Placebo (N = 12)
Age — yr	22.4±3.0	24.7±6.2	23.4±2.4	23.7±4.6	24.6±4.3	22.8±3.4	25.1±8.2	23.6±2.6	23.8±5.0	24.4±5.1
Body-mass index	25.4±2.3	23.8±3.0	23.9±2.4	24.4±2.7	22.4±1.6	25.4±2.0	22.7±2.2	23.5±2.6	23.9±2.5	22.7±1.7
Male sex — no. (%)	10 (71)	12 (63)	9 (82)	31 (71)	14 (78)	6 (75)	5 (71)	7 (88)	18 (78)	9 (75)
Race — no. (%)†										
White	13 (93)	16 (84)	10 (91)	39 (89)	13 (72)	7 (88)	5 (71)	8 (100)	20 (87)	8 (67)
Asian	0	1 (5)	1 (9)	2 (5)	1 (6)	0	1 (14)	0	1 (4)	1 (8)
Black	0	2 (11)	0	2 (5)	1 (6)	0	1 (14)	0	1 (4)	0
Other	1 (7)	0	0	1 (2)	3 (17)	1 (13)	0	0	1 (4)	3 (25)
Viral load (log ₁₀ PFUe/ ml)‡	1.2±1.4	1.1±1.6	1.7±1.6	1.3±1.5	1.1±1.4	2.1±1.2	2.9±1.3	2.4±1.4	2.4±1.3	1.6±1.4

* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. ITT denotes intention to treat; LD loading dose, MD maintenance dose, and PFUe plaque-forming-unit equivalents.

[†] Race was self-reported.

[‡] Baseline samples were obtained from the last nasal wash collected before treatment was initiated; the samples were frozen and shipped to a central laboratory. Viral load was assessed with the use of a quantitative reverse-transcriptase–polymerase-chain-reaction assay.

Table 2. Efficacy Results for the ITT-Infected Population.*

End Point	Group 1 (N=8) ALS-008176 750 mg LD + 500 mg MD	Group 2 (N=7) ALS-008176 750 mg LD + 150 mg MD	Group 3 (N=8) ALS-008176 375 mg	Placebo (N=12)
Primary				
AUC viral load from baseline through day 12 (log ₁₀ PFUe × hr/ml)	59.9±69.5	73.7±48.3	133.4±118.4	500.9±219.9
P value	P<0.001	P<0.001	P<0.001	
Reduction relative to placebo (%)	88.0	85.4	73.4	
Secondary				
Time to nondetectability of RSV RNA (days)	1.3±1.3	1.4±0.5	2.3±1.5	7.2±3.1
P value	P<0.001	P<0.001	P<0.001	
Viral load slope: baseline to 24 hr after first dose (log ₁₀ PFUe/ml/24 hr)	-1.7±1.1	-1.7±1.2	-0.2±1.0	0.6±1.8
P value	P<0.001	P>0.02	P=0.66	
Baseline to 48 hours post 1st dose (log ₁₀ PFUe/ml/48 hr)	-1.0±0.5	-1.1±0.9	-0.6±0.5	1.1±1.0
P value	P<0.001	P<0.001	P<0.001	
Peak viral load (log ₁₀ PFUe/ml)	2.3±1.3	3.1±1.1	3.1±1.3	5.3±1.2
P value	P<0.001	P<0.001	P<0.001	
Viral load at 3.5 days after dose 1 (log ₁₀ PFUe/ml)†	0.6±1.1	0.0±0.1	0.8±1.4	4.3±2.1
P value	P<0.001	P<0.001	P<0.001	
AUC of symptom score from baseline through day 16 (change in score × hr)	111.7±94.0	73.2±63.4	113.1±110.3	606.9±564.8
P value	P=0.12	P<0.01	P>=0.01	
AUC of mucus weight from baseline through day 12 (g × no. days)	3.0±2.0*	5.9±6.3	5.4±7.6	18.6±18.4
P value	P>0.02	P=0.09	P=0.06	

* Plus-minus values are means ±SD. The area under the curve (AUC) was calculated with the use of log₁₀ values for viral load. Baseline values were obtained immediately before the first dose of the study drug. P values were calculated for the comparison with placebo. RSV denotes respiratory syncytial virus.

† The viral load at 3.5 days after administration of the first dose represents the time at which the peak mean viral load occurred in the placebo group.

008176 groups were observed within the first 12 hours after the initiation of treatment (i.e., the time between administration of the study drug and the first post-treatment nasal wash) (Fig. 1). The clearance rate of RSV RNA (the slope of the viral load) was most rapid in the two regimens that incorporated a loading dose, but the clearance rates for all three regimens were significantly more rapid during the first 48 hours than the rates for placebo (Table 2 and Fig. 1). There was no evidence of rebound of viral load in any of the treatment regimens after the completion of dosing.

The mean time to nondetectability of RSV

RNA ranged from 1.3 to 2.3 days for the three ALS-008176 regimens as compared with 7.2 days for placebo (P <0.001 for all comparisons). RSV RNA became undetectable in all participants in the ALS-008176 regimens within 4.5 days after the initiation of ALS-008176, except in one participant who received the 375-mg regimen, in whom levels of RSV RNA did not become undetectable until 7 days after the initiation of dosing. In contrast, most participants in the placebo group still had detectable levels of RSV RNA at the end of the 5-day dosing period, and it was not until 11 days after the initiation of dosing that RSV RNA levels became undetectable in all

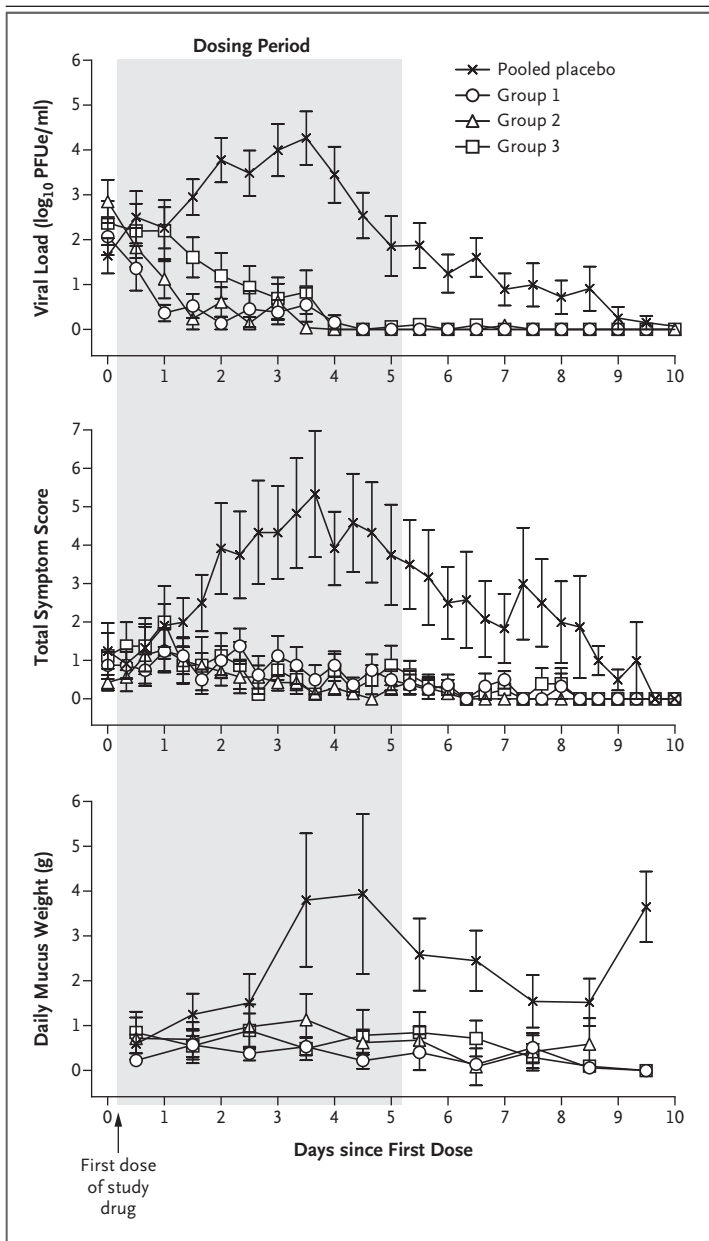


Figure 1. Viral Load, Symptom Score, and Daily Mucus Weight over Time.

Mean viral loads, symptom scores, and mucus weights are shown from the time immediately before administration of the first dose until 10 days afterward (i.e., study day ≥ 12) in the intention-to-treat infected population. Respiratory syncytial virus (RSV) RNA could not be detected in any participant 16 or 28 days after inoculation. Although participants were inoculated with RSV on the same day, they became infected on different days; consequently, they also began treatment on different days. Viral loads were determined with the use of a quantitative reverse-transcriptase–polymerase-chain-reaction assay of nasal-wash samples, which were collected twice daily and analyzed in a central laboratory. Participants recorded symptoms in diaries three times daily. Mucus weights were measured daily and plotted at the time corresponding to the midpoint of the mucus-collection period each day (i.e., weights plotted midway between the first and second days of treatment are from facial tissues collected between the morning of the first day of study treatment and the morning of the second day). After the loading doses were administered in participants in groups 1 and 2, they received maintenance doses every 12 hours until the conclusion of treatment. Treatment group 1 received a loading dose of 750 mg followed by nine maintenance doses of 500 mg, and treatment group 2 received a loading dose of 750 mg followed by nine maintenance doses of 150 mg. Treatment group 3 received 375 mg every 12 hours for 5 days. Plus–minus values are means $\pm$ SE. PFUe denotes plaque-forming-unit equivalents.

participants who received placebo. Mean peak viral loads were lower in each ALS-008176 treatment group than in the placebo group ($P \leq 0.001$ for all comparisons). At the time that the peak viral load occurred in the placebo group, the mean viral load in each of the three ALS-008176 treatment groups was more than 1000 times as low (Fig. 1).

The severity of RSV disease in the three ALS-008176 treatment groups was lower than that in the placebo group as assessed by means of symptom scores and quantity of nasal mucus pro-

duced (Fig. 1). The AUC for the total score for RSV symptoms was significantly reduced in each of the three ALS-008176 treatment groups as compared with placebo ($P \leq 0.05$ for all comparisons), and symptom scores and mucus weights in the treatment groups declined in tandem with the decline in viral load.

Sequence analysis of the RSV *L* gene region encoding the polymerase domain did not detect any of the amino acid mutations associated with in vitro resistance to ALS-008112 (M628L, A789V, L795I, and I796V). In addition, no new mutations associated with the potential emergence of resistance to ALS-008112 were identified.

SAFETY

No serious adverse events, premature discontinuations of the study drug, or clinically significant, treatment-related adverse events were observed in any participants in the ITT population. Adverse events were generally balanced in terms of frequency and intensity across recipients of ALS-008176 and placebo, and all but seven ad-

Table 3. Adverse Events.*

Event or Abnormality	Group 1 (N=14) ALS-008176 750 mg LD + 500 mg MD	Group 2 (N=19) ALS-008176 750 mg LD + 150 mg MD	Group 3 (N=11) ALS-008176 375 mg	All ALS-008176 Groups (N=44)	Placebo (N=18)
Adverse event (%)					
Epistaxis†	4 (29)	5 (26)	1 (9)	10 (23)	2 (11)
Upper respiratory tract infection	1 (7)	2 (11)	0	3 (7)	2 (11)
Cough	2 (14)	0	0	2 (5)	1 (6)
Laboratory abnormality (%)‡					
Elevated alanine aminotransferase level§	3 (21)	2 (11)	2 (18)	7 (16)	3 (17)
Elevated aspartate aminotransferase level	2 (14)	0	0	2 (5)	2 (11)
Low platelet count†¶	1 (7)	0	2 (18)	3 (7)	0
Elevated creatine kinase level	0	2 (11)	0	2 (5)	0

* Safety analyses were based on the primary safety analysis (ITT) population, which was defined as those participants who were inoculated with the challenge virus and received at least one dose of the study drug. An adverse event was listed in this table if it occurred after the start of the study medication in two or more participants receiving a treatment regimen or placebo. Participants were assessed from the time of RSV inoculation through day 28 (± 3). See Section 3.0 in the Supplementary Appendix for further details on evaluations of safety.

† Epistaxis is a recognized complication of upper respiratory tract infection.¹⁷ Epistaxis did not occur in participants whose platelet count was low enough to qualify as an adverse event. All episodes of epistaxis resolved without the need for treatment.

‡ When a laboratory abnormality was considered to be an adverse event, the Division of Acquired Immunodeficiency Syndrome (DAIDS) toxicity grading system was used to define the severity of the event except for cases in which there was no DAIDS criterion for the particular abnormality.

§ A single asymptomatic grade 3 event occurred in treatment group 1 in which the alanine aminotransferase level peaked at 3.6 times the upper limit of the normal range. This peak occurred on day 5 of dosing, and the principal investigator indicated that it was unlikely to be related to the study drug. No potentially hepatotoxic concomitant medications or other causes were identified. Overall, elevations of grades 1–2 (mild to moderate) were balanced across the treatment groups.

¶ The lowest platelet count (116,000 per cubic millimeter) was observed in a participant in whom thrombophlebitis developed at an intravenous cannula site on the same day as the day of sample collection. The lowest values observed in the two remaining participants for whom a low platelet count was defined as an adverse event were 129,000 per cubic millimeter and 134,000 per cubic millimeter. (The lower limit of a normal platelet count was defined as 150,000 per cubic millimeter.) All three events resolved without the need for treatment. The principal investigator at the quarantine unit considered it possible that the count of 116,000 per cubic millimeter was related to the study drug and unlikely that the other two events were related to the study drug.

|| Elevated levels of creatine kinase were reported 9 to 10 days after the completion of dosing with ALS-008176. Both events occurred after the participants were discharged from the quarantine unit (on study day 16), and each was preceded by strenuous exercise. None of these participants had an elevation of grade 1 or higher during dosing or at any time before discharge from quarantine on study day 12. The principal investigator considered it unlikely that either event was related to the study drug.

verse events were mild in severity. Among these seven events, five events — one instance of low platelet levels (in treatment group 1), three instances of elevated alanine aminotransferase levels (in one participant each in treatment group 1, treatment group 2, and the placebo group), and one instance of elevated creatine kinase levels (in treatment group 2) — were moderate. Two events — one instance of elevated alanine aminotransferase levels in group 1 and one instance of elevated creatine kinase levels in group 2 — were severe in intensity. Neither severe adverse event was considered by the investigator to be related to the study drug. The most commonly reported adverse events (more than two partici-

pants reporting an event in any one treatment group) are listed in Table 3. (See Table S4 in the Supplementary Appendix for a comprehensive listing of all adverse events reported after the initiation of dosing; see Section 3.0 in the Supplementary Appendix for further descriptions of safety data in a phase 1 study of ALS-008176.) No clinically relevant findings were identified from laboratory analyses, electrocardiography, or physical examination, including vital signs.

PHARMACOKINETICS

As would be expected for a prodrug that is rapidly metabolized to its parent compound, ALS-008176 concentrations were below the limit of

Table 4. Pharmacokinetic Measures of ALS-008112 after Oral Dosing for ALS-008176.*

Measure	Group 1 (N=14)		Group 2 (N=19)		Group 3 (N=11)	
	ALS-008176 750 mg LD + 500 mg MD		ALS-008176 750 mg LD + 150 mg MD		ALS-008176 375 mg	
	Dose 1	Dose 9 or 10	Dose 1	Dose 9 or 10	Dose 1	Dose 9 or 10
C _{max} (ng/ml)	1740±655	1670±528	1730±750	601±210	1160±555	1580±485
T _{max} (hr)	1.1±0.6	1.1±0.6	1.5±1.4	0.8±0.6	1.0±0.7	0.7±0.3
AUC _{0–12 hr} (ng × hr/ml)	5660±1060	5400±881	5960±1620	1780±263	2710±584	4300±569
C _{min} (ng/ml)	NA	151±48	NA	65±16	NA	114±23

* Levels of ALS-008112 in plasma samples were determined with the use of high-performance liquid chromatography and tandem mass spectrometry. ALS-008176 is a oral prodrug and therefore was rapidly absorbed and efficiently converted to ALS-008112. The active antiviral is formed intracellularly after the triphosphorylation of ALS-008112. Antiviral effects are related to the intracellular concentrations of this triphosphorylated form of ALS-008112, which has an intracellular half-life of approximately 29 hours. The pharmacokinetic population was defined as all participants who received at least one dose of ALS-008176 (ITT population) and from whom at least one measurement of drug concentration was obtained. Actual sample times were used for all analyses. For each of the three regimens, ALS-008176 was administered orally every 12 hours for 5 days. Sampling for pharmacokinetic data occurred on all 5 days of the study. If the first daily dose was administered in the morning, sampling for pharmacokinetic data occurred before administration and at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours after administration. If the first daily dose was administered in the evening, sampling for pharmacokinetic data occurred before administration and at 0.5, 1, 2, 4, and 6 hours after administration. Steady-state pharmacokinetic sampling occurred after a morning dose (maintenance dose 9 or 10) at the following time points: before administration of the dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours after administration. Plus-minus values are means ±SD. AUC_{0–12 hr} denotes area under the concentration–time curve from time 0 to 12 hours, C_{max} the maximum observed concentration, C_{min} the minimum concentration (trough), NA not assessed, and T_{max} the time to reach the maximum plasma concentration.

quantitation at most time points. After administration of the first dose of 750 mg or 375 mg, the T_{max} of the parent nucleoside, ALS-008112, was approximately 1.0 hour and, at steady state (doses 9 or 10), exposures of ALS-008112 appeared to increase in a dose-proportional manner (Table 4). The terminal half-life of ALS-008112 was 63 hours. The pharmacokinetic assessments of the major metabolite of ALS-008112 are shown in Table S1 in the Supplementary Appendix.

DISCUSSION

As compared with placebo, the administration of ALS-008176 resulted in a reduction of viral load, the AUC for viral load, peak viral load, and duration of viral shedding in the 23 infected participants. These effects were associated with concomitant reductions in the severity of clinical disease.

The reason for the antiviral effect probably reflects the mechanism of action of ALS-008176, which inhibits RSV replication within cells already infected in addition to protecting uninfected host respiratory epithelial cells. Other RSV antiviral drugs (e.g., monoclonal antibodies^{19–21}

and small-molecule fusion inhibitors²²) prevent the infection of uninfected cells by blocking cellular entry of the virus, but these drugs do not inhibit viral replication within cells that have already been infected.

Consistent with this mechanism of action, treatment with ALS-008176 resulted in antiviral effects that were different from those observed with a fusion inhibitor in an RSV challenge study with a similar design.¹⁷ First, reduction in viral load was observed to occur more rapidly. The first assessment of viral load, performed 12 hours after ALS-008176 dosing, revealed that the load was already lower than the predose load by 0.5 log₁₀ PFUe per milliliter. In contrast, administration of the fusion inhibitor GS-5806 was associated with an increase in viral load for 24 hours after administration, at which point the load began to decline. Second, the extent of suppression of viral replication was greater with ALS-008176. The reduction in the AUC for viral load in participants treated with ALS-008176 was 73 to 88% as compared with the AUC for viral load for placebo, and the virus was undetectable in all but one participant within 4.5 days of the start of treatment. In contrast, in participants treated with the fusion inhibitor, mean

reduction in the AUC for viral load as compared with placebo was 38 to 67%, and participants continued to have mean viral loads of approximately $0.5 \log_{10}$ PFUe per milliliter for up to 9.5 days after the initiation of treatment. These differences in antiviral effects may translate into clinical benefit or expansion of the therapeutic window, but therapeutic activity and dosing regimens must be determined in clinical trials in naturally infected populations that include immunocompromised patients.

Nucleoside analogues typically have higher barriers to emerging resistance for viruses with higher mutation rates, including the hepatitis C and hepatitis B viruses.^{23,24} A higher barrier to resistance was also observed with ALS-008176 in vitro but not with RSV fusion inhibitors.^{25,26} Although we observed no emergence of resistant viruses, the sample size was quite small for the purposes of such detection. The potential for the emergence of resistance is lower in immunocompetent hosts than in immunocompromised patients, who are known to have prolonged and elevated levels of RSV replication. The emergence of resistance during therapy with RSV monoclonal antibodies has been documented.²⁷ In such situations, nucleoside analogues may offer advantages. More definitive conclusions regarding viral resistance to ALS-008176 should be drawn from patients who become infected in natural settings.

Our proof-of-concept trial had several limitations in addition to the small number of participants. Despite waiting approximately 12 hours after viral detection before starting treatment, we did provide treatment early in the course of infection. In addition, the participants' infections were limited to their upper respiratory tract, and all had preexisting immune memory, which may have aided the eradication of the virus. Patients, particularly infants, who are infected in natural circumstances are likely to present later in the course of disease, with greater disease severity and with more limited preexisting immunity. Therefore, it may be inappropriate to directly extrapolate the results of the study to a clinical setting. The relatively small study size limited our ability to identify potential concerns about the safety of ALS-008176.

In conclusion, this anti-RSV compound shows potential for inhibiting viral replication, reducing clinical disease severity, and clearing virus in infected patients. Clinical trials evaluating ALS-008176 in these patient populations are needed.

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REFERENCES

1. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;375:1545-55.
2. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009;360:588-98.
3. Leader S, Kohlhasse K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr* 2003;143:Suppl:S127-S132.
4. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179-86.
5. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005;352:1749-59.
6. Lee N, Lui GC, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. *Clin Infect Dis* 2013;57:1069-77.
7. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis* 2012;206:56-62.
8. Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev* 2007;1:CD000181.
9. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics* 2014;134:415-20.
10. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics* 2014;134(2):e620-e638.
11. Buckingham SC, Bush AJ, Devincenzo JP. Nasal quantity of respiratory syncytial virus correlates with disease severity in hospitalized infants. *Pediatr Infect Dis J* 2000;19:113-7.
12. DeVincenzo JP, El Saleeby CM, Bush AJ. Respiratory syncytial virus load predicts disease severity in previously healthy infants. *J Infect Dis* 2005;191:1861-8.
13. El Saleeby CM, Bush AJ, Harrison LM, Aitken JA, Devincenzo JP. Respiratory syncytial virus load, viral dynamics, and disease severity in previously healthy naturally infected children. *J Infect Dis* 2011; 204:996-1002.
14. DeVincenzo JP, Wilkinson T, Vaishnaw A, et al. Viral load drives disease in humans experimentally infected with respiratory syncytial virus. *Am J Respir Crit Care Med* 2010;182:1305-14.
15. DeVincenzo J, Lambkin-Williams R, Wilkinson T, et al. A randomized, double-

- blind, placebo-controlled study of an RNAi-based therapy directed against respiratory syncytial virus. *Proc Natl Acad Sci U S A* 2010;107:8800-5.
16. Kim YI, DeVincenzo JP, Jones BG, et al. Respiratory syncytial virus human experimental infection model: provenance, production, and sequence of low-passaged memphis-37 challenge virus. *PLoS One* 2014;9(11):e113100.
 17. DeVincenzo JP, Whitley RJ, Mackman RL, et al. Oral GS-5806 activity in a respiratory syncytial virus challenge study. *N Engl J Med* 2014;371:711-22.
 18. Perkins SM, Webb DL, Torrance SA, et al. Comparison of a real-time reverse transcriptase PCR assay and a culture technique for quantitative assessment of viral load in children naturally infected with respiratory syncytial virus. *J Clin Microbiol* 2005;43:2356-62.
 19. Johnson S, Griego SD, Pfarr DS, et al. A direct comparison of the activities of two humanized respiratory syncytial virus monoclonal antibodies: MEDI-493 and RSHZL9. *J Infect Dis* 1999;180:35-40.
 20. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. *J Infect Dis* 1997;176:1215-24.
 21. Wu H, Pfarr DS, Johnson S, et al. Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. *J Mol Biol* 2007;368:652-65.
 22. Douglas JL, Panis ML, Ho E, et al. Small molecules VP-14637 and JNJ-2408068 inhibit respiratory syncytial virus fusion by similar mechanisms. *Antimicrob Agents Chemother* 2005;49:2460-6.
 23. McCown MF, Rajyaguru S, Le Pogam S, et al. The hepatitis C virus replicon presents a higher barrier to resistance to nucleoside analogs than to nonnucleoside polymerase or protease inhibitors. *Antimicrob Agents Chemother* 2008;52:1604-12.
 24. Zoulim F. Hepatitis B virus resistance to antiviral drugs: where are we going? *Liver Int* 2011;31:Suppl 1:111-6.
 25. Lundin A, Bergström T, Bendrioua L, Kann N, Adamiak B, Trybala E. Two novel fusion inhibitors of human respiratory syncytial virus. *Antiviral Res* 2010;88:317-24.
 26. Yan D, Lee S, Thakkar VD, Luo M, Moore ML, Plemper RK. Cross-resistance mechanism of respiratory syncytial virus against structurally diverse entry inhibitors. *Proc Natl Acad Sci U S A* 2014;111(33):E3441-E3449.
 27. Grad YH, Newman R, Zody M, et al. Within-host whole-genome deep sequencing and diversity analysis of human respiratory syncytial virus infection reveals dynamics of genomic diversity in the absence and presence of immune pressure. *J Virol* 2014;88:7286-93.

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Factors Associated With Pneumonia Severity in Children: A Systematic Review

Preston Dean¹ and Todd A. Florin^{2,3}

¹Cincinnati Children's Hospital Medical Center Residency Training Program, Cincinnati Children's Hospital Medical Center, Ohio; ²Division of Emergency Medicine, Cincinnati Children's Hospital Medical, Ohio; ³Department of Pediatrics, University of Cincinnati College of Medicine, Ohio

Community-acquired pneumonia in children is associated with significant morbidity and mortality; however, data are limited in predicting which children will have negative outcomes, including clinical deterioration, severe disease, or development of complications. The Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) pediatric pneumonia guideline includes criteria that were modified from adult criteria and define pneumonia severity to assist with resource allocation and site-of-care decision-making. However, the PIDS/IDSA criteria have not been formally developed or validated in children. Definitions for mild, moderate, and severe pneumonia also vary across the literature, further complicating the development of standardized severity criteria. This systematic review summarizes (1) the current state of the evidence for defining and predicting pneumonia severity in children as well as (2) emerging evidence focused on risk stratification of children with pneumonia.

Keywords: children; pneumonia; risk stratification; severity.

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality in children worldwide [1]. In the United States, CAP is one of the most frequent and costly reasons for childhood hospitalization [2, 3]. Despite its impact, significant variation exists in the diagnosis and management of children with pneumonia [4–6]. Although practice guidelines can assist with clinical decision making [1, 7, 8], no validated severity criteria exist for children with CAP. The objective of this systematic review is to summarize the current state of evidence for defining and predicting pneumonia severity in children.

PNEUMONIA SEVERITY SCORES

Numerous severity scores have been developed in adults with CAP (Table 1) [9–14]. They have been shown to reduce hospitalizations and administration of broad-spectrum antibiotics [15, 16], but they predict other outcomes with varied success.

The World Health Organization (WHO) defines “pneumonia” in children as presence of cough or difficulty breathing associated with fast breathing or chest indrawing in children 2–59 months of age, whereas “severe pneumonia” is defined as pneumonia plus inability to drink, persistent vomiting, convulsions, lethargy, stridor, or severe malnutrition [1]. These criteria

were developed for use in countries with limited resources, and they are highly sensitive at the cost of specificity.

In the developed world, pediatric CAP guidelines include severity criteria intended to assist site-of-care decision making. The British Thoracic Society (BTS) [8] and the Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) [7] criteria were developed by author consensus (Table 2) and have not been formally derived and validated in children. A recent study found that >50% of children who met PIDS/IDSA severity criteria were safely discharged home from the emergency department (ED) [17].

There are few severity scoring systems developed in children with CAP. A 2016, large-scale, multicenter, prospective cohort study developed a prediction model for severe outcomes (defined as death or need for mechanical ventilation or vasoactive medications) in children hospitalized with CAP [18]. Age extremes, vital signs, chest indrawing, and radiographic infiltrate pattern were the most important predictors. Given its derivation in hospitalized children, its applicability to the ED or clinic is currently unknown.

In a developing nation, Araya et al [19] developed a scoring system (based on age, comorbidities, hypoxemia, hypotension, bacteremia, multilobar/complicated pneumonia, kidney/liver failure, and acute respiratory distress syndrome) to predict mortality in children hospitalized with pneumonia. The application of this system in developed nations is limited.

METHODS

We conducted a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology [20].

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Corresponding Author: Preston Dean, MD, 3333 Burnet Ave, MLC 5018, Cincinnati, OH 45229. E-mail: preston.dean@cchmc.org.

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Table 1. Summary of Existing Pneumonia Severity Scores^a

Severity Score	Components	Area Under the Receiver Operator Characteristic Curve
PSI [10]	Age, Nursing Home, Comorbidities, AMS, Tachypnea, Hypotension, Hypo- or Hyperthermia, Tachycardia, pH <7.35, BUN ≥30, Na <130, Glucose ≥250, Hematocrit <30%, Partial pressure of arterial oxygen <60 mmHg, Pleural Effusion	30-day Mortality: 0.70–0.89 CAP Complications: 0.58–0.85
CURB-65 [11]	Confusion, Urea ≥7 mmol/L, Tachypnea, Hypotension and Age ≥65	30-day Mortality: 0.73–0.87 CAP Complications: 0.60–0.78
IDSA/ATS 2007 [14]	Minor Criteria: Tachypnea, PaO ₂ /FiO ₂ ≤250, Multilobar Infiltrates, Confusion, BUN ≥20, WBC ≤4000, Platelets ≤100 000, Hypothermia, Hypotension Major Criteria: Invasive Mechanical Ventilation, Need for Vasopressors	30-day Mortality: 0.63–0.67 CAP Complications: 0.85–0.88
SMART-COP [9]	Hypotension, Multilobar Infiltrates, Albumin <3.5 g/dL, Tachypnea, Tachycardia, Confusion, Hypoxemia and Arterial pH <7.35	30-day Mortality: Not assessed CAP Complications: 0.83–0.87
SCAP [12]	Major Criteria: pH <7.30, Hypotension Minor Criteria: Confusion, Urea >30 mg/dL, Tachypnea, Multilobar Infiltrates, Hypoxemia, Age ≥80	30-day Mortality: Not assessed CAP Complications: 0.75–0.83
Williams et al [18] (Pediatric)	Age ^{RE} , Sex ^E , Race ^E , Comorbidities ^R , Household smoke exposure, Season, Symptom Duration, Vomiting/feeding refusal, Hypo/Hyperthermia ^E , Tachypnea ^{RE} , Tachycardia ^{RE} , Hypotension ^{RE} , Hypoxemia ^{RE} , AMS ^R , Chest Indrawing ^R , Asymmetric breath sounds, Wheezing, White blood cell count ^E , Infiltrate Pattern ^R , Pleural Effusion ^R	Death or CAP Complications: 0.78–0.81
Araya et al [19] (Pediatric)	Age, Comorbidities, Hypoxemia, Hypotension, Bacteremia, Multilobar/Complicated Pneumonia, Kidney/Liver Failure and Acute Respiratory Distress Syndrome	Death: 0.94

Abbreviations: AMS, altered mental status; CAP, community-acquired pneumonia; ^E, components of electronic health record-based variable model; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; PSI, pneumonia severity index; ^R, components of reduced variable model; SCAP, severe CAP.

^aTable adapted from Pereira JM, Paiva JA, Rello J. Assessing severity of patients with community-acquired pneumonia. *Semin Respir Crit Care Med*. 2012;33:272. CAP complications defined as need for intensive care unit admission, need for mechanical ventilation, or need for vasopressor support.

Literature Search

We searched PubMed, Embase, EBM Reviews, CINAHL, and SCOPUS in February 2018. We limited our search to English language articles in children over the past 20 years. We excluded studies in which a high percentage of subjects had wheezing or diarrhea, use of WHO-definitions of pneumonia without requiring focality on exam or chest x-ray confirmation, or if severe

comorbidities (ie, human immunodeficiency virus [HIV] or malaria) affected generalizability. Our search strategy and results are listed in [Figure 1](#). Included studies are listed in [Table 3](#).

CLINICAL FACTORS

Hypoxemia

The PIDS/IDSA guideline recommends that children who require a fraction of inspired oxygen (FiO₂) of ≥0.50 to maintain an oxygen saturation of >92%, or those with an arterial oxygen partial pressure (PaO₂)/FiO₂ <250, should be admitted to the intensive care unit (ICU) or a unit with continuous cardiorespiratory monitoring [7]. Hypoxemia is also a component of the Pediatric Early Warning Score (PEWS), a validated general early warning score to predict need for ICU care in children [21]. Although the association with hypoxemia with severe outcomes is well recognized, exact thresholds for defining hypoxemia are variable (BTS <92%, PIDS/IDSA <90%) [7, 8].

Numerous studies in developing countries show a consistent association between hypoxemia and mortality in childhood pneumonia [19, 22–25]. In the developed world, supplemental oxygen requirement was the most significant determinant in predicting time to clinical stability in hospitalized children with CAP [26]. The PF ratio has also been shown to be the factor most strongly associated with severe outcomes [18].

Age

The PIDS/IDSA guideline states that infants and young children are at highest risk for severe disease [7]. In the developed world, 1-year-olds have increased odds of severe disease compared with 2-year-olds [18], and infants are more likely to have pneumonia-specific readmissions (adjusted odds ratio [aOR], 1.36; 95%

Table 2. Summary of BTS and PIDS/IDSA Criteria for Severe Pneumonia

British Thoracic Society [8]	Pediatric Infectious Diseases Society/Infectious Diseases Society of America [7]
Temperature >38.5°C	Major Criteria:
Respiratory rate	Invasive mechanical ventilation
• >70 in infants	Fluid refractory shock
• >50 in older children	Acute need for noninvasive positive pressure ventilation
Moderate/severe recession in infants	Hypoxemia requiring FiO ₂ at a higher concentration or flow feasible in general care area
Severe difficulty in breathing in children	Minor Criteria:
Not feeding in infants	Tachypnea for age:
Nasal flaring	• 0–2 months: respiratory rate >60
Cyanosis	• 2–12 months: respiratory rate >50
Apnea	• 1–5 years: respiratory rate >40
Grunting	• >5 years: respiratory rate >20
Tachycardia	Apnea
Signs of dehydration	Increased work of breathing
Capillary refill ≥2 seconds	PaO ₂ /FiO ₂ <250
	Multilobar infiltrates
	Pediatric Early Warning Score >6
	Altered mental status
	Hypotension
	Pleural effusion
	Comorbid conditions
	Unexplained metabolic acidosis

Abbreviations: BTS, British Thoracic Society; FiO₂, fraction of inspired oxygen; IDSA, Infectious Diseases Society of America; PaO₂, oxygen partial pressure; PIDS, Pediatric Infectious Diseases Society.

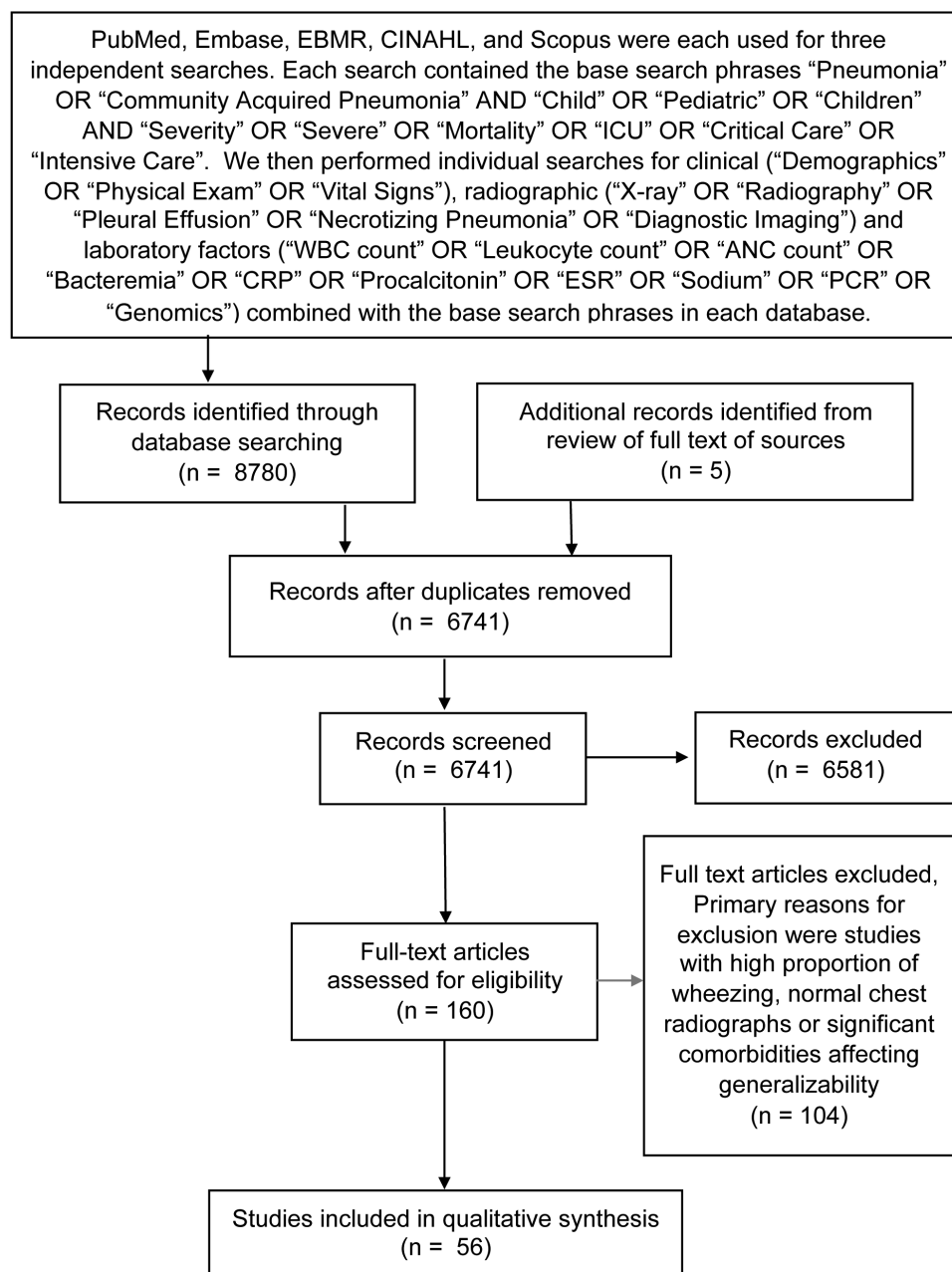


Figure 1. Results from literature search.

confidence interval [CI], 1.14–1.61) [27]. In children hospitalized with pneumonia in the developing world, age <6 months was the strongest factor associated with enteral treatment failure (aOR, 5.15; 95% CI, 2.94–9.02) among children 3–59 months [28], age <4 months was associated with mortality (relative risk [RR], 3.5; 95% CI, 3.0–4.2) among children <24 months [23], and age <6 months was associated with mortality (OR, 2.2; 95% CI, 1.1–4.2) among children <15 years [19].

Tachypnea

Tachypnea is included in the WHO definition, the BTS and PIDS/IDSA severity criteria, and in PEWS [21]. In the

developing world, WHO-defined tachypnea-for-age is associated with mortality [19]. In the developed world, studies found tachypnea-for-age was not associated with severe disease in infants but showed increasing association as children got older (aOR = 0.99–1.53, depending on age) [18].

The use of tachypnea as a severity sign has important limitations, including association with fever, dehydration, and acidosis [29]; physician impression of tachypnea has only fair interrater reliability (kappa 0.42) [30]; and age-based respiratory rate thresholds vary, including conflicting definitions from WHO [1], Pediatric Advanced Life Support [31], and Advanced Pediatric Life Support [32] (Table 4). Recent studies

Table 3. Studies Included in Systematic Review

Study, Year	Region, Setting	Study Design	Age	n	Limitations and Potential Biases
Florin et al [17], 2018	Single center, US, ED	Retrospective	3 months–18 years old	518	Single center, use of ICD coding may have introduced misclassification bias
Williams et al [18], 2016	Multicenter, US, inpatient	Prospective	<18 years old	2319	Definition of mild, moderate, and severe pneumonia based on author opinion, limited to hospitalized patients
Araya et al [19], 2016	Single center, Paraguay, inpatient	Retrospective	<15 years old	860	Single center, retrospective, exclusively inpatient, significant rates of comorbidities
Duke et al [22], 2001	Single center, Papua New Guinea, inpatient	Prospective	28 days–5 years old	703	High rates of malnourished children, lack of invasive interventions available, elevation of 1600 m, use of WHO severity criteria
Djelantik et al [23], 2003	Single center, Indonesia, inpatient	Retrospective	<24 months	4531	Possible selection bias, high rates of malnourishment, lack of invasive interventions, use of WHO severity criteria
Nantanda et al [24], 2008	Single Center, US, ICU and General Wards	Retrospective	2–59 months	157	Retrospective, single center, developing nation with high rates of malnourishment limiting generalizability, used WHO definitions but required either CXR confirmation or excluded children with wheezing with negative CXR
Reed et al [25], 2012	Single center, South Africa, inpatient	Retrospective	<24 months	4148	Limited to young infants, high rates of malnourished children
Wolf et al [26], 2015	Single center, US, inpatient	Post hoc analysis of prospective population-based study	<18 years old	336	Single-site analysis of a multicenter study introducing possible selection bias
Neuman et al [27], 2012	Large-scale Multicenter, US, inpatient	Retrospective	<18 years old	82 566	Children may have been readmitted at nonincluded facility, admission decisions can show great variation between institutions
Mamtani et al [28], 2009	Multicenter, 8 developing countries, inpatient	Post hoc analysis of previous RCT	3–59 months	889	Developing countries, use of WHO severity criteria, treatment dose of amoxicillin 45 mg/kg per day, did not comment on percentage of children with wheezing (bronchiolitis, reactive airway disease) or HIV status
Tiewsoh et al [34], 2009	Single center, India, inpatient	Prospective	2–60 months	200	Use of WHO severity criteria, high rates of malnourishment and overcrowding, high proportion of children had wheezing, possible recall bias
Basnet et al [35], 2006	Single center, Nepal, outpatient/ED	Retrospective	2–60 months	250	Use of WHO severity criteria, developing country, 1300+m above sea level likely influencing degree of hypoxemia
Kuti et al [36], 2013	Single center, Gambia, inpatient	Prospective	2–59 months	420	Used WHO definitions for pneumonia diagnosis and severity, and did not require CXR confirmation (however, did exclude children with wheezing or cough for >2 weeks), single center and developing nation limiting generalizability
Demers et al [37], 2000	Single center, Central African Republic, inpatient	Prospective	<5 years old	395	Developing nation with limited resources and high rates of malnourishment, possible observer bias as “alteration of general status” based on physician opinion and not validated scoring system, possible selection bias (significant proportion of patients absconded due to military uncertainty during the study, and not all patients had CXR performed)
Chisti et al [38], 2013	Single center, Bangladesh, ICU	Retrospective	<5 years old	140	Developing nation, high rates of malnourishment, retrospective, limited to ICU
Hsu et al [41], 2015	Multicenter, Taiwan, ICU	Retrospective	<18 years old	12 577	Retrospective, dependent upon ICD-9 coding, only ICU setting limiting generalizability
Hirsch et al [42], 2016	Multicenter, US, inpatient	Retrospective	Children	12 097	Retrospective, used administrative database relying on ICD coding, all sites are tertiary care referral centers limiting generalizability
Champatiray et al [43], 2017	Single center, India, inpatient	Prospective	2 months–5 years old	141	Single center, exclusively inpatient, use of WHO definitions, CXR were obtained on admission, but study does not mention whether cases were radiographically confirmed, study did not comment on rate of wheezing, history of present illness/social history subject to recall bias, much longer LOS (8–9 days) and much higher mortality rate (22%) than US studies
Muszynski et al [44], 2011	Single Center, US, ICU	Retrospective	<18 years old	23	Retrospective, single center, small n, limited to ICU setting
Grafakou et al [48], 2004	Single center, Greece, inpatient	Retrospective	1–14 years old	167	Single center and only inpatient limiting generalizability, markers for severity were duration of fever and LOS
Kin et al [49], 2009	Single center, Brazil, inpatient	Prospective	<5 years old	113	Single center, excluded bilateral pulmonary infiltrates that could present with more severe disease, severity criteria were WHO and BTS guidelines that are not validated, CXR interpreted by single radiologist

Table 3. Continued

Study, Year	Region, Setting	Study Design	Age	n	Limitations and Potential Biases
Patria et al [50], 2013	Single center, Italy, ED	Retrospective	<14 years old	335	Single center, not all children with CAP during the study period had CXR performed introducing possible selection bias for more severe disease, CXR interpreted by single radiologist, higher than expected mean age (7.5 years old)
McLain et al [51], 2014	Multicenter, US, inpatient	Retrospective	60 days–18 years old	406	Retrospective, CXR interpreted by single radiologist, potential selection bias as this was a sampling of a larger cohort
Ferrero et al [52], 2010	Multicenter, Developing nations, inpatient	Prospective	3–59 months	2536	Exclusively inpatient, use of WHO severity criteria, patients not vaccinated against pneumococcus significantly limiting generalizability, each CXR interpreted by 1 reviewer (possible interobserver bias)
Tapisiz et al [53], 2011	Single center, Turkey, inpatient	Retrospective	<18 years old	501	Single center, retrospective, pre-pneumococcal and <i>Haemophilus</i> vaccination era in this region
Erllichman et al [56], 2017	Multicenter, Jerusalem, inpatient	Retrospective	<18 years old	144	Retrospective, demographics limit generalizability
Langley et al [57], 2008	Multicenter, Canada, inpatient	Retrospective	<18 years old	251	Retrospective, reliant upon chart review and ICD-coding, did not require specific WBC cutoff in pleural fluid to verify diagnosis of empyema
Goldbart et al [58], 2009	Single center, Israel, inpatient	Retrospective	≤8 years old	112	Retrospective, single center, and patients not vaccinated against pneumococcus significantly limiting generalizability, each CXR interpreted by 1 reviewer (possible interobserver bias)
Sawicki et al [61], 2008	Single center, US, inpatient	Retrospective	Children	80	Single-center and retrospective design limit generalizability
Bender et al [62], 2008	Single center, US, inpatient	Retrospective	<18 years old	33	Small n, single-center and retrospective design limit generalizability
Krenke et al [63], 2015	Single center, Poland, inpatient	Retrospective	1 months–18 years old	32	Small n, single-center and retrospective design limit generalizability
Donnelly et al [64], 1998	Single center, US, inpatient	Retrospective	6 months–16 years old	17	Very small n, single center, retrospective
Hacimustafaoglu et al [65], 2004	Single center, Turkey, inpatient	Prospective	6 months–14 years old	108	Single center, each radiographic study interpreted by 1 reviewer (possible interobserver bias)
Hsieh et al [66], 2011	Single center, Taiwan, inpatient	Retrospective	<18 years old	112	Retrospective, single center, relatively few number of cases with BPF (18)
Hsieh et al [67], 2015	Multicenter, Taiwan, inpatient	Prospective	<18 years old	94	All cases limited to 1 region, images were not independently reviewed by 2 pediatric radiologists
Chen et al [70], 2017	Single center, Taiwan, inpatient	Retrospective	6 months–18 years old	142	Single center, retrospective, exclusively inpatient, not all patients during study had an ultrasound performed introducing possible selection bias, intrinsic limitation of ultrasound is that quality of images are operator-dependent (significant number of cases were excluded due to suboptimal images)
Lai et al [71], 2015	Single center, Taiwan, inpatient	Retrospective	Children	236	Retrospective, single center, potential selection bias as children who had lung ultrasound were likely to have more severe pneumonia, ultrasound inherently is operator-dependent
Williams et al [72], 2015	Multicenter, US, inpatient	Retrospective	<18 years old	153	Sampling from larger cohort that only included patients that had CRP and WBC performed thus introducing possible selection bias, retrospective
Don et al [74], 2009	Single center, Italy, ED	Prospective	Children	100	Used hospital admission (institutional and provider differences can play a role) and alveolar infiltrate (vs interstitial) as markers for severity, single center
Prat et al [75], 2003	Single center, Spain, ED	Prospective	6 months–10 years old	85	Primarily studied PCT, ESR, and WBC's ability to predict etiology of CAP; however, secondary analyses revealed no association between WBC and bacteremic patients, which may indicate a more severe disease course, limitations include a relatively small n at a single center limiting generalizability
Wu et al [76], 2015	Single center, China, inpatient	Retrospective	Children	865	Use of WHO definition and severity criteria that are not specific, single center, no mention of exclusion criteria, no mention of how many patients had CXR and what the results of those potential imaging studies may have been, no mention of additional outcomes of cases (ie, mortality, ICU admission, invasive interventions)

Table 3. Continued

Study, Year	Region, Setting	Study Design	Age	n	Limitations and Potential Biases
Agnello et al [78], 2015	Single center, Italy, inpatient	Retrospective	1–14 years old	119	Single center, excluded patients who were hospitalized for more than 48 hours introducing selection bias against more severe cases, clinical markers for severity were hypoxemia (SpO ₂ <92%), dyspnea and tachycardia but not more severe markers or outcomes
Stockmann et al [79], 2017	Multicenter, US, inpatient	Post hoc analysis of prospective study	<18 years old	532	Possible selection bias as only those with residual serum available for analysis were included (patients in the ICU were more likely to have residual serum), median time during admission PCT obtained was 1 day, thus limiting applicability to risk stratification on initial presentation
Yadav et al [80], 2015	Single center, India, inpatient	Prospective	2 months–5 years old	50	Single center, small n
Korppi et al [81], 2003	Multicenter, Finland, Primary Care	Retrospective	≤15 years old	190	Retrospective, serum samples run for PCT over 15 years after they were collected, pre-pneumococcal and <i>Haemophilus</i> vaccination era, performed in 1 region of Finland limiting generalizability
Singhi et al [82], 1992	Single center, India, inpatient	Prospective	Children	264	Single-center study in a developing nation during the pre-routine vaccination era significantly limiting generalizability, LOS much longer than average LOSs in current studies in the developed world
Wrotek et al [83], 2013	Single center, Poland, inpatient	Retrospective	<18 years old	312	Significant number of patients did not have sodium measured introducing possible selection bias, retrospective, single center, severity assessment based on clinical factors and inflammatory markers but did not evaluate for more severe outcomes, average hospitalization length (8–9 days), significantly longer than other current studies in the developed world
Don et al [84], 2008	Single center, Italy, ED	Prospective	Children	108	Small percentage of patients did not have sodium samples introducing possible selection bias, single center, severity assessment based on clinical factors and inflammatory markers but did not evaluate for more severe outcomes
Wang et al [85], 2013	Single center, Taiwan, inpatient	Retrospective	<18 years old	84	Single center, retrospective, pre-pneumococcal and <i>Haemophilus</i> vaccination era
Shah et al [86], 2011	Multicenter, US, ED	Retrospective	≤18 years old	291	Few number of bacteremic patients (6) limits statistical power of assessment of severity
Neuman et al [88], 2017	Multicenter, US, ED	Retrospective	3 months–18 years old	2568	Retrospective, wide variation between sites in rates of obtaining blood cultures, which introduces possible selection bias, primary objective of study was to evaluate rate of bacteremia in hospitalized children with CAP and determine susceptibility of pathogens to standard care, evaluation of +blood culture impact on severity came via rates of +cultures in complicated vs noncomplicated CAP and did not evaluate for other outcomes
Myers et al [90], 2013	Multicenter, US, inpatient	Retrospective	60 days–18 years old	369	Retrospective, inpatient study limiting generalizability, evaluated severity based on hypoxemia, LOS, ICU admission, and complicated pneumonia including respiratory failure but no mention of assessment on mortality
Banerjee et al [91], 2011	Multicenter, North America, inpatient	Retrospective survey	Children	37	Retrospective survey of pediatric infectious disease physicians thus potential for reporting bias with potential preference to report more severe cases
Muñoz et al [93], 2011	Single center, Spain, inpatient	Prospective	<18 years old	206	Single center, evaluated severity by LOS and ICU admission but not by other clinical factors or more severe outcomes
Shen et al [94], 2011	Single center, Taiwan, inpatient	Retrospective	Children	119	Single center, retrospective, only pneumococcal and exclusively inpatient limiting generalizability, urinary antigen tests may have detected colonization and not acute infection in some cases
Pettigrew et al [95], 2016	Single center, US, inpatient	Retrospective	6 months to <18 years old	363	Single center, retrospective, exclusively inpatient, approximately 50% of children had asthma/reactive airway disease, ethnic distribution not representative of general population, 20% had received antibiotics before sputum collection, limited generalizability

Abbreviations: BPF, bronchopleural fistulas; BTS, British Thoracic Society; CAP, community-acquired pneumonia; CRP, C-reactive protein; CXR, chest radiographs; ED, emergency department; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; ICU, intensive care unit; LOS, length of stay; PCR, polymerase chain reaction; PCT, procalcitonin; RCT, randomized clinical trial; SpO₂, blood oxygen saturation; US, United States; WBC, white blood cells; WHO, World Health Organization.

Table 4. Respiratory Rate Cutoffs to Define Age-Specific Tachypnea

Source	Respiratory Rate Thresholds Defining Tachypnea-for-Age
WHO [1]	0–2 months: >60
	2–12 months: >50
	1–5 years: >40
	Older than 5 years: >20
PALS [31]	Infant: >53
	Toddler: >37
	Preschooler: >28
	School-aged child: >25
	Adolescent: >20
APLS [32]	0–3 months: >50
	3–6 months: >45
	6–18 months: >40
	18–24 months: >35
	2–8 years: >30
	8–12 years: >25
	Older than 12 years: >24
Bonafide et al [33] ^a	0–3 months: >62
	3–6 months: >58
	6–9 months: >54
	9–12 months: >51
	12–18 months: >48
	18–24 months: >45
	2–3 years: >42
	3–4 years: >40
	4–6 years: >37
	6–8 years: >35
	8–12 years: >31
	12–15 years: >28
	15–18 years: >26

Abbreviations: APLS, Advanced Pediatric Life Support; PALS, Pediatric Advanced Life Support; WHO, World Health Organization.

^a95th percentile-for-age cutoffs used for study by Bonafide et al [38].

suggest thresholds could be broken down into smaller groupings, because respiratory rate shows significant variation based on age [33].

Dyspnea

Examination findings associated with dyspnea include accessory muscle use, retractions, nasal flaring, and grunting. Williams et al [18] found that chest indrawing was associated with severe outcomes (aOR, 2.12; 95% CI, 1.62–2.78). Reed et al [25] found that chest indrawing was an independent predictor of mortality in HIV-negative children <24 months old hospitalized with lower respiratory tract infections (LRTIs) in South Africa (aOR, 4.6; 95% CI, 2.2–9.4). In children hospitalized with WHO-defined severe or very severe pneumonia in a developing nation, head bobbing was associated with mortality (RR, 8.3; 95% CI, 2.71–12.77) and mechanical ventilation (RR, 4.7; 95% CI, 1.50–6.36) [34]. Grunting is associated with hypoxemia [35, 36] and can suggest impending respiratory failure [7]. Retractions have fairly strong interrater reliability (kappa 0.62)

among children with suspected CAP; however, nasal flaring, head bobbing, and grunting have only fair reliability (kappa 0.49, 0.25, and 0.33, respectively) [30].

Tachycardia

Tachycardia may be due to multiple factors including pain, anxiety/fear, fever, dehydration, and underlying disease processes. Tachycardia is included in PEWS [21] and as a severity marker in the BTS guideline [8]. The PIDS/IDSA guideline recommends admission to the ICU or continuous cardiopulmonary monitoring for sustained tachycardia [7].

Data specifically investigating tachycardia in pediatric pneumonia severity are limited. Although Williams et al [18] found that tachycardia was one of the factors associated with severe pneumonia (aOR = 1.59–2.90, depending on age), Reed et al [25] found that admission heart rate >170 was not associated with mortality (OR, 0.9; 95% CI, 0.3–3.2) in HIV-negative infants <24 months old.

Altered Mental Status

Altered mental status (AMS) in children with CAP is often multifactorial, and it can be due to hypercarbia, hypoxemia, severe dehydration, sepsis, or a combination. It is included in the WHO and PIDS/IDSA guidelines [1, 7]. Altered mental status was one of the factors most associated with severe outcomes in the Williams et al [18] study (aOR, 11.9; 95% CI, 6.41–22.23). Araya et al [19] found that a Glasgow Coma Score <13 was the factor most associated with mortality in children admitted with pneumonia (OR, 324; 95% CI, 131–805). In the ED, AMS was highly specific for hospital admission in children with pneumonia (LR+ 10.6) [17]. In children admitted with WHO-defined severe or very severe pneumonia, AMS was associated with mortality (RR, 5.44; 95% CI, 1.34–17.56) [34], and in children admitted with WHO-defined pneumonia in a developing nation, “alteration of general status” based on clinician impression was also associated with mortality (aOR, 3.23; 95% CI, 1.17–8.94) [37].

Temperature

Resolution of fever is a common sign of appropriate therapy and is often used to monitor clinical improvement; however, data are limited to suggest an association between height or duration of fever and pneumonia severity. The BTS guideline uses >38.5°C as a marker for severe pneumonia [8]. The PIDS/IDSA and WHO guidelines do not include fever in their severity criteria [1, 7]. Multiple studies in developing nations have found no association between degree of fever and pneumonia severity in children [22, 23, 25]. Hypothermia may be more indicative of severe disease, as Williams et al [18] found that temperature >39°C (aOR, 0.50; 95% CI, 0.39–0.65) was a protective factor against severe outcomes, whereas hypothermia (<35°C) was associated with severity (aOR, 2.0; 95% CI, 1.54–2.59).

Dehydration and Decreased Perfusion

In developing countries, clinical dehydration in malnourished children with radiographically confirmed pneumonia admitted to the ICU was associated with death (OR, 9.48; 95% CI, 2.42–37.19) [38]. Delayed capillary refill is one sign that dehydration has progressed to decreased perfusion. It is included in the BTS guideline (≥ 2 seconds) [8] and in PEWS [21]. Although widely used, the interrater reliability of capillary refill in suspected CAP is fair to poor (kappa 0.18) [30] and is highly variable in assessing dehydration (kappa 0.15–0.64) [39].

Hypotension

Age-specific hypotension is the defining factor of uncompensated septic shock [40]. Data examining hypotension specifically in pediatric pneumonia is limited and conflicting. Williams et al [18] found that systolic blood pressure < 5 th percentile-for-age was not associated with severe outcomes (aOR, 0.95–1.15). In developing nations, Chisti et al [38] found no association between hypotension and CAP severity in children; however, Araya et al [19] found a significant association between mean arterial pressure > 2 standard deviation below mean-for-age and mortality in children hospitalized with pneumonia (OR, 48.7; 95% CI, 24.8–95.6).

Comorbidities

Araya et al [19] found that significant comorbidities (malnutrition, HIV, congenital heart disease [CHD], asthma, and Down syndrome) were associated with mortality (OR, 4.9–6.2). A retrospective study of children in the ICU with pneumonia found that cerebral palsy, epilepsy, and CHD were associated with mortality (OR, 1.49–2.37), whereas asthma was protective (OR, 0.17; 95% CI, 0.09–0.31) [41]. In a multicenter retrospective study comparing children hospitalized with aspiration pneumonia versus CAP, Hirsch et al [42] found that children with aspiration pneumonia had longer hospital length of stay (LOS) and were more likely to receive ICU care.

Duration of Symptoms/Time to Correct Antibiotic Therapy

Champatiray et al [43] found that in Indian children hospitalized with WHO-defined severe/very severe pneumonia, delayed presentation was associated with mortality, although the mortality rate in the study was high overall (22%). Muszynski et al [44] found that in children with pneumonia requiring invasive mechanical ventilation, time to correct antibiotic selection based on bacterial cultures was independently associated with duration of mechanical ventilation, hospital, and ICU LOS.

RADIOGRAPHIC FACTORS

Despite the widespread use of chest radiographs (CXR), challenges limit their accuracy and utility [45, 46], and clinical factors such as hydration status, degree of atelectasis, and time of presentation can influence interpretation [47]. International

single-center studies suggest that various anatomic locations are associated with CAP severity in children (left lung [48], upper lobes [49], bilateral multifocal, and right hilum [50]). These studies evaluated severity based on LOS, duration of fever, dyspnea, tachypnea, and hydration status and did not consider more severe markers [51]. More recently, studies in developing and developed nations (including well powered prospective multicenter studies) have shown multilobar infiltrates are associated with severe outcomes including ICU admission, mechanical ventilation, vasoactive medications, and death [18, 19, 51].

In a recent multicenter cohort, pleural effusions of any size were associated with longer LOS (aOR, 2.6; 95% CI, 1.9–3.6) and duration of supplemental oxygen (aOR, 3.0; 95% CI, 1.4–6.5). Moderate or large effusions were associated with ICU admission (aOR, 3.2; 95% CI, 1.1–8.9) and mechanical ventilation (aOR, 14.8; 95% CI, 9.8–22.4) [51]. In a large multicenter study of children unvaccinated against *Streptococcus pneumoniae* hospitalized with WHO-defined severe pneumonia, Ferrero et al [52] found that pleural effusions were associated with pneumococcal bacteremia (OR, 3.1; 95% CI, 1.23–7.98). In children hospitalized with pneumonia, pleural effusions were the factors most associated with empiric parenteral ampicillin/sulbactam treatment failure (aOR, 5.74; 95% CI, 2.17–15.15) [53]. Complex loculated effusions contribute to treatment failure with conservative measures leading to increased LOS and need for surgical interventions [54, 55].

Empyema is also associated with severity including prolonged hospitalizations, bacteremia, and need for ICU admission, but not mortality [56, 57]. Goldbart et al [58] found that empyema was associated with LOS, ICU admission, and mechanical ventilation compared with children with nonpurulent effusions.

Necrotizing pneumonia is an increasingly recognized complication of CAP, defined by parenchymal liquefaction and necrosis, later replaced by air or fluid-filled cavities. Lung necrosis and abscesses are generally a result of bacterial pathogens, particularly *S pneumoniae* and *Staphylococcus aureus*, the latter of which is associated with a more severe disease course [59, 60]. Retrospective studies suggest that necrotizing pneumonia in children is associated with prolonged hospital stays, ICU admission, and surgical interventions, but not with mortality [56, 61–65]. Necrosis can extend through pleura leading to bronchopleural fistulas (BPF), which are associated with duration of fever, LOS, and mechanical ventilation when compared with culture-proven pneumococcal pneumonia without BPF [66, 67]. Pneumothoraces in children admitted with pneumonia are also associated with mortality (OR, 15; 95% CI, 2.9–76.6) [19].

Emerging evidence suggests that lung ultrasound is highly sensitive and specific for diagnosing pneumonia in children compared with CXR [68, 69]. Evidence of multifocal disease and fluid bronchograms on transthoracic ultrasound are associated

with severity [70]. Lai et al [71] found that degree of impaired perfusion on ultrasound is associated with severity of necrosis and need for resection.

LABORATORY MARKERS

Complete Blood Count

Studies have consistently shown that leukocytosis alone is a poor predictor of pneumonia etiology and severity [7, 18, 19, 72–76]; however, Araya et al [19] found that leukopenia (<4000) was associated with mortality (OR, 6.5; 95% CI, 2.7–15.6). The PIDS/IDSA guideline recommends, with low-quality evidence, that a complete blood count should only be performed in severe CAP [7] to evaluate for severe complications such as hemolytic-uremic syndrome (HUS).

Inflammatory Markers

C-reactive protein (CRP) is an acute phase reactant that is associated with disease severity in bacterial infections in children [77]; however, studies have not shown substantial associations between CRP and CAP severity. A single-center cross-sectional study found that elevated CRP was not associated with hypoxemia, dyspnea, or tachycardia [78]. Another retrospective observational study of children admitted with CAP found that admission CRP was minimally associated with LOS and duration of fever (adjusted ratio of means 1.03 and 1.08, respectively) [72]. In children admitted with WHO-defined pneumonia, CRP was not associated with WHO severity criteria (OR, 1.01; 95% CI, 0.99–1.02) [76]. Reed et al [25] found that admission CRP was not associated with mortality in young children hospitalized with LRTIs.

Procalcitonin is a precursor of calcitonin that can increase in bacterial infections and inflammatory states. A multicenter, prospective study found increasing levels of procalcitonin were associated with ICU admission and empyema requiring drainage, and values <0.25 ng/mL were associated with decreased risk of ICU admission [79]. An Indian study found that elevation in admission procalcitonin in radiographically confirmed and WHO-defined severe or very severe pneumonia was associated with increased LOS and pneumonia complications [80]. In a prospective study of children diagnosed with CAP in the ED, Don et al [74] found that elevated procalcitonin was associated with hospitalization, whereas a cross-sectional study of hospitalized children found no association with markers for severity including tachycardia, hypoxemia, and dyspnea [78]. A primary care study found that procalcitonin was not associated with hospitalization in children with radiographically confirmed pneumonia [81]. These conflicting studies are limited by heterogeneous populations, study settings, and varied outcomes.

Electrolytes

Several studies suggest that hyponatremia may be associated with CAP severity in children, although limitations prevent

definitive conclusions. In a small-scale, single-center Indian study, hyponatremia was associated with LOS, complications, and mortality, although LOS and mortality rates were high overall [82]. More recently, 2 European studies (a retrospective study of children hospitalized with CAP [83] and a prospective ED-based study [84]) found that hyponatremia was associated with hospitalization, LOS, inflammatory markers, and degree of fever but not with respiratory rate, tachycardia, capillary refill, or defervescence.

Acidosis

Araya et al [19] found that $\text{HCO}_3^- < 15$ was associated with mortality (OR, 26.7; 95% CI, 13–54), and Wang et al [85] found that metabolic acidosis was independently associated with mortality in children hospitalized with pneumonia (aOR, 8.5; 95% CI, 2.82–25.6).

Bacteremia

In the developed world, bacteremia in childhood pneumonia is uncommon, with rates <1% for outpatients, 2.5% for hospitalized children, and 13% in complicated pneumonia [7, 86–88]. Although blood cultures upon admission are recommended by the PIDS/IDSA guideline, the majority of organisms isolated from blood cultures in children with pneumonia were sensitive to guideline-recommended therapy (ie, penicillin) and rarely changed management [86, 88]. Bacteremia in childhood pneumonia has been associated with hypoxemia, LOS, and complications including effusions and empyema; however, data are limited for more severe measures [86, 89, 90].

Concern for Hemolytic-Uremic Syndrome

A 2011 survey of pediatric infectious disease physicians found that cases of *S pneumoniae*-associated HUS (diagnosed by microangiopathic hemolytic anemia, renal injury, and platelets <150 000/mL) were associated with severe outcomes including ICU admission, invasive procedures/mechanical ventilation, and dialysis [91].

Molecular Diagnostics/Genomics

Molecular diagnostic tools are likely to improve severity classification in pediatric CAP. An association has been shown between pneumococcal load and pneumonia severity in adults [92]. In children, plasma pneumococcal load is associated with prolonged hospital stays (aOR, 3.53; 95% CI, 1.43–8.70) [93], and pleural pneumococcal load is associated with worsening necrosis including progression to BPF [67]. Urinary antigen tests have shown promise, and Shen et al [94] found that time to positivity and intensity of band reactions may correlate with pneumococcal CAP severity based on dyspnea, hypoxemia, bacteremia, LOS, and ICU admission. In addition, sputum microbiota profiles using 16S ribosomal ribonucleic acid may

influence pneumonia severity, likely due to complex interactions between bacteria and a child's immune response [95].

FUTURE DIRECTIONS

This systematic review highlights the current evidence regarding the factors that influence pneumonia severity in children. The current evidence suggests that hypoxemia, AMS, age <3–6 months, dyspnea, multilobar infiltrates, and moderate/large pleural effusions are the factors most predictive of pneumonia severity in children. The development and validation of pediatric pneumonia severity scoring systems for use in settings where site-of-care decisions are made have the potential to improve risk stratification.

Emerging technologies and molecular diagnostics will likely play an increasing role in severity assessment. Quantitative pneumococcal load and pneumococcal urinary antigen tests have shown promise in severity assessment in children [67, 93, 94], although pneumococcal pneumonia represents only one cause of CAP [96]. Gene expression profiling and other -omics approaches will provide new insights into CAP etiology and severity [97]. In nonpneumococcal cases, quantitative urinary metabolites have shown the potential to assess for mortality risk, although further research is still needed [98]. As the use of both rapid viral testing and polymerase chain reaction have become more common, viral coinfections have shown an association with CAP severity in children and may play a role in risk stratification [99, 100]. Assessing for impaired perfusion on lung ultrasound has shown promise in predicting pneumonia complications (necrosis) and may play a larger role in severity assessment going forward [71]. The development of a validated pneumonia severity scoring system across outpatient, ED, and inpatient settings, in combination with emerging technologies, will improve risk stratification and resource allocation.

Notes

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References

- World Health Organization. Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Evidence Summaries. Geneva: World Health Organization; 2014.
- Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization. *N Engl J Med* 2015; 373:2382.
- Pfuntner A, Wier L, Stocks C. Most Frequent Conditions in U.S. Hospitals, 2011. HCUP Statistical Brief #162. Rockville, MD: Agency for Healthcare Research and Quality, 2013.
- Florin TA, French B, Zorc JJ, et al. Variation in emergency department diagnostic testing and disposition outcomes in pneumonia. *Pediatrics* 2013; 132:237–44.
- Brogan TV, Hall M, Williams DJ, et al. Variability in processes of care and outcomes among children hospitalized with community-acquired pneumonia. *Pediatr Infect Dis J* 2012; 31:1036–41.
- Handy LK, Bryan M, Gerber JS, et al. Variability in antibiotic prescribing for community-acquired pneumonia. *Pediatrics* 2017; 139:pii: 20162331.
- Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 53:e25–76.
- Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax* 2011; 66(Suppl 2):iii1–23.
- Charles PG, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis* 2008; 47:375–84.
- Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336:243–50.
- Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58:377–82.
- España PP, Capelastegui A, Gorordo I, et al. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med* 2006; 174:1249–56.
- Pereira JM, Paiva JA, Rello J. Assessing severity of patients with community-acquired pneumonia. *Semin Respir Crit Care Med* 2012; 33:272–83.
- Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44(Suppl 2):S27–72.
- Jo S, Kim K, Jung K, et al. The effects of incorporating a pneumonia severity index into the admission protocol for community-acquired pneumonia. *J Emerg Med* 2012; 42:133–8.
- Chalmers JD, Singanayagam A, Akram AR, et al. Safety and efficacy of CURB65-guided antibiotic therapy in community-acquired pneumonia. *J Antimicrob Chemother* 2011; 66:416–23.
- Florin TA, Brokamp C, Mantyla R, et al. Validation of the PIDS/IDSA severity criteria in children with community-acquired pneumonia. *Clin Infect Dis* 2018. doi: 10.1093/cid/ciy031.
- Williams DJ, Zhu Y, Grijalva CG, et al. Predicting severe pneumonia outcomes in children. *Pediatrics* 2016; 138:e20161019.
- Araya S, Lovera D, Zarate C, et al. Application of a prognostic scale to estimate the mortality of children hospitalized with community-acquired pneumonia. *Pediatr Infect Dis J* 2016; 35:369–73.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6:e1000100.
- Parshuram CS, Hutchison J, Middaugh K. Development and initial validation of the Bedside Paediatric Early Warning System score. *Crit Care* 2009; 13:R135.
- Duke T, Mgone J, Frank D. Hypoxaemia in children with severe pneumonia in Papua New Guinea. *Int J Tuberc Lung Dis* 2001; 5:511–9.
- Djelantik IG, Gessner BD, Sutanto A, et al. Case fatality proportions and predictive factors for mortality among children hospitalized with severe pneumonia in a rural developing country setting. *J Trop Pediatr* 2003; 49:327–32.
- Nantanda R, Hildenwall H, Peterson S, et al. Bacterial aetiology and outcome in children with severe pneumonia in Uganda. *Ann Trop Paediatr* 2008; 28:253–60.
- Reed C, Madhi SA, Klugman KP, et al. Development of the Respiratory Index of Severity in Children (RISC) score among young children with respiratory infections in South Africa. *PLoS One* 2012; 7:e27793.
- Wolf RB, Edwards K, Grijalva CG, et al. Time to clinical stability among children hospitalized with pneumonia. *J Hosp Med* 2015; 10:380–3.
- Neuman MI, Hall M, Gay JC, et al. Readmissions among children previously hospitalized with pneumonia. *Pediatrics* 2014; 134:100–9.
- Mamtani M, Patel A, Hibberd PL, et al. A clinical tool to predict failed response to therapy in children with severe pneumonia. *Pediatr Pulmonol* 2009; 44:379–86.
- Smyth A, Carty H, Hart CA. Clinical predictors of hypoxaemia in children with pneumonia. *Ann Trop Paediatr* 1998; 18:31–40.
- Florin TA, Ambroggio L, Brokamp C, et al. Reliability of examination findings in suspected community-acquired pneumonia. *Pediatrics* 2017; 140:pii: e20170310.
- American Heart Association. In: Chameides L, Samson RA, Schexnayder SM, Hazinski MF, eds. Pediatric Advanced Life Support Provider Manual. Dallas, TX: American Heart Association, 2016.
- Advanced Life Support Group. In: Samuels M, Wieteska S, eds. Advanced Paediatric Life Support: A Practical Approach to Emergencies. 6th ed. Chichester: John Wiley and Sons, 2016.
- Bonafide CP, Brady PW, Keren R, et al. Development of heart and respiratory rate percentile curves for hospitalized children. *Pediatrics* 2013; 131:e1150–7.
- Tiewsoh K, Lodha R, Pandey RM, et al. Factors determining the outcome of children hospitalized with severe pneumonia. *BMC Pediatr* 2009; 9:15.
- Basnet S, Adhikari RK, Gurung CK. Hypoxemia in children with pneumonia and its clinical predictors. *Indian J Pediatr* 2006; 73:777–81.

36. Kuti BP, Adegoke SA, Ebruke BE, et al. Determinants of oxygen therapy in childhood pneumonia in a resource-constrained region. *ISRN Pediatr* **2013**; 2013:435976.
37. Demers AM, Morency P, Mbeyo-Yaah F, et al. Risk factors for mortality among children hospitalized because of acute respiratory infections in Bangui, Central African Republic. *Pediatr Infect Dis J* **2000**; 19:424–32.
38. Chisti MJ, Salam MA, Ashraf H, et al. Clinical risk factors of death from pneumonia in children with severe acute malnutrition in an urban critical care ward of Bangladesh. *PLoS One* **2013**; 8:e73728.
39. Fleming S, Gill P, Jones C, et al. Validity and reliability of measurement of capillary refill time in children: a systematic review. *Arch Dis Child* **2015**; 100:239–49.
40. Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* **2005**; 6:2–8.
41. Hsu CL, Lee YS, Chen CJ, et al. A population-based analysis of children with pneumonia among intensive care units in Taiwan. *J Microbiol Immunol Infect* **2015**; 48:153–9.
42. Hirsch AW, Monuteaux MC, Fruchtman G, et al. Characteristics of children hospitalized with aspiration pneumonia. *Hosp Pediatr* **2016**; 6:659–66.
43. Champatiray J, Satapathy J, Kashyap B, Mondal D. Clinico-aetiological study of severe and very severe pneumonia in two months to five years children in a Tertiary Health Care Centre in Odisha, India. *J Clin Diagn Res* **2017**; 11:SC06–10.
44. Muszynski JA, Knatz NL, Sargel CL, et al. Timing of correct parenteral antibiotic initiation and outcomes from severe bacterial community-acquired pneumonia in children. *Pediatr Infect Dis J* **2011**; 30:295–301.
45. Neuman MI, Lee EY, Bixby S, et al. Variability in the interpretation of chest radiographs for the diagnosis of pneumonia in children. *J Hosp Med* **2012**; 7:294–8.
46. Williams GJ, Macaskill P, Kerr M, et al. Variability and accuracy in interpretation of consolidation on chest radiography for diagnosing pneumonia in children under 5 years of age. *Pediatr Pulmonol* **2013**; 48:1195–200.
47. Gereige RS, Laufer PM. Pneumonia. *Pediatr Rev* **2013**; 34:438–56.
48. Grafakou O, Moustaki M, Tsoia M, et al. Can chest X-ray predict pneumonia severity? *Pediatr Pulmonol* **2004**; 38:465–9.
49. Kin Key N, Araújo-Neto CA, Nascimento-Carvalho CM. Severity of childhood community-acquired pneumonia and chest radiographic findings. *Pediatr Pulmonol* **2009**; 44:249–52.
50. Patria MF, Longhi B, Lelii M, et al. Association between radiological findings and severity of community-acquired pneumonia in children. *Ital J Pediatr* **2013**; 39:56.
51. McClain L, Hall M, Shah SS, et al. Admission chest radiographs predict illness severity for children hospitalized with pneumonia. *J Hosp Med* **2014**; 9:559–64.
52. Ferrero F, Nascimento-Carvalho CM, Cardoso MR, et al. Radiographic findings among children hospitalized with severe community-acquired pneumonia. *Pediatr Pulmonol* **2010**; 45:1009–13.
53. Tapisiz A, Özdemir H, Çiftçi E, et al. Ampicillin/sulbactam for children hospitalized with community-acquired pneumonia. *J Infect Chemother* **2011**; 17:504–9.
54. Margenthaler JA, Weber TR, Keller MS. Predictors of surgical outcome for complicated pneumonia in children: impact of bacterial virulence. *World J Surg* **2004**; 28:87–91.
55. Ozelik C, Inci I, Nizam O, Onat S. Intrapleural fibrinolytic treatment of multiloculated postpneumonic pediatric empyemas. *Ann Thorac Surg* **2003**; 76:1849–53.
56. Erlichman I, Breuer O, Shoseyov D, et al. Complicated community acquired pneumonia in childhood: different types, clinical course, and outcome. *Pediatr Pulmonol* **2017**; 52:247–54.
57. Langley JM, Kellner JD, Solomon N, et al. Empyema associated with community-acquired pneumonia: a Pediatric Investigator's Collaborative Network on Infections in Canada (PICNIC) study. *BMC Infect Dis* **2008**; 8:129.
58. Goldbart AD, Leibovitz E, Porat N, et al. Complicated community acquired pneumonia in children prior to the introduction of the pneumococcal conjugated vaccine. *Scand J Infect Dis* **2009**; 41:182–7.
59. Spencer DA, Thomas ME. Necrotizing pneumonia in children. *Paediatr Respir Rev* **2014**; 15:240–5.
60. Taffarel P, Bonetto G, Penazzi M, et al. Severe *Staphylococcus aureus* infection in three pediatric intensive care units: analysis of cases of necrotizing pneumonia. *Arch Argent Pediatr* **2014**; 112:163–8.
61. Sawicki GS, Lu FL, Valim C, et al. Necrotizing pneumonia is an increasingly detected complication of pneumonia in children. *Eur Respir J* **2008**; 31:1285–91.
62. Bender JM, Ampofo K, Korgenski K, et al. Pneumococcal necrotizing pneumonia in Utah: does serotype matter? *Clin Infect Dis* **2008**; 46:1346–52.
63. Krenke K, Sanocki M, Urbankowska E, et al. Necrotizing pneumonia and its complications in children. *Adv Exp Med Biol* **2015**; 857:9–17.
64. Donnelly LF, Klosterman LA. Cavitary necrosis complicating pneumonia in children: sequential findings on chest radiography. *AJR Am J Roentgenol* **1998**; 171:253–6.
65. Hacimustafaoglu M, Celebi S, Sarimehmet H, et al. Necrotizing pneumonia in children. *Acta Paediatr* **2004**; 93:1172–7.
66. Hsieh YC, Wang CW, Lai SH, et al. Necrotizing pneumococcal pneumonia with bronchopleural fistula among children in Taiwan. *Pediatr Infect Dis J* **2011**; 30:740–4.
67. Hsieh YC, Chi H, Chang KY, et al. Increase in fitness of *Streptococcus pneumoniae* is associated with the severity of necrotizing pneumonia. *Pediatr Infect Dis J* **2015**; 34:499–505.
68. Guerra M, Cricchiutti G, Pecile P, et al. Ultrasound detection of pneumonia in febrile children with respiratory distress: a prospective study. *Eur J Pediatr* **2016**; 175:163–70.
69. Pereda MA, Chavez MA, Hooper-Miele CC, et al. Lung ultrasound for the diagnosis of pneumonia in children: a meta-analysis. *Pediatrics* **2015**; 135:714–22.
70. Chen IC, Lin MY, Liu YC, et al. The role of transthoracic ultrasonography in predicting the outcome of community-acquired pneumonia in hospitalized children. *PLoS One* **2017**; 12:e0173343.
71. Lai SH, Wong KS, Liao SL. Value of lung ultrasonography in the diagnosis and outcome prediction of pediatric community-acquired pneumonia with necrotizing change. *PLoS One* **2015**; 10:e0130082.
72. Williams DJ, Hall M, Auger KA, et al. Association of white blood cell count and C-reactive protein with outcomes in children hospitalized for community-acquired pneumonia. *Pediatr Infect Dis J* **2015**; 34:792–3.
73. Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. *Eur Respir J* **1997**; 10:1125–9.
74. Don M, Valent F, Korppi M, Canciani M. Differentiation of bacterial and viral community-acquired pneumonia in children. *Pediatr Int* **2009**; 51:91–6.
75. Prat C, Dominguez J, Rodrigo C, et al. Procalcitonin, C-reactive protein and leukocyte count in children with lower respiratory tract infection. *Pediatr Infect Dis J* **2003**; 22:963–8.
76. Wu J, Jin YU, Li H, et al. Evaluation and significance of C-reactive protein in the clinical diagnosis of severe pneumonia. *Exp Ther Med* **2015**; 10:175–80.
77. Rey C, Los Arcos M, Concha A, et al. Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. *Intensive Care Med* **2007**; 33:477–84.
78. Agnello L, Bellia C, Di Gangi M, et al. Utility of serum procalcitonin and C-reactive protein in severity assessment of community-acquired pneumonia in children. *Clin Biochem* **2016**; 49:47–50.
79. Stockmann C, Ampofo K, Killpack J, et al. Procalcitonin accurately identifies hospitalized children with low risk of bacterial community-acquired pneumonia. *J Pediatric Infect Dis Soc* **2018**; 7:46–53.
80. Yadav KK, Awasthi S, Takia L, et al. Procalcitonin and C-reactive protein in WHO defined severe and very severe community acquired pneumonia: a hospital based cross-sectional study. *Clin Epidemiol Glob Health* **2015**; 3:S3–9.
81. Korppi M, Remes S, Heiskanen-Kosma T. Serum procalcitonin concentrations in bacterial pneumonia in children: a negative result in primary healthcare settings. *Pediatr Pulmonol* **2003**; 35:56–61.
82. Singhi S, Dhawan A. Frequency and significance of electrolyte abnormalities in pneumonia. *Indian Pediatr* **1992**; 29:735–40.
83. Wrotek A, Jackowska T. Hyponatremia in children hospitalized due to pneumonia. *Adv Exp Med Biol* **2013**; 788:103–8.
84. Don M, Valerio G, Korppi M, Canciani M. Hyponatremia in pediatric community-acquired pneumonia. *Pediatr Nephrol* **2008**; 23:2247–53.
85. Wang LJ, Mu SC, Lin CH, et al. Fatal community-acquired pneumonia: 18 years in a medical center. *Pediatr Neonatol* **2013**; 54:22–7.
86. Shah SS, Dugan MH, Bell LM, et al. Blood cultures in the emergency department evaluation of childhood pneumonia. *Pediatr Infect Dis J* **2011**; 30:475–9.
87. St Peter SD, Tsao K, Spilde TL, et al. Thoracoscopic decortication vs tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial. *J Pediatr Surg* **2009**; 44:106–11.
88. Neuman MI, Hall M, Lipsett SC, et al. Utility of blood culture among children hospitalized with community-acquired pneumonia. *Pediatrics* **2017**; 140:pii: e20171013.
89. Iroh Tam PY, Bernstein E, Ma X, Ferrieri P. Blood culture in evaluation of pediatric community-acquired pneumonia: a systematic review and meta-analysis. *Hosp Pediatr* **2015**; 5:324–36.
90. Myers AL, Hall M, Williams DJ, et al. Prevalence of bacteremia in hospitalized pediatric patients with community-acquired pneumonia. *Pediatr Infect Dis J* **2013**; 32:736–40.
91. Banerjee R, Hersh AL, Newland J, et al. *Streptococcus pneumoniae*-associated hemolytic uremic syndrome among children in North America. *Pediatr Infect Dis J* **2011**; 30:736–9.

92. Rello J, Lisboa T, Lujan M, et al. Severity of pneumococcal pneumonia associated with genomic bacterial load. *Chest* **2009**; 136:832–40.
93. Muñoz-Almagro C, Gala S, Selva L, et al. DNA bacterial load in children and adolescents with pneumococcal pneumonia and empyema. *Eur J Clin Microbiol Infect Dis* **2011**; 30:327–35.
94. Shen CF, Wang SM, Liu CC. A new urinary antigen test score correlates with severity of pneumococcal pneumonia in children. *J Formos Med Assoc* **2011**; 110:613–8.
95. Pettigrew MM, Gent JF, Kong Y, et al. Association of sputum microbiota profiles with severity of community-acquired pneumonia in children. *BMC Infect Dis* **2016**; 16:317.
96. West DM, McCauley LM, Sorensen JS, et al. Pneumococcal urinary antigen test use in diagnosis and treatment of pneumonia in seven Utah hospitals. *ERJ Open Res* **2016**; 2. doi: 10.1183/23120541.00011-2016.
97. Mejias A, Dimo B, Suarez NM, et al. Whole blood gene expression profiles to assess pathogenesis and disease severity in infants with respiratory syncytial virus infection. *PLoS Med* **2013**; 10:e1001549.
98. Ambroggio L, Florin TA, Shah SS, et al. Emerging biomarkers of illness severity: urinary metabolites associated with sepsis and necrotizing methicillin-resistant *Staphylococcus aureus* pneumonia. *Pharmacotherapy* **2017**; 37:1033–42.
99. Williams DJ, Hall M, Brogan TV, et al. Influenza coinfection and outcomes in children with complicated pneumonia. *Arch Pediatr Adolesc Med* **2011**; 165:506–12.
100. Dawood FS, Chaves SS, Perez A, et al. Complications and associated bacterial coinfections among children hospitalized with seasonal or pandemic influenza, United States, 2003–2010. *J Infect Dis* **2014**; 209:686–94.

Is Higher Viral Load in the Upper Respiratory Tract Associated With Severe Pneumonia? Findings From the PERCH Study

Daniel R. Feikin,^{1,2} Wei Fu,^{1,3} Daniel E. Park,^{1,4} Qiuyan Shi,¹ Melissa M. Higdon,¹ Henry C. Baggett,^{5,6} W. Abdullah Brooks,^{7,8} Maria Deloria Knoll,¹ Laura L. Hammit,^{1,9} Stephen R. C. Howie,^{10,11,12} Karen L. Kotloff,¹³ Orin S. Levine,^{1,14} Shabir A. Madhi,^{15,16} J. Anthony G. Scott,^{9,17} Donald M. Thea,¹⁸ Peter V. Adrian,^{15,16} Martin Antonio,^{10,19,20} Juliet O. Awori,³ Vicky L. Baillie,^{15,16} Andrea N. DeLuca,^{1,21} Amanda J. Driscoll,¹ Bernard E. Ebruke,¹⁰ Doli Goswami,⁷ Ruth A. Karron,²² Mengying Li,^{1,23} Susan C. Morpeth,^{9,17,24} John Mwaba,^{25,26} James Mwansa,^{25,26} Christine Prosper,¹ Pongpun Sawatwong,⁵ Samba O. Sow,²⁷ Milagritos D. Tapia,¹³ Toni Whistler,^{5,6} Khalequ Zaman,⁷ Scott L. Zeger,²⁸ Katherine L. O'Brien,¹ and David R. Murdoch^{29,30}, for the PERCH Study Group^a

¹Department of International Health, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; ²Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; ³Department of Rheumatology, Johns Hopkins School of Medicine, Baltimore, Maryland; ⁴Milken Institute School of Public Health, Department of Epidemiology and Biostatistics, George Washington University, District of Columbia; ⁵Global Disease Detection Center, Thailand Ministry of Public Health–US Centers for Disease Control and Prevention Collaboration, Nonthaburi; ⁶Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia; ⁷International Centre for Diarrhoeal Disease Research, Bangladesh (icddr), Dhaka and Matlab; ⁸Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; ⁹Kenya Medical Research Institute–Wellcome Trust Research Programme, Kilifi; ¹⁰Medical Research Council Unit, Basse, The Gambia; ¹¹Department of Paediatrics, University of Auckland, and ¹²Centre for International Health, University of Otago, Dunedin, New Zealand; ¹³Division of Infectious Disease and Tropical Pediatrics, Department of Pediatrics, Center for Vaccine Development, Institute of Global Health, University of Maryland School of Medicine, Baltimore; ¹⁴Bill & Melinda Gates Foundation, Seattle, Washington; ¹⁵Medical Research Council, Respiratory and Meningeal Pathogens Research Unit, and ¹⁶Department of Science and Technology/National Research Foundation, Vaccine Preventable Diseases Unit, University of the Witwatersrand, Johannesburg, Johannesburg, South Africa; ¹⁷Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, United Kingdom; ¹⁸Center for Global Health and Development, Boston University School of Public Health, Massachusetts; ¹⁹Department of Pathogen Molecular Biology, London School of Hygiene & Tropical Medicine, and ²⁰Microbiology and Infection Unit, Warwick Medical School, University of Warwick, Coventry, United Kingdom; ²¹Department of Epidemiology, ²²Department of International Health, Center for Immunization Research, and ²³Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; ²⁴Microbiology Laboratory, Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand; ²⁵Department of Pathology and Microbiology, University Teaching Hospital, and ²⁶Zambia Center for Applied Health Research and Development, Lusaka; ²⁷Centre pour le Développement des Vaccins (CVD-Mali), Bamako; ²⁸Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; ²⁹Department of Pathology, University of Otago, and ³⁰Microbiology Unit, Canterbury Health Laboratories, Christchurch, New Zealand

Background. The etiologic inference of identifying a pathogen in the upper respiratory tract (URT) of children with pneumonia is unclear. To determine if viral load could provide evidence of causality of pneumonia, we compared viral load in the URT of children with World Health Organization–defined severe and very severe pneumonia and age-matched community controls.

Methods. In the 9 developing country sites, nasopharyngeal/oropharyngeal swabs from children with and without pneumonia were tested using quantitative real-time polymerase chain reaction for 17 viruses. The association of viral load with case status was evaluated using logistic regression. Receiver operating characteristic (ROC) curves were constructed to determine optimal discriminatory viral load cutoffs. Viral load density distributions were plotted.

Results. The mean viral load was higher in cases than controls for 7 viruses. However, there was substantial overlap in viral load distribution of cases and controls for all viruses. ROC curves to determine the optimal viral load cutoff produced an area under the curve of <0.80 for all viruses, suggesting poor to fair discrimination between cases and controls. Fatal and very severe pneumonia cases did not have higher viral load than less severe cases for most viruses.

Conclusions. Although we found higher viral loads among pneumonia cases than controls for some viruses, the utility in using viral load of URT specimens to define viral pneumonia was equivocal. Our analysis was limited by lack of a gold standard for viral pneumonia.

Keywords. pneumonia; viral load; viral density; RSV; PERCH.

For diagnosing viral pneumonia, upper respiratory tract (URT) specimens have become the most common specimen type due

to their logistical ease of collection [1, 2]. However, detection of viruses in URT specimens has low specificity as this finding might simply reflect an URT infection without lower respiratory tract involvement or coincidental asymptomatic or past infection [2–4].

A possible solution to the lack of specificity of simply detecting the presence or absence of a virus in the URT of pneumonia patients is to determine whether the density of a virus in the URT can better distinguish its causative role in pneumonia. There are reports that a higher pathogen load in the URT is associated with pneumonia, for both *Streptococcus pneumoniae*

^aMembers of the PERCH Study Group are listed in the Acknowledgments.

Correspondence: D. R. Feikin, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, 415 N Washington St, Room 563, Baltimore, MD 21231 (drf3217@gmail.com).

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and some respiratory viruses [5–8]. In addition, for some viruses, higher viral load in the URT has been associated with worse outcomes [7, 9–11].

In this analysis, we describe viral load in nasopharyngeal/oropharyngeal (NP/OP) specimens from cases and community controls from a large multicountry childhood pneumonia study (Pneumonia Etiology Research for Child Health [PERCH]), as well as demographic and clinical characteristics associated with higher viral load and disease severity. An overarching aim was to explore whether the incorporation of viral load data into the main PERCH etiology analysis might improve the assignment of the etiology of pneumonia cases.

METHODS

The PERCH study design and enrollment strategy has been previously described [12]. In brief, PERCH is a case-control study of the etiology of World Health Organization (WHO)–defined severe and very severe pneumonia among hospitalized children aged 1–59 months and age frequency-matched community controls. Enrollment took place during August 2011–January 2014 for 24 months at each of 9 study sites located in 7 countries—Dhaka and Matlab, Bangladesh; Basse, The Gambia; Kilifi, Kenya; Bamako, Mali; Soweto, South Africa; Nakhon Phanom and Sa Kaeo, Thailand; and Lusaka, Zambia [13].

Case and Control Definitions

For this analysis, we included only cases with evidence of pneumonia on chest radiograph, defined as consolidation and/or any other infiltrate assessed according to the WHO radiological pneumonia criteria [14]. A control participant was considered to have a respiratory tract illness (RTI) if cough or runny nose was reported. RTI was also considered present if a child had (1) at least 1 of ear discharge, wheezing, or difficulty breathing and (2) either a measured temperature of $\geq 38.0^{\circ}\text{C}$ within the previous 48 hours or a history of sore throat. Controls who did not meet the definition of RTI are referred to as non-RTI controls.

Specimen Collection and Laboratory Testing

Nasopharyngeal and oropharyngeal swabs were collected from PERCH cases and controls at enrollment. Nasopharyngeal specimens were collected by inserting flocked swabs (Copan ETC) into the posterior nasopharynx and rotating 180° for 2–3 seconds. Oropharyngeal specimens were then collected by rubbing Rayon swabs (Fisher Scientific) over both tonsillar pillars and the posterior oropharynx for several seconds. Following collection, swabs were placed together in the same 3-mL vial of universal transport media (Copan) and processed within 24 hours of collection. Specimens were left at room temperature for no more than 2 hours or at 4°C for no more than 24 hours, before freezing at -70°C .

All specimens were tested in-country using a standardized methodology, and details are described elsewhere [15]. Specimens were evaluated using the Fast-track Diagnostics Respiratory Pathogens 33 test (FTD Resp 33, Fast-track Diagnostics, Sliema, Malta), a 33-target, 8-multiplex real-time polymerase chain reaction (PCR) platform for the detection of viruses, bacteria, and fungi. The 18 viruses or virus classes included influenza A, B, and C viruses; parainfluenza virus (PIV) types 1, 2, 3, and 4; coronaviruses NL63, 229E, OC43, and HKU1; human metapneumovirus (HMPV) A and B (A and B not differentiated); rhinovirus; respiratory syncytial virus (RSV) A and B (A and B not differentiated); adenovirus; enterovirus and parechovirus (not differentiated); human bocavirus (HBOV); and cytomegalovirus. Cytomegalovirus is not included in this analysis but is discussed in a separate publication of the pathogen load of pathogens commonly detected in both cases and controls [16].

Some sites (Bangladesh, The Gambia, Mali, South Africa) collected lung aspirates from children with consolidation on chest radiograph who met clinical and radiologic criteria for the

Table 1. Characteristics of Chest Radiograph–Positive Children With Severe and Very Severe Pneumonia and Controls—Pneumonia Etiology Research for Child Health (PERCH) Study, August 2011–January 2014

Characteristic	CXR+Cases ^a (n = 1733)	All Controls (n = 4986)	χ^2 P Value ^b
Site			
Kenya	282 (16.3)	855 (17.2)	<.001
The Gambia	273 (15.8)	624 (12.5)	
Mali	239 (13.8)	724 (14.5)	
Zambia	189 (10.9)	535 (10.7)	
South Africa	433 (25.0)	823 (16.5)	
Thailand	98 (5.7)	657 (13.2)	
Bangladesh	219 (12.6)	768 (15.4)	
Age			
1–5 mo	680 (39.2)	1555 (31.2)	<.001
6–11 mo	415 (24.0)	1187 (23.8)	
12–23 mo	424 (24.5)	1235 (24.8)	
24–59 mo	214 (12.4)	1009 (20.2)	
Female sex	756 (43.6)	2477 (49.7)	<.001
Prior antibiotic use ^c	597 (42.4)	84 (1.7)	<.001
Respiratory tract illness ^d	NA	1185 (23.8)	NA
No. of viruses detected			
0 viruses	180 (10.4)	1048 (21.0)	
1 virus	628 (36.2)	1928 (38.7)	<.001
2 viruses	616 (35.6)	1420 (28.5)	
≥ 3 viruses	309 (17.8)	590 (11.8)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CXR+, chest radiograph positive; NA, not applicable.

^aCXR+ defined as having radiographic evidence of pneumonia.

^bComparing distribution of characteristics between CXR+ cases and controls. Bolded values are significant ($P < .05$).

^cPrior antibiotic use: administered antibiotics at the study facility prior to the collection of specimens (cases only), antibiotics at a referral facility (cases only), or positive serum bioassay (cases and controls).

^dSee Methods for respiratory tract illness definition.

procedure [17]. Lung aspirate specimens were tested for viral targets using the same method described for NP/OP specimens.

Statistical Analysis

Human immunodeficiency virus (HIV)-positive cases were excluded from analyses unless stated otherwise. PCR quantification was $\log_{10}$ -transformed. Demographic characteristics of cases and controls were compared using the χ^2 test. All controls, both RTI and non-RTI, were included in the main analysis. All analyses of viral load were restricted to children positive for each virus. Among children positive for each virus, *t* tests adjusted for site and age were performed to compare mean cycle threshold (Ct) values between cases and controls. For each virus, a trend analysis, using simple linear regression, was performed to test if viral density increased with age for cases and for controls. Among cases only, mean Ct values were also compared by days since onset, severity, vital status, and HIV status. Multivariable logistic regression, adjusting for age and site, was performed to compare odds of being a case for each 3.4-unit drop in Ct value, which was approximately equivalent to a 1 $\log_{10}$ increase in viral copies/mL; Ct values instead of viral density were used for regression because viral density was only accurate within the linear range of the assay (10^4 – 10^8 copies/mL). Kernel density distribution plots were created

to show distributions of viral density by case/control status. Receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were generated to investigate the performance of viral load in determining case status among children positive by NP/OP PCR for each virus, and the Youden index was calculated to determine the optimized diagnostic cutoffs to differentiate cases and controls [18]. To guard against bias in the estimates of sensitivity due to having a small number of some viruses detected among cases, the Youden index was calculated using leave-one-out cross-validation where sample size was sufficient [19]. Redefining positivity using the optimal cutpoints, we calculated odds ratios associated with case status for children above vs below the optimal cutpoint including negatives. The proportion of radiographically confirmed cases attributable to each virus [population attributable fraction: population prevalence $\times$ (1 – 1 / OR)] was calculated using 2 methods: (1) any positive vs negative and (2) positive above vs below the optimal cutpoint, the former method being optimal for laboratory sensitivity and the latter for a balance of epidemiological sensitivity and specificity. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary North Carolina) and R Statistical Software 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). All *P* values are 2 sided.

Table 2. Mean Nasopharyngeal/Oropharyngeal Polymerase Chain Reaction Cycle Threshold Values for Chest Radiograph-Positive Cases and Controls and Odds Ratios for Viral Load Being Predictive of Case Status—Pneumonia Etiology Research for Child Health (PERCH) Study, August 2011–January 2014

Virus	CXR+ Cases ^a (n = 1733)			All Controls (n = 4986)			<i>P</i> Value ^d	OR per 1 $\log_{10}$ Increase, Copies/mL (95% CI) ^e
	No. ^b	(%) ^b	Ct Value Mean ^c (95% CI)	No. ^b	(%) ^b	Ct Value Mean ^c (95% CI)		
Adenovirus	164	(9.5)	27.7 (26.8–28.5)	594	(11.9)	29.5 (29.2–29.8)	<.001	1.27 (1.10–1.46)
Coronavirus 229	18	(1.1)	31.1 (28.6–33.5)	54	(1.1)	30.2 (28.3–32.0)	.58	0.89 (.62–1.26)
Coronavirus 43	38	(2.2)	26.4 (24.4–28.5)	192	(3.9)	28.0 (27.1–28.8)	.30	1.13 (.91–1.39)
Coronavirus 63	36	(2.1)	27.0 (25.3–28.7)	158	(3.2)	28.5 (27.7–29.3)	.26	1.18 (.90–1.55)
Coronavirus HKU	37	(2.2)	29.2 (27.0–31.4)	111	(2.2)	27.7 (26.5–28.9)	.40	0.91 (.74–1.13)
Influenza A	62	(3.6)	28.5 (27.7–29.4)	57	(1.2)	29.8 (28.4–31.2)	.31	1.21 (.85–1.72)
Influenza B	18	(1.1)	27.6 (25.7–29.5)	29	(0.6)	28.5 (26.7–30.3)	.82	1.07 (.63–1.83)
Influenza C	10	(0.6)	28.1 (24.8–31.4)	29	(0.6)	27.3 (25.3–29.3)	.14	0.44 (.17–1.15)
HBOV	231	(13.4)	30.5 (29.6–31.3)	660	(13.3)	31.7 (31.3–32.1)	.007	1.13 (1.03–1.24)
HMPV A/B	185	(10.8)	28.1 (27.6–28.7)	206	(4.1)	28.9 (28.2–29.5)	.02	1.23 (1.03–1.46)
Parainfluenza 1	89	(5.2)	26.1 (24.9–27.2)	49	(1.0)	29.4 (27.6–31.2)	.008	1.37 (1.08–1.74)
Parainfluenza 2	23	(1.3)	34.0 (31.7–36.3)	53	(1.1)	35.1 (33.9–36.3)	.70	1.10 (.71–1.69)
Parainfluenza 3	104	(6.1)	25.0 (24.0–25.9)	142	(2.9)	29.0 (28.0–30.0)	<.001	1.47 (1.22–1.77)
Parainfluenza 4	44	(2.6)	31.7 (30.3–33.1)	86	(1.7)	32.2 (31.3–33.1)	.88	0.98 (.73–1.31)
PV/EV	131	(7.6)	30.1 (29.5–30.8)	423	(8.5)	30.4 (30.0–30.7)	.45	1.08 (.89–1.31)
Rhinovirus	365	(21.2)	31.7 (31.3–32.0)	1056	(21.2)	32.4 (32.3–32.6)	.003	1.21 (1.08–1.35)
RSV	461	(26.8)	22.2 (21.8–22.5)	140	(2.8)	27.0 (26.1–28.0)	<.001	2.02 (1.71–2.37)

Abbreviations: CI, confidence interval; Ct, cycle threshold; CXR+, chest radiograph positive; HBOV, human bocavirus; HMPV, human metapneumovirus; OR, odds ratio; PV/EV, parechovirus/enterovirus; RSV, respiratory syncytial virus.

^aCXR+ defined as having radiographic evidence of pneumonia.

^bNo. (%) positive in the nasopharynx/oropharynx among those with available results for the given virus.

^cAmong those with a positive density.

^dComparing mean cycle threshold value of CXR+ cases vs all controls using linear regression adjusting for age and site. Bolded values are significant (*P* < .05).

^eOdds ratio is for approximately each 3.4-unit drop in Ct value (equivalent to approximately 1 $\log_{10}$ increase in copies/mL) adjusting for age and site using logistic regression. Bolded values are significant (*P* < .05).

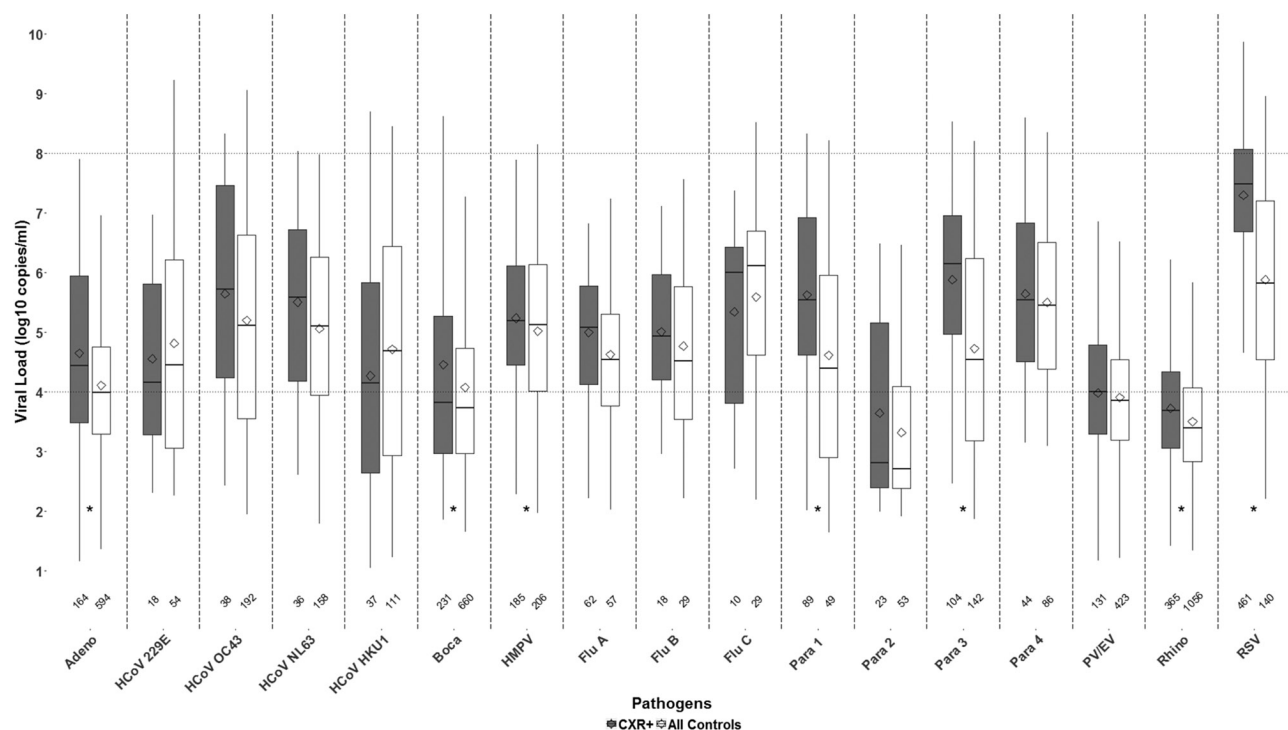


Figure 1. Nasopharyngeal/oropharyngeal viral load ($\log_{10}$ copies/mL) for chest radiograph–positive (CXR+) cases and all controls among those in which the virus was detected—Pneumonia Etiology Research for Child Health (PERCH) study, August 2011–January 2014. CXR+ defined as having radiographic evidence of pneumonia. Box-and-whiskers plot features include the following: central line in box is median, bottom line of box is first quartile (25%), top line of box is third quartile (75%), diamond is mean, and top and bottom of whiskers represent 95% confidence intervals. Area above the upper dotted line and below the lower dotted line indicate areas outside the linear range of the assay for calculation of viral load from cycle threshold (Ct) values where there is a greater degree of uncertainty in viral density calculations. Numbers on x-axis indicate number of positive results for that virus. * *P* value comparing mean Ct value between controls and CXR+ cases < .05 after adjusting for age and site. Abbreviations: Adeno, adenovirus; Boca, human bocavirus; CXR, chest radiograph; Flu, influenza virus; HCoV, human coronavirus; HMPV, human metapneumovirus; Para, parainfluenza virus; PIV1, parainfluenza virus 1; PIV3, parainfluenza virus 3; PIV4, parainfluenza virus 4; Rhinovirus, rhinovirus; RSV, respiratory syncytial virus.

Ethical Considerations

The PERCH study protocol was approved by the institutional review board or ethical review committee at each of the study site institutions and at the Johns Hopkins Bloomberg School of Public Health. Parents or guardians of all participants provided written informed consent.

RESULTS

Of 1935 radiographically confirmed cases and 5325 controls in PERCH, 1733 cases (1227 severe, 506 very severe) and 4986 controls (1185 RTI and 3801 non-RTI) were not known to be HIV infected and had viral density results available for analysis (Table 1).

Overall, 89.6% of cases and 79.0% of controls had at least 1 virus detected, and 53.4% and 40.3%, respectively, had ≥ 2 viruses detected (Table 1). Among the 17 viruses tested, RSV was the most commonly detected among cases (27%) but was uncommon among controls (3%) (Table 2). Rhinovirus was the next most commonly detected virus in cases but was present at a similar frequency among controls (21% for both).

Analysis of Viral Load Among Cases and Controls

RSV had the highest mean viral load among cases (7.3 log copies/mL; Figure 1); no viruses other than RSV had a mean viral

load >6 log copies/mL. Among controls, no viruses had a mean viral load >6 log copies/mL. Eight viruses among cases (RSV, influenza C, PIV1, PIV3, PIV4, coronavirus 43, coronavirus 63, and HMPV) had mean viral loads >5 log copies/mL vs 5 viruses among controls (RSV, influenza C, PIV4, coronavirus 43, and coronavirus 63). There were 7 viruses that had significantly higher mean viral density among cases after adjusting for site and age—adenovirus, HCoV, HMPV, PIV1, PIV3, rhinovirus, and RSV. After adjusting for age and site, there was a significant increase in the odds of being a case (vs a control) for each 3.4-unit drop in Ct value (approximately 1 log increase in copies/mL) for the same 7 viruses, ranging from a 13% increased odds for HCoV to a 102% increased odds for RSV (Table 2).

Viral load was similar between RTI and non-RTI controls for most viruses with the exception of RSV, where the mean viral load was significantly higher for RTI controls (Supplementary Figure 1).

Despite the differences in viral load between cases and controls noted above, there was substantial overlap in the viral density distribution between cases and controls in which virus was detected, as shown in the box plots and kernel density distribution plots (Figures 1 and 2). Kernel density distribution plots were examined for a bimodal distribution with a smaller subset

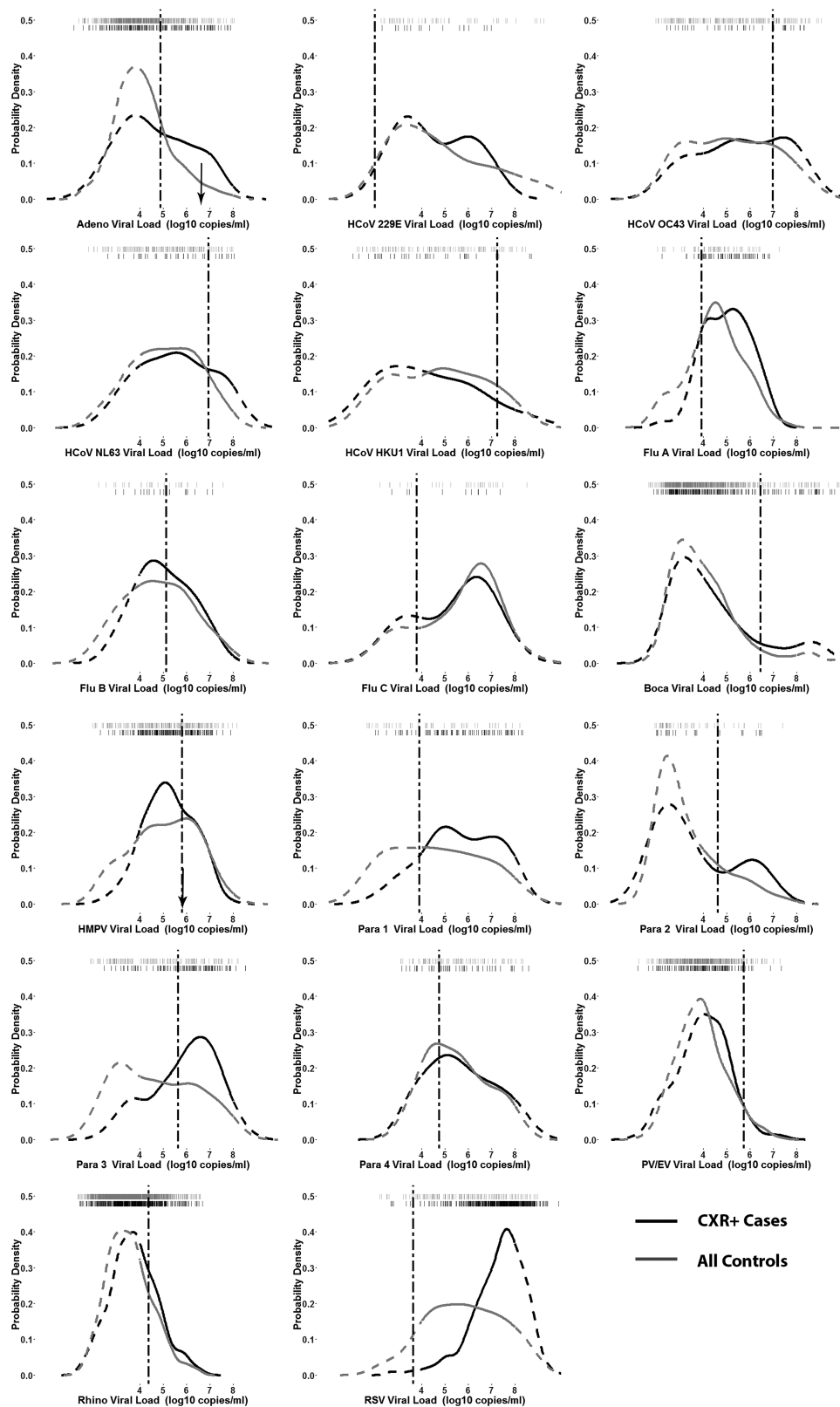


Figure 2. Kernel density distribution plots comparing nasopharyngeal/oropharyngeal (NP/OP) viral load among chest radiograph-positive (CXR+) cases and all controls for each viral polymerase chain reaction (PCR) target—Pneumonia Etiology Research for Child Health (PERCH) study, August 2011–January 2014. Tick marks across the top of each plot indicate viral load of each individual (first row of black ticks for cases and second row of gray ticks for controls). Dashed curves indicate areas outside the linear range of the assay for calculation of viral load from cycle threshold values. Dotted dashed vertical lines indicate optimal cutpoint distinguishing cases and controls calculated using Youden index. Black arrows in adenovirus and human metapneumovirus plots indicate NP/OP viral load of cases whose lung aspirate specimen was available and PCR positive for that virus. Abbreviations: Adeno, adenovirus; Boca, human bocavirus; CXR, chest radiograph; Flu, influenza virus; HCoV, human coronavirus; HMPV, human metapneumovirus; Para, parainfluenza virus; PV/EV, parechovirus/enterovirus; Rhino, rhinovirus; RSV, respiratory syncytial virus.

of cases having viruses at a higher viral load that might be indicative of those with pneumonia due to that virus. Adenovirus, coronavirus 229, and PIV1–3 had a suggestion of a bimodal distribution among cases. The NP/OP viral load for the 2 cases with viruses detected in PCR of lung aspirates (ie, HMPV and adenovirus) fell within the distribution of viral loads for other cases, as well as controls, positive for that virus (Figure 2).

When constructing ROC curves, no virus had an AUC >0.8 (Table 3). RSV had the highest AUC at 0.76, with only 3 other viruses having an AUC between 0.6 and 0.7 (influenza A, PIV1, and PIV3). Despite the low values for the AUC, when redefining positive for a virus as those with viral loads above the ROC optimal cutpoint value as determined by the Youden index, the odds ratio for predicting case status increased substantially for some viruses, approximately doubling for adenovirus, coronavirus 63, PIV2, and RSV (Table 4). Although the odds ratios increased, the population attributable fraction for most viruses did not change substantially, or even decreased (eg, influenza A, RSV) due to the lower frequency of cases with densities above the optimal cutpoint (Figure 3). This is because while the odds ratios are higher at the higher density cutoff, the prevalence of cases above the higher threshold was lower, and thus the proportion of PERCH cases assigned to the virus would not change appreciably by using the higher cutoff.

Table 3. Receiver Operating Characteristic Areas Under the Curve, Optimal Nasopharyngeal/Oropharyngeal Polymerase Chain Reaction Density Cutpoints for Determining Case Status, and Associated Positive Rate in Cases and Negative Rate in Controls by Virus Among Chest Radiograph–Positive Cases and Controls With Positive Densities—Pneumonia Etiology Research for Child Health (PERCH) Study, August 2011–January 2014

Virus ^a	AUC	Optimal Cutpoint ^b (Log ₁₀ Copies/ mL)	Proportion of CXR+ ^c Cases Above Cutpoint	Proportion of Controls Below Cutpoint
Adenovirus	0.60	4.88	0.44	0.78
Coronavirus 43	0.57	6.94	0.36	0.74
Coronavirus 63	0.58	7.24	0.22	0.89
Influenza A	0.61	5.12	0.50	0.68
Influenza B	0.55	3.79	0.89	0.28
HBOV	0.54	5.81	0.20	0.89
HMPV A/B	0.54	3.9	0.91	0.20
Parainfluenza 1	0.65	4.62	0.75	0.55
Parainfluenza 2	0.54	5.64	0.26	0.91
Parainfluenza 3	0.69	4.75	0.81	0.54
PV/EV	0.53	4.38	0.40	0.71
Rhinovirus	0.56	3.64	0.55	0.56
RSV	0.76	6.30	0.84	0.59

Abbreviations: AUC, area under the curve; CXR+, chest radiograph positive; HBOV, human bocavirus; HMPV, human metapneumovirus; PV/EV, parechovirus/enterovirus; RSV, respiratory syncytial virus.

^aViruses with adjusted odds ratios <1 (see Table 2) were excluded from table (coronavirus 229, coronavirus HKU, influenza C, and parainfluenza 4).

^bCalculated using Youden index and, where possible, leave-one-out cross-validation. Leave-one-out cross-validation was not performed for influenza B, parainfluenza 2, or parechovirus/enterovirus.

^cCXR+ defined as having radiographic evidence of pneumonia.

Predictors of Viral Load

We explored several potential predictors of viral density among cases. When NP/OP specimens were collected earlier in the course of illness, mean viral load was higher for RSV, PIV1, and PIV3 and was lower for adenovirus; no significant difference was observed for the other viruses (Supplementary Table 1). The viral load among cases did not vary by age for most viruses, including RSV, but a significant trend toward decreasing viral load with increasing age was observed for a few viruses, including adenovirus and RSV, which was also observed among controls (Supplementary Figure 2). A slight, but significant trend toward increasing viral load with increasing age was seen for rhinovirus among cases, but a significant trend in the opposite direction was observed for controls. In general, viral load did not vary by study site. One notable exception was higher PIV1 viral load in The Gambia site (the only site with a PIV1 outbreak, data not shown). HIV-infected cases had a higher mean viral load for coronavirus 43 and a lower viral load for HMPV, PIV3, and RSV (Supplementary Table 2). There were no significant differences in the viral load between cases who were normally nourished vs malnourished (except PIV1 viral load was higher in normally nourished, data not shown).

We assessed whether viral load was associated with pneumonia severity. Rhinovirus was the only virus with higher mean viral load for very severe pneumonia compared to severe pneumonia (Supplementary Figure 3). Influenza A was the only virus with higher mean viral load in fatal compared with surviving cases (Supplementary Figure 4). Furthermore, we compared mean viral densities between cases with evidence of an other infiltrate (without alveolar consolidation) on chest radiograph to cases with evidence of alveolar consolidation (without evidence of an other infiltrate). No significant differences were found for any virus after adjusting for site and age.

DISCUSSION

In the PERCH study, the evidence for the utility of NP/OP viral load in distinguishing radiographically confirmed cases of severe or very severe pneumonia from controls was mixed. On the one hand, we found a higher mean viral load in NP/OP samples from severe and very severe pneumonia cases than from community controls without pneumonia for several respiratory viruses. Moreover, for many viruses, using a higher viral load threshold to define positivity that maximized the combination of sensitivity and specificity increased the odds ratio for case status over a simple binary (presence/absence) definition of positivity based on viral detection, which has high sensitivity but low specificity. On the other hand, there was substantial overlap in the distribution of NP/OP viral load densities among cases and controls, even for RSV, the virus most strongly associated with case status. No cutoffs clearly distinguished cases from controls.

Table 4. Nasopharyngeal/Oropharyngeal Prevalence of Viruses in Chest Radiograph–Positive Cases and Controls, Defining Positive as Any Detection of Virus and Detection of Virus Above an Optimal Viral Load Cutpoint as Determined by Receiver Operating Characteristic Curves; Odds of Determining Case Status Using Both Definitions of Positive—Pneumonia Etiology Research for Child Health (PERCH) Study, August 2011–January 2014

Virus ^a	Negative		Weak Positive ^c (Below Optimal Cutpoint)		Strong Positive ^d (Above Optimal Cutpoint)		AOR ^e (95% CI) Any Positive vs Negative ^f	AOR ^e (95% CI) Strong Positive vs Weak Positive/ Negative ^g
	CXR+ Cases ^b	Controls	CXR+ Cases ^b	Controls	CXR+ Cases ^b	Controls		
Adenovirus	1556 (90.5)	4384 (88.0)	92 (5.3)	470 (9.4)	72 (4.2)	126 (2.5)	0.88 (.73–1.07)	1.74 (1.28–2.36)
Coronavirus 43	1681 (97.7)	4785 (96.1)	25 (1.5)	149 (3.0)	14 (0.8)	43 (0.9)	0.52 (.36–.74)	0.81 (.44–1.49)
Coronavirus 63	1684 (97.9)	4819 (96.8)	28 (1.6)	147 (3.0)	8 (0.5)	11 (0.2)	0.63 (.43–.91)	1.78 (.71–4.47)
Influenza A	1658 (96.4)	4920 (98.9)	31 (1.8)	41 (0.8)	31 (1.8)	16 (0.3)	3.11 (2.15–4.49)	5.32 (2.87–9.85)
Influenza B	1702 (99.0)	4948 (99.4)	2 (0.1)	8 (0.2)	16 (0.9)	21 (0.4)	1.82 (1.00–3.32)	2.24 (1.15–4.36)
HBOV	1488 (86.6)	4316 (86.7)	184 (10.7)	593 (11.9)	47 (2.7)	68 (1.4)	1.11 (.94–1.31)	2.02 (1.38–2.96)
HMPV A/B	1534 (89.2)	4771 (95.9)	16 (0.9)	47 (0.9)	169 (9.8)	159 (3.2)	2.59 (2.09–3.21)	3.02 (2.40–3.82)
Parainfluenza 1	1630 (94.8)	4928 (99.0)	23 (1.3)	27 (0.5)	66 (3.8)	22 (0.4)	5.19 (3.60–7.49)	8.09 (4.92–13.32)
Parainfluenza 2	1697 (98.7)	4927 (98.9)	18 (1.0)	48 (1.0)	5 (0.3)	5 (0.1)	1.2 (.73–1.97)	2.55 (.72–9.04)
Parainfluenza 3	1616 (94.0)	4838 (97.1)	21 (1.2)	78 (1.6)	83 (4.8)	64 (1.3)	2.13 (1.63–2.77)	3.52 (2.51–4.92)
PV/EV	1589 (92.4)	4555 (91.5)	79 (4.6)	303 (6.1)	52 (3.0)	122 (2.4)	0.91 (.74–1.12)	1.22 (.87–1.71)
Rhinovirus	1260 (73.3)	3675 (73.8)	211 (12.3)	743 (14.9)	249 (14.5)	559 (11.2)	0.94 (.82–1.07)	1.26 (1.07–1.48)
RSV	1259 (73.2)	4840 (97.2)	73 (4.2)	83 (1.7)	388 (22.6)	57 (1.1)	12.55 (10.24–15.38)	24.72 (18.52–33.01)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; CXR+, chest radiograph positive; HBOV, human bocavirus; HMPV, human metapneumovirus; PV/EV, parechovirus/enterovirus; RSV, respiratory syncytial virus.

^aViruses with adjusted odds ratios <1 for association of density (log copies/mL) with case status excluded from table (coronavirus 229, coronavirus HKU, influenza C, and parainfluenza virus 4 as noted in Table 2).

^bCXR+ defined as having radiographic evidence of pneumonia.

^cWeakly positive: positive density below optimal cutpoint determined by Youden index. See Table 3.

^dStrongly positive: density above optimal cutpoint determined by Youden index. See Table 3.

^eOdds ratios adjusted for site and age. Bolded values are significant ($P < .05$).

^fAny positive includes those below and above optimal cutoff.

^gStrong positives are compared with combined negatives and weak positives.

Previous studies have also shown that the median or mean RSV concentration of NP/OP specimens among children is higher in cases of severe illness than among a healthy or mildly ill control population [7–10, 20, 21]. However, few of these studies compared the distribution of viral loads between severe

cases and controls. Those that did compare these 2 groups showed an overlapping distribution similar to our study [8, 22]. Some studies of RSV viral load failed to show an association with severe lower respiratory tract infection [23, 24], but these studies included older children and adolescents in whom the

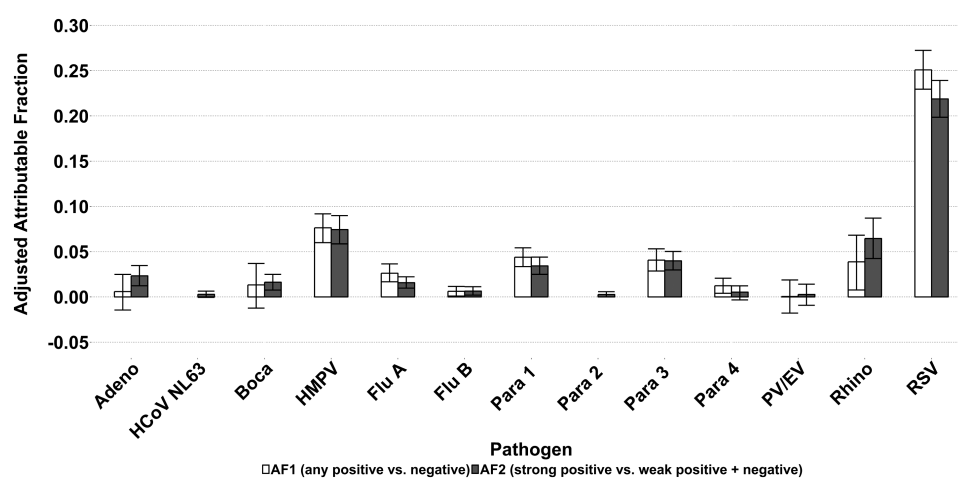


Figure 3. Adjusted population attributable fraction (PAF) for chest radiograph–positive cases using 2 methods: any positive vs negative (AF1) and positive above optimal cutpoint vs positive below optimal cutpoint and negative (AF2)—Pneumonia Etiology Research for Child Health (PERCH) study, August 2011–January 2014. PAF = population prevalence $\times (1 - 1 / \text{odds ratio})$. Odds ratio (OR) is adjusted for other viruses, site, and age. Confidence intervals calculated using bootstrapping method. PAF not shown where adjusted OR was <1 resulting in negative PAF. Abbreviations: Adeno, adenovirus; AF, attributable fraction; Boca, human bocavirus; Flu, influenza virus; HCoV, human coronavirus; HMPV, human metapneumovirus; Para, parainfluenza virus; PV/EV, parechovirus/enterovirus.

pathogenic significance of detecting RSV in the NP/OP is less clear. One study of RSV viral load in infants showed no association with severe bronchiolitis [25] while another suggested that viral load only influences clinical severity for first RSV infections in young infants [10].

In some studies, influenza viral load was associated with severe disease [4, 26–29], while in others there was no association [8, 23, 27, 30–32]. A few studies have shown a higher viral load in severe cases for HMPV [24, 33, 34]. Higher viral loads of HBOV in nasopharyngeal aspirates were associated with greater severity of illness among Chinese children [35]. Rhinovirus viral load has been associated with more severe illness [22], but not in some studies [8, 21]. Again, the majority of these studies looked only at the central tendency of the viral load and did not demonstrate a clear dichotomy in the distribution of viral loads based on case status or severity category.

We did not find a higher viral load associated with greater severity among pneumonia cases for most viruses. Cases who died had a similar viral load as those who survived, and those with very severe pneumonia had similar viral loads to those children with severe pneumonia. This is in contrast with some other studies of viruses in which higher viral load was observed among RSV-infected children requiring mechanical ventilation [9], and severe acute respiratory syndrome coronavirus- and Middle East respiratory syndrome coronavirus-infected adults who died [36, 37].

We undertook this analysis, in part, to determine if viral loads of NP/OP specimens could be incorporated into the PERCH analysis to identify etiologies of severe/very severe pneumonia. Using a higher density threshold also did not have an appreciable effect on the population attributable fraction for most viruses, suggesting that using higher thresholds to assign viral etiology to cases would likely have little impact on the analysis of the etiologic distribution among the population of PERCH cases [38]. In the final PERCH analyses, we will be able to run sensitivity analyses to assess the impact of incorporating viral density thresholds on the assessment of etiology.

In contrast to the accompanying analyses of bacterial pneumonia, our conclusions about the interpretation of viral load and whether to include it in the main PERCH etiology analysis were limited by the lack of a gold standard to diagnose viral pneumonia [5, 16]. There were few PERCH cases who underwent lung aspirate procedures and even fewer who had a lung aspirate in which a virus was detected in their lungs. Among a population of pneumonia cases in which a virus was detected in the NP/OP, there was likely a mixture of those in whom the virus had a causal role in pneumonia and those in whom it did not. The inability to identify which children had pneumonia due to which virus hampered the study's ability to determine if higher viral loads in the NP/OP were associated with pneumonia.

Besides the lack of a gold standard, other limitations might have affected our results. First, specimens were taken at one point in time on admission to the hospital. We observed that viral load varied with the time since illness onset, with higher viral load earlier in the course of symptomatic illness for some viruses. Taking sequential samples in which we could compare the peak viral load between cases of different clinical severity would have been optimal. Second, our design precluded us from assessing the role of viral load in the lung. Upper respiratory tract viral load might reflect the amount of replication in the local epithelial cells rather than the viral burden in the lung parenchyma. Evaluation of viral load of specimens from the lung, either through lung aspirates or bronchoalveolar lavage, would provide more direct evidence of the role of viral load in pneumonia severity.

The widespread use of sensitive PCR assays for testing NP/OP specimens has led to a higher reported prevalence of pneumonias attributed to respiratory viruses in both adults and children [2]. Due to the high prevalence of viral infections of the URT itself, however, it is difficult to conclude that detection of a virus in the URT of a pneumonia patient is equivalent to having pneumonia due to that virus. In the PERCH study, the viral loads in the NP/OP of pneumonia patients are unlikely to further clarify the role of that virus in causing pneumonia. However, the PERCH study design was not optimal to answer this question definitively. Further research, such as longitudinal studies and animal models, is needed to better elucidate the interpretation of viral load in the diagnosis and clinical management of viral pneumonia.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Author contributions. D. R. F. led the analysis, interpreted results, and drafted initial manuscript. W. F. and Q. S. performed the analysis. W. F., Q. S., D. E. P., M. M. H., and D. R. M. provided significant guidance on the development of the manuscript. O. S. L., K. L. O., D. R. F., L. L. H., R. A. K., D. R. M., M. D. K., H. C. B., W. A. B., S. R. C. H., K. L. K., S. A. M., J. A. G. S., D. M. T. conceived and designed the study and supervised study conduct. W. F., D. E. P., Q. S., M. M. H., P. V. A., M. A., J. O. A., V. L. B., A. N. D., A. J. D., B. E. E., D. G., M. L., S. C. M., J. M., J. M., C. P., P. S., S. O. S., M. D. T., T. W., and K. Z. were involved in study conduct. S. L. Z. provided statistical expertise and led the integrated etiology analysis. All authors reviewed and approved the manuscript. D. R. F. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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PERCH Study Group. Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland: Katherine L. O'Brien (principal investigator [PI]), Orin S. Levine (former PI, current affiliation Bill & Melinda Gates Foundation, Seattle, Washington), Maria Deloria Knoll (co-PI), Daniel R. Feikin (joint affiliation with Centers for Disease Control and Prevention [CDC], Atlanta, Georgia), Andrea N. DeLuca, Amanda J. Driscoll, Nicholas Fancourt, Wei Fu, Laura L. Hammitt, Melissa M. Higdon, E. Wangeci Kagucia, Ruth A. Karron, Mengying Li, Daniel E. Park, Christine Prosperi, Zhenke Wu, Scott L. Zeger; Emmes Corporation, Rockville, Maryland: Nora L. Watson; Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom: Jane Crawley; University of Otago, Christchurch, New Zealand: David R. Murdoch; icddr, Dhaka and Matlab, Bangladesh: W. Abdullah Brooks (site PI), Hubert P. Endtz, Khalequ Zaman, Doli Goswami, Lokman Hossain, Yasmin Jahan, Hasan Ashraf; Medical Research Council, Basse, The Gambia: Stephen R. C. Howie (site PI), Bernard E. Ebruke, Martin Antonio, Jessica McLellan, Eunice Machuka, Arifin Shamsul, Syed M. A. Zaman, Grant Mackenzie; KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya: J. Anthony G. Scott (site PI and PERCH co-PI), Juliet O. Awori, Susan C. Morpeth, Alice Kamau, Sidi Kazungu, Micah Silaba Ominde; Division of Infectious Disease and Tropical Pediatrics, Department of Pediatrics, Center for Vaccine Development, Institute of Global Health, University of Maryland School of Medicine, Baltimore, Maryland and Centre pour le Développement des Vaccins (CVD-Mali), Bamako, Mali: Karen L. Kotloff (site PI), Milagritos D. Tapia, Samba O. Sow, Mamadou Sylla, Boubou Tamboura, Uma Onwuchekwa, Nana Kourouma, Aliou Toure; Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg, South Africa: Shabir A. Madhi (site PI), David P. Moore, Peter V. Adrian, Vicky L. Baillie, Locadiah Kuwanda, Azwifarwi Mudau, Michelle J. Groome, Nasreen Mahomed; Thailand Ministry of Public Health–US CDC Collaboration, Nonthaburi, Thailand: Henry C. Baggett (site PI), Somsak Thamthitwat, Susan A. Maloney (former site PI), Charatdao Bunthi, Julia Rhodes, Pongpun Sawatwong, Pasakorn Akarasewi (site co-PI, Ministry of Public Health); Boston University School of Public Health, Boston, Massachusetts and University Teaching Hospital, Lusaka, Zambia: Donald M. Thea (site PI), Lawrence Mwananyanda, James Chipeta, Phil Seidenberg, James Mwansa, Somwe wa Somwe, Geoffrey Kwenda. Canterbury Health Laboratory, Christchurch, New Zealand: Trevor P. Anderson, Joanne Mitchell.

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References

- Hammit LL, Murdoch DR, Scott JA, et al; Pneumonia Methods Working Group. Specimen collection for the diagnosis of pediatric pneumonia. *Clin Infect Dis* **2012**; 54(suppl 2):S132–9.
- Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet* **2011**; 377:1264–75.
- Murdoch DR, O'Brien KL, Scott JA, et al. Breathing new life into pneumonia diagnostics. *J Clin Microbiol* **2009**; 47:3405–8.
- Jansen RR, Wieringa J, Koekkoek SM, et al. Frequent detection of respiratory viruses without symptoms: toward defining clinically relevant cutoff values. *J Clin Microbiol* **2011**; 49:2631–6.
- Baggett HC, Watson NL, Deloria Knoll M, et al. Density of upper respiratory colonization with *Streptococcus pneumoniae* and its role in the diagnosis of pneumococcal pneumonia among children aged <5 years in the PERCH study. *Clin Infect Dis* **2017**; 64(suppl 3):S317–27.
- Albrich WC, Madhi SA, Adrian PV, et al. Use of a rapid test of pneumococcal colonization density to diagnose pneumococcal pneumonia. *Clin Infect Dis* **2012**; 54:601–9.
- Fuller JA, Njenga MK, Bigogo G, et al. Association of the CT values of real-time PCR of viral upper respiratory tract infection with clinical severity, Kenya. *J Med Virol* **2013**; 85:924–32.
- Utokaarch S, Marchant D, Gosselink JV, et al. The relationship between respiratory viral loads and diagnosis in children presenting to a pediatric hospital emergency department. *Pediatr Infect Dis J* **2011**; 30:e18–23.
- Buckingham SC, Bush AJ, Devincenzo JP. Nasal quantity of respiratory syncytial virus correlates with disease severity in hospitalized infants. *Pediatr Infect Dis J* **2000**; 19:113–7.
- DeVincenzo JP, El Saleeby CM, Bush AJ. Respiratory syncytial virus load predicts disease severity in previously healthy infants. *J Infect Dis* **2005**; 191:1861–8.
- DeVincenzo JP, Wilkinson T, Vaishnav A, et al. Viral load drives disease in humans experimentally infected with respiratory syncytial virus. *Am J Respir Crit Care Med* **2010**; 182:1305–14.
- Deloria-Knoll M, Feikin DR, Scott JA, et al; Pneumonia Methods Working Group. Identification and selection of cases and controls in the pneumonia etiology research for child health project. *Clin Infect Dis* **2012**; 54(suppl 2):S117–23.
- Scott JA, Wonodi C, Moisi JC, et al; Pneumonia Methods Working Group. The definition of pneumonia, the assessment of severity, and clinical standardization in the Pneumonia Etiology Research for Child Health study. *Clin Infect Dis* **2012**; 54(suppl 2):S109–16.
- Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bull World Health Organ* **2005**; 83:353–9.
- Driscoll AJ, Karron RA, Morpeth SC, et al. Standardization of laboratory methods for the pneumonia etiology research for child health study. *Clin Infect Dis* **2017**; 64(suppl 3):S245–52.
- Park DE, Baggett HC, Howie SRC, et al. Colonization density of the upper respiratory tract as a predictor of pneumonia—*Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pneumocystis jirovecii*. *Clin Infect Dis* **2017**; 64(suppl 3):S328–36.
- Falade AG, Mulholland EK, Adegbola RA, Greenwood BM. Bacterial isolates from blood and lung aspirate cultures in Gambian children with lobar pneumonia. *Ann Trop Paediatr* **1997**; 17:315–9.
- Youden WJ. Index for rating diagnostic tests. *Cancer* **1950**; 3:32–5.
- Leeftang MMG, Moons KGM, Reitsma JB, Zwinderman AH. Bias in sensitivity and specificity caused by data-driven selection of optimal cutoff values: mechanisms, magnitude, and solutions. *Clin Chem* **2008**; 54:729–37.
- Fodha I, Vabret A, Ghedira L, et al. Respiratory syncytial virus infections in hospitalized infants: association between viral load, virus subgroup, and disease severity. *J Med Virol* **2007**; 79:1951–8.
- Houben ML, Coenjaerts FE, Rossen JW, et al. Disease severity and viral load are correlated in infants with primary respiratory syncytial virus infection in the community. *J Med Virol* **2010**; 82:1266–71.
- Jansen RR, Schinkel J, Dek I, et al. Quantitation of respiratory viruses in relation to clinical course in children with acute respiratory tract infections. *Pediatr Infect Dis J* **2010**; 29:82–4.
- Franz A, Adams O, Willems R, et al. Correlation of viral load of respiratory pathogens and co-infections with disease severity in children hospitalized for lower respiratory tract infection. *J Clin Virol* **2010**; 48:239–45.
- Martin ET, Kuypers J, Heugl J, Englund JA. Clinical disease and viral load in children infected with respiratory syncytial virus or human metapneumovirus. *Diagn Microbiol Infect Dis* **2008**; 62:382–8.
- Wright PF, Gruber WC, Peters M, et al. Illness severity, viral shedding, and antibody responses in infants hospitalized with bronchiolitis caused by respiratory syncytial virus. *J Infect Dis* **2002**; 185:1011–8.

26. Hall CB, Douglas RG Jr, Geiman JM, Meagher MP. Viral shedding patterns of children with influenza B infection. *J Infect Dis* **1979**; 140:610–3.
27. Lee CK, Lee HK, Loh TP, et al. Comparison of pandemic (H1N1) 2009 and seasonal influenza viral loads, Singapore. *Emerg Infect Dis* **2011**; 17:287–91.
28. Li CC, Wang L, Eng HL, et al. Correlation of pandemic (H1N1) 2009 viral load with disease severity and prolonged viral shedding in children. *Emerg Infect Dis* **2010**; 16:1265–72.
29. Lu PX, Deng YY, Yang GL, et al. The relationship between chest CT findings and viral load in patients with novel influenza A (H1N1). *Natl Cent Biotechnol Inf* **2010**; 33:746–9.
30. Duchamp MB, Casalegno JS, Gillet Y, et al. Pandemic A(H1N1)2009 influenza virus detection by real time RT-PCR: is viral quantification useful? *Clin Microbiol Infect* **2010**; 16:317–21.
31. Meschi S, Selleri M, Lalle E, et al. Duration of viral shedding in hospitalized patients infected with pandemic H1N1. *BMC Infect Dis* **2011**; 11:140.
32. To KKW, Hung IFN, Li IWS, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. *Clin Infect Dis* **2010**; 50:850–9.
33. Bosis S, Esposito S, Osterhaus AD, et al. Association between high nasopharyngeal viral load and disease severity in children with human metapneumovirus infection. *J Clin Virol* **2008**; 42:286–90.
34. Gerna G, Sarasini A, Percivalle E, et al. Prospective study of human metapneumovirus infection: diagnosis, typing and virus quantification in nasopharyngeal secretions from pediatric patients. *J Clin Virol* **2007**; 40:236–40.
35. Zhao B, Yu X, Wang C, et al. High human bocavirus viral load is associated with disease severity in children under five years of age. *PLoS One* **2013**; 8:e62318.
36. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med* **2004**; 10(12 suppl):S88–97.
37. Feikin DR, Al-Raddadi B, Qutub M, et al. Association of higher MERS-CoV virus load with severe disease and death, Saudi Arabia, 2014. *Emerg Infect Dis* **2015**; 21:2029–35.
38. Deloria Knoll M, Fu W, Shi Q, et al. Bayesian estimation of pneumonia etiology: epidemiologic considerations and applications to pneumonia etiology research for child health study. *Clin Infect Dis* **2017**; 64(suppl 3):S213–27.

Revised WHO classification and treatment of childhood pneumonia at health facilities

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Revised WHO classification and treatment of childhood pneumonia at health facilities

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Executive Summary

In the early 1980s, the global burden of childhood mortality due to pneumonia led the World Health Organization (WHO) to develop a pneumonia control strategy suitable for countries with limited resources and constrained health systems. Management of pneumonia cases formed the cornerstone of this strategy. Simple signs were identified to classify varying severities of pneumonia in settings with little or no access to diagnostic technology; the classifications determined the appropriate case management actions. Children with fast breathing were classified as having “pneumonia” and were given an oral antibiotic (at that time oral cotrimoxazole) to take at home for five days. Children who had chest indrawing with or without fast breathing were classified as having “severe pneumonia” and were referred to the closest higher-level health facility for treatment with injectable penicillin. Children who had any general danger signs were classified as having “severe pneumonia or very severe disease”. These children received a first dose of oral antibiotic and were then urgently referred to a higher-level health facility for further evaluation and treatment with parenteral antibiotics.

These pneumonia classification and management guidelines had been developed based on evidence generated in the 1970s and early 1980s, and were incorporated into the original version of Integrated Management of Childhood Illness (IMCI). In the intervening time, new evidence has emerged which prompted the development of revised guidelines.

Research results provided solid scientific evidence to guide and support the revision of the pneumonia guidelines. During two related consultations, a panel of experts assessed the new evidence according to the GRADE methodology (“Grading of Recommendations, Assessment, Development and Evaluation”). The consultations aimed to summarize the new WHO recommendations for policy and practice, to review GRADE evidence profiles, and to discuss the factors that determined the strength of the recommendations. The first consultation resulted in updated recommendations for preventing and managing pneumonia in HIV-infected and -exposed infants and children; these were published in 2010.¹ The second resulted in updated recommendations for managing pneumonia in non-HIV affected infants and children, published in 2012.²

The revisions include changing the recommendation for the first-line antibiotic and re-defining the classification of pneumonia severity. The data show that oral amoxicillin is preferable to oral cotrimoxazole for the treatment of “fast breathing pneumonia” and is equivalent to injectable penicillin/ampicillin in cases of “chest indrawing pneumonia”. Hence, in a programmatic context, the distinction between previously defined “pneumonia” (fast breathing) and “severe pneumonia”

¹ Integrated Management of Childhood Illness (IMCI). WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241548083/en).

² Recommendations for management of common childhood conditions, Evidence for technical update of pocket book recommendations. Geneva: World Health Organization; 2012 (http://www.who.int/maternal_child_adolescent/documents/management_childhood_conditions/en).

(chest indrawing) loses its significance. The new classification is therefore simplified to include only two categories of pneumonia; “pneumonia” with fast breathing and/or chest indrawing, which requires home therapy with oral amoxicillin, and “severe pneumonia”, pneumonia with any general danger sign, which requires referral and injectable therapy.

Dosages for pneumonia treatment at health facilities have been revised to reflect three age bands: 2 months up to 12 months (4–<10 kg); 12 months up to 3 years (10–<14 kg); 3 years up to 5 years (14–19 kg). Dosages and age bands for treatment of fast breathing pneumonia by community health workers (CHWs) have not changed.

National child health programmes will benefit from the revised recommendations and are encouraged to incorporate them into their existing guidelines for care at health facilities. The recommendations concerning the use of amoxicillin should also be included in guidelines for integrated community case management (iCCM). Programmes should recognize the importance of these revisions, which will result in a substantially lower need for referral, and in better treatment outcomes. Local adaptations may be required, particularly the arrangements to include amoxicillin as the first-line therapy; facility-level health workers will also need to be re-trained in the new system of classification and treatment.

The purpose of this document is to provide a summary of WHO-approved recommendations,^{1,2} and the evidence supporting them, and to assist national child health programmes in revising their guidelines to conform to the new recommendations.

The revised recommendations are:

Recommendation 1

Children with fast breathing pneumonia with no chest indrawing or general danger sign should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily (80mg/kg/day) for five days. In areas with low HIV prevalence, give amoxicillin for three days.

Children with fast-breathing pneumonia who fail on first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.

Recommendation 2

Children age 2–59 months with chest indrawing pneumonia should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily for five days.

Recommendation 3

Children aged 2–59 months with severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.

- Ampicillin: 50 mg/kg, or benzyl penicillin: 50 000 units per kg IM/IV every 6 hours for at least five days
- Gentamicin: 7.5 mg/kg IM/IV once a day for at least five days

Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.

Recommendation 4

Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and -exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.

For HIV-infected and -exposed infants and for children with chest indrawing pneumonia or severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second-line treatment.

Recommendation 5

Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with chest indrawing or severe pneumonia.

Empirical cotrimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended for HIV-infected and -exposed children over 1 year of age with chest indrawing or severe pneumonia.

Introduction

Pneumonia continues to be the biggest killer worldwide of children under five years of age. Although the implementation of safe, effective and affordable interventions has reduced pneumonia mortality from 4 million in 1981 (1) to just over one million in 2013 (2,3), pneumonia still accounts for nearly one-fifth of childhood deaths worldwide.

Case management is a cornerstone of pneumonia control strategies (4). It consists of classifying the severity of illness using simple clinical signs such as fast breathing, chest indrawing and general danger signs,³ and then applying the appropriate treatment. Treatment includes home care advice, antibiotics for home therapy, or referral to a higher-level health facility.

The recommendations for the management of pneumonia in health facilities have recently been modified (5–7). The revisions are a result of new evidence generated from research carried out in the last decade including in those low- and middle-income countries with the largest burden of pneumonia mortality. Integrated Management of Childhood Illness (IMCI) at health facility level has been updated accordingly. Integrated Community Case Management (iCCM) by lay community health workers (CHWs) has not been changed.

The original guidelines classified the respiratory symptoms of children 2 to 59 months of age into four categories (8,9). Children with cough and cold who did not have signs of pneumonia were classified as “no pneumonia”, and their caregivers were advised on appropriate home care. Children with fast breathing were classified as “pneumonia” and were given an oral antibiotic (at that time oral cotrimoxazole) to take at home for five days. Children who had chest indrawing with or without fast breathing were classified as “severe pneumonia” and were referred to the closest health facility for treatment with injectable penicillin. Children who had any general danger signs were classified as “severe pneumonia or very severe disease”. These children received a first dose of oral antibiotic and were then urgently referred to a health facility for further evaluation and treatment with parenteral antibiotics.

Data shows that the majority of childhood pneumonia deaths are due to severe pneumonia/severe disease (10); management of these cases requires early identification, prompt referral and the availability of good-quality higher-level care. However, in many low-resource settings, referral is difficult and often does not take place (11–15). On the basis of this information, WHO undertook a review of the evidence, with the aim of developing a simplified approach that could increase the number of children receiving correct treatment for pneumonia.

³ Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

In two consultations, experts updated recommendations for 1) preventing and managing pneumonia in HIV-infected and -exposed infants and children (9) and 2) for managing pneumonia in non-HIV-affected infants and children (5). The recommendations were published in 2010 and 2012 respectively.

This document presents a summary of recommendations and of the research that forms the technical basis of the revised guidelines; it also suggests implications for implementation in countries. Its purpose is to assist national child health programmes in revising their guidelines to conform to the new recommendations. These revisions, implemented in countries with a high pneumonia burden, will result in a higher proportion of children receiving care at the outpatient or community levels, and a reduced number of pneumonia-related deaths.

1. Scientific basis of WHO recommendations for treatment of pneumonia

1.1 Recommendation 1

Children with fast breathing pneumonia⁴ with no chest indrawing or general danger sign should be treated with oral amoxicillin: at least 40 mg/kg/dose twice daily (80mg/kg/day) for five days. In areas with low HIV prevalence, give amoxicillin for three days.

Children with fast-breathing pneumonia who fail on first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.

1.1.1 The effectiveness of various antibiotics in community-acquired childhood pneumonia: a systematic review

Kabra et al (16) systematically reviewed literature comparing various antibiotics, in order to identify effective drug therapy for community-acquired pneumonia in children. All randomized controlled trials (RCTs) that compared at least two antibiotics for community-acquired pneumonia in children in hospital or ambulatory settings were selected.

The review showed that for treatment of pneumonia, cotrimoxazole was inferior in efficacy to both amoxicillin (clinical failure rates odds ratio (OR) 1.33; 95% CI 1.05 to 1.67) and procaine penicillin (clinical cure rates OR 2.64; 95% CI 1.57 to 4.45). Injectable penicillin in conjunction with injectable gentamicin was more effective than injectable chloramphenicol alone (re-hospitalization rates OR 1.61; 95% CI 1.02 to 2.55). Co-amoxycyclavulanic acid was more effective than amoxicillin alone (cure rates OR 10.44; 95% CI 2.85 to 38.21). There were no differences between injectable penicillin and oral amoxicillin (failure rates OR 1.03; 95% CI 0.81 to 1.31); between azithromycin and erythromycin; between cefodoxime and amoxicillin; or between azithromycin and co-amoxycyclavulanic acid.

The authors concluded that for treatment of ambulatory patients with community-acquired pneumonia, amoxicillin was more effective than cotrimoxazole. Moreover, in hospitalized patients, penicillin was found to be more effective than cotrimoxazole; and the combination of penicillin and gentamicin was superior to chloramphenicol. Injectable penicillin and oral amoxicillin had similar clinical failure rates.

Another systematic review (17) was conducted by nine clinicians and researchers with extensive experience in the field of childhood pneumonia. The review aimed to identify appropriate first- and second-line antimicrobial agents for the empirical treatment of fast breathing pneumonia in children by first-level health care providers, in addition to defining treatment failure and criteria for referral. For the first-line treatment oral amoxicillin was found to be most effective in the treatment of fast breathing pneumonia. The review suggested that treatment failure for fast breathing pneumonia should be redefined as “clinical deterioration” only, instead of changing therapy when the child’s condition is the “same” on follow-up after two or three days of treatment. It was sug-

⁴ Previously classified as pneumonia (IMCI Chart Booklet 2008).

gested that once classified as “treatment failure” each child should be assessed independently for referral as not all cases will mandate immediate referral. The review recommended the development of an algorithm to determine the best course of action when treatment failure occurs.

1.1.2 A three-day course of antibiotics is as effective as a five-day course in treating children with fast breathing pneumonia

A systematic review by Haider et al (18) reviewed three randomized controlled trials evaluating the efficacy of short-course versus long-course treatment of fast breathing pneumonia in children age 2–59 months. Two of the studies (19,20) examined treatment with oral amoxicillin, while the third (21) examined treatment with oral cotrimoxazole. All studies compared the duration of two courses of treatment, one lasting three days and the other five days, while holding the antibiotic constant. The three studies were double blind, randomized, placebo controlled trials with a total of 6210 participants. Data was available for 5763 cases. The primary outcome was clinical cure at the end of the treatment. The studies found no significant differences in clinical cure rates between the two groups (RR 0.99; 95% CI 0.97 to 1.01). Nor were there significant differences in either the treatment failure or relapse rates between groups. The review recommended a shorter course of antibiotic therapy, keeping in mind the benefits to the individual as well as to the health system, especially in settings with limited resources.

1.2 Recommendation 2

Children age 2–59 months with chest indrawing pneumonia⁴ should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily (80mg/kg/day) for five days.

Previous guidelines by WHO for the management of chest indrawing pneumonia in children (22) recommended parenteral antibiotics for at least three days. A study by Straus et al (23) published in 1998 found that treatment failure rate with oral amoxicillin was significantly lower than with oral cotrimoxazole (18% and 33% respectively) in children with chest indrawing pneumonia ($p=0.009$). It was concluded that although oral cotrimoxazole was effective in fast breathing pneumonia, it was less effective in treating chest indrawing pneumonia. Multi-country studies, using a randomized controlled trial design and an adequate sample size, were then undertaken to assess the effectiveness of oral amoxicillin in chest indrawing pneumonia. A summary of the evidence that has led to the revised recommendation is presented below.

1.2.1 Oral amoxicillin is as effective as injectable penicillin in the treatment of chest indrawing pneumonia in children in low-resource settings

A multicentre, randomized, open-label trial by Addo-Yobo et al (24) (APPIS Study) compared the efficacy of oral amoxicillin and injectable penicillin. The study was conducted at nine tertiary health facilities in eight developing countries and enrolled 1702 children age from 3 to 59 months with chest indrawing. Children were randomly assigned to receive either a five-day course of oral amoxicillin ($n=857$) or parenteral penicillin ($n=845$). Evaluations were carried out at 48 hours, five days and 14 days. The primary outcome of the study was clinical treatment failure at 48 hours. The study found treatment failure rates of 19% in each treatment group ($n=161$ penicillin; $n=167$ amoxicillin; risk difference -0.4%; 95% CI -4.2 to 3.3). The study described a number of advantages of oral treatment over parenteral treatment, including reduced risk of injection-related morbidity, and fewer needs for medical supplies such as needles, and suggested that oral treatment be considered as an equally effective alternative to parenteral treatment. Although this study proved the

effectiveness of oral amoxicillin, it did not fully address the issue of safety, as all enrolled children were hospitalized for 48 hours and kept under close supervision. More research was needed to test the hypothesis under a wider range of circumstances.

1.2.2 Oral amoxicillin is equally effective for pneumonia of various severities in a high-resource setting

A study in England in 2007 (PIVOT Trial) (25) compared oral amoxicillin and intravenous (IV) benzyl penicillin in the management of severe pneumonia. The randomized, controlled, non-blinded equivalence trial was conducted in eight paediatric centres (district general and tertiary hospitals) and enrolled children with all but the most severe cases of pneumonia. Additional exclusion criteria were: wheeze, oxygen saturation less than 85%, shock, immunodeficiency, pleural effusion at presentation requiring drainage, chronic lung condition (excluding asthma), penicillin allergy, and age less than 6 months. Children were randomly assigned to a 7-day treatment of either oral amoxicillin or IV benzyl penicillin. The primary outcome was the time required for temperature to be below 38 °C for 24 continuous hours. The study found the two treatments to be equivalent, each having a median time of 1.3 days to achieve the primary outcome. While equivalence between oral and parenteral antibiotics itself was not a new development, this study was unique in the scope of varying severities of pneumonia treated. It was also the first study of its kind for children in a high-resource setting with radiologically confirmed pneumonia. The study recommended that children be treated with oral amoxicillin instead of IV benzyl penicillin, as oral treatment was both painless and non-invasive.

1.2.3 It is safe to treat chest indrawing pneumonia at home with oral amoxicillin

Hazir et al (26) (NO-SHOTS Study) carried out a randomized, open-label equivalency trial at seven sites in Pakistan, comparing hospitalization with parenteral ampicillin to home treatment with oral amoxicillin. Children with chest indrawing pneumonia were randomized to treatment in hospital (n=1012) with two days of injectable ampicillin followed by three days of oral amoxicillin (80–90 mg/kg/day), or were sent home with a five-day twice daily course of oral amoxicillin (n=1025). The primary outcome was clinical treatment failure. Follow-up assessments were conducted at 1, 3, 6, and 14 days after enrolment. At day 6 there were 87 (8.6%) treatment failures in the hospitalized group and 77 (7.5%) treatment failures in the home-treatment group (risk difference 1.1%, 95% CI – 1.3–3.5). In addition to finding equivalence between the two treatments, the authors suggested that in cases of chest indrawing pneumonia without underlying complications, home treatment with a short course of high-dose oral amoxicillin was preferable to parenteral treatment because of the associated reduction in referral, admission, and treatment costs as well as the reduced invasiveness of oral treatment.

1.2.4 Home therapy with oral amoxicillin is effective in a range of settings

To test whether the interpretation that chest indrawing pneumonia can be treated safely and effectively at home was generalizable across communities and geographic regions, a multicentre observational study was conducted in Bangladesh, Egypt, Ghana and Viet Nam (27). Outcome was ascertained on a total of 823 children age 3 to 59 months old, with chest indrawing pneumonia, who were given oral amoxicillin (80–90 mg/kg/day) twice daily for five days. Follow-up at home was carried out on days 1, 2, 3 and 6 to assess treatment failure, and at the health facility on day 14 to assess relapse. Overall treatment failure was 9.2%, varying from 6.4% in Ghana to 13.2% in Vietnam. The common reasons for failure were persistence of chest indrawing at day 6 (3.8%),

abnormally sleepy or difficult to wake (1.3%) and central cyanosis (1.3%). The authors concluded that among children with chest indrawing pneumonia treated at home with oral amoxicillin, clinical treatment failure and adverse event rates did not differ across geographic areas. This argues in favour of the option of home-based therapy of chest indrawing pneumonia in a wide variety of settings.

In these studies, the children with chest indrawing pneumonia were identified and treated on an outpatient basis by qualified doctors, and were followed up either in an outpatient facility or at home. This made it difficult to generalize to situations where pneumonia is treated within the community, by CHWs who may have little or no formal education. Data were needed to assess the effectiveness of community case management of chest indrawing pneumonia.

1.2.5 Efficacy of higher dose (80–90 mg/kg/day) vs. lower dose (45 mg/kg/day) of amoxicillin

1.2.5.1 Amoxicillin is more effective when given in higher doses

The major parameter determining the *in vivo* efficacy of many antibiotics is the duration of time that serum level exceeds the mean inhibiting concentration (MIC), and studies have demonstrated the effect of increasing concentrations of antimicrobials on their bactericidal activity. A clinical review and other reports showed that for *Streptococcus pneumoniae* and *Haemophilus influenzae* in patients with otitis media (28–34), serum levels must be above the MIC for more than 40% of the time the child is in treatment in order to achieve a bacteriological cure rate of 85% to 100%. The review also showed that amoxicillin and cefuroxime provided adequate duration above the MIC for penicillin-intermediate resistant strains. In contrast, for penicillin-resistant strains, only amoxicillin provided levels above the MIC for more than 40% of the dosing interval. The review also showed that a four-fold higher dose given every eight hours results in a much higher peak/MIC ratio than a dose administered every two hours.

The evidence-based practice guidelines of the American Academy of Pediatrics and the American Academy of Family Physicians for the treatment of community-acquired pneumonia recommend an amoxicillin dose of 75–100 mg/kg/day (35). This recommendation was based on extrapolation from microbiology studies on acute otitis media (AOM). Amoxicillin can be given in a twice-daily regimen.

The main causal organisms of AOM and childhood pneumonia are *S. pneumoniae* and *H. influenzae*. Keeping in mind the penicillin-intermediate and penicillin resistant strains of these organisms, the revised guidelines recommend 80mg/kg/day of amoxicillin in two divided doses for the treatment of chest indrawing pneumonia.

1.2.5.2 Amoxicillin can be given twice instead of thrice daily for children with fast breathing and chest indrawing pneumonia

Fonseca W et al (36) compared levels of oral amoxicillin in a 15 mg/kg/body weight/dose given thrice daily with a regimen of 25 mg/kg/dose twice daily in 66 children age 3 to 59 months. Amoxicillin concentrations were determined by high performance liquid chromatography after the first daily dose on days 1 and 3. For amoxicillin, the mean area under the concentration time curve after the 25 mg/kg/dose was 54.7 µg/ml x h, whereas after the 15 mg/kg/dose it was 24.9 µg/ml x h. The study concluded that oral amoxicillin twice daily is a feasible alternative to thrice daily dosing. It was suggested that in order to lengthen the time above the MIC at higher concentration levels, a 30 to 40 mg/kg/dose twice daily should be considered instead of the 25 mg/kg/dose used in this study.

Valtonen M et al (37) compared the clinical efficacy and side effects of amoxicillin (40 mg/kg/day) in two groups of children randomly assigned to a regimen of either two or three doses per day. In the group with two daily doses, 82% of the patients with otitis media were cured; in the group with three daily doses this figure was 86%. Side effects were equal in both groups. The trial concluded that “the same total daily dose of amoxicillin given either three times daily or two times daily is comparably effective and tolerated in children with acute respiratory infections”.

Daschner FD et al (38) compared the effects of giving amoxicillin (50 mg/kg/day) twice or four times per day in 34 children with respiratory tract infections. Peak and trough antibiotic concentrations were determined. Eradication of bacteria, clinical improvement and side effects were compared in both groups. The authors concluded that the same total daily dosage of amoxicillin given either twice or four times daily was equally effective and safe.

The Catchup study group (39) compared the clinical effectiveness of twice-daily oral amoxicillin with twice-daily oral cotrimoxazole in 1459 children with fast breathing pneumonia in a randomized, double blind trial in seven outpatient departments and one community health service in Pakistan. 730 children were randomly assigned to receive a 25 mg/kg/dose of amoxicillin, and 741 to receive 4 mg/kg trimethoprim plus 20 mg/kg sulphamethoxazole (cotrimoxazole). Treatment failure in the amoxicillin group was 16.1% as compared to 18.9% in the cotrimoxazole group (OR 0.83, 95%CI 0.63–1.08, $p=0.160$). The authors concluded that both amoxicillin and cotrimoxazole provided equally effective therapy for fast breathing pneumonia in twice-daily dosing regimens.

Hazir et al (26) compared high dose oral amoxicillin (80–90 mg/kg/day) with injectable penicillin in children with chest indrawing pneumonia, using a twice-daily regimen. This study showed that amoxicillin given two times a day was effective in treating children with chest indrawing pneumonia.

These studies demonstrate that amoxicillin given in a twice-daily dosage regimen is as effective as regimens of three- or four-times daily, provided that the total daily dosage of amoxicillin is the same. A twice-daily schedule has advantages for caregivers and programmes as it may result in improved adherence.

1.3 Recommendation 3

Children aged 2–59 months with severe pneumonia¹ should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.

- **Ampicillin: 50 mg/kg, or benzyl penicillin: 50 000 units per kg IM/IV every six hours for at least five days**
- **Gentamicin: 7.5 mg/kg IM/IV once a day for at least five days**

Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.

One systematic review (40) that included two large randomised controlled trials (RCT) comparing beta-lactam and gentamicin versus chloramphenicol for very severe pneumonia showed high-quality evidence that ampicillin/penicillin and gentamicin reduce clinical failure rates compared to

¹ Previously classified as very severe pneumonia (Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources. First edition. Geneva: World Health Organization; 2005).

chloramphenicol. There was moderate-quality evidence of a trend towards reduced death rates for treatment with ampicillin/penicillin and gentamicin compared to chloramphenicol.

1.3.1 Penicillin/gentamicin vs chloramphenicol at high altitude

The first of these RCTs (41), conducted in the highlands of Papua New Guinea (1600–1800 m above sea level), included 1116 children aged 1–59 months with WHO-defined very severe pneumonia (modified to include heart failure as a danger sign). Enrolled children had a median oxygen saturation of 71%. Five hundred and fifty-nine (559) children were treated with 100 mg/kg/day chloramphenicol; 557 children were treated with penicillin (200 mg/kg/day) plus gentamicin (7.5 mg/kg/day). Duration of treatment was 14 days. Measured outcomes were: death, treatment failure by day 5, and readmission. More children in the penicillin/gentamicin group required a change of antibiotic (60 versus 49), while 147 (26%) children treated with chloramphenicol and 123 (22%) treated with penicillin and gentamicin had adverse outcomes ($p = 0.11$, not significant). Thirty-six children treated with chloramphenicol and 29 treated with penicillin and gentamicin died (difference not significant). More children treated with chloramphenicol presented again with severe pneumonia within one month of hospital discharge ($p = 0.03$), as compared to those treated with penicillin and gentamicin.

1.3.2 Penicillin/gentamicin vs chloramphenicol at low altitude

The second of the RCTs (42) was a multi-country study, with 80% of children residing at sea level. Children aged 2–59 months were enrolled: 479 were randomized to receive chloramphenicol (75 mg/kg/day), and 479 to receive ampicillin (200 mg/kg/day) and gentamicin (7.5 mg/kg/day). Median oxygen saturation on admission was higher than for the Papua New Guinea study (88%) (41). Duration of treatment was 10 days. More children in the chloramphenicol group required a change in antibiotic (45 versus 26). Measured outcomes were death or treatment failure by days 5, 10, and 21. More children failed treatment with chloramphenicol at day 5 (16% versus 11%; relative risk 1.43, 95% CI 1.03 to 1.97) as well as at days 10 and 21. There was a trend towards reduced death rates in children treated with ampicillin plus gentamicin, but this was not significant.

1.3.3 Ceftriaxone as second-line treatment

Although there were no data on the use of ceftriaxone in the treatment of pneumonia with general danger signs, the WHO Guidelines Development Group recognized the need to include ceftriaxone as a second-line treatment for children with severe pneumonia with general danger signs, especially for hospital care.

1.4 Recommendation 4

Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and -exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.

For HIV-infected and -exposed infants and for children with chest indrawing pneumonia or severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second-line treatment.

While there has been no randomized controlled trial designed on the basis of an a-priori hypothesis to examine the efficiency of antibiotic regimens or case management, a subgroup analysis was conducted in one randomized controlled trial in which oral amoxicillin was compared with paren-

teral penicillin for chest indrawing pneumonia in children (43). The response rates with the two regimens were comparable, but the treatment failure rate was significantly higher for HIV-infected infants at day 14 (40.7% versus 24.3%; OR, 2.8; 95% CI 1.35; 3.5).

Therefore, it was recommended that HIV-infected or -exposed children with chest indrawing pneumonia be hospitalized and treated as patients with severe pneumonia (pneumonia with general danger signs).

1.5 Recommendation 5

Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with severe or very severe pneumonia.

Empirical cotrimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended for HIV-infected and -exposed children over 1 year of age with chest indrawing or severe pneumonia.

Two reviews led to this decision, that was based on those guidelines previously approved by the WHO Guidelines Review Committee (9). One review examined the evidence for the management of pneumonia in HIV-infected children (44). The second review, which evaluated etiological agents for pneumonia (45), was comprised of nine descriptive studies, two post-mortem studies, and 15 analytical studies, of which five were post-mortem.

In a cohort study of HIV-infected children in Malawi (46), the incidence of severe pneumonia was high, mostly in children older than two years. No cases of PCP were diagnosed in this age group. In autopsy studies in South Africa and Zimbabwe (47,48) the mean age of all 46 cases of PCP was reported to be 3–4 months. The findings of these and subsequent autopsy and clinical studies in the region provided consistent evidence that most cases of PCP occur in young infants. Of 130 autopsy cases of PCP reported, only 5% were in children over 12 months of age.

In the 1990s, data reported from Europe, Thailand and the United States of America also showed that the peak prevalence of PCP in children was in infants under 12 months of age, with the highest prevalence under 6 months (49,50). A report from Ireland and the United Kingdom showed that, before 1998, 27% of HIV-infected infants had PCP or cytomegalovirus as a first indicator; 91% of these were young infants (51).

Based on the systematic review, the WHO Guidelines Development Group recognized the importance of covering clinically suspected PCP in infants younger than 1 year of age and thus recommended empirical treatment with cotrimoxazole of all HIV-infected and -exposed children under one year of age.

1.6 Additional information on implementing the management of pneumonia at community level

1.6.1 Management of pneumonia at community level

According to the WHO/UNICEF joint statement on management of pneumonia in community settings (52), an important strategy to increase access to quality care for pneumonia is to train and deploy CHWs to assess and treat children with pneumonia. There is strong scientific and programmatic evidence to support the effectiveness of this approach.

Two large-scale studies, in Bangladesh and Nepal, assessed the ability of volunteer CHWs with intensive basic training and close supervision to properly diagnose and treat pneumonia. Hadi et al (53) showed that the sensitivity, specificity, and overall agreement rates in pneumonia diagnosis and treatment were significantly higher among those health volunteers in Bangladesh who had intensive basic training and routine supervision than among those who had not. Ghimire et al (54) showed a significant trend towards a decrease in the proportion of pneumonia and severe pneumonia cases from 2004 to 2006 in districts of Nepal where the volunteers were given special training to manage pneumonia.

In addition, numerous countries implement community case management of childhood pneumonia. For example, the Gambia has a nationwide programme addressing pneumonia in the community (52). In Honduras, pneumonia treatment has been incorporated into the national integrated community child care programme where community volunteers – in addition to their other responsibilities – provide treatment for pneumonia and diarrhoea in more than 1800 communities (52). In 2008, the government of Malawi initiated activities to deliver community-level treatment of common childhood illnesses including suspected pneumonia. By September 2011, 3296 health surveillance assistants (HSAs) had been trained, and 2709 village health clinics were functional. Evaluation has shown that HSAs are able to treat sick children with a quality similar to that provided by professional health personnel in fixed facilities. Monitoring data also showed that communities were utilising the HSA services (55). Large-scale, national-level programmes supporting CHWs to treat illness including childhood pneumonia are also implemented in Ethiopia and Pakistan.

The current WHO/UNICEF tools for CHWs recommend oral amoxicillin in two daily doses. Because the CHW is not expected to treat chest indrawing pneumonia, these guidelines will retain two age bands and will not be revised at the present time. Some data from Asia (56,57) shows that CHWs can manage chest indrawing pneumonia with oral amoxicillin. However, current CHW guidelines will not be changed until more evidence becomes available from additional regions and countries.

1.6.2 Community management of chest indrawing pneumonia

Two studies have shown that CHWs, when properly trained and supported, can effectively and safely treat chest indrawing pneumonia at home with oral amoxicillin.

Bari et al (56) aimed to compare community management of children with chest indrawing pneumonia by lady health workers (LHWs), using oral amoxicillin, to the standard of care: a first dose of cotrimoxazole followed by referral. Twenty-eight clusters in the Haripur district of Pakistan were randomly assigned equally in a 1:1 ratio to either intervention or control. Children age 2 to 59 months with chest indrawing pneumonia were included. In the intervention clusters, LHWs provided mothers with oral amoxicillin (80–90 mg/kg/day in two divided doses) for five days, and gave specific guidance on its use. In the control clusters, LHWs gave the first dose of oral cotrimoxazole and referred the child for standard care to the nearest health facility. The primary outcome was treatment failure by day 6. A total of 1995 children participated in the 14 intervention clusters and 1477 in the 14 control clusters. Treatment failure rates were significantly reduced in the intervention clusters (165 [9%] vs 241 [18%], risk difference –8.9%). Most of the risk reduction was in the occurrence of fever and chest indrawing on day 3 (–6.7%, –10.0 to –3.3). Two deaths were reported in the control clusters and one in the intervention cluster. It was concluded that community case management by LHWs could result in appropriate treatment for children with chest indrawing pneumonia, reduce delays in initiating treatment, and reduce costs for families and health systems.

Similar evidence on the management of severe pneumonia by LHWs was generated in a cluster-randomized controlled trial in Matiari district of rural Sindh, Pakistan (57). Public-sector LHWs undertook community management of chest indrawing pneumonia. In the intervention clusters children with suspected pneumonia were screened by LHWs, and identified cases of chest indrawing pneumonia were prescribed oral amoxicillin (90 mg/kg per day in two doses) for five days at home. Children in control clusters were given one dose of oral cotrimoxazole and were referred to their nearest health facility for further management. In both groups, follow-up visits at home were conducted at days 2, 3, 6, and 14 by the LHWs. The primary outcome was treatment failure by day 6 after enrolment. 2341 children in the intervention clusters and 2069 children in the control clusters participated in the study. Treatment failure by day 6 was 8% in the intervention group and 13% in the control group. After adjusting for clustering, the risk difference for treatment failure was -5.2% (95% CI -13.7% to 3.3%). Two deaths by day 6 and one between days 7 and 14 were recorded; no serious adverse events were witnessed. The authors concluded that properly trained LHWs were able to satisfactorily diagnose and treat chest indrawing pneumonia at home in rural Pakistan. This strategy could effectively increase access to care for pneumonia in settings where referral is difficult, and could become a key component of community detection and management strategies for childhood pneumonia.

2. Costs of treating pneumonia using the revised recommendations

One potential barrier to access to case management in low-resource settings is the cost of treatment. Understanding the relevant costs can help public sector programmes and ministries of health reduce them by rationalizing the use of available resources and focusing on those interventions with the greatest public health benefit.

A number of studies carried out in countries with a high burden of childhood pneumonia compared the cost of pneumonia therapy at household, outpatient and hospital levels. The general conclusion is that costs of hospitalization are far greater than the costs of home therapy.

2.1 Household treatment costs for pneumonia

Sadrudin et al (58) compared household costs for chest indrawing pneumonia cases referred to a health facility with those managed directly by LHWs in Pakistan. Data on direct and indirect costs were collected through interviews and record reviews. The average household cost of each LHW-managed case was US\$ 1.46, while the average cost for a referred case was US\$ 7.60. After excluding the cost of the antibiotic provided, the cost per case came to US\$ 0.25 for each LHW-managed case and US\$ 7.51 per referred case; this is a 30-fold difference. The authors concluded that expanding the treatment of chest indrawing pneumonia to community level could significantly reduce household costs, improve access to treatment, and ultimately prevent many deaths.

2.2 Outpatient treatment costs for pneumonia

Chola et al (59) collected data on annual economic and financial costs from urban health centres in Zambia in 2005–06. The average cost of providing outpatient services was US\$ 3 per visit, while the cost per outpatient visit for childhood pneumonia was US\$48. In a study in the Northern Areas of Pakistan, Hussain H et al (60,61) calculated that the average cost of treating childhood pneumonia was US\$ 13.44.

2.3 Inpatient treatment costs for pneumonia

Chola et al (59) calculated the cost of inpatient treatment in Zambia to be US\$ 18 per bed day; for childhood pneumonia this increased to US\$ 215 per bed day. Hussain et al (60,61) calculated that in northern Pakistan each in-patient episode of pneumonia cost the health system US\$ 71; each in-patient case of severe pneumonia cost US\$ 235. Outpatient costs averaged US\$ 13 and US\$ 86 respectively for pneumonia and severe pneumonia. The same authors showed that, when the provider costs (excluding inpatient care) and household costs were added together, the total societal average cost per episode was US\$ 22.62 for fast breathing pneumonia, and US\$ 142.90 for chest indrawing pneumonia (60,61). It should be clarified here that the costs quoted in the latter example are per episode of illness; thus they are slightly higher than the cost per visit cost shown in the earlier paper.

A cost minimization analysis from eight paediatric centres in England (62) published in 2010 concluded that treatment of community-acquired pneumonia with oral amoxicillin could result in savings of between £ 473 and £ 518 per case.

2.4 Comparison of inpatient costs for pneumonia at different tiers of health facilities

Madsen et al (63) looked at the health-care provider cost and household cost of the treatment of severe pneumonia in infants and young children admitted to secondary and tertiary level health-care facilities in Vellore, India. The total cost to the health system for one episode of hospitalized childhood pneumonia treated at secondary level was US\$ 84.0 (INR 3524); an episode treated at tertiary level cost US\$ 147.0 (INR 6158). At both levels the greatest single cost was the hospital stay itself, comprising 74% and 56% of the total costs respectively.

Ayieko et al (64) calculated the costs of treatment for childhood pneumonia at different tier hospitals in Kenya. A sensitivity analysis was conducted using WHO-CHOICE values for cost per bed day. From the provider perspective the mean cost per admission for childhood pneumonia at the national hospital was US\$ 177.0, at district hospitals was between US\$ 54.1 to US\$ 99.3 and at mission hospitals ranged from US\$ 43.4 to US\$ 142.2. In public sector hospitals, households provide partial subsidies to the provider costs through payment of user fees; within the private sector the total amount of provider costs may be passed on to households. The authors suggested that these findings could be used in cost effectiveness analysis of health interventions.

3. Flexible Solid Oral Dosage: Dispersible formulations of amoxicillin

Amoxicillin has been recognized as a “priority essential” medicine by WHO and UNICEF (65). The dosage of amoxicillin is based on the child’s weight. There is a potential risk of microbial resistance with under-dosing, and of toxicity with over-dosing. It is therefore crucial that the paediatric formulation have flexibility for dose adjustment, while at the same time remaining within the effective therapeutic range. One of the current challenges is the suitability of existing formulations of amoxicillin for children in resource-constrained settings. The use of solid preparations often involves breaking an adult tablet into smaller pieces, then crushing and adding it to food or liquid; this can lead to inaccuracies in dosing. There is a widespread expectation from both end-users and clinicians that medicines for children should be liquid, as it is generally believed that children prefer this formulation. In addition, liquid formulations make weight-based dosing much easier. However, the accurate administration of a liquid medicine is not assured even if the dose is correctly calculated. There is evidence that measuring spoons and other devices supplied with liquid medicines are not always accurate and that significant under- or over-dosing can occur (66–68).

In order to reach consensus on the most suitable formulations of medicines for children, with particular attention to conditions in developing countries, in 2006 WHO hosted a meeting of pediatricians, pharmacists, clinical pharmacologists, and representatives of the European Medicines Agency, the International Federation of Pharmaceutical Manufacturers and Associations, the Medicines for Malaria Venture, the National Institutes of Health, UNICEF, and the Bill & Melinda Gates Foundation. The group recommended that in general, the dosage forms of medicines that are likely to prove most ‘suitable’ particularly for developing countries are flexible solid dosage forms, such as tablets that are oro-dispersible and/or that can be used for preparation of oral liquids (for e.g. suspension or solution). Provided the product can be dispersed in breast milk from the mother, it could potentially be used for very young children (0–6 months). This type of product is feasible to manufacture in facilities that produce conventional tablets, but requires excipients that ensure stability and palatability. Examples of existing dispersible tablet product suggest that they can be more affordable than standard liquid dosage forms (69).

In September 2010, the UNICEF Supply Division and WHO brought together experts in paediatric medicine from academia, the pharmaceutical industry (both innovator and generic), regulators, programme managers and implementers. The meeting aimed to reach consensus on priority essential medicines for children, and to identify the steps required to ensure that these medicines are available and affordable. The group concluded, “Liquid formulations can be difficult to use and store, which can make their use impractical in some areas. Solid formulations and flexible solid oral dosage forms, such as dispersible tablets, that can be given whole to older children or dispersed in water for ease of administration to younger children are preferred” (65).

Based on these consultations, WHO recommended ‘Flexible Solid Oral Dosage’ forms as the optimum formulation for children’s medicines administered orally, as they have better stability and shelf life than liquids, in addition to being less bulky to ship and store (70).

4. Implications for implementation

The revised recommendations present a number of advantages.

- Oral amoxicillin can be used to treat both fast breathing pneumonia and chest indrawing pneumonia (see Table).
- Pneumonia classification and management are simplified to two categories instead of three (see Figure).
- Access to antibiotic treatment closer to home is increased.
- The need for referrals to higher level facilities is decreased.
- The probability of hospitalization and thus the risk of nosocomial and injection borne diseases is reduced.
- The probability of antimicrobial resistance is diminished, due to better adherence to the simplified treatment.
- Training of health workers is simplified.

Adoption of the revised guidelines will have a number of implications for policy as well as for implementation at different levels of the health system.

4.1 Implications for policy

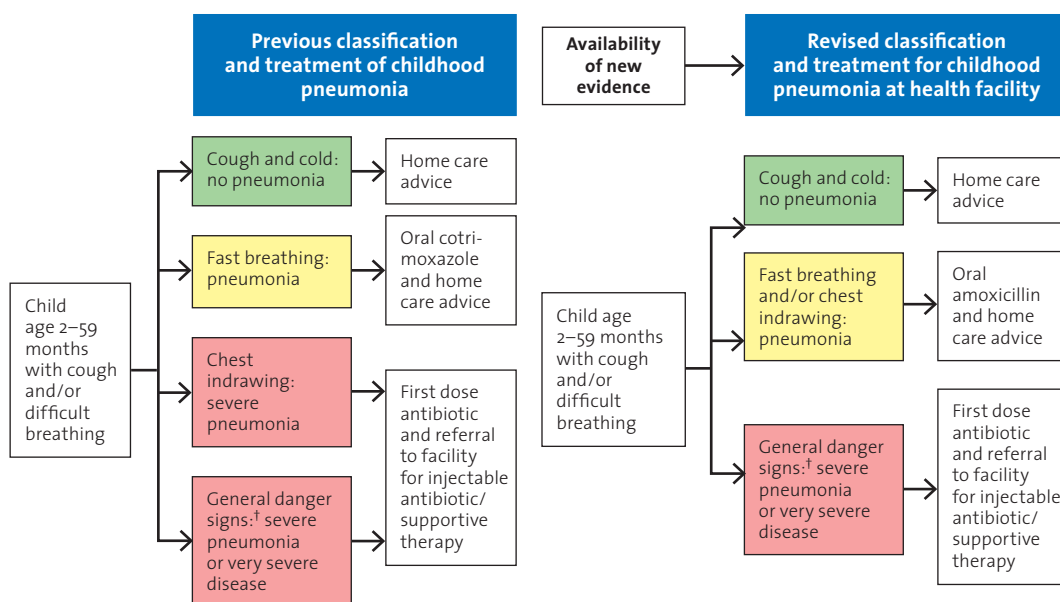
- National programmes will need to switch from oral cotrimoxazole to oral amoxicillin. Because of this:
 - ✓ *retraining of healthcare providers will be required (with training materials and job aids appropriately revised);*
 - ✓ *reduction in overall costs of pneumonia treatment by promoting outpatient/home therapy will help offset the additional costs of switching to oral amoxicillin from oral cotrimoxazole.*
- Combining the two previous categories of “pneumonia” (fast breathing) and “severe pneumonia” (chest indrawing) under a single classification of “pneumonia” simplifies classification. Because of this:
 - ✓ *training will be simplified;*
 - ✓ *the process of local adaptation of training materials and job aids will be easier.*
- It is crucial that the policy makers, administrators and officials of relevant programmes understand the significance of these modifications. Because of this:
 - ✓ *widespread dissemination of technical updates is of utmost importance to ensure adoption and adherence.*
- In order to pre-empt the possible over-use of antibiotics, programmes will need to invest in careful monitoring procedures. Because of this:
 - ✓ *close monitoring will be essential in areas implementing the new guidelines at large scale.*

Table

Doses of amoxicillin for children 2–59 months of age with pneumonia

TOOLS	CATEGORY OF PNEUMONIA	AGE/WEIGHT OF CHILD	DOSAGE OF AMOXICILLIN DISPERSIBLE TABLETS (250 mg)
iCCM tool for community health workers: no change	Fast breathing pneumonia	2 months up to 12 months (4–<10 kg)	1 tab twice a day x 5 days (10 tabs)
		12 months up to 5 years (10–19 kg)	2 tabs twice a day x 5 days (20 tabs)
IMCI tool for professional health workers at health facilities: revised	Fast breathing and chest indrawing pneumonia	2 months up to 12 months (4–<10 kg)	1 tab twice a day x 5 days (10 tabs)
		12 months up to 3 years (10–<14 kg)	2 tabs twice a day x 5 days (20 tabs)
		3 years up to 5 years (14–19 kg)	3 tabs twice a day x 5 days (30 tabs)

Figure

Comparison of previous and revised classification and treatment of childhood pneumonia at health facility

† Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

4.2 Implications for implementation at community level (integrated Community Case Management)

The WHO/UNICEF joint statement *Management of pneumonia in community settings* (52) recommends the training and deployment of CHWs as a central strategy for increasing access to quality care for pneumonia. Research showed that educated community members could be trained to detect and manage pneumonia in their communities; large-scale studies confirmed that the sensitivity, specificity, and overall agreement rates in pneumonia diagnosis and treatment were high among health volunteers who had intensive basic training and routine supervision. This led to a substantial decrease in the proportion of severe pneumonia cases and deaths.

It has also been shown that properly trained and supervised CHWs can appropriately manage chest indrawing pneumonia with oral amoxicillin at community level, resulting in increased access to treatment and reduced costs for families. As evidence is limited, the iCCM guidelines are not currently being updated to include the management of chest indrawing pneumonia. In situations where referral is not possible, however, CHWs may treat chest indrawing pneumonia with oral amoxicillin, if local health policy allows them to do so.

Thus, at the **community level** the revised recommendations imply that:

- all children with fast breathing are classified as having “pneumonia” and treated with oral amoxicillin;
- children with “chest indrawing” pneumonia should be referred to a higher level. However, in situations where referral is not possible and if local health policy allows, CHWs may treat chest indrawing pneumonia with oral amoxicillin;
- dispersible amoxicillin is the preferred treatment for children.

4.3 Implications for implementation at health facility Level

The revised recommendations can be encapsulated into the following statements, each with a short description of the supporting evidence:

It is safe to treat chest indrawing pneumonia at home with oral amoxicillin. A comparison of the use of parenteral ampicillin in hospital to oral amoxicillin at home found that the two treatments were equivalent. In cases of chest indrawing pneumonia without underlying complications, home treatment with a short course of high-dose oral amoxicillin is preferable to parenteral treatment because of the associated reduction in referral, admission, and treatment costs as well as the reduced invasiveness of oral treatment.

A three-day course of antibiotics is as effective as a five-day course in treating children with fast breathing pneumonia in areas of low HIV prevalence. A systematic review of trials evaluating the efficacy of short-course versus long-course treatment of fast breathing pneumonia in children age 2 to 59 months recommended a shorter course of antibiotic therapy, keeping in mind the benefits to the individual as well as to the health system, especially in settings with limited resources.

Amoxicillin is more effective when given in higher doses. Increasing concentrations of antimicrobials improves their bactericidal activity. Clinical reviews show that, for community-acquired pneumonia, oral amoxicillin should be given in a regimen of at least 80 mg/kg/day in two divided doses.

Amoxicillin can be given twice instead of thrice daily for children. Amoxicillin given in a twice-daily dosage regimen is as effective as regimens of three- or four-times daily, provided that the total daily dosage of amoxicillin is the same. A twice-daily schedule has advantages for caregivers and programmes as it may result in improved adherence to treatment.

Dispersible amoxicillin is the most suitable formulation for children. Because the dosage of amoxicillin is based on the child's weight, and because of the risks associated with under- or over-dosing, it is crucial that the paediatric formulation have flexibility for dose adjustment. The use of solid preparations often involves breaking an adult tablet into smaller pieces, then crushing and adding it to food or liquid; this can lead to inaccuracies in dosing. Liquid formulations make weight-based dosing much easier, however there is evidence that measuring devices supplied with liquid medicines are not accurate and that significant under- or over-dosing can occur. A multidisciplinary consensus supports the recommendation of 'Flexible Solid Oral Dosage' forms for children's oral medicines, as they are less costly than tablets, they have better stability and shelf life than liquids, and they are less bulky to ship and store.

Thus, at the **health facility level**, changes in the management of ARI implied by these new recommendations can be summarized as follows:

- all children with fast breathing and/or chest indrawing are classified as having "pneumonia" and treated with oral amoxicillin; the recommended dosage is 80 mg/kg for five days (40 mg/kg twice a day); in settings of low HIV prevalence the duration of treatment for 'fast breathing pneumonia' can be reduced to three days;
- only those children who have either general danger signs or who are HIV positive and have chest indrawing need to be referred to higher level facility for inpatient treatment with injectable antibiotics;
- dispersible amoxicillin is the preferred treatment for children.

4.4 Implications for implementation at hospital level

Children with chest indrawing pneumonia in settings of low HIV prevalence will be treated at the outpatient level and will no longer need to be referred for hospitalization.

References

1. Leowski J. Mortality from acute respiratory infections in children under 5 years of age: Global estimates. *World Health Statistics Quarterly*. 1986; 39:138–44.
2. Levels and Trends in Child Mortality: Report 2014. United Nations Inter Agency Group for Child Mortality Estimation. UNICEF, WHO, The World Bank, United Nations Population Division. New York, 2014.
3. Global Health Observatory. Proportions of child deaths by cause. (http://www.who.int/gho/child_health/en/index.html), WHO, Geneva Accessed on 24 July 2014.
4. Integrated Global Action Plan for Prevention and Control of Pneumonia and Diarrhoea (GAPPD). Geneva: World Health Organization and The United Nations Children's Fund (UNICEF); 2013 (http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en).
5. Recommendations for management of common childhood conditions, Evidence for technical update of pocket book recommendations. Geneva: World Health Organization; 2012 (http://www.who.int/maternal_child_adolescent/documents/management_childhood_conditions/en).
6. Pocket book of hospital care for children: Guidelines for the management of common illnesses. Second edition. Geneva: World Health Organization; 2013 (http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en).
7. Integrated Management of Childhood Illness (IMCI) (revised). Geneva, World Health Organization/ The United Nation Children's Fund (UNICEF), 2014 (http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/).
8. Chart booklet: Integrated Management of Childhood Illness (IMCI). Geneva, World Health Organization/The United Nation Children's Fund (UNICEF), 2008.
9. Integrated Management of Childhood Illness (IMCI). WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241548083/en).
10. Rudan I et al. Epidemiology and etiology of childhood pneumonia. *Bulletin of the World Health Organization*. 2008; 86:408–416.
11. Bang AT, Bang RA, Reddy HM. Home-based neonatal care: summary and applications of the field trial in rural Gadchiroli, India (1993 to 2003). *Journal of Perinatology*. 2005; 25:S108–S122.
12. The Multi-Country Evaluation of IMCI Effectiveness, Cost and Impact (MCE) – Progress Report', May 2001–April 2002, Geneva: World Health Organization; 2002 (WHO/FCH/CAG/02.16).
13. Aguilar AM et al. Mortality Survey of Bolivia: The Final Report: Investigating and identifying the causes of death for children under five. Published for USAID by the Basic Support for Institutionalizing Child Survival (BASICS) Project, Virginia, 1998.

14. Schumacher R et al. Mortality Study in Guinea: Investigating the causes of death in children under 5. Published by Save the Children and the Basic Support for Institutionalizing Child Survival (BASICS II) Project, Virginia, 2002.
15. Schellenberg JA et al. Inequalities among the very poor. Health care for children in rural southern Tanzania. *Lancet*. 2003; 361:561–66.
16. Kabra SK, Lodha R, Pandey RM. Antibiotics for community-acquired pneumonia in children. *Cochrane Database of Systematic Reviews*. 2010; (3): CD004874.
17. Grant GB et al. Recommendations for treatment of childhood non-severe pneumonia. *Lancet Infectious Diseases*. 2009; 9:185–196.
18. Haider BA, Saeed MA, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. *Cochrane Database of Systematic Reviews*. 2008; CD:005976.
19. Hazir T et al. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. *Lancet*. 2002; 360:835–41.
20. Agarwal G et al. Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial. *British Medical Journal*. 2004; 328:791.
21. Consultative meeting to review evidence and research priorities in the management of acute respiratory infections. Geneva, 29 September–1 October 2003. Geneva: World Health Organization; 2004 (WHO/FCH/CAH/04.2).
22. Pocket book of hospital care for children: Guidelines for the management of common illnesses. Geneva: World Health Organization; 2005.
23. Straus W et al. Antimicrobial resistance and clinical effectiveness of cotrimoxazole versus amoxicillin for pneumonia among children in Pakistan: randomised controlled trial. *Lancet*. 1998; 352:270–74.
24. Addo-Yobo E et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. *Lancet*. 2004; 364:1141–8.
25. Atkinson M et al. A multicentre randomised controlled equivalence trial comparing oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children PIVOT Trial. *Thorax*. 2007; 62:1102–6.
26. Hazir T et al. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. *Lancet*. 2008; 371:49–56.
27. Addo-Yobo E et al. Outpatient treatment of children with severe pneumonia with oral amoxicillin in four countries: the MASS study. *Tropical Medicine and International Health*. 2011; 16:995–1006.
28. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clinical Infectious Diseases*. 1998; 26: 1–10.
29. Craig WA. Antimicrobial resistance issues of the future. *Diagnostic Microbiology and Infectious Diseases*. 1996; 25:213–7.
30. Howie VM, Dillard R, Lawrence B. In vivo sensitivity test in otitis media: efficacy of antibiotics. *Pediatrics*. 1985; 75:8–13.
31. Howie V. Eradication of bacterial pathogens from middle ear infections. *Clinical Infectious Diseases*. 1992; 14(suppl 2):S209–11.
32. Klein JO. Microbiologic efficacy of antibacterial drugs for acute otitis media. *Pediatric Infectious Diseases Journal*. 1993; 12:973–5.

33. Dagan R et al. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. *Pediatric Infectious Diseases Journal*. 1996; 15: 980–5.
34. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatric Infectious Diseases Journal*. 1996; 15:255–9,38.
35. Lieberthal AS et al. The diagnosis and management of acute otitis media. *American Academy of Pediatrics and American Academy of Family Physicians. Pediatrics*. 2013; 131:e964–99. doi: 10.1542/peds.2012–3488.
36. Fonseca W et al. Comparing pharmacokinetics of amoxicillin given twice or three times per day to children older than 3 months with pneumonia. *Antimicrobial Agents and Chemotherapy*. 2003; 47: 997–1001.
37. Valtonen M et al. Comparison of amoxicillin given two and three times a day in acute respiratory tract infections in children. *Scandinavian Journal of Primary Health Care*. 1986; 4:201–4.
38. Daschner FD, Behre U, Dalhoff A. Prospective clinical trial on the efficacy of amoxicillin administered twice or four times daily in children with respiratory tract infections. *Journal of Internal Medicine Research*. 1981; 9:274–6.
39. Catchup Study Group. Clinical efficacy of cotrimoxazole versus amoxicillin twice daily for treatment of pneumonia: a randomized controlled clinical trial in Pakistan. *Archives of Diseases in Childhood*. 2002; 86: 113–18.
40. Lassi ZS et al. Systematic review on antibiotic therapy for pneumonia in children less than 59 months of age. *Archives of Diseases in Childhood*. 2014;99:687–93.
41. Duke T et al. Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial. *Lancet*. 2002; 359:474–80.
42. Asghar R et al. Severe Pneumonia Evaluation Antimicrobial Research Study Group. Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2–59 months in low resource settings: multicentre randomised controlled trial (SPEAR study). *British Medical Journal*. 2008; 336:80–4.
43. Jeena P et al. Amoxicillin Penicillin Pneumonia International Study (APPIS Group). Failure of standard antimicrobial therapy in children aged 3–59 months with mild or asymptomatic HIV infection and severe pneumonia. *Bulletin of the World Health Organization*. 2006; 84:269–75.
44. Punpanich W et al. Antibiotic and systemic therapies for pneumonia in human immunodeficiency virus (HIV)-infected and HIV-exposed children. *Journal of Infection in Developing Countries*. 2012; 6:109–19.
45. Punpanich W et al. Systematic review on the etiology and antibiotic treatment of pneumonia in human immunodeficiency virus-infected children. *Pediatric Infectious Diseases Journal*. 2011; 30:e192–202. doi:10.1097/INF.0b013e1822d989c.
46. Laufer MK. Observational cohort study of HIV-infected African children. *Pediatric Infectious Disease Journal*. 2006; 25:623–7.
47. Jeena PM, Coovadia HM, Chrystal V. *Pneumocystis carinii* and cytomegalovirus infections in severely ill, HIV-infected African infants. *Annals of Tropical Paediatrics*. 1996; 16:361–8.
48. Ikeogu MO, Wolf B, Mathe S. Pulmonary manifestations in HIV seropositivity and malnutrition in Zimbabwe. *Archives of the Diseases of Childhood*. 1997; 76:124–8.
49. Simonds RJ et al. *Pneumocystis carinii* pneumonia among U.S. children with perinatally acquired HIV infection. *Journal of American Medical Association*. 1993; 270:470–3.

50. Chokephaibulkit K. *Pneumocystis carinii* severe pneumonia among human immunodeficiency virus-infected children in Thailand: the effect of a primary prophylaxis strategy. *Pediatric Infectious Disease Journal*. 1999; 18:147–52.
51. Williams AJ et al. *Pneumocystis carinii* pneumonia and cytomegalovirus infection in children with vertically acquired HIV infection. *AIDS*. 2001; 15:335–9.
52. WHO/UNICEF joint statement. Management of pneumonia in community settings. New York/ Geneva: The United Nations Children's Fund/World Health Organization, 2004 (http://www.who.int/maternal_child_adolescent/documents/fch_cah_04_06/en).
53. Hadi A. Management of acute respiratory infections by community health volunteers: experience of Bangladesh Rural Advancement Committee (BRAC). *Bulletin of the World Health Organization*. 2003; 81: 183–89.
54. Ghimire M, Pradhan YV, Maskey MK. Community based intervention for diarrhoeal diseases and acute respiratory infections in Nepal. *Bulletin of the World Health Organization*. 2010; 88:216–21.
55. Nsona H et al. Scaling up integrated community case management of childhood illness: Update from Malawi. *American Journal of Tropical Medicine and Hygiene*. 2012;87:54–60.
56. Bari A et al. Community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Haripur district, Pakistan: a cluster randomised trial. *Lancet*. 2011; 378:1796–803.
57. Soofi S et al. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. *Lancet*. 2012;379:729–37.
58. Sadruddin S et al. Household costs for treatment of severe pneumonia in Pakistan. *American Journal of Tropical Medicine and Hygiene*, 2012; 87:5137–43.
59. Chola L, Robberstad B. Estimating average inpatient and outpatient costs and childhood pneumonia and diarrhoea treatment costs in an urban health centre in Zambia. *Cost Effectiveness and Resources Allocation*. 2009; 7:16.
60. Hussain H et al. Economic analysis of childhood pneumonia in Northern Pakistan. *Health Policy and Planning*. 2008; 23:438–42.
61. Hussain H et al. The cost of treatment for child pneumonias and meningitis in the Northern Areas of Pakistan. *The International Journal of Health Planning and Management*. 2006; 21:229–38.
62. Lorgelly PK et al. Oral versus i.v. antibiotics for community acquired pneumonia in children: a cost minimization analysis. *European Respiratory Journal*. 2010; 35:585–64.
63. Madsen HO et al. Costing of severe pneumonia in hospitalized infants and children aged 2–36 months, at a secondary and tertiary level hospital of a not-for-profit organization. *Tropical Medicine and International Health*. 2009; 14:1315–22.
64. Ayieko P et al. The economic burden of inpatient pediatric care in Kenya: household and provider costs for treatment of pneumonia, malaria and meningitis. *Cost Effectiveness and Resources Allocation*. 2009; 7:3.
65. Priority essential medicines for child survival. Copenhagen, The United Nations Children's Fund/ World Health Organization. 2010.
66. Griebmann K et al. Dosing accuracy of measuring devices provided with antibiotic oral suspensions. *Paediatric and Perinatal Drug Therapy*. 2007; 8: 61–70.

67. Falagas et al. Inaccuracies in dosing with teaspoons and tablespoons. *The International Journal of Clinical Practice*. 2010; 64:1185–9.
68. Monk PM, Ball PA. The accuracy of a paediatric dosing device. *The Australian Journal of Hospital Pharmacy*. 1997; 27: 323–324.
69. Report of the informal expert meeting on dosage forms of medicines for children. Geneva: World Health Organization; 2008.
70. Priority medicines for mothers and children 2011. Ensuring access to priority medicines for mothers and children improves health and saves lives. Geneva: World Health Organization; 2011 (WHO/EMP/MAR/2011.1) (http://www.who.int/maternal_child_adolescent/documents/emp_mar2011.1/en/).



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For more information please contact:

Department of Maternal, Newborn, Child and Adolescent Health (MCA)
World Health Organization
20 Avenue Appia, 1211 Geneva 27, Switzerland

Tel: + 41 22 791 32 81; Fax: + 41 22 791 48 53

E-mail: mncah@who.int

Website: http://www.who.int/maternal_child_adolescent

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Application of a Prognostic Scale to Estimate the Mortality of Children Hospitalized with Community-acquired Pneumonia

Soraya Araya, MD,*† Dolores Lovera, MD,*† Claudia Zarate, MD,*† Silvio Apodaca, MD,*†
Julia Acuña, MD,*† Gabriela Sanabria, BS,* and Antonio Arbo, MD, MSc*†

Background: Pneumonia is a major cause of mortality in children. The objective of this study was to construct a prognostic scale for estimation of mortality applicable to children with community-acquired pneumonia (CAP).

Methods: This observational study included patients younger than 15 years with a diagnosis of CAP who were hospitalized between 2004 and 2013. A point-based scoring system based on the modification of the PIRO scale used in adults with pneumonia was applied to each child hospitalized with CAP. It included the following variables: predisposition (age <6 months, comorbidity), insult [hypoxia (O_2 saturation < 90), hypotension (according to age) and bacteremia], response (multilobar or complicated pneumonia) and organ dysfunction (kidney failure, liver failure and acute respiratory distress syndrome). One point was given for each feature that was present (range, 0–10 points). The association between the modified PIRO score and mortality was assessed by stratifying patients into 4 levels of risk: low (0–2 points), moderate (3–4 points), high (5–6 points) and very high risk (7–10 points).

Results: Eight hundred sixty children hospitalized with CAP were eligible for study. The mean age was 2.8 ± 3.2 years. The observed mortality was 6.5% (56/860). Mortality ranged from 0% for a low PIRO score (0/708 pts), 18% (20/112 pts) for a moderate score, 83% (25/30 pts) for a high score and 100% (10/10 pts) for a very high modified PIRO score ($P < 0.001$).

Conclusion: The present score accurately discriminated the probability of death in children hospitalized with CAP, and it could be a useful tool to select candidates for admission to intensive care unit and for adjunctive therapy in clinical trials.

Key Words: pneumonia, prognostic scale, mortality, children

(*Pediatr Infect Dis J* 2016;35:369–373)

Community-acquired pneumonia (CAP) is one of the most common infections in children and continues to be one of the leading causes of hospital admission worldwide.^{1–3}

Mortality associated with pneumonia varies around the world, with an annual incidence of 3.0–3.6 cases per 100 inhabitants in developed countries and 7–40 cases per 100 in developing countries.⁴ Even though the associated death rate has fallen in the decades since the introduction of penicillin and vaccines (for measles, *Bordetella pertussis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b), it is estimated that pneumonia and other associated conditions can cause approximately 18% of deaths of children younger than 5 years worldwide.^{1–4}

One of the greatest challenges in assessing children hospitalized with CAP is the identification of children at risk of sepsis and death, as well as those patients who would benefit from placement in an intensive care unit (ICU) or require adjunctive therapy. Therefore, it is important to have a tool based on a score-stratification system to identify the risk and severity of the pneumonia on admission. In addition, this score system would guide the appropriate antibiotic treatment as well as the early admission in intensive care.

Recently, an interesting tool called PIRO,⁵ which uses most of the prognostic factors identified by other sepsis scales, has been developed for prognostic stratification of adult patients with pneumonia. The acronym PIRO, used throughout this study, stands for predispositions which are the factors present at the time of admission and can modify the course of the disease and substantially impact the outcome of pneumonia; insults, which are the effects over the vital variable caused by infectious process including hypoxia (the impact of hypoxia on the metabolism is recognized), hypotension and bacteremia, with this last included because of the sequence of events leading to sepsis probably beginning with bacteremia; response, based on the observation that multilobar involvement and complications such as pleural effusion can be associated with higher mortality and organ dysfunction, a critical marker of the severity of infectious disease.

This scale, as well as others such as the pneumonia severity index (PSI),⁶ SMART-COP⁷ and CURB-65,⁸ has been widely used and validated for prediction of mortality in large adult and elderly populations with pneumonia. However, the comorbidities and the response of children to infectious insult can be different from those in adult or elderly patients. Consequently, the characteristics of elderly patients with pneumonia differ from those of younger patients.⁹ For this reason, we present a study based on a modified PIRO scale to be used on admission for stratification of children with CAP into mortality-risk group.

MATERIALS AND METHODS

Study Site

The study was conducted in the Department of Pediatrics of the Instituto de Medicina Tropical in Asunción, Paraguay—a national reference center for infectious and tropical diseases in the country.

Study Design

This was a retrospective observational study based on a review of medical records of patients diagnosed on admission with CAP and hospitalized in the department between January 2004 and June 2013. Only those patients younger than 15 years were included. Cases of CAP were defined by the presence of respiratory signs and symptoms and a history of fever with the presence of consolidation in chest radiography (CXR) at admission in patients who had not been hospitalized within the previous 30 days. Patients with respiratory infections of other types such as pulmonary tuberculosis, bronchiolitis, laryngitis and laryngotracheobronchitis were excluded. Patients were also excluded when diagnosis of pneumonia was done more than 48 hours after hospitalization, in cases when

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From the *Department of Pediatrics, Institute of Tropical Medicine, Avda. Venezuela y Florida, Asunción, Paraguay; and †Facultad de Ciencias Médicas, Universidad Nacional de Asunción, Av. Mcal. Francisco Solano Lopez, San Lorenzo, Paraguay.

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Address for correspondence: Antonio Arbo, MD, Department of Pediatric, Instituto de Medicina Tropical, Avda. Venezuela y Florida, Asunción, Paraguay. E-mail: antonioarbo@hotmail.com.

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radiographically diagnosed pneumonia resolved within 72 hours, or when a diagnosis of pneumonia was not confirmed by CXR.

Variables Analyzed

Demographic variables, the presence of comorbidities, clinical signs and symptoms and lab and radiographic studies were all included in the study, with outcome (survival or death) treated as an independent variable. Among the demographic variables were included age, sex and day-care attendance. Comorbidities were classified by severity as grades I, II or III. Grade I comorbidities included being overweight or obese and mild malnutrition or at risk of malnutrition (Z score < -1)¹⁰; grade II included congenital heart disease, asthma, Down syndrome and moderate malnutrition (Z score between -2 and -3); grade III comorbidities included predisposing conditions such as HIV infection, immunosuppressant treatment (for prednisone a dose of 2 mg/kg/day for more than 15 days), cancer or severe malnutrition (Z score < -3). Malnutrition grade was determined by weight–age ratio in patients younger than 2 years, whereas determined by weight–height ratio in patients older than 2 years.^{10,11} Among those clinical variables recorded, the presence of tachypnea, hypotension, shock, consciousness level, hypoxemia and renal or liver failure was considered. Tachypnea was defined as a respiratory rate >60/min in patients younger than 2 months, >50 breaths/min for patients aged 2–12 months and >40 breaths/min for patients older than 12 months; hypotension was defined as a mean arterial pressure under the fifth percentile for age or less than 2 standard deviation (SD) for age; shock was defined by the requirement for antihypotensive agents for more than 4 hours after adequate fluid replacement to achieve appropriate arterial pressure; impairment of consciousness was defined as Glasgow score ≤13 upon admission; hypoxaemia needing oxygen delivery was defined as arterial oxygen saturation (SpO₂) less than 90% found by pulse oximetry measured while the patient was breathing room air for 15 minutes; renal failure was deemed as urine production <0.6 mL/kg/h with increased urea and serum creatinine. Liver failure was defined as the presence of clinical findings secondary to liver failure with signs of encephalopathy, bleeding disorders, metabolic disorders and jaundice with transaminase >5 times normal value, increased direct bilirubin and altered prothrombin time.

Laboratory parameters included were a complete blood count and blood sodium and potassium—both at admission and on day 3 of hospitalization; arterial blood gas (pH, arterial PaO₂ and PaCO₂, and bicarbonate); coagulation time; liver and kidney function and blood culture. Bacterial pneumonia was diagnosed by isolation of a respiratory pathogen in blood culture. Pneumonia was defined as lobar upon radiographic detection of consolidation in 1 lobe and multilobar when consolidation was present in more than 1 pulmonary lobe. Complicated pneumonia was defined as multilobar involvement on CXR or the existence of pleural empyema, pneumatocele or pyopneumothorax.

Statistical Analysis

Discrete variables are described as counts (%) and continuous variables as the mean with SD. For comparative analysis, χ^2 test (proportion testing), Student's *t* test (parametric variables) and Mann–Whitney *U* test (nonparametric variables) were used. Regression analysis was done to study the relationship of the variables with mortality and odds ratio (OR) calculated with a confidence interval (CI) of 95%. Following analysis of the variables in the study population, significant variables (*P* < 0.05) were considered, and a point scale of risk was created that classified outcomes as patients surviving or deceased. The PIRO scale was used as a

base,⁵ with modifications to include as variables within P: age <6 months, grade II or III comorbidity (malnutrition, gastroesophageal reflux, asthma, cardiopathy, Down syndrome and congenital or acquired immunodeficiency); within I: hypoxia (O₂ saturation <90), hypotension (for age) and bacteremia; within R: multilobar pneumonia, complicated pneumonia (pneumothorax, bullae or empyema) and O in case of presence of multiple organ dysfunction (acute renal failure, acute respiratory distress syndrome and acute liver failure). A point was assigned to each variable presented by the patient, creating thereby a scale of 0–10 to correlate with mortality. Discrimination of PIRO score for mortality of CAP was assessed using the area under the receiver operating characteristic (ROC) curve. The ROC curve was plotted for each score using sensitivity and specificity values for true prediction of the mortality across the whole range of possible cut-off of predictive mortality. The area under the ROC curve ranges from 0.5 to 1, with higher values indicating better discrimination. The association between the modified PIRO and mortality was studied also by stratifying patients into different mortality-risk groups (0–2 points, 3–4 points, 5–6 points and 7–10 points). The data were analyzed using SPSS version 11 for Windows (SPSS Inc., Chicago, IL).

RESULTS

During the study period, 860 patients younger than 15 years met the inclusion criteria for the study. The mean age of patients was 2.8 ± 3 years, with a range of 35 days to 15 years. One hundred ten patients (13%) were younger than 6 months of age, 627 (73%) were cases between 6 months to 5 years of age, and 123 (14%) cases were older than 5 years. There was no predominance of sex (56% males; 44% females).

Classical symptoms of pneumonia such as fever, respiratory symptoms and tachypnea were observed in 79.7%, 100% and 57.6% of cases, respectively, and 112 patients (13%) had hypoxemia at admission. Underlying illnesses or coexisting conditions were present in 62% of the cases (534/860). The most common underlying illnesses were genetics disorders (mainly Down syndrome), congenital heart diseases, HIV infection, gastroesophageal reflux and malnutrition (Table 1). The microorganism responsible of the pneumonia was identified in 141 cases (16%), being the most common pathogens detected *S. pneumoniae* (in 10.4% of patients) and *Staphylococcus aureus* (in 5.8% of patients). A total of 102 patients (12%) required admission to the ICU, 77 (8.9%) required invasive mechanical ventilation and 56 (6.5%) died during hospitalization (Table 1).

Analysis of the demographic and clinical findings showed that an age younger than 6 months (OR: 2.2; 95% CI: 1.14–4.2; *P* = 0.018), presence of grades II comorbidity (OR: 4.9; 95% CI: 2.8–8.5; *P* < 0.001) or grade III comorbidity (OR: 6.18; 95% CI: 3.4–10.9; *P* < 0.001), apyrexia (OR: 2.3; 95% CI: 1.3–4.1; *P* 0.003), tachypnea (OR: 3.2; 95% CI: 1.6–6.3; *P* < 0.0001), hypotension (OR: 48.7; 95% CI: 24.8–95.6; *P* < 0.0001), seizures (OR: 10.6; 95% CI: 4.9–23; *P* < 0.0001) or Glasgow score ≤13 (OR: 324; 95% CI: 131–805; *P* < 0.0001) upon admission were associated with greater mortality (Table 2).

When laboratory and CXR findings were assessed, it was observed that a white blood cell count <4000/mm³ (OR: 6.5; 95% CI: 2.7–15.6; *P* < 0.0001), pH ≤7.2 (OR: 77; 95% CI: 35–171; *P* < 0.0001), HCO₃ ≤15 (OR: 26.7; 95% CI: 13–54; *P* < 0.0001), O₂ saturation <90% (OR: 11; 95% CI: 6.2–19.6; *P* < 0.0001), multilobar involvement on CXR (OR: 4.9; 95% CI: 2.7–8.9; *P* < 0.0001), pleural empyema (OR: 2.6; 95% CI: 1.1–6.2; *P* < 0.05) or pneumothorax (OR: 15; 95% CI: 2.9–76.6; *P* < 0.01) were significantly associated with death (Table 3). In the course of treatment, risk of death was also associated with need for mechanically assisted

TABLE 1. Demographic, Clinical and Radiographic Characteristics of Children Hospitalized with Pneumonia

Characteristic	No. of patients, N = 860 (%)
Age (mean $\pm$ SD), yr	2.8 $\pm$ 3.2
Age groups	
<6 mo	110 (13)
7 mo to 5 yr	627 (73)
>5 to 15 yr	123 (14)
Male sex	480 (55)
Underlying disease*	
HIV	77 (9)
Down syndrome	33 (4)
Congenital heart disease	14 (1.6)
Gastroesophageal reflux disease	26 (3)
Leukemia	2 (0.2)
Risk of malnutrition	280 (32.5)
Moderate malnutrition	100 (11.6)
Severe malnutrition	39 (4.5)
Obesity	47 (5)
Clinical characteristics	
Axillary temperature $>38^{\circ}\text{C}$	685 (79.7)
Tachypnea (according to age)	495 (57.6)
Hypoxemia (O_2 saturation <90)	112 (13)
Hypotension	56 (6.5)
Laboratory findings	
White blood cell/mm ³ (media $\pm$ SD)	16,328 $\pm$ 2378
Leukocytosis ($>15,000/\text{mm}^3$)	355 (41.3)
Leukopenia ($<4000/\text{mm}^3$)	28 (3.3)
Blood positive culture	141 (16.4)
Bacteria isolated	
<i>Streptococcus pneumoniae</i>	90 (10.5)
<i>Staphylococcus aureus</i>	50 (5.8)
<i>Haemophilus influenzae</i> type b	1 (0.1)
CXR findings	
Patchy consolidation	476 (55)
Unilobar consolidation	241 (28)
Multilobar consolidation	95 (11)
Pleural empyema	48 (5.6)
Pneumothorax or pneumatocele†	6 (0.7)
Admission to ICU	102 (12)
Requirement for mechanical ventilation	77 (8.9)
Mortality	56 (6.5)

*Some patients had 2 coexisting conditions.

†In 3 patients with unilobar condensation and in 3 patients with multilobar condensation.

ventilation (OR: 66; 95% CI: 32.9–132, $P < 0.0001$), as well as with the development of hepatic (OR: 19; 95% CI: 7–51.6; $P < 0.0001$) and renal impairment (OR: 15.2; 95% CI: 5.8–39; $P < 0.0001$; Table 3). When the microbiological findings were taken in consideration, no association with mortality was observed.

The median of PIRO score at admission of the series was 2, being the mean higher (5 ± 4.8) in nonsurvivors than survivors (1 ± 1.3 ; $P < 0.001$). It was noted that in parallel with the rise of the PIRO score, the mortality rate increased significantly ($P < 0.001$). So, among patients with a PIRO score of 0 ($n = 221$), 1 ($n = 350$) and 2 ($n = 137$), any deaths was observed. But, in children with score of 3 ($n = 68$), 4 ($n = 44$), 5 ($n = 11$) and 6 ($n = 19$), the mortality rate was 14.7%, 25%, 82% and 85%, respectively. All patients with a PIRO score of 7 ($n = 2$), 8 ($n = 3$), 9 ($n = 3$) and 10 ($n = 2$) died. When the area under ROC curve was determined, it showed consistent mortality discrimination by PIRO score (0.94; 95% CI: 0.90–0.98; Fig. 1). Because of the observed mortality for each PIRO score, the patients were stratified in 4 levels of risk: (a) low, 0–2 points; (b) mild, 3–4 points; (c) high, 5–6 points and (d) very high, 7–10 points. We found that 708 patients (82.3%) had a score of 0–2 points, 112 patients (13%) a score of 3–4 points, 30 patients (3.6%) 5–6 points and 10 patients (1.2%) had ≥ 7 points. No patient with a modified PIRO score of 0–2 died; but progressively greater mortality rates were found as the point score rose; 20 (18%) of 112 patients with a score of 3–4 died; 25 (83%) of 30 patients with a score of 5–6 died; all 10 patients (100%) with a score ≥ 7 points died ($P < 0.001$). When other significant variables were added to this score (for instance, seizures and age older than 5 years), we do not observed an improvement of the discriminatory power in the PIRO score.

DISCUSSION

A number of point scales have been developed for measuring the severity of CAP. These scales stratify patients into different mortality-risk classifications, generally according to demographic, clinical and laboratory findings. The objective of these scales is to determine the severity of pneumonia at admission and especially to identify patients requiring admission to intensive care for adequate monitoring. Examples of these point scales are the PSI,⁶ SMART-COP⁷ and CURB-65⁸; however, most scales are designed with only adult patients in mind.

TABLE 2. Relationship Between Demographic and Clinical Variables with Mortality in Children with CAP

Variable	Survivors, N = 804	Deceased, N = 56	OR	95% CI	P
Age groups					
<6 mo	97 (12)	13 (23)	2.2	1.14–4.2	0.018
7 mo to 5 yr	560 (70)	25 (45)	0.36	0.2–0.6	<0.001
>5 to 15 yr	147 (18)	18 (32)	2.1	1.17–3.8	<0.05
Comorbidity*					
Grade I	326 (41)	1 (1.8)	0.02	0.003–0.19	<0.001
Grade II	144 (18)	29 (52)	4.9	2.8–8.5	<0.001
Grade III	87 (11)	24 (43)	6.18	3.4–10.9	<0.001
Clinical variables					
Apyrexia	155 (19)	20 (36)	2.3	1.3–4.1	0.003
Tachypnea	450 (56)	45 (80)	3.2	1.6–6.3	<0.001
Hypotension	23 (2.8)	33 (59)	48.7	24.8–95.6	<0.0001
Seizures	20 (2.5)	12 (21)	10.6	4.9–23	<0.0001
Glasgow ≤ 13	10 (1.2)	45 (80)	324	131–805	<0.0001

*Grade: I (overweight and risk of malnutrition); grade II (congenital heart disease, Down syndrome, moderate malnutrition and gastroesophageal reflux); grade III (HIV, hematological cancer and severe malnutrition).

TABLE 3. Relationship Between Laboratory Variables, CXR Findings and Complications with Mortality in Children with CAP

Variable	Survivors, N = 804	Deceased, N = 56	OR	95% CI	P
Laboratory variables					
Leukopenia (<4000/mm ³)	20 (2.5)	8 (14)	6.5	2.7–15.6	<0.0001
Leukocytosis (>15,000/mm ³)	349 (43)	6 (10.7)	0.15	0.06–0.36	<0.0001
pH < 7.2	11 (1.4)	29 (51.7)	77	35–171	<0.0001
HCO ₃ <15	19 (2.4)	22 (39)	26.7	13–54	<0.0001
Saturated O ₂ <90	81 (10)	31 (55)	11	6.2–19.6	<0.0001
CXR finding					
Unilobar consolidation	221 (27.5)	20 (36)	1.5	0.8–2.6	0.18
Patchy consolidation	466 (58)	7 (12.5)	0.1	0.04–0.23	<0.0001
Multilobar consolidation	76 (9.5)	19 (34)	4.9	2.7–8.9	<0.0001
Pleural effusion	41 (5)	7 (12.5)	2.6	1.1–6.2	<0.05
Pneumothorax	3 (0.4)	3 (5)	15	2.9–76.6	<0.01
Others variables					
Mechanical ventilation	35 (4.4)	42 (75)	66	32.9–132	<0.0001
Hepatic impairment	8 (1)	9 (16)	19	7–51.6	<0.0001
Renal impairment	10 (1.2)	9 (16)	15.2	5.8–39	<0.0001

The PSI is a prognostic model that calculates a severity-of-illness score based on 20 separate characteristics (demographic, clinical and laboratory) of the patients, including underlying comorbidities.⁶ The SMARTCOP scale was proposed by Australian researchers. Its name is derived from the components of the scale, with the S referring to systemic arterial pressure, the M to multilobar involvement on radiography, A to albumin, R to respiratory rate, T for tachycardia, C to confusion (altered mental state), O to oxygenation and P to arterial pH.⁷ The value assigned to the findings held in common, arterial pressure, oxygen saturation, arterial pH and radiographic finding of involvement is indisputable.

Another greatly simplified scale, CURB-65, has been proposed for achieving a prognosis for adults with CAP, with C referring to confusion, U to urea, R to respiratory rate and B to blood pressure, while '65' is the point at which age itself becomes a risk factor.⁸ Recently, CRB-65, which drops the requirement for determining blood urea replaced CURB-65.¹²

A joint statement by the Infectious Disease Society of America and American Thoracic Society¹³ recommended for adults the use of different clinical, radiographic and laboratory criteria, along with initial treatment requirements ordered by importance according to the severity of findings, to guide the clinical physician in determining a prognosis and need for placement of the patient

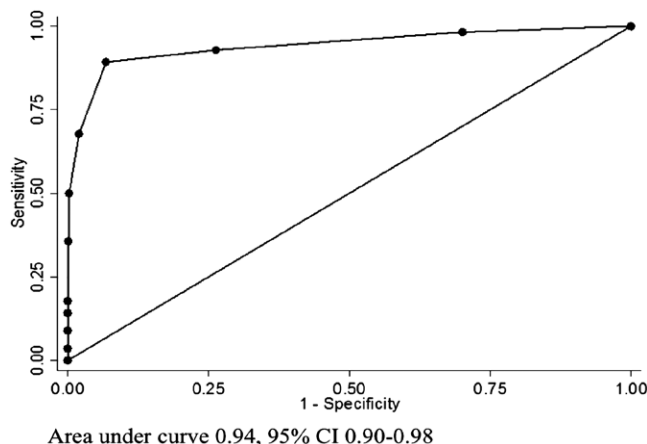
in intensive care. In the same line, the Pediatrics Infectious Society and Infectious Disease Society of America recommend almost similar criteria for hospitalization of children with CAP in ICU.¹⁴

Although several point scale are being used to classify adult patients with pneumonia on admission, scale that can be used in children with pneumonia are scarce. The respiratory index of severity in children (RISC) scale was published by Reed et al.¹⁵ The RISC scale predicts mortality in children younger than 2 years with respiratory tract infections, using 2 models for patients according to the presence or absence of HIV. The variables considered in HIV-negative patients were O₂ saturation <90%, presence of chest indrawing, presence of wheezing, refusal to feed and weight-age Z score. In HIV-positive patients, all the above were included, as well as the HIV clinical classification. They showed that a simple combination of these factors in a scoring model provides good discrimination and calibration for predicting mortality in young children with pneumonia.¹⁵ However, the RISC score study included participants with bronchiolitis as well as children in whom the diagnosis of pneumonia was done based only on clinical criteria (only 16.5% of the patients had alveolar consolidation on CXR).¹⁵

In this study, we have used a new scale to predict mortality in children with CAP. The variables used in the creation of the scale is an adaptation of the PIRO scale previously used for prognostic stratification of adult patients with pneumonia.⁵ This scale includes aspects of host response to the infection as well as predisposing conditions, in recognition that immunodeficient or chronically ill children represent a significant proportion of the real population.

The mean age of patients in our series is similar to those reported in other studies of CAP in children, with a predominance of patients younger than 5 years. The high mortality (6.5%) found in our study series may have been influenced by the high proportion diagnosed as immunodeficient, primarily secondary to HIV infection and by the fact that our institution is a referral center.

Of the patients who died, approximately 60% showed hypotension on admission, 80% required mechanically assisted ventilation and one-third showed multilobar involvement in radiography. The presence of significant (grades II or III) comorbidity and age younger than 6 months were statistically associated with death. These findings are not surprising because conditions such as malnutrition, cancer and HIV profoundly impact the innate and adaptive immune response of the host while patients in the earliest stages of life have not yet achieved full development.

**FIGURE 1.** ROC curve and discrimination of PIRO score for mortality of CAP in children.

The point scale we present strongly correlates with the mortality rates in CAP and helps to discriminate the probability of death in children hospitalized with pneumonia. Its additional advantages are simplicity and absence of sophisticated laboratory determinations. Although any patient with a score of 2 or less died, it was noted that to the extent that increased the score on the scale, at the same time increased mortality. So, in patients with a modified PIRO score of 3–4, the mortality rate was 18%, increasing significantly to 83% in patients with a score of 5–6 and to 100% in patients with a modified PIRO score of 7 or higher.

Our study has a number of limitations, including its retrospective design and the fact that data were collected from a referral center. Thus, the results may not be applicable to community healthcare settings. All selected variables were chosen arbitrary, although all of them were significantly associated with mortality. Several other variables (for instance, seizure and age older than 5 years) that were significantly associated with mortality were not included because when they were taken in, we did not observe an improvement of the discriminatory power in the PIRO score.

Prospective studies applying the present modified PIRO scale in children with CAP are needed to confirm these results. The broad predictive value of mortality of the scale presented here could provide a useful tool for identification of patients with a greater risk of death and guide a more effective early treatment.

REFERENCES

1. Rudan I, Tomaskovic L, Boschi-Pinto C, et al; WHO Child Health Epidemiology Reference Group. Global estimate of the incidence of clinical pneumonia among children under five years of age. *Bull World Health Organ*. 2004;82:895–903.
2. Rudan I, Boschi-Pinto C, Biloglav Z, et al. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ*. 2008;86:408–416.
3. Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013;381:1405–1416.
4. Rudan I, O'Brien KL, Nair H, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Global Health*. 2013;3:10401.
5. Rello J, Rodriguez A, Lisboa T, et al. PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. *Crit Care Med*. 2009;37:456–462.
6. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.
7. Charles PG, Wolfe R, Whitby M, et al; Australian Community-Acquired Pneumonia Study Collaboration. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis*. 2008;47:375–384.
8. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–382.
9. McCracken GH Jr. Diagnosis and management of pneumonia in children. *Pediatr Infect Dis J*. 2000;19:924–928.
10. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/Height-for-age, Weight-for-age, Weight-for-length, Weight-for-height and Body Mass Index-for-age: Methods and Development. Geneva, World Health Organization; 2006. Available at: http://www.who.int/childdgrowth/standards/technical_report/en/index.html. Accessed January 6, 2016.
11. Niles M, Mehta NM, Corkins MR, et al. Defining pediatric malnutrition: paradigm shift toward etiology-related definitions. *JPEN J Parent Enter Nutr*. 2013;37:460–481.
12. Macfarlane JT, Boldy D. 2004 update of BTS pneumonia guidelines: what's new? *Thorax*. 2004;59:364–366.
13. Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44 (Suppl 2):S27–S72.
14. Bradley JS, Byington CL, Shah SS, et al. Executive summary: the management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53:617–630.
15. Reed C, Madhi SA, Klugman KP, et al. Development of the Respiratory Index of Severity in Children (RISC) Score among young children with respiratory infections in South Africa. *PLoS One*. 2012;7:e27793.

Human Rhinoviruses

Samantha E. Jacobs,^a Daryl M. Lamson,^b Kirsten St. George,^b Thomas J. Walsh^a

Transplantation-Oncology Infectious Diseases Program, Division of Infectious Diseases, Weill Cornell Medical College, New York, New York, USA^a; Laboratory of Viral Diseases, Wadsworth Center, Albany, New York, USA^b

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Address correspondence to Samantha E. Jacobs, sej9006@med.cornell.edu.

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SUMMARY

Human rhinoviruses (HRVs), first discovered in the 1950s, are responsible for more than one-half of cold-like illnesses and cost billions of dollars annually in medical visits and missed days of work. Advances in molecular methods have enhanced our understanding of the genomic structure of HRV and have led to the characterization of three genetically distinct HRV groups, designated groups A, B, and C, within the genus *Enterovirus* and the family *Picornaviridae*. HRVs are traditionally associated with upper respiratory tract infection, otitis media, and sinusitis. In recent years, the increasing implementation of PCR assays for respiratory virus detection in clinical laboratories has facilitated the recognition of HRV as a lower respiratory tract pathogen, particularly in patients with asthma, infants, elderly patients, and immunocompromised hosts. Cultured isolates of HRV remain important for studies of viral characteristics and disease pathogenesis. Indeed, whether the clinical manifestations of HRV are related directly to viral pathogenicity or secondary to the host immune response is the subject of ongoing research. There are currently no approved antiviral therapies for HRVs, and treatment remains primarily supportive. This review provides a comprehensive, up-to-date assessment of the basic virology, pathogenesis, clinical epidemiology, and laboratory features of and treatment and prevention strategies for HRVs.

INTRODUCTION

Human rhinoviruses (HRVs) were first discovered in the 1950s in an effort to identify the etiology of the common cold. Nearly 60 years later, the search for a “cure” for the common cold virus is still ongoing. Worldwide and nearly year-round, HRV is

the most common cause of upper respiratory tract infection (URI), leading to considerable economic burdens in terms of medical visits and school and work absenteeism (1–4). However, while once thought to cause relatively benign upper respiratory tract illness, HRVs are now linked to exacerbations of chronic pulmonary disease, asthma development, and, more recently, severe bronchiolitis in infants and children as well as fatal pneumonia in elderly and immunocompromised adults. Our enhanced understanding of the spectrum of illness of HRVs draws largely from advances in molecular methods that have facilitated the detection and characterization of HRV groups and strains. Indeed, a growing number of clinical laboratories are adopting multiplex PCR-based assays for the detection of respiratory viruses that include HRVs (5).

There are currently no approved antiviral agents for the prevention or treatment of HRV infection. Clinical trials of antiviral therapies have been limited by drug toxicities, drug interactions, and a lack of efficacy when applied to the natural setting. Efforts at vaccine development are hindered by the existence of more than 100 HRV serotypes with high-level sequence variability in the antigenic sites. The treatment of HRV infection remains primarily supportive, including over-the-counter products aimed at symptom relief. Given the frequency of HRV infections and our expanding knowledge of their clinical spectrum, effective control of this virus through treatment and prevention would have significant public health impacts.

In this paper, we provide an up-to-date review of HRVs, including their clinical and molecular epidemiology and disease pathogenesis, laboratory diagnostics, and the status of preventative and therapeutic interventions.

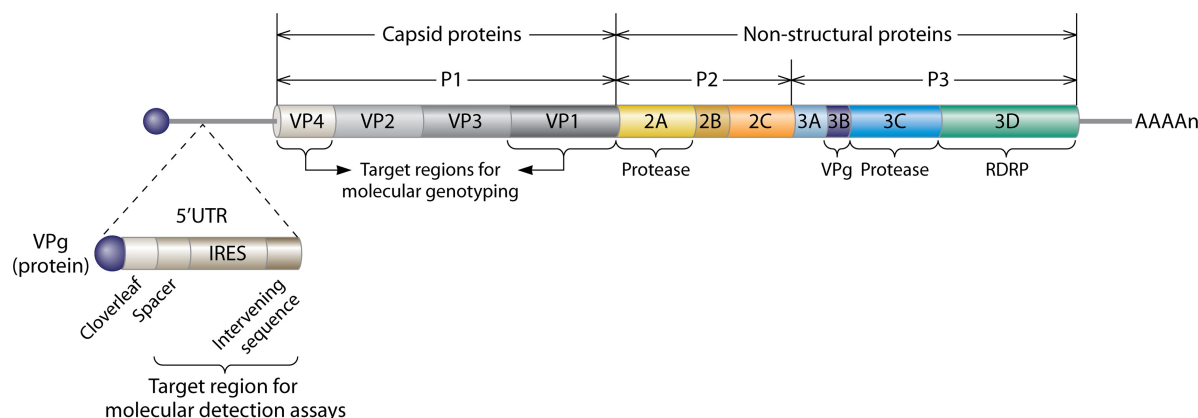


FIG 1 HRV genomic structure. HRV is a 7.2-kb single-stranded, positive-sense RNA virus with a single open reading frame joined to a 5' untranslated region and a short viral priming protein (VPg). The P1 protein is processed to form the HRV capsid, and P2 and P3 are processed to produce VPg, protease, and RNA-dependent RNA polymerase (RDRP) (6). IRES, internal ribosomal entry subunit.

BASIC VIROLOGY

Virion Structure and Genomic Organization

HRVs, members of the family *Picornaviridae* and the genus *Enterovirus*, are positive-sense, single-stranded-RNA (ssRNA) viruses of approximately 7,200 bp. The viral genome consists of a single gene whose translated protein is cleaved by virally encoded proteases to produce 11 proteins (6) (Fig. 1). Four proteins, VP1, VP2, VP3, and VP4, make up the viral capsid that encases the RNA genome, while the remaining nonstructural proteins are involved in viral genome replication and assembly. The VP1, VP2, and VP3 proteins account for the virus' antigenic diversity, while VP4 anchors the RNA core to the capsid. There are 60 copies each of the four capsid proteins, giving the virion an icosahedral structure, with a canyon in VP1 that serves as the site of attachment to cell surface receptors. More than 90% of known HRV serotypes, the "major group," utilize the cell surface receptor intercellular adhesion molecule 1 (ICAM-1), while the "minor group" attaches to and enters cells via the low-density lipoprotein receptor (LDLR). Some of the major-group HRVs also use heparan sulfate as an additional receptor.

Viral Replication

Depending on the receptor type, virus uptake occurs via clathrin-dependent or -independent endocytosis or via macropinocytosis (Fig. 2). The virions subsequently undergo conformational changes that yield hydrophobic subviral particles. This process is initiated by ICAM-1 and/or the low-pH environment in endosomes. It is thought that the RNA genome crosses the endosome membrane into the cytosol through a pore formed by viral proteins or following membrane rupture. Once inside the cytosol, the host cell ribosome translates the positive-sense, single-stranded RNA into a polyprotein that is eventually processed into its various parts (7).

Serotypes/Genotypes

Until recently, HRVs were classified into two species, HRV-A and -B, based on phylogenetic sequence criteria. Clinical specimens in the 1960s and 1970s yielded approximately 100 different HRV

strains (known as the reference or prototype set), which were subsequently serotyped (6). Partial sequencing of viral capsid-encoding regions, noncoding regions, and a limited number of complete genomes led to a division of the original 99 strains into two species: HRV-A (containing 74 serotypes) and HRV-B (containing 25 serotypes). To understand further the molecular and evolutionary biology of the virus and aid in epidemiological investigations, the sequencing of the full genomes of these 99 serotypes was recently completed (8).

The development of highly sensitive molecular techniques for the identification of HRV in clinical specimens led to the identification and designation of a novel species, HRV-C, by the International Committee on Taxonomy of Viruses in 2009 (9). HRV-C strains do not grow in standard cell culture, likely postponing their discovery; therefore, a genetically based classification system was developed. HRV-C strains have a genomic organization similar to that of HRV-A and HRV-B; however, there are several distinct characteristics supporting their classification as a new species. To date, at least 50 different types of HRV-C have been identified by using a threshold of a 13% nucleotide difference in VP1 or at least a 10% nucleotide difference in the VP4/VP2 region if the VP1 sequence is unavailable (10, 11). In 2011, Bochkov et al. were the first to grow HRV-C *in vitro* by utilizing sinus mucosal tissue, and they demonstrated that the species uses a distinct cell attachment mechanism (12). At present, the specific cellular receptor and unique pathogenic mechanisms of HRV-C strains are not known.

Transmission

HRVs are transmitted from person to person via contact (either direct or through a fomite) or aerosol (small or large particle) (13, 14). HRV infection is efficiently initiated by intranasal and conjunctival inoculation but not by the oral route. In studies of natural and experimental HRV infection, the virus is regularly deposited onto the hands and introduced into the environment. HRV is detected in 40% of naturally infected volunteers' hands and 6% of objects in the home (15). In a study of 24 married couples with one experimentally infected partner, the transmission of HRV infection occurred in 9 couples during contact periods ranging from 63

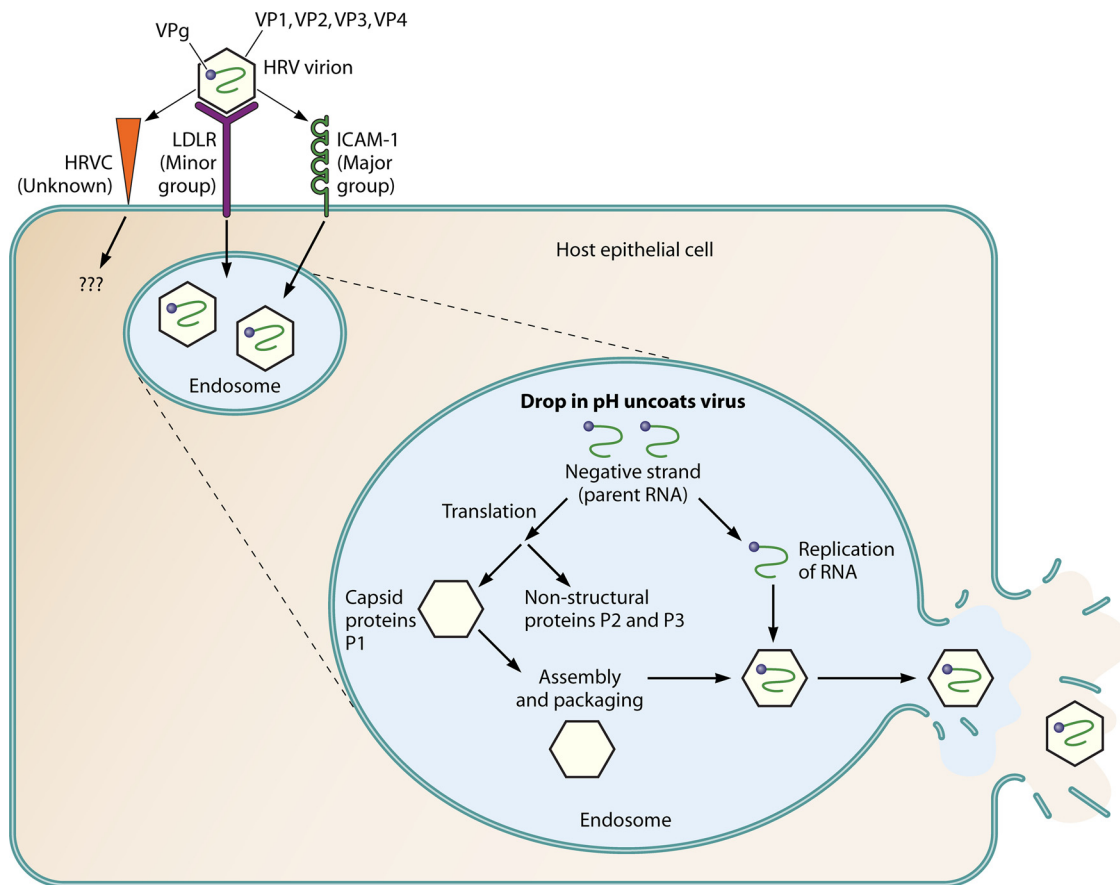


FIG 2 Viral replication in airway epithelial cells. Depending on the receptor type, virus uptake occurs via clathrin-dependent or -independent endocytosis or via macropinocytosis. A drop in the pH leads to viral uncoating. Negative-strand (parental) RNA is replicated as well as translated into structural (capsid) and nonstructural proteins. The virion is then assembled and packaged prior to cellular export via cell lysis (6, 7). LDLR, low-density-lipoprotein receptor; ICAM-1, intercellular adhesion molecule 1.

to 149 h (16). Under experimental conditions, HRV will survive in an indoor environment for hours to days at an ambient temperature and on undisturbed skin for 2 h (17). The frequency and duration of HRV shedding in aerosols are not well understood. In one study, HRV was transmitted via an aerosolized route to 56% of 18 volunteers who played cards for 12 h with experimentally infected subjects (18).

PATHOGENESIS AND HOST RESPONSE

Infection of Nasal Epithelial Cells

To understand how HRV is introduced into the nasal mucosa, Winther et al. delivered 25 μ l of a viral inoculum to the right conjunctival sac near the tear duct or to the posterior nasopharyngeal wall of healthy volunteers (19). Cultures for HRV were obtained daily from the inferior turbinates and the nasopharynx via epithelial brush sampling. In general, HRV was initially detected at the nasopharynx and then spread anteriorly to one or both inferior turbinates. One potential mechanism for this pattern of spread is nose blowing, which may propel virus-laden mucus anteriorly (20). The nasopharynx also serves as the endpoint of mucociliary clearance from the nose, paranasal sinuses, and middle ear cavities (20).

Using *in situ* hybridization, HRV replication has been localized to a small proportion of cells in the nasal epithelium and nasopharynx (21), perhaps due to the limited expression of ICAM-1

(22). The majority of HRV-A and -B serotypes (the major receptor group) enter airway epithelial cells via ICAM-1, a member of the immunoglobulin superfamily. In adenoid and nasopharyngeal tissues of healthy children and adults, ICAM-1 is detected in small numbers of single nonciliated lymphoepithelial cells as well as the basal layer of the ciliated epithelium; however, ICAM-1 is not normally expressed on squamous epithelial cells and on the luminal surface of the ciliated epithelium. However, in normal primary human bronchial epithelial cells (HBECs), HRV upregulates membrane-bound ICAM-1 expression via a NF- κ B-dependent mechanism (23) while downregulating the release of soluble ICAM-1 (24). ICAM-1 upregulation was also observed *in vivo* on nasal epithelial cells following experimental HRV-39 infection of healthy volunteers (25).

While other respiratory viruses, such as influenza virus and respiratory syncytial virus (RSV), cause a destruction of airway epithelial cells, HRV is seldom associated with cytopathology of the upper respiratory tract. Using light and scanning electron microscopy of nasal biopsy specimens from subjects with natural colds, Winther et al. found that epithelial cells were sloughed; however, the epithelial cell lining and borders remained structurally intact (26). A similar preservation of cell morphology and composition was observed for the nasal epithelium during studies of experimental HRV infection, where the amount of viral shedding did not correlate

with the severity of symptoms (19, 27). However, HRV does disrupt epithelial cell barrier function by the dissociation of zona occludens 1 from the tight junction complex (28), thereby facilitating the transmigration of bacteria and exposing basolateral epithelial cell receptors such as Toll-like receptors (TLRs) (29).

Infection of Lower Airway Epithelium

There is mounting evidence from experimental and observational studies to support the role of HRV as a lower respiratory tract pathogen. Although early experiments with HRV-2 suggested that viral replication was optimal at 33°C and markedly reduced at 37°C to 39°C, clinical studies which showed an association between HRV infection and asthma exacerbations prompted researchers to reexamine the temperature sensitivity of HRVs. In 1999, Papadopoulos et al. determined that there were minimal differences in replication capacities at 33°C and 37°C for eight different HRV strains, including when viruses were cultured and titrated at the same temperature (30). Furthermore, virus titers at 37°C for all strains were significantly higher than those required to initiate infection.

In a follow-up study, that same group demonstrated effective HRV replication *in vitro* using primary HBECs and *in vivo* in bronchial biopsy specimens of experimentally infected healthy volunteers via *in situ* hybridization (31). A characteristic cytopathic effect (CPE) was also observed when low-confluence cell cultures of HBECs were exposed to high titers of virus. Moreover, infection of HBECs with rhinovirus type 7 (RV-7) resulted in a significant increase over baseline expression levels for interleukin-6 (IL-6), IL-8, IL-16, and regulated upon activation, normal T cell expressed, and secreted (RANTES).

Gern et al. experimentally infected eight adult allergic volunteers with HRV-16 (32). All subjects developed cold symptoms and had HRV-16 cultured from nasal specimens. In addition, in all subjects, HRV-16 was detected by reverse transcription-PCR (RT-PCR) in lower airway cells obtained via bronchoalveolar lavage (BAL) at 2 to 4 days following infection. Transient abnormal pulmonary function, such as a compliance that is frequency dependent, has also been observed for healthy adults following experimental HRV infection (33).

In the few reported cases of HRV lower respiratory tract infection with human histology, HRV was capable of causing both interstitial and alveolar processes. In those reports, pathological findings included bronchiolitis obliterans with organizing pneumonia (34), interstitial pneumonitis (35; S. E. Jacobs, R. Soave, T. B. Shore, M. J. Satlin, A. N. Schuetz, C. Magro, S. G. Jenkins, and T. J. Walsh, submitted for publication), acute and chronic inflammation with fibrinopurulent alveolar debris (36), and hyperplasia and desquamation of alveolar cells (37). Together, these experiments, as well as clinical observations, confirm that HRV infects the lower airways and induces a proinflammatory response.

Innate and Adaptive Host Response

In addition to a direct effect on respiratory epithelial cells, the innate and adaptive host responses also have a role in the pathogenesis of HRV infection (Fig. 3). Triantafilou et al. conducted a series of *in vitro* experiments with primary HBECs to elucidate the specific recognition of HRV by the innate immune system (38). Those authors determined that the HRV-6 capsid is recognized via TLR2; subsequently, upon HRV-6 ssRNA internalization, the vi-

rus genome is recognized by endosomally located TLR7 and TLR8. Once double-stranded RNA (dsRNA) is generated, the type I interferon (IFN) response is mediated by melanoma differentiation-associated gene 5 (MDA-5) and retinoic acid-inducible gene 1 (RIG-1). The engagement of these receptors maximizes HRV-induced IFN- β and IFN- γ and proinflammatory cytokine gene expression, including RANTES, IP-10, IL-6, IL-8, and epithelial cell-derived neutrophil-activating peptide 78 (ENA-78) (38, 39). In particular, IL-8, which has neutrophil chemotactic and activation properties, is an important determinant of the clinical outcome of HRV infection. The HRV-induced stimulation of IL-8 production has been demonstrated for upper and lower airway epithelial cells (40, 41) and is mediated in part by an NF- κ B-dependent transcriptional activation pathway (42). Levels of IL-8 in nasal lavage fluid specimens from experimentally infected subjects correlated with symptom severity (rhinorrhea and nasal obstruction) (40) and peaked at 48 to 72 h after virus inoculation.

Evaluations of promoter polymorphisms of cytokine genes and the associated protein production may provide new insights into symptom expression during HRV infection. IL-6 levels are consistently increased in nasal lavage fluid specimens in controlled studies of experimental and natural HRV infections (42–44). Studies of children and adults with RSV infection found that the C/C genotype of a single-nucleotide polymorphism in the IL-6 promoter at position –174 correlated with illness severity (45, 46). Doyle et al. therefore recently examined the relationship between IL-6 promoter genotypes and the magnitudes of symptoms during HRV infection (47). Following experimental HRV-39 infection, subjects with a phenotype of a low level of production of IL-6 (position –174, C/C genotype) experienced greater symptom severity, although there was no effect on nasal secretion production and mucociliary clearance time. That study also found that the IFN- γ (position +874) phenotype predicted the frequency of seroconversion. There was no relationship between IL-10 or tumor necrosis factor alpha (TNF- α) polymorphisms and seroconversion or symptom outcomes. The observed IL-6 genotype associations are consistent with those of RSV studies; however, they are also unexpected given previous reports that higher IL-6 levels predicted the magnitude of symptoms. Those authors noted that the cytokine phenotypes were assigned based on *in vitro* data, which may not correlate with *in vivo* cytokine production in the more complex nasal mucosa and blood during a viral upper respiratory tract infection. Furthermore, other cytokine polymorphisms that were not measured in the *in vivo* studies may interact with IL-6 genotypes to influence cytokine production. These experiments highlight the complexity in deriving genotype-phenotype associations as well as the challenge of elucidating the complex interactions of cytokines in producing common cold symptoms.

Kinins also play a role in the pathogenesis of symptomatic HRV infections. In both experimental and natural HRV colds, symptomatic subjects show significantly increased levels of kinins, specifically bradykinin and lysylbradykinin, in nasal lavage fluid compared to levels in sham-infected and/or healthy controls (48, 49). Elevated kinin levels are associated with increases in vascular permeability, as indicated by elevated albumin levels and the influx of neutrophils. Of note, histamine levels do not change in symptomatic HRV infection, suggesting that mast cells and basophils do not contribute to the pathogenicity of HRV.

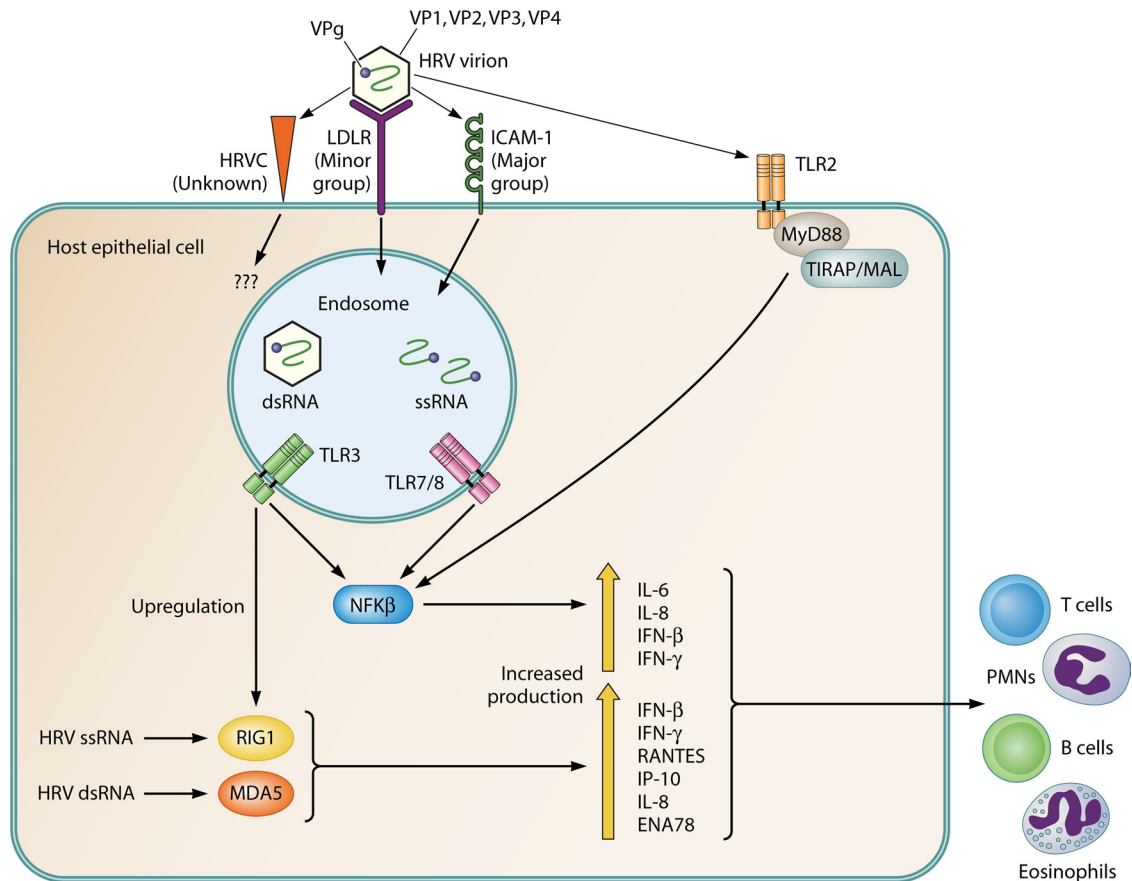


FIG 3 Signal transduction pathways and activation of the innate immune response. In the endosome, viral dsRNA and ssRNA are recognized by TLR3 and TLR7/8, respectively. An interaction with TLR3 triggers the upregulation of the pattern recognition receptors (retinoic acid-inducible gene 1 [RIG-1] and melanoma differentiation-associated protein 5 [MDA-5]) (RNA helicases) in the intracellular compartment. RIG-1 and MDA-5 also recognize newly synthesized viral dsRNA and ssRNA in the cytoplasm. RIG-1 and MDA-5 stimulate HRV-induced IFN gene expression as well as the increased production of T cell and neutrophil cytokines, including regulated, normal T cell expressed, and secreted (RANTES); IFN- γ -induced protein 10 (IP-10); IL-8; and epithelial cell-derived neutrophil-activating peptide 78 (ENA78). An interaction with TLR2 on the cell surface initiates a proinflammatory cytokine response via a MyD88-dependent pathway (38, 39). LDLR, low-density-lipoprotein receptor; ICAM-1, intercellular adhesion molecule 1; TIRAP, Toll–interleukin-1 receptor (TIR) domain containing adaptor protein; PMNs, polymorphonuclear leukocytes.

Humoral immune responses are important for preventing HRV infection, although the precise mechanism is unknown. HRV infection in antibody-naïve subjects is followed by the development of serotype-specific neutralizing serum antibodies (IgG) as well as secretory antibodies (IgA) in the airways. When seronegative subjects are experimentally infected with HRV-2, specific antibodies are detectable at 1 to 2 weeks, and levels of these antibodies may remain elevated for 1 or more years after infection (50, 51). The persistence of high-titer serotype-specific antibody is associated with protection from infection as well as reduced symptom severity following experimental challenge with the same serotype (52). However, there is little cross-neutralization among serotypes, which presents a challenge to vaccine development, given that there are more than 100 different known HRV serotypes (53). Further support for the role of humoral immunity in the prevention and control of HRV infection was observed in a study of patients with primary hypogammaglobulinemia. These patients experienced more frequent and severe HRV infections than their healthy spouses despite the administration of replacement immunoglobulin therapy (54).

T cells contribute to antiviral immunity through the recognition of viral antigens, which trigger both cytotoxic and antibody-mediated immune responses. HRV-infected endothelial cells secrete RANTES and IP-10, which promote T cell chemotaxis (289). IP-10 is a chemokine secreted by bronchial epithelial cells, monocytes, lymphocytes, and neutrophils in response to the cytokines IFN- γ and TNF- α , the levels of which are elevated by HRV infection. Increased numbers of lymphocytes and neutrophils are present in nasal secretions, and bronchial biopsy specimens of HRV-infected subjects with asthma and controls show T cell infiltration of the airway epithelium and submucosa (55) with concomitant lymphopenia. To determine a potential role of circulating lymphocytes in the pathogenesis of HRV infection, Levandowski et al. challenged 15 healthy volunteers with HRV-25 (56). Lymphocyte subsets in peripheral blood leukocytes were classified and quantified by using monoclonal antibodies at baseline and at day 3 and day 7 following HRV inoculation. Among the subsets of T cells, numbers of both T4⁺ (T helper/inducer) and T8⁺ (T suppressor/cytotoxic) lymphocytes declined over time, but only the change in the T4⁺ subset was significant. The duration of virus shedding was

also inversely related to changes in lymphocyte counts. No changes were observed for B cells. In addition, the total leukocyte count increased, likely due to an increased number of neutrophils. A potential explanation for these results is that the lymphocytes migrated to the site of HRV infection, while neutrophils were released from the marginal pools in response to the inflammatory process.

Human T cell clones of HRV-specific T cells are activated by not only serotype-specific but also shared viral epitopes (57). Cross-reactivity among T cells may lead to more potent T cell responses and subsequent cytokine release upon reinfection with different HRV serotypes. In addition, T cell recruitment may facilitate viral clearance via Th1 cytokine production, including IFN- γ and IL-2 (58).

A clinical approach to elucidating the role of the immune system in HRV infection and pathogenesis is to study the effects of pharmacological agents with known mechanisms of action. For example, the cyclooxygenase inhibitor naproxen was evaluated in a randomized, placebo-controlled trial of experimental HRV infection in healthy adults (59). Subjects receiving naproxen had reduced headache, malaise, myalgias, and cough, suggesting that prostaglandins may have a causal role in HRV pathogenesis. Naproxen did not affect the duration of virus shedding or serum-neutralizing antibody responses.

Animal Models

The development of small-animal models is useful to understand further the pathogenesis of HRV infection in both the upper and lower airways; however, there are no known murine rhinoviruses. Experimental animal models using either minor-group receptor HRVs in wild-type mice or major-group receptor HRVs in mice that are transgenic for ICAM-1 have been developed recently (60). Mice were inoculated with 5×10^6 50% tissue culture infective doses of minor-group HRV (HRV-1B) or major-group HRV (HRV-16). Infection with both HRV-1B and HRV-16 resulted in BAL fluid neutrophilia and lymphocytosis; increased Muc5B protein in BAL fluid; increased viral RNA levels in BAL fluid and lung tissue; and the induction of IFNs, chemokines, IL-1 β , and virus-specific antibodies. An examination of stained lung sections revealed areas of extensive peribronchial and perivascular cellular infiltration. One limitation to these murine models is that HRV titers exhibit a steep decline within 12 to 24 h, limiting the ability to investigate viral replication and HRV-induced inflammation and airway dysfunction.

A major focus of animal models has been to elucidate the immunology of HRV-induced asthma exacerbations. Using combined mouse models of allergic airway disease and HRV infection, Nagarkar et al. inoculated ovalbumin (OVA)-sensitized and -challenged BALB/c mice with HRV-1B (61). Those authors found that the levels of production of proinflammatory cytokines, including eotaxin-1/CCL11, IL-4, and IL-13, increased following viral infection. Furthermore, levels of bronchoalveolar and lung neutrophils, eosinophils, and macrophages, as well as airway responsiveness, were elevated in the HRV-infected, OVA-treated mice compared to control mice. Activated macrophages played a key role in eosinophilic infiltration and airway responsiveness in HRV-infected OVA-treated versus phosphate-buffered saline (PBS)-treated mice.

Another recently reported strategy is the use of genetically modified mengovirus, a picornavirus that has a phenotype similar to

that of poliovirus in its natural murine host (62). The deletion of the poly(C) tract in the distal portion of the 5' untranslated region (5'UTR) of mengovirus causes an infection in wild-type mice that more closely resembles HRV infection of humans. This murine model of picornaviral infection may be useful for elucidating HRV pathogenesis in humans.

Mechanisms in Chronic Pulmonary Disease

Asthma. Several plausible mechanisms for HRV-induced asthma development have been proposed. Experimental HRV-16 infections in patients with mild atopic asthma and allergic subjects led to a significant reduction in the forced expiratory volume in 1 second (FEV1) in home recordings and potentiated airway inflammation after bronchoprovocation, respectively (63). Potential mechanisms for lower airway dysfunction following HRV infection include the direct infection of the lower airway or the stimulation of inflammatory, immunological, or neurogenic mechanisms. *In vitro* data suggest impaired innate and acquired immune responses in subjects with asthma, including deficient IFN induction and impaired Th1 responses (64–66). Furthermore, HRV can stimulate the synthesis of factors that regulate airway remodeling and alveolar development, including vascular endothelial growth factor, nitric oxide, transforming growth factor β , and fibroblast growth factor (67).

Chronic obstructive pulmonary disease. In order to investigate a causal relationship between HRV and chronic obstructive pulmonary disease (COPD) exacerbations, Mallia et al. experimentally infected 13 patients with COPD and 13 nonobstructed smoker controls (68). Three patients (2 with COPD and 1 control) were excluded from further analysis because HRV was not detected after experimental infection. Of the remaining 11 COPD patients, 10 fulfilled symptom criteria for COPD exacerbation. Pulmonary function tests demonstrated significant reductions in postbronchodilator peak expiratory flow and carbon monoxide diffusion capacity from baseline to HRV infection in COPD patients but no change in controls. Neutrophil elastase and IL-8 levels in sputum supernatants and IL-6 levels in BAL fluid also increased from baseline to HRV infection in COPD patients, whereas the TNF- α levels did not increase significantly in either group. Finally, pulmonary alveolar macrophages from BAL fluid demonstrated deficient IFN- β responses in COPD patients compared to controls, suggesting a potential mechanism for the increased severity of HRV infection in COPD patients. There was a nonsignificant trend toward reduced levels of IFN- α and IFN- γ production ($P = 0.09$ and 0.1 , respectively).

Recently, Quint et al. examined serum IP-10 as a potential biomarker of HRV infection during COPD exacerbations (69). At baseline, 136 COPD patients had higher serum IP-10 levels than 70 age-matched controls without COPD. During 2 years of follow-up, serum IP-10 levels increased significantly from baseline during HRV-positive COPD exacerbations and demonstrated no change during HRV-negative exacerbations. Serum IP-10 levels also correlated with sputum HRV viral load. Of note, among 13 COPD patients with HRV positivity at baseline and during exacerbations, serum IP-10 levels and sputum HRV viral loads were significantly higher during exacerbations.

Cystic fibrosis. Mechanisms of HRV-induced pulmonary exacerbations in patients with cystic fibrosis (CF) are not well understood. Two recent studies suggested an impairment in innate immunity, specifically IFN production (70, 71). After infecting CF

and non-CF bronchial epithelial cell lines and primary nasal and bronchial epithelial cells from CF patients and healthy controls, Vareille et al. found that CF cells produced significantly less IFN- β and IFN- γ than did normal cells (70). Deficient IFN production was associated with reduced expression levels of IFN-stimulated genes, including myxovirus resistance A, 2',5'-oligoadenylate synthetase, viperin, and nitric oxide synthase 2. Secondary viral infections in the setting of chronic bacterial infection are also common and may increase the severity of lung disease in patients with CF. Chattoraj et al. demonstrated *in vitro* that mucoid *Pseudomonas aeruginosa* preinfection impairs HRV clearance by suppressing the antiviral IFN response in primary HBEs from CF patients but not in normal cells (71). Deficient IFN responses occurred via the inhibition of HRV-stimulated Akt phosphorylation and decreased levels of IFN regulatory factor 3 (IRF3) phosphorylation. An exaggerated inflammatory response to viral infection was also postulated to be a mechanism for virus-induced CF exacerbations (72, 73). However, a recent study found no difference in levels of cytokine transcription or production in CF and control nasal and bronchial epithelial cells; indeed, there was a trend toward a reduced cytokine response associated with increased cell death in CF cells (74).

In conclusion, *in vitro* and clinical data indicate that HRVs are a significant upper and lower respiratory tract pathogen. However, the relative roles of the virus itself and the host immune response in HRV pathogenicity and symptomatic illness are still under debate. In the upper airways, HRV has not been shown to cause direct cytopathology; clinical symptoms are likely the result of local and systemic immune responses. In cultured epithelial cells from the lower airways, cytopathology has been observed by using low-confluence monolayers and high viral inocula (31), perhaps suggesting a dose-response relationship to HRV-associated lower respiratory tract infection, to which patients with immune dysregulation (e.g., deficient IFN responses in individuals with asthma and cystic fibrosis) and immunosuppressive conditions are particularly predisposed.

EPIDEMIOLOGY AND CLINICAL SYNDROMES

Seasonal Patterns and Geographic Distribution

HRVs cause respiratory illness throughout the world and throughout the year. Beginning in the 1960s, longitudinal studies of the epidemiology and clinical features of HRV infection in temperate climates reported a peak in incidence in the early fall, with a smaller peak in the spring (75). More recent prospective studies employing molecular detection methods (RT-PCR) have replicated these findings (76–78). In general, HRVs are the most common cause of respiratory viral illness during the spring, summer, and fall months, while influenza virus and RSV predominate in the winter.

Following the identification of a novel HRV genotype, HRV species C (9, 79, 80), studies from diverse geographic regions have attempted to characterize the molecular epidemiology of HRV and identify distinguishing clinical features according to species. All HRV species have been identified in all months, in temperate, tropical, subtropical, and semiarid regions (81–85). HRV-C appears to show seasonality, with peaks in the fall or winter in most temperate or subtropical countries but a possible peak incidence during the rainy season in the tropics. HRV-A and HRV-B may show a similar seasonality (86). Additional longer-duration, large

epidemiological studies with symptomatic and asymptomatic subjects are needed to enhance our understanding of the seasonality of HRVs.

Clinical Syndromes

Asymptomatic infections. With the increasing use of molecular methods of viral detection, asymptomatic HRV infection has been noted to be relatively common, particularly in children. The frequent detection of HRV in asymptomatic individuals may also reflect one of several states: prolonged virus shedding after a symptomatic respiratory illness has resolved; mild, unrecognized symptoms; or the incubation period prior to the onset of symptoms. In children less than 4 years old, rates of asymptomatic infection range from 12 to 32% (87–91) and tend to be higher in the youngest age groups (91). A study conducted in Alaska's Yukon-Kuskokwim Delta to characterize the etiology of lower respiratory tract-associated hospitalizations in children less than 3 years old selected controls from the community if they had no respiratory symptoms in the previous 2 weeks. Among 425 community control children, 33% tested positive for HRV by real-time PCR of nasopharyngeal swab specimens (87); this rate was not significantly different from that observed for children hospitalized with lower respiratory tract illness. In contrast, Iwane et al. (90) detected HRV in nasal and throat swab specimens from 12.5% of asymptomatic children less than 5 years old recruited at well-child primary care visits in three different regions of the United States (Rochester, NY; Nashville, TN; and Cincinnati, OH). This difference in observed rates of asymptomatic HRV infection may be attributed to the higher prevalence of HRV in the youngest age groups or to environmental factors in the Alaska Native community, including household crowding and a lack of running water, that predispose individuals to respiratory illnesses (92).

Among middle-aged and elderly adults, rates of asymptomatic HRV carriage are less well studied but are considerably lower than those for children. Two studies (91, 93) detected HRV in 0% and 2% of asymptomatic adults, although rates were higher in adult household members of HRV-infected children (94). Of note, the above-mentioned studies were typically conducted over at least a 1-year period, and seasonal differences in rates of asymptomatic infection have not been described.

Upper respiratory infections. (i) Common cold. Studies using both molecular methods and viral culture demonstrated that HRV is the etiology of one-half to two-thirds of common colds (95, 96). The common cold is primarily a self-limited illness in immunocompetent hosts, with an average incubation period of 2 days (97, 98) and a symptom duration period of 7 to 14 days (5, 99). However, in one experimental study, subjects reported nasal irritation and sore or scratchy throat at 2 and 10 h, respectively, after virus inoculation (100). Common symptoms include rhinorrhea, nasal congestion, sore throat, cough, headache, subjective fevers, and malaise. Compared to patients with coronavirus-associated colds, there is no difference in respiratory symptom severity or duration (96). Despite the relatively mild course of illness, the economic burden is considerable. In a survey of 4,051 U.S. households, the economic impact of non-influenza virus respiratory tract infections was estimated to be \$40 billion annually in direct and indirect costs (4).

(ii) Acute otitis media. In both experimental and natural settings, HRV is linked to otitis media (OM), which complicates

approximately one-third of cold-like illnesses in early childhood (101). Among healthy volunteers undergoing intranasal inoculation with HRV, otologic manifestations of HRV infection include Eustachian tube dysfunction, abnormal middle ear pressure, and OM (102, 103). In the Finnish Otitis Media Cohort study of 329 children monitored prospectively from ages of 2 months to 2 years, there were 458 episodes of OM. HRV was detected by real-time PCR in nasopharyngeal aspirate or middle ear fluid (MEF) specimens in 41% of episodes (104). Further support for the role of HRV in upper respiratory tract infections and OM is derived from investigations of adenoid tissue. Using *in situ* hybridization of adenoid tissue removed from children with histories of recurrent OM or adenoid hypertrophy, HRV RNA was detected in 45% of specimens (105). Of note, clinical outcomes of acute OM may not vary according to viral etiology. Among 92 children aged 3 months to 7 years with acute OM, rates of treatment failure or recurrence, defined as recurrent symptoms within 7 to 30 days after initial clinical improvement, were not significantly different between those with HRV detected in MEF specimens (18%), those with RSV or coronavirus detected in MEF specimens (21%), and those with no detectable viral RNA in MEF specimens (27%) (106).

Coinfection with bacterial pathogens is also common during HRV-associated OM episodes. In one study of children with tympanostomy tubes and acute OM onset within the previous 2 days, bacterial-viral coinfection occurred in 66% of patients, with picornaviruses accounting for two-thirds of cases (107). Another prospective study of 121 otitis-prone children tested nasopharyngeal swabs by PCR for respiratory viruses and by culture for bacterial pathogens during three study visits over a 6-month period (108). HRV was detected in 30% and 19% of baseline and follow-up specimens, respectively, and HRV positivity correlated with the culturing of *Moraxella catarrhalis* and *Streptococcus pneumoniae* but not nontypeable *Haemophilus influenzae*. Of note, HRV and bacterial pathogens were found in otitis-prone children even in the absence of clinical symptoms. Further potential mechanisms of HRV-bacterial coinfection are reviewed in "Coinfections with Other Respiratory Pathogens."

(iii) Rhinosinusitis. Sinus abnormalities are frequently detected by computed tomography (CT) (109) and magnetic resonance imaging (MRI) (110) of patients with the common cold. The maxillary and ethmoid sinuses were most commonly involved in healthy young adults challenged with HRV-39 and monitored by serial MRI over several weeks (110). In one study, HRV RNA was detected by RT-PCR of maxillary aspirate specimens and nasal swab specimens in 50% of patients with acute community-acquired sinusitis (111). Furthermore, using *in situ* hybridization, HRV RNA was found in the maxillary sinus epithelium in 7 out of 14 adults with acute sinusitis (112). Nose blowing is one potential mechanism for the spread of nasal fluid carrying viruses and other pathogens to the sinuses in patients with cold symptoms. Gwaltney et al. measured intranasal pressure in adults during nose blowing, coughing, and sneezing (113). In addition, CT scans were performed after the instillation of radiopaque contrast medium into the nasopharynx followed by nose blowing, coughing, and sneezing. Nose blowing, but not coughing or sneezing, generated sufficient pressure to propel nasal fluid into the paranasal sinuses (mean maximum intranasal pressures $\pm$ standard deviations of 66 ± 14 mm Hg versus 7 ± 3 mm Hg and 5 ± 4 mm Hg, respectively).

Lower respiratory infections. (i) Croup. Although most commonly caused by parainfluenza viruses (PIVs), croup has occasionally been reported in children with HRV infection. In a study of U.S. children less than 5 years old hospitalized with acute respiratory infections, 10% and 3% of admission and discharge diagnoses, respectively, were croup among those children with HRV alone isolated from respiratory specimens (77, 90). Croup is a similarly rare manifestation of HRV infection among children and young adults in Japan (81). Another study of children presenting to the emergency department with signs and symptoms of croup detected HRV in 12% of cases, although rates were similar among control children with wheezing illnesses (114). Reflecting patterns of other microbiological surveys for respiratory viruses, HRV was detected more often in samples obtained during the fall (September to November), whereas influenza A virus and RSV were more common in winter (December to February), and PIVs were found most often in winter and spring (December to April).

(ii) Bronchiolitis. Bronchiolitis is the most common clinical manifestation of HRV infection in hospitalized children (115) and accounts for 14% of HRV-associated lower respiratory tract infection admissions to pediatric intensive care units (ICUs) (116). Following RSV, HRV is the second most common cause of bronchiolitis in hospitalized children, as demonstrated in a recent U.S. multicenter prospective study (117). Among 2,207 children less than 2 years old, HRV was detected alone, in combination with RSV, and in combination with non-RSV pathogens in 9%, 15%, and 6% of cases, respectively. Compared to children with RSV infection alone, a hospital length of stay of 3 or more days was less likely for children with HRV infection alone or for children with infection by HRV and non-RSV pathogens but was more likely for those with RSV-HRV coinfection. These findings challenge the notion that the viral etiology of severe bronchiolitis does not affect short-term outcomes and support further research to guide cohorting and therapeutic strategies (117, 118).

Among very-low-birth-weight infants in Argentina, HRV detection (40%) exceeded RSV detection (7%) during bronchiolitis episodes (119). The incidence of HRV infection in this population was 75 per 100 infant years of follow-up. In a multivariable analysis model including bronchopulmonary dysplasia (BPD), weight, breastfeeding status, parental asthma, smoking in the home, and maternal age, BPD was independently associated with a higher risk of HRV-associated bronchiolitis (relative risk, 2.2). The adjusted relative risk of any HRV-associated hospitalization was also increased for infants with BPD and those who were not breastfed.

HRV-associated bronchiolitis in infancy is an independent risk factor for recurrent wheezing at 1 year of age (120) and for the development of asthma. A follow-up study of 81 children conducted 6 years after hospitalization as infants for wheezing found that the risk of childhood asthma was four times higher for children with a history of HRV-associated wheezing than for children with wheezing of a different viral etiology (121). Viral respiratory infections have been shown to induce cell damage as well as alter immune responses. As lung development begins at 4 weeks of gestation and continues through early childhood, HRV infection may have severe direct and indirect effects on lung tissues, leading to chronic lung disease (67).

(iii) Community-acquired pneumonia. Several clinical studies of children hospitalized with community-acquired pneumonia (CAP) have established HRV as a common pathogen in viral CAP,

with rates ranging from 18 to 26%, although it may be difficult to establish a causal role in the presence of bacterial and viral coinfection, which occurs in up to 60% of cases (122–124). Clinical manifestations are potentially severe (125), particularly in children with underlying chronic medical conditions. Indeed, HRV was detected in 49% of children admitted to ICUs with lower respiratory tract infection; in approximately one-half of cases, no other respiratory pathogen was identified (116). Among adults, HRV is identified in only approximately 5% of cases of viral CAP (126, 127). However, in two outbreaks of HRV-associated acute respiratory illness among elderly residents in long-term-care facilities, HRV caused substantial morbidity and one fatality (128, 129).

Infections in Immunocompromised Hosts

With the increasing use of newer molecular platforms for respiratory virus detection, including multiplex real-time PCR assays, HRV is increasingly being recognized as a significant cause of acute respiratory illness in immunocompromised hosts (130, 131). A recent study of patients presenting to the emergency department with influenza-like illness found that the severity of HRV infection in immunocompromised patients, including those with diabetes, human immunodeficiency virus (HIV) infection, malignancy, or organ transplantation, was similar to that of pandemic H1N1 influenza virus. Nearly 40% of patients with HRV-associated respiratory symptoms were admitted to the hospital, and 11% required ICU admission. Two (3%) patients died; however, mortality was due to concurrent illness and was not directly attributable to HRV infection (132).

Lung transplant recipients. Lung transplant recipients provide a unique opportunity to study HRV infection of the lower airways because these patients undergo frequent bronchoscopy and BAL for graft rejection surveillance as well as during episodes of respiratory illness. Kaiser et al. demonstrated active and chronic HRV infection (8 to 15 months) of the lower respiratory tract in three highly immunosuppressed lung transplant patients. HRV was identified by RT-PCR of lower respiratory tract specimens and by using antibodies specifically directed against the infecting HRV strain in interstitial and epithelial cells (133). In a study of 36 adult lung transplant recipients in Italy, HRV was detected in 13% of all BAL fluid specimens obtained from 15 (42%) patients over a 2-year period. All patients were symptomatic at the time of HRV detection, including those with low viral loads of 10^3 to 10^4 RNA copies/ml, and all patients had coinfection with bacterial and/or viral pathogens (134). Compared to adults, HRV is common in pediatric lung transplant recipients, accounting for 22% and 30% of respiratory viral illnesses at 1 year and a median of 22 months, respectively, following transplantation (135, 136). Whether HRV affects transplant outcomes, such as acute rejection and the development of bronchiolitis obliterans syndrome (BOS), is not well understood due to the small numbers of patients under study. In a recent pooled analysis of 34 studies evaluating respiratory viral infection and graft dysfunction, posttransplant BOS occurred in 18% of patients with a history of respiratory viral infection and in 11.6% of patients with no such history (137). In pediatric patients, respiratory viral infection is independently associated with decreased 1-year survival rates (136).

Patients with hematologic malignancy and hematopoietic stem cell transplant recipients. HRV causes both upper and lower respiratory tract infections in hematologic malignancy pa-

tients (130, 138–140); however, the relative frequency and severity of HRV infection compared to those of other respiratory viral pathogens remain to be elucidated. Milano et al. obtained weekly surveillance nasopharyngeal swab specimens for HRV and coronavirus testing by real-time RT-PCR and recorded respiratory symptoms in a cohort of allogeneic hematopoietic stem cell transplant (HSCT) recipients. The cumulative incidence of HRV infection was 22% in the first 100 days posttransplantation. In a multivariable regression model, a positive HRV sample within the last week was significantly associated with rhinorrhea, sinus congestion, postnasal drip, sputum production, and cough (139). One-third of HSCT recipients will have clinical and/or radiographic evidence of sinusitis (35). Asymptomatic infection also occurs in a minority of patients (139, 140).

Progression to HRV pneumonia is uncommon but is associated with substantial morbidity and mortality (35, 139, 141). In the majority of reported cases of HRV in the lower airways, coinfection with one or more bacterial, viral, and/or fungal copathogens is present (35, 141). Recently, our group described 63 HSCT recipients with one or more HRV infections since our institution implemented multiplex PCR testing of respiratory viruses in 2008 (Jacobs et al., submitted). We identified 25 HSCT recipients with pneumonia and HRV detected in BAL fluid, of which 10 (40%) patients had no other respiratory pathogen identified via culture or molecular methods. A review of the CT scan findings for these 10 patients revealed a characteristic peribronchiolar patchy ground-glass infiltrate in the majority of cases. For the remaining 15 cases, copathogens were bacterial ($n = 7$), fungal ($n = 5$), and viral ($n = 3$). Compared to patients with respiratory coinfection detected in BAL fluid, patients with HRV alone detected in BAL fluid were not significantly different in terms of age, symptoms, ICU admission, transplant type, conditioning regimen, graft-versus-host disease, or receipt of antibiotics. The mortality rate at 1 year following the first posttransplantation HRV infection was 55% in patients with BAL-confirmed HRV pneumonia, versus 41% in the total cohort of 63 patients. Risk factors for HRV pneumonia may include lymphopenia (absolute lymphocyte count of <500 cells/ μ l) (142) and hypoalbuminemia (Jacobs et al., submitted); however, further research is needed to elucidate fully the epidemiology and pathogenesis of HRV pneumonia in this patient population.

Exacerbations of Chronic Pulmonary Diseases

Asthma. Wheezing illnesses during infancy are associated with recurrent wheezing and the development of asthma in childhood. In a prospective cohort study of 259 children monitored from birth to 6 years of age, children with outpatient HRV-associated wheezing illnesses from birth to 3 years of age were 10 times more likely to have developed asthma at 6 years of age. Nearly 90% of children who wheezed with HRV in year 3 had asthma by 6 years of age (143). Infants hospitalized with viral bronchiolitis have a 2- to 3-fold-increased risk of asthma later in childhood. This risk appears to be greatest with HRV compared to RSV, PIV, and influenza virus infections (144).

HRV is also associated with exacerbations of asthma. Subjects with asthma do not have more cold illnesses than nonasthmatic individuals, nor are there differences in the severity or duration of HRV-associated upper respiratory tract symptoms; however, they do experience more frequent and severe lower respiratory tract symptoms (144, 145). On average, approximately two-thirds of

respiratory virus-associated asthma exacerbations are due to HRV. In a cross-sectional study of children hospitalized with asthma exacerbations and controls hospitalized with acute respiratory illnesses, HRV was detected in 85% of cases and 33% of controls. Of note, HRV-C was associated with asthma exacerbations, whereas rates of HRV-A and HRV-B detection were similar between groups (146).

Chronic obstructive pulmonary disease. Several longitudinal studies have demonstrated a significant association between respiratory viral infections and exacerbations of COPD in both inpatient and outpatient settings. In a study of 62 patients with COPD monitored for a mean of 26 months, 58% of office visits and 6% of emergency room visits were associated with respiratory viral infections (147). Among patients hospitalized with acute exacerbations of COPD (AECOPD), respiratory viruses were detected in 37% of AECOPD patients, compared to 12% of control subjects with stable COPD and 12% of nonobstructed smokers. HRV was the most common respiratory viral infection, isolated in 24% of AECOPD patients. HRV was also detected in 4% of stable COPD patients and zero nonobstructed smokers. Therefore, compared to stable COPD patients, those with COPD exacerbations were 4.4 times more likely to have a respiratory viral infection (148). Two additional prospective studies of patients hospitalized with AECOPD found that picornaviruses were the most common viral infection detected by RT-PCR in nasal lavage fluid, nasopharyngeal swab, or induced sputum specimens, occurring in 36 to 50% of cases (149, 150). In the outpatient setting, approximately two-thirds of AECOPD cases are associated with common cold symptoms (increased nasal congestion and/or increased rhinorrhea) in the 18 days preceding the onset of the exacerbation, and HRV remains the most common cause of viral infection (151). The presence of common cold symptoms appears to be associated with prolonged recovery in patients with a moderate to severe obstruction (152).

Compared to patients with nonviral causes of AECOPD, fever is more frequent in those with documented viral infection (148, 149). Two studies also found increased lengths of stay for patients hospitalized with AECOPD and respiratory viral infection (151, 153). Another study found no difference in lengths of stay among AECOPD patients with and without respiratory viral infection; however, rates of bacterial infection were higher in the nonviral infection group (150). Respiratory viral infections do not occur more commonly according to baseline COPD severity (0.38 and 0.52 respiratory viral infections per year in patients with mild obstruction and moderate to severe obstruction, respectively) (147).

Cystic fibrosis. Several studies have examined the effects of respiratory viruses on respiratory exacerbations in CF patients. Among patients with a proven viral etiology, HRV is the most commonly detected pathogen when molecular detection methods are employed; in one study, HRV was detected during 16% of all respiratory exacerbations (154, 155). Unlike other respiratory viruses, including influenza virus, PIV, and RSV, HRV was not associated with decrements in pulmonary function (154). However, the effects of HRV on the lower airways may be species or strain dependent. In a study of 103 Brazilian children with CF tested for respiratory viruses during routine visits or respiratory exacerbations over a 1-year period, HRV-C but not HRV-A or HRV-B was significantly associated with respiratory exacerbations (156).

Health Care-Associated Infections

Data are limited on the frequency and risk factors for the health care-associated transmission of HRV infection, including health care worker (HCW)-to-patient and patient-to-patient transmission, perhaps due to limited methods for HRV detection at facilities that do not use molecular detection methods. Hospital HRV outbreaks have been reported primarily in neonatal ICUs (157–159). In one study, 7 out of 11 infected infants acquired HRV infection during their hospital stay (159). The most common symptoms were respiratory distress, apnea, rhinorrhea, and hypothermia; all infants required respiratory support. Chest radiographs revealed perihilar streakiness, atelectasis, focal consolidation, and hyperinflation.

HRV outbreaks have also been described in long-term-care facilities, where they have been linked to pneumonia, hospitalization, and, rarely, death (128, 129, 160). One of the first studies to report an HRV outbreak described an investigation in a nursing home in rural Wisconsin in 1993. In this elderly population, 66% of residents had lower respiratory signs and symptoms, including productive cough, dyspnea, hoarseness, and abnormalities upon lung auscultation (wheezing, rhonchi, and rales) (161). More recently, using data from an active surveillance network in Ontario, Canada, Longtin et al. identified 297 respiratory disease outbreaks in long-term-care facilities reported to the Ontario Public Health Laboratory from 1 July to 31 December 2009 (160). Among the 234 (79%) outbreaks for which a pathogen was identified, 174 (59%) pathogens were determined to be HRV by using multiplex PCR. Deaths were potentially associated with the HRV outbreak in four facilities. Among the 13 patients who died, 7 had clinical data available; 6 of these 7 patients died from pneumonia/respiratory illness (162). In all of the above-described outbreaks, different strains of HRV were identified.

Although HCWs have a higher risk of acquisition and transmission of respiratory viruses, few studies have thoroughly assessed their role in health care-associated HRV outbreaks. In a 2-year prospective study in Sao Paulo, Brazil, 203 HCWs presenting to the Health Care Worker Medical Assistance Service with acute respiratory illness of a possible viral etiology were tested for a panel of respiratory viruses, including influenza virus (163). HRV testing was performed by using RT-PCR on influenza virus-negative samples. Overall, HRV was the most frequently detected virus (38%). Sixteen of the HRV-infected HCWs, representing 77% of HRV cases, worked with high-risk patients, including immunocompromised and obstetric patients and those with cardiovascular and pulmonary diseases. Another study involving an outbreak of HRV in an intensive care nursery found that 42% and 31% of clinical staff reported upper respiratory symptoms in the previous 4 weeks and 1 week, respectively, preceding the onset of symptoms in the infants (158). Of 29 nasal washes performed in 29 clinical staff, HRV was isolated from one nurse via cell culture; cross-neutralization testing could not confirm if the strain was the same as that isolated from the infected infants.

The U.S. Centers for Disease Control and Prevention Healthcare Infection Control Practices Advisory Committee 2007 guidelines for hospital isolation recommend droplet precautions for patients with HRV infection, with the addition of contact precautions if “copious moist secretions” are present or if close contact is likely to occur (164).

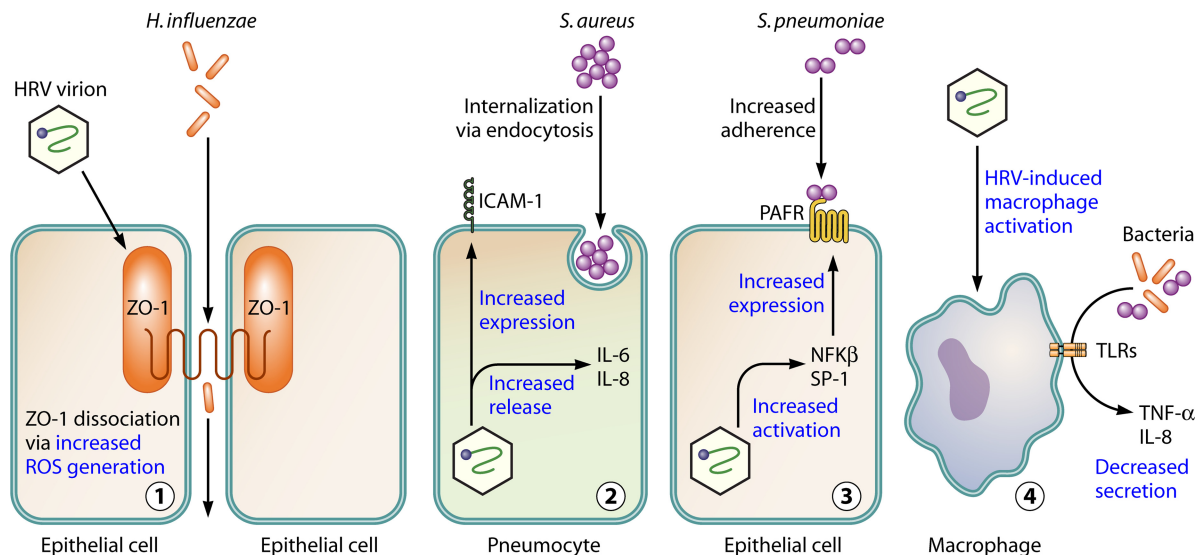


FIG 4 Mechanisms by which HRV increases susceptibility to bacterial infection. (1) HRVs disrupt epithelial cell barrier function by the dissociation of zona occludens 1 (ZO-1) from the tight junction complex via the increased generation of reactive oxygen species (ROS), thereby facilitating the transmigration of bacteria (28). (2) HRVs promote *Staphylococcus aureus* internalization into non-fully permissive cultured pneumocytes via the increased release of IL-6 and IL-8 and expression of intercellular adhesion molecule 1 (ICAM-1) on neighboring uninfected cells (175). (3) HRVs stimulate *Streptococcus pneumoniae* adhesion to human tracheal epithelial cells by inducing the surface expression of platelet-activating factor receptor (PAFR) via NF-κB expression (173) and to nasal epithelial cells via increased gene and protein expression levels of fibronectin, PAFR, and carcinoembryonic antigen-related cell adhesion molecule (174). (4) Compared to non-HRV-activated macrophages, HRV-activated macrophages demonstrate reduced levels of secretion of TNF-α and IL-8 when exposed to bacterial Toll-like receptors (TLRs) (lipopolysaccharide and lipoteichoic acid) (176). SP-1, promoter-specific transcription factor 1.

Clinical Microbiology Correlations

HRV species. Several early reports suggested that HRV-C causes more severe respiratory illness in adults and children as well as more asthma hospitalizations than HRV-A or -B (84, 165, 166). In addition, two recent case reports described systemic HRV-C infection involving BAL and pericardial fluid, plasma, urine, and feces (125, 167). Also of note, when serum specimens from hospitalized children with HRV-associated severe respiratory illness were tested for HRV viremia, 12% of specimens were positive for HRV. Among children with HRV-C infection, 31% were viremic, compared to 3% and 0% of children with HRV-A and HRV-B infections, respectively (168). More recently, however, well-designed studies found that the clinical manifestations and prevalences of lower respiratory tract infection among children with HRV-A and HRV-C infections appear to be similar (90, 122, 169). Whether illness severity is virus or host (e.g., immune status) dependent requires further study.

HRV viral load. The quantification of the HRV viral load may predict disease severity at higher levels. Piralla et al. found that a viral load higher than 10^7 RNA copies/ml in nasopharyngeal aspirate specimens and patient age less than 5 years were independently associated with lower respiratory tract infection among children and adults hospitalized for acute respiratory illness (170). The viral load also correlated with illness severity scores for children more than 11 months old with lower respiratory tract illnesses (171). In other patient populations and clinical settings, however, lower viral loads of 10^3 to 10^4 RNA copies/ml have been variably associated with symptomatic infection (134), and serial measurements are not useful for monitoring illness resolution (172). Furthermore, results from individual studies are difficult to interpret due to differences in real-time PCR methods and sampling techniques, and therefore, they may not be generalizable to

other patient populations and clinical settings. For further discussion of the utility of quantitative real-time RT-PCR as a clinical and research tool, please see “Quantitative real-time RT-PCR” below.

Coinfection with Other Respiratory Pathogens

Bacterial pathogens. Several potential mechanisms through which HRV increases susceptibility to bacterial infection have been demonstrated *in vitro* in epithelial cells of the upper and lower airways (Fig. 4). HRVs stimulate *Streptococcus pneumoniae* adhesion to human tracheal epithelial cells via increases in levels of platelet-activating factor receptors (PAFRs) (173) and to nasal epithelial cells via increased gene and protein expression levels of fibronectin, PAFR, and carcinoembryonic antigen-related cell adhesion molecule (174). HRVs also promote *Staphylococcus aureus* internalization into non-fully permissive cultured pneumocytes (175) and disrupt epithelial cell barrier function by the dissociation of zona occludens 1 from the tight junction complex, thereby facilitating the transmigration of bacteria (28). HRV also impairs immune responses to bacterial products in human alveolar macrophages (176). Compared to non-HRV-activated macrophages, HRV-activated macrophages demonstrate reduced levels of secretion of TNF-α and IL-8 when exposed to bacterial TLRs.

A large ecological study in Finland identified a temporal association between HRV infection in the community and the incidence of invasive pneumococcal disease (IPD) in children (177). Using data from national registries and large epidemiological cohort studies, the authors of that study determined that the mean IPD rates in children less than 5 years old were 2.9 cases per week (95% confidence interval [CI], 2.5 to 3.3) during periods of high-level HRV activity (September to November) and 1.4 (95% CI, 1.2 to 1.6) during periods of low-level HRV activity (April and May)

($P < 0.001$). In comparison, the mean IPD rate was only moderately increased during periods of high- versus low-level RSV activity (2.1 versus 1.7 cases per week; $P = 0.008$) and was unchanged during periods of high- and low-level influenza virus activity.

Viral pathogens. HRV-virus coinfection is common in prospective observational studies; several studies have attempted to elucidate the significance and directionality of this association. Greer et al. (178) showed a statistically significant reduction in HRV-virus codetection compared to other respiratory viruses. Among 1,247 clinical respiratory specimens from all seasons of 2003 tested for 17 respiratory viruses using PCR-based analyses, 131 (11%) contained two or more viruses. HRV was the most commonly detected virus, and 24% of HRV-positive specimens demonstrated virus coinfection. HRV detection was associated with a reduced probability of detection of human adenoviruses, coronaviruses, bocavirus, metapneumovirus, RSV, PIV, influenza A virus, and the KI and WU polyomaviruses. Those authors suggested that the HRV mediation of IFN-stimulating genes may induce a protective antiviral state.

The above-described findings are in contrast to those of Tanner et al., who demonstrated a significant positive association between HRV and PIV, HRV and RSV, and HRV and adenovirus during the 2009 and 2010 winter seasons (179). A negative association was found only between HRV and influenza A virus, which has been observed in other settings (180). These differences may be due to geographical location, seasonality, or the host response and warrant further study. The clinical significance of virus codection is also unknown. In one study, hospitalized children with bronchiolitis with HRV and RSV coinfection had longer hospital stays than those with HRV infection alone or HRV coinfection with non-RSV pathogens (117).

Fungal pathogens. With the exception of immunocompromised hosts, HRV-fungus coinfection has not been described. *Aspergillus* species are the most common fungal pathogens identified in patients with hematological malignancy and HSCT recipients (35, 141) but has not been associated with HRV infection.

LABORATORY DIAGNOSTICS

Specimen Collection and Processing

Specimens should be collected for laboratory diagnosis as soon as possible after the onset of symptoms. HRV titers are highest in the respiratory tract during the first 2 days of presentation, although the virus may be isolated from 1 day before to 6 days after the onset of symptoms (181). For the investigation of upper respiratory tract infections, nasopharyngeal swabs or aspirates rather than oropharyngeal swabs are preferred, with flocked swabs generally yielding higher virus recovery rates than wrapped swabs, especially for adult patients (182). Nasal wash specimens are also a good source of virus for HRV detection (183, 184), although they are suboptimal for some other respiratory viruses and therefore are not recommended unless no other pathogens are being investigated. Swabs should be placed into viral transport medium.

For lower respiratory tract infections, samples may include tracheal or bronchial aspirate, BAL fluid, or, less frequently, lung biopsy specimens. In a recent study, Harvala et al. reported the detection of HRV in approximately 10% of stool samples from hospitalized patients with enteric disease, predominantly from children under the age of 2 years or adults over 65 years of age

(185). In contrast, that study detected HRV in only 1 of 1,500 cerebrospinal fluid (CSF) samples collected from patients with central nervous system disease. However, in general, HRV is not usually suspected of causing infections at other anatomical sites. If respiratory specimens are being transported to an off-site facility, they should be refrigerated and shipped on cold packs, or if delays of more than 2 days are anticipated, they should be frozen at -70°C and shipped on dry ice.

Antigen Detection and Serology

There is no common antigen among HRVs, and an increasingly large number of serotypes have been described; therefore, antigen detection assays are not used for routine detection. Antibodies are measured in both serum and nasal secretions by neutralization, plaque reduction, complement fixation, and enzyme-linked immunosorbent assays (ELISAs) in research settings (104, 186). As with antigen assays, however, the lack of a common antigen across all strains of HRV makes the detection of antibody responses impractical for diagnostic purposes. Furthermore, antibodies are not detectable for 1 to 3 weeks postinfection. Therefore, while antibody measurement is useful for epidemiological studies (187), it is not useful for diagnosing acute infections.

Virus Culture

Conventional virus culture. While well-designed molecular methods are clearly more sensitive for overall detection, HRVs occasionally grow in culture that were otherwise missed due to oligonucleotide mismatches or technical errors. Additionally, cultured isolates are important for studies of virus characteristics and disease pathogenesis (12). HRVs were originally isolated from primary monkey kidney cells, although these cells will support the growth of only some strains (181). Human fetal embryonic lung fibroblast cell lines, certain HeLa cell clones, and human embryonic kidney cell lines are most commonly used for HRV culture in clinical laboratories. In a recent study, HRV-infected susceptible HeLa cells were shown to be a good model compared to HBECs for the study of viral RNA synthesis, translation, protein processing, intracellular protein localization, and disruption of host cell functions (188). In a study of HRV recovery from nasal wash specimens, WI-38 and an HRV-susceptible HeLa clone (with high levels of ICAM-1 expression) were found to be the most sensitive cell types for HRV culture (183). As noted by other investigators (189), those authors suggested a combination of different cell lines as the best approach for the optimal recovery of HRV.

Inoculated cultures are maintained at a neutral pH, since HRVs are acid sensitive (181). Early studies showed enhanced growth with incubation at 33°C rather than at 36°C or 37°C (190, 191). However, a later study demonstrated that for the majority of several serotypes, replication was enhanced only slightly by incubation at the lower temperature and in some instances was equal or better at 37°C (30). Continuous rotation has been demonstrated to provide clear improvements in the detection and virus yields of HRV for many years (192–194).

CPE is usually visible in most cell lines, although CPE-negative strains have been reported (195). Morphological changes are easiest to observe in fibroblast lines and include foci of small and large rounded, refractile cells with pyknotic nuclei and cellular debris (181).

Conventional cultures should be incubated for up to 14 days, and presumptive identification is usually made on the basis of CPE

in appropriate cell lines, although the appearance is the same or very similar to that of enteroviruses (EVs). The viruses are distinguished by acid stability testing: EVs are relatively resistant to low pHs compared to HRV, and a 2- to 3-log reduction in titers after exposure to pH 3.0 will indicate that the virus is HRV (181). A more rapid confirmation method was recently reported, utilizing a combination of staining with a pan-enterovirus reagent which cross-reacts with EV- and HRV-positive cultures and non-cross-reactive EV antibodies (196). Serotyping with specific antisera can be performed with immunofluorescence-labeled antisera but is increasingly being replaced by molecular genotyping (described below).

Rapid culture methods. Rapid culture methods for the detection of infectious HRV have been described. These methods include multichamber slides with HRV-susceptible HeLa cells combined with virus antigen detection using immunofluorescence at 48 h postinfection (197). However, despite reports of a reasonable detection sensitivity compared to that of conventional culture, rapid methods are not commonly used in routine clinical practice. While respiratory screening panels have been developed with pools of labeled antibodies for the simultaneous immunofluorescence detection of many other cultured respiratory agents, HRV is usually not included on the list of detectable viruses (198). Again, the absence of a common antigen makes the development of reliable and specific immunofluorescence reagents difficult. Centrifugation-enhanced cultures can be stained prior to the development of CPE with some EV detection reagents that cross-react with HRV; however, laboratories are left without a specific diagnosis.

A large prospective study reported the use of a centrifugation-enhanced culture method with HuH7 cells in 48-well microplates followed by RT-PCR for HRV on cultures that were CPE positive within 4 days (199). This method had been previously validated for a very large number of HRV genotypes as well as many other respiratory viruses. Over three winter seasons, 4,032 nasal aspirate specimens that had tested negative for respiratory viruses by a direct fluorescence assay were tested for HRV and other respiratory viruses by the rapid culture method, and 272 specimens tested positive for HRV. However, the authors of that study did not report the detection sensitivity compared to that of the direct application of the HRV RT-PCR assay to specimens or how it compared to conventional culture with other cell lines.

Organ culture. Historically, organ cultures of fetal nasal or tracheal epithelia were used to isolate HRVs (200, 201), but these techniques are not used in clinical laboratories. Nasal and tracheal mucosa organ cultures are still used in research settings for pathogenesis research (202), and sinus organ culture has been used to grow an isolate of HRV-C (12).

Molecular Methods

Conventional and real-time RT-PCR. HRVs are somewhat fastidious *in vitro*, and due to the specific conditions required for optimal culture, isolation rates have been generally low except in large reference virology laboratories. Furthermore, since the viruses were believed to cause only “common colds,” most laboratories did not consider the detection and identification of HRV infections worth their time and effort. In the late 1980s, methods for PCR-based assays capable of detecting HRV in primary respiratory samples were reported (203–206). The use of these early molecular tests resulted in an increased HRV detection rate. Al-

though identification had to be confirmed with dideoxy sequencing due to cross-reactivity with human DNA, these tests shortened the time to diagnosis from up to 2 weeks to a few days. However, HRV testing continued to be performed primarily in specialized laboratories under limited clinical circumstances or, for specific studies, for many years.

Multiple RT-PCR and real-time RT-PCR techniques have been developed for the detection of HRV since the late 1980s. In general, most of these assays target the 5'UTR, a region highly conserved among all HRVs and EVs, causing cross-reactivity between assays for the two viruses and making their differentiation difficult. RT-PCR tests that can differentiate HRV from EV by amplicon size (207, 208), restriction fragment length polymorphism (RFLP) (206), hybridization with HRV-specific probes (205), RT-PCR followed by sequencing (209), and real-time RT-PCR (210) have also been reported. Since the International Committee on Taxonomy of Viruses reclassified all HRVs into the EV genus, however, the reporting of diagnostic test results as HRV or EV without further testing has become acceptable.

Quantitative real-time RT-PCR assays. While some reports have indicated a correlation between higher viral loads and symptomatic disease (172, 211), which makes quantitative testing attractive for verifying the clinical relevance of positive results, there are currently no commercially available quantitative molecular HRV tests. Additionally, due to the intertypic variability of HRV, there is no standard for the quantification of all HRV types, although some studies have used a chimeric HRV internal standard to limit assay variability between types (212). Other challenges that arise when attempting to provide an accurate and relevant quantification include factors such as the sample type and collection procedure, test methodology, age of the patient, and immune status. All these factors affect viral load and the potential standardization of assays and collectively impact the clinical interpretation of quantitative HRV data such that generally applicable guidelines are not feasible with any reasonable level of confidence.

Additional amplification techniques. Isothermal and other nucleic acid amplification chemistries, in addition to RT-PCR, have also been employed for the molecular detection of HRV. In clinical laboratories, the most commonly used of the alternative chemistries is nucleic acid sequence-based amplification (NASBA). First developed in the late 1990s (213), NASBA assays for HRV were improved several years later by the generation of additional sequence data and appropriate changes to primers (214). A clinical evaluation showed a performance comparable to that of RT-PCR and a sensitivity superior to that of culture, with sensitivity and specificity values of 85.1% and 98.3%, respectively, for the NASBA assay and 82.9% and 93.4%, respectively, for RT-PCR (215). Recently, a quantitative real-time NASBA assay using molecular beacon probes was reported (216), which provides a simplified format and the additional benefit of viral load assessment. However, reports on its clinical evaluation have not yet been published.

Respiratory virus detection panels. With the expanding number of highly multiplexed respiratory virus detection arrays available in recent years and their increasing simplicity of operation, respiratory virus detection has entered a new era (217). Numerous agents that previously could be tested at only a few sophisticated molecular laboratories can now be detected rapidly in most microbiology facilities. As data accumulated on the involvement of HRV in more serious clinical disease, the importance of the inclu-

sion of assays for the virus in these new panels became clear. In turn, as these new assays have been introduced into clinical practice, more data have emerged on the high incidence of HRV infection, resulting in the further awareness of the widespread and sometimes serious disease manifestations. Additionally, some HRVs, such as the group C viruses, are uncultivable by routine culture techniques. Many studies have now demonstrated that HRV infection can lead to an influenza-like illness, lower respiratory tract infections, chronic infections, and secondary bacterial infections, especially in immunocompromised patients (132), children with asthma (218–221), and adults with COPD (152).

Genotyping. HRVs were originally characterized by their growth patterns in human embryonic and monkey kidney cells (222, 223). However, this system demonstrated limited use, since growth characteristics changed with time *in vitro* (224). A subsequent classification system, based on cell receptors, divided HRVs into a major group that utilizes ICAM and a minor group that utilizes LDL (225). An additional system grouped 100 HRV types into 2 groups, designated groups A and B, based on the activities of 15 antiviral compounds (226, 227). Serotyping was also attempted but, due to the large amount of cross-reactivity, did not produce a clear delineation between types.

Since the discovery of PCR in the 1980s, multiple investigators have employed PCR to amplify different genes and nontranslated regions, to further characterize HRV. Three groups of HRVs are now genetically distinguished: group A, group B, and the more recently discovered group C (9). This characterization is best demonstrated by the amplification and sequence analysis of either the VP1 (91) or VP4 (208) gene of the virus. While VP4 sequence data are generally more easily obtained and readily distinguish different HRV groups, the VP1 sequence usually provides more powerful data for HRV strain comparisons of viruses within a group. Sequence analysis can be performed on other regions in the HRV genome, such as the RNA-dependent RNA polymerase (3D) gene and the 5'UTR. However, while analyses of these regions can differentiate groups A, B, and C, they do not have the power to distinguish related strains within the same genetic group.

The motivations for genetic characterizations of HRV include outbreak source determinations and investigations of relatedness or the emergence of a previously uncharacterized strain. In laboratories that perform phylogenetic analyses, RT-PCR amplification and sequence analysis of either the VP1 or VP4 gene are commonly used for this purpose.

Whole-genome sequencing. In 2009, the full-length genomic sequences of all known human HRV serotypes, including the group C viruses, were published (8). A recently updated phylogenetic tree, generated from full-genome HRV sequences, is shown in Fig. 5 (228). This work has harmonized genetic characterizations and provided a reference for the comparison of multiple gene sequences and the determination of type for all subsequently detected HRVs. The importance of full-length genomic sequencing has become increasingly evident with recent studies that demonstrated HRV recombination (229, 230). In such cases, the HRV type determined based on one specific gene would be misleading.

With the increasing availability of techniques for whole-genome sequencing (WGS), it is feasible that more laboratories could perform these methods on clinical isolates of HRV. The increased volume of WGS data will help identify additional genomic regions for analysis. Furthermore, it could provide a bet-

ter understanding of HRV evolutionary changes, including recombination (229, 230), and help us understand what makes strains of HRV more virulent, prone to causing chronic infections, exhibit tropism for certain tissues or cell types, or target patients with particular underlying conditions or genetic predispositions for more severe outcomes.

ANTIVIRAL AGENTS

Table 1 summarizes the outcomes of clinical trials of agents for HRV/enterovirus prevention and treatment.

Capsid-Binding Agents

The viral capsid was one of the first viral proteins targeted for the development of inhibitors of viral replication. These compounds bind to the hydrophobic pocket of the viral capsid, inducing a conformational change that increases the stability of the virion and interferes with its ability to interact with the cellular receptor (231). Selection for drug resistance is of concern among this class of agents due to the error-prone nature of the viral polymerase and variable conservation of the viral structural proteins (231). To reduce the risk of resistance, the combined use of antiviral therapies with different mechanisms of action may be a useful strategy (232).

Pleconaril. Pleconaril has 70% bioavailability, a long half-life, and good central nervous system penetration, making it an attractive therapy for EV infections (233). A case series of 38 patients treated under a compassionate plea with pleconaril showed that 78% had favorable clinical responses. Clinical syndromes included chronic enterovirus meningoencephalitis and agammaglobulinemia or hypogammaglobulinemia, neonatal enterovirus sepsis, myocarditis, vaccine-associated or wild-type poliovirus infection, postpolio muscular atrophy syndrome, or enterovirus encephalitis as well as bone marrow transplant patients infected with EV (234).

The most rigorous studies of pleconaril were conducted with patients with respiratory illnesses. Two phase 3 multicenter studies in the United States and Canada randomized 2,096 healthy subjects with self-diagnosed colds into groups receiving pleconaril at 400 mg orally twice daily or matching placebo for 5 days. The primary endpoint was the duration of illness. In the primary-efficacy population, which included 1,363 subjects with picornavirus RNA detected in nasal mucus, pleconaril-treated subjects experienced a 1-day reduction in the duration of illness (7.3 days versus 6.3 days; $P < 0.001$) compared to the placebo group (235). In subsequent analyses of subjects with cultivable picornavirus at baseline, pleconaril treatment was associated with a more rapid loss of cultivable virus. In addition, pleconaril-treated subjects infected with more highly susceptible viruses experienced a greater reduction in the duration of symptoms than subjects with reduced viral susceptibility (236). Despite these results, the Food and Drug Administration declined to license pleconaril due to concerns about resistance and safety, including interactions with hormonal contraception and drugs used to treat HIV (233, 237). Pleconaril was subsequently developed into a nasal spray. A phase 2 study evaluating the efficacy of pleconaril nasal spray in preventing asthma exacerbations and common cold symptoms was completed in 2007; results have not yet been disclosed (ClinicalTrials.gov identifier NCT00394914 [<http://www.clinicaltrials.gov/> {accessed 20 September 2012}]).

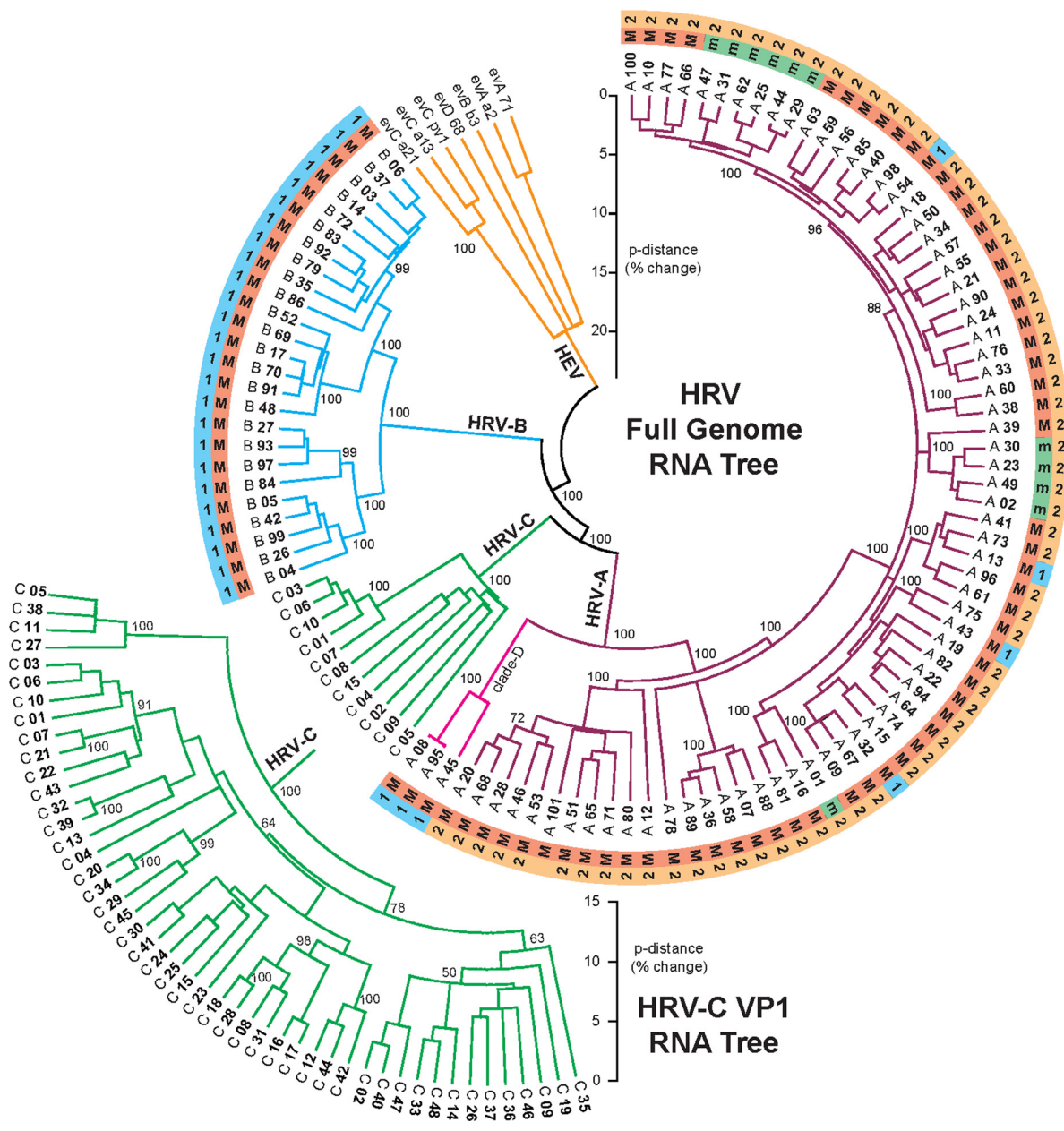


FIG 5 Phylogenetic tree. Shown are circle phylogram relationships for known genotypes of HRV-A, HRV-B, and HRV-C. The tree was calculated with neighbor-joining methods from aligned, full-genome RNA sequences and rooted with data for human enterovirus species A, B, and C. The outer ring ("1" or "2") indicates anticapsid drug group types, if known. The inner ring shows members of the major ("M") (ICAM-1) and minor ("m") (LDLR) receptor groups. The HRV-C receptor is unknown. Since few HRV-C strains are fully sequenced, the determination of relationships among these genotypes relies on partial VP1 RNA data (bottom left). Bootstrap values (percentages of 2,000 replicates) are indicated at key nodes. (Reprinted from reference 228 with permission of Wolters Kluwer Health/Lippincott Williams & Wilkins.)

Vapendavir. Vapendavir is a novel orally administered investigational agent that binds to the HRV VP1 capsid protein, thus preventing the release of viral RNA into the target cell. Vapendavir exhibits antiviral activity against known HRV-A and HRV-B serotypes as well as selected EVs; activity against HRV-C has not yet been established. In a phase 2a clinical trial with healthy volunteers inoculated with HRV-39 2 days after randomization into vapendavir treatment or placebo groups, vapendavir was well tolerated and reduced the incidence of HRV and the peak viral load (238). A phase 2b treatment study with asthmatic adults to assess

the effect of vapendavir on URI symptom severity and asthma exacerbations was recently completed; results have not yet been disclosed (ClinicalTrials.gov identifier NCT01175226 [<http://www.clinicaltrials.gov/>] {accessed 20 September 2012})).

Pirodavir. Pirodavir is an intranasal capsid-binding agent that reached phase 3 clinical trials for HRV prevention and treatment in the 1990s. Although the compound decreased viral replication and shedding, it failed to show a significant reduction in the duration or severity of symptoms (239, 240). The development of pirodavir has been discontinued (241).

TABLE 1 Agents for HRV/enterovirus prevention and treatment^b

Drug or therapy	Mechanism of action	Formulation	Study objective(s) ^a	Status	Result(s)	Comments	Source or reference(s)
Vapendavir	Capsid binder	Oral	Prevention of asthma exacerbations and reduction in URI symptom severity and duration	Phase 2b completed	Results not yet disclosed		ClinicalTrials.gov
Pleconantril	Capsid binder	Oral	Treatment of natural HRV colds	Phase 3 completed	1-day reduction in illness duration compared to placebo	U.S. FDA licensing withheld due to safety concerns	233, 236
Pirodavir	Capsid binder	Intranasal spray	Prevention of exptl HRV colds; treatment of exptl and natural HRV colds	Phase 3 completed	For prevention, reduced HRV infection rates when administered 6 times daily but not when given 3 times daily; for treatment, no difference in symptom severity or duration	Compound development discontinued	239, 240
Ruprintivir	3C protease inhibitor	Intranasal spray	Prevention and treatment of exptl HRV infection	Phase 2 completed	For prevention, reduced frequency of positive viral cultures but not of colds; for treatment, reduced symptom severity by 33%	No effect on viral load or symptom severity in natural HRV infection (data not reported)	242
IFN- α 2, IFN- β	Immunomodulatory and possible mediation of viral replication	Intranasal spray or drops	Prevention and treatment of exptl and natural HRV colds	Studies completed	For prevention, reduced HRV colds using IFN- α 2, no benefit using IFN- β ; for treatment, no difference in symptom severity or duration	Limited use as prophylaxis due to nasal irritation and nasal mucosal friability and bleeding	246, 274–278
<i>Echinacea</i>	Immunomodulatory	Oral	Prevention and treatment of exptl and natural HRV colds in adults and children	Phase 3 completed	For prevention, no reduction in HRV infection rates; for treatment, majority of studies showed no reduction in symptom severity or duration using various <i>Echinacea</i> extracts	EMA approved <i>E. purpurea</i> for treatment of respiratory tract infections in 2010	248–254
Vitamin C	Antioxidant	Oral	Prevention and treatment of natural colds in adults and children	Phase 3 completed	For prevention, no reduction in HRV colds; for treatment, modest reduction in symptom severity and duration	Treatment benefit may be limited to higher doses of vitamin C and to subjects undergoing brief physical stress	281
Zinc	Unknown ^c	Oral	Prevention and treatment of natural colds in adults and children	Phase 3 completed	For prevention, reduced cold incidence, school absenteeism, and antibiotic prescriptions in children; for treatment, reduced symptom severity and duration when taken within 24 h of symptom onset	Optimal dosages, formulation, and duration are unknown; side effects of zinc lozenges include bad taste and nausea	261
Antihistamines	H ₁ receptor inverse agonist	Oral	Treatment of exptl and natural HRV colds	Phase 3 completed	Reduced sneezing and rhinorrhea with no change in total symptom severity scores	Use limited by side effects of dry eyes, nose, and mouth; generally not recommended for treatment of HRV colds	263–265
Tremacamra	Recombinant sICAM-1	Intranasal spray or inhaled powder	Treatment of exptl HRV infection	Study completed	Reduced symptom severity and nasal mucus wt	Potential concerns of 6-times-daily administration affecting adherence and antibody response to sICAM-1; no further development currently reported	284
Enviroxime	Unknown; targets protein 3A	Intranasal spray or oral	Prevention of exptl HRV infection; treatment of exptl and natural HRV colds	Phase 2 completed	For prevention, no reduction in HRV infection; for treatment, no difference in symptom severity or wt of nasal secretions	Oral formulation with gastrointestinal side effects; lack of response to intranasal spray may be due to inconsistent drug levels	285–288

^a All agents were evaluated in adults only unless otherwise specified.^b HRV, human rhinovirus; FDA, Food and Drug Administration; ICAM-1, intercellular adhesion molecule 1; sICAM-1, soluble ICAM-1; IFN, interferon; EMA, European Medicines Agency.^c See the text.

Proteolytic Enzyme Inhibitors

Rupintrivir. A virally encoded enzyme, 3C protease, cleaves viral proteins from precursor polypeptides and is essential for viral replication and the assembly of the virion. Rupintrivir was one of the most potent compounds to inhibit 3C protease *in vitro* and was active against a broad panel of HRVs and EVs. In an HRV challenge trial, rupintrivir was well tolerated and reduced viral loads and respiratory symptoms (242). However, in trials of natural infection, rupintrivir did not significantly affect viral loads and symptom severity (243).

Alpha-2 Interferon

Interferons have antiviral, antiproliferative, and immunological effects that impact host cell susceptibility to infection. All of these effects are mediated through cell receptor signal transduction pathways (244). Although intranasal IFN- α 2 has shown some benefit for the prevention of HRV colds, studies focusing on treatment have yielded equivocal results. Hayden and Gwaltney randomized healthy adult volunteers to receive recombinant IFN- α 2 or placebo via intranasal spray or drops 28 h after experimental HRV infection. Both treatment modalities were associated with significant reductions in the quantity and duration of viral shedding; however, only nasal drops were associated with a significant albeit modest reduction in nasal symptom scores on days 2 and 3 only after viral challenge (245). Subsequently, a placebo-controlled trial using two different doses of recombinant IFN- α 2b nasal spray was performed with subjects with naturally occurring colds to determine the effect of interferon after symptoms are established as well as household transmission rates. The treatment arms showed no benefit for symptom severity or duration. In fact, subjects receiving the higher dose of interferon nasal spray experienced a longer duration of symptoms and more severe sore throat and nasal congestion, likely a toxicity of the treatment (246). Given the limited clinical benefit and the side effects, including nasal mucosal bleeding, intranasal interferon has not been adopted as a therapy for HRV infections.

Echinacea

Echinacea preparations are among the most widely used herbal medicines. Preparations include mainly the leaves and roots of dried or fresh *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida* and are manufactured by using a range of extraction methods. Chemical constituents that may be important in *Echinacea* health effects include alkylamides, polysaccharides, and caffeic acid derivatives. *Echinacea* is best known for its immune effects, including the stimulation of macrophages, other monocytes, and natural killer cells. Despite the *in vitro* demonstration of immunomodulatory properties, human clinical trials of *Echinacea* therapy for experimental and natural clinical colds yielded conflicting results (247). When healthy volunteers were challenged with HRV-39, three different *E. angustifolia* extracts did not affect rates of infection or symptom severity compared to placebo (248). Among 282 healthy adults with common cold symptoms randomized in a double-blind fashion to treatment with *E. purpurea* extract or placebo, total daily symptom scores were 23% lower in subjects treated with *Echinacea* than in subjects treated with placebo (249). However, in two similarly well-designed studies of children and college students using a dried extract of *E. purpurea* juice of the herb and a dried mixture of *E. angustifolia* root, respectively, *E. purpurea* root and *E. purpurea* herb failed to show a

reduction in URI symptom severity or duration (250, 251). More recently, a trial of *E. purpurea* and *E. angustifolia* root extract for the treatment of common cold symptoms employed a two-way factorial design, randomizing subjects into groups with various degrees of clinical interactions and with no pills, blinded placebo, blinded *Echinacea*, or unblinded open-label *Echinacea*. That study found a nonstatistically significant trend toward reduced symptom severity and duration in subjects assigned to the *Echinacea* treatment group (252).

Explanations for the conflicting study results include variations in extracts, medication regimens, and study design, including the timing of administration relative to the onset of symptoms. A Cochrane review concluded that despite some studies that showed a benefit, there is no conclusive evidence that *Echinacea* products effectively treat or prevent the common cold (253). That review cited concerns about publication bias, poor study quality, and the variability of study results. The European Medicines Agency Committee on Herbal Medicinal Products recently assessed *in vitro* and *in vivo* pharmacological and clinical data for *E. purpurea* root and herb, *E. pallida* root, and *E. angustifolia* root for the prevention and treatment of respiratory infections. The committee concluded that herbal drug preparations of *E. purpurea* can be considered safe and effective for the treatment of respiratory tract infections. However, there are insufficient pharmacological and/or clinical data to support the efficacy and clinical use of *E. purpurea*, *E. pallida*, and *E. angustifolia* root (254–256). The U.S. Food and Drug Administration has not evaluated *Echinacea* for safety and efficacy.

Zinc

Zinc has activity against HRVs, although its exact mechanism of action is unknown. Zinc has been shown to inhibit viral replication *in vitro* (257), block HRV binding to ICAM-1 molecules (258), alter the configuration of viral capsid proteins to prevent their role in proteolysis and virus assembly (259), and decrease histamine release (260). A recent Cochrane review included 966 subjects from 13 randomized controlled trials in which all subjects began zinc therapy within 3 days of the onset of symptoms and continued treatment for at least 5 days (261). Formulations included zinc sulfate tablets, zinc sulfate syrup, or zinc gluconate or zinc acetate lozenges. The authors of that study found that zinc supplementation within 24 h of the onset of a cold was associated with significantly reduced symptom severity and duration. Another systematic review and meta-analysis similarly showed a dose-dependent reduction in the duration of symptoms among subjects exposed to zinc (262). However, the benefits were limited to adults, and zinc did not impact symptom severity. Significant trial heterogeneity and a lack of adequate blinding may contribute to the different conclusions of the reviews. When utilized for prevention, zinc supplementation for at least 5 months was associated with reduced cold incidences, school absenteeism, and antibiotic prescriptions in children (261).

Antihistamines

First-generation (i.e., nonselective) antihistamines, including clemastine fumarate and brompheniramine maleate, were evaluated in the 1990s for the treatment of experimental HRV colds. In two separate randomized, placebo-controlled trials of adult subjects with experimental HRV infection, clemastine and brompheniramine reduced sneeze scores and rhinorrhea scores by up to

50% and 62%, respectively, compared to placebo when administered daily for 4 days (263, 264). However, neither the severity of other cold symptoms, including cough, nasal obstruction, and sore throat, nor the total symptom severity scores were significantly different between groups. A Cochrane review of 32 trials confirmed a mild effect of first-generation antihistamines on rhinorrhea and sneezing, but this benefit was not replicated with nonsedating antihistamines (265). Furthermore, in clinical practice, their use is limited by side effects such as dry eyes, nose, and mouth.

Other Agents

Tremacamra, targeting recombinant soluble ICAM-1, and enviroxime, with an unknown mechanism, are two compounds evaluated for HRV prevention and treatment that failed to show a benefit in clinical trials. More information on these agents is available in Table 1.

PREVENTION

Potential modes of person-to-person HRV transmission include small-particle aerosols, large-particle aerosols (18), and contact spread either directly or through a fomite (13, 15). Behavioral strategies to reduce respiratory viral transmission include social distancing, the use of respiratory masks, and hand hygiene. Efforts to develop prophylactic medications and vaccinations specifically for HRV prevention have been unsuccessful.

Social Distancing and Respiratory Masks

Behavioral strategies such as social distancing and respiratory mask application have been evaluated primarily in the context of pandemic influenza A virus and influenza-like illness prevention. Social distancing includes school closures and the avoidance of public gatherings. An assessment of the effectiveness of social distancing in real-world settings is challenging due to the lack of randomization, inadequate reporting, and changing interventions over time (266, 267). Broderick et al. evaluated febrile respiratory illness (FRI) transmission rates in a military training setting where some units were open to potentially infectious convalescents and some units were closed to the entry of potentially infected individuals (268). They found that there was no significant difference in FRI rates between open and closed units; however, any effect of social distancing may have been mitigated by the finding that there was also considerable environmental pathogen contamination in the housing units. Such studies highlight the complexity of systematic evaluations of population-based interventions in natural settings, rather than disprove their efficacy. Indeed, computer simulations have demonstrated that social distancing can be an effective public health prevention measure, reducing epidemic attack rates by as much as 90%, depending on the infectivity of the pathogen (269, 270). The use of masks, particularly among health care workers, is an established effective intervention to reduce respiratory virus transmission (266). It remains uncertain whether N95 respirators confer additional protection over surgical masks, and the degree of difference may vary by pathogen. A well-designed randomized controlled trial designed to show non-inferiority found that surgical masks offer protection similar to that of N95 respirators among nurses at the highest risk for exposure to influenza virus (271).

Hand Hygiene

Hand-to-hand HRV transmission appears to be highly efficient, and individuals may also self-inoculate if a contaminated hand contacts nasal secretions. Therefore, the interruption of direct contact in viral transmission presents a potential target for intervention. In a series of experiments with healthy volunteers challenged with HRV-39 on the fingertips, Turner et al. demonstrated that ethanol hand sanitizer was more effective than soap and water in removing detectable virus from the hand (the efficacy rate for the ethanol group of 80%, versus 31% for the group using soap and water) and that the addition of organic acids (2% malic acid and 2% citric acid in a 70% solution of ethanol) provided additional virucidal activity that persisted for at least 4 h (272).

In order to evaluate the efficacy of hand disinfection on HRV prevention in the natural setting, Turner et al. (273) conducted an unblinded, randomized trial with 212 healthy young-adult volunteers. The hand treatment contained 2% citric acid and 2% malic acid in 62% ethanol and was applied every 3 h for 9 weeks during the fall of 2009. In both the intention-to-treat and per-protocol analyses, there was no difference between treatment groups in the primary endpoint, HRV-associated illness, or the secondary endpoint, the incidence of HRV infection. Despite evidence supporting virucidal hand treatments for HRV prevention in the experimental setting, those authors provided several potential explanations for the discrepancy in the results: a lack of control in the natural setting for variables such as compliance and modes of transmission, potential protective effects of nasal secretions, and the potential for routes of virus transmission other than direct-contact self-inoculation. Nonetheless, a systematic review of physical interventions to reduce the transmission of respiratory viruses found that hand washing with or without antiseptic was effective (266). The results were most robust for children, who are least capable of performing hygienic behaviors by themselves.

Alpha-2 and Beta Interferons

Several studies in the 1980s demonstrated that intranasal IFN- α 2 reduced respiratory illness when administered either continuously during a respiratory virus season or intermittently as post-exposure prophylaxis in the family setting (274–276). However, local adverse reactions, including nasal irritation, mucosal friability, and bleeding, have limited its use (275, 276). In one study, IFN- β serine appeared to be better tolerated (277); however, a follow-up prophylaxis study in the natural setting failed to show a benefit of IFN- β serine compared to placebo (278).

Echinacea

Several double-blinded, placebo-controlled studies have found that different preparations of *Echinacea* are ineffective for the prevention of HRV infection or the development of HRV colds (248, 279, 280). A 2009 Cochrane review of *Echinacea* for prophylaxis and treatment including three prevention trials in the natural setting confirmed these negative findings (253).

Vitamin C

Vitamin C has been studied for the prevention and treatment of the common cold since 1942 and has been marketed as such since the 1970s. As an antioxidant, vitamin C may protect against the generation of oxidative stress during infections; in animal studies, vitamin C reduces the incidence and severity of bacterial and viral infections. The belief that these benefits extend to human subjects

has existed for many years. In 2010, the Cochrane Library conducted a systematic review and meta-analysis of vitamin C for the prevention and treatment of the common cold (281). Only placebo-controlled trials using doses of 0.2 mg/day vitamin C were included. Twenty-nine trials including more than 11,000 subjects found no difference in the incidences of colds between subjects treated with vitamin C and those given placebo; however, the duration and severity of colds were reduced albeit modestly. Of note, the benefit was most pronounced in subjects undergoing brief periods of high physical stress, e.g., marathon runners. Seven therapeutic trials showed no difference in the severity or duration of symptoms, with the exception of one trial showing that high-dose vitamin C (8 g/day) was associated with more “short” colds (symptom duration of <1 day) than lower-dose vitamin C (4 g/day).

Vaccination

To date, there have been no HRV vaccines evaluated in clinical trials. Challenges to vaccine development include the presence of more than 100 different HRV serotypes, the lack of epidemiological data to identify the most commonly circulating HRV strains, the incomplete understanding of antigenic differences between the recently discovered HRV-C species and known serotypes, and limited animal models of HRV infection to understand viral pathogenesis (282). Effective vaccine development calls for the elucidation of antigenic epitopes common to most known HRV serotypes to induce the production of cross-reactive antibodies (53). Recent work has focused on deriving antigenic peptides from one of the viral capsid proteins, VP1, which plays a central role in receptor binding and subsequent epithelial cell infection and is recognized by HRV-neutralizing antibodies (283). However, no studies have moved beyond the *in vitro* phase; due to the challenges noted above, we are still far from clinical vaccine development.

CONCLUSIONS

Substantial advances in the field of HRV research have occurred in the last decade, due primarily to improvements in molecular diagnostics. HRV is not just a cause of benign upper respiratory illness; rather, it is a significant lower respiratory tract pathogen in patients with chronic pulmonary disease, children, and immunocompromised hosts. Our understanding of HRV pathogenesis, drawn largely from *in vitro* data and *in vivo* studies of experimental infection of healthy adults, implicates both direct viral effects and tissue damage due to the host immune response. The recently published full-length genomic sequences of all known HRV serotypes, including the group C viruses, will facilitate characterizations of HRV strains detected in the future. Additionally, whole-genome sequencing may provide insight into the observed differences in clinical symptoms and outcomes according to the HRV strain. There is also a need to identify other modifiable risk factors for the acquisition and severity of HRV infection. A better understanding of the mechanisms leading to manifestations of HRV infection and the role of the host immune response is needed to guide future efforts at HRV prevention and treatment.

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REFERENCES

- Nichol KL, D’Heilly S, Ehlinger E. 2005. Colds and influenza-like illnesses in university students: impact on health, academic and work performance, and health care use. *Clin. Infect. Dis.* 40:1263–1270.
- Roelen CAM, Koopmans PC, Notenbomer A, Groothoff JW. 2011. Job satisfaction and short sickness absence due to the common cold. *Work* 39:305–313.
- Bertino JS. 2002. Cost burden of viral respiratory infections: issues for formulary decision makers. *Am. J. Med.* 112:42S–49S. doi:10.1016/S0002-9343(01)01063-4.
- Fendrick AM, Monto AS, Nightengale B, Sarnes M. 2003. The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch. Intern. Med.* 163:487–494.
- Pappas DE, Hendley JO, Hayden FG, Winther B. 2008. Symptom profile of common colds in school-aged children. *Pediatr. Infect. Dis. J.* 27:8–11.
- Palmenberg A, Rathe J, Liggett S. 2010. Analysis of the complete genome sequences of human rhinovirus. *J. Allergy Clin. Immunol.* 125:1190–1201.
- Fuchs R, Blaas D. 2010. Uncoating of human rhinoviruses. *Rev. Med. Virol.* 20:281–297.
- Palmenberg AC, Spiro D, Kuzmickas R, Wang S, Djikeng A, Rathe JA, Fraser-Liggett CM, Liggett SB. 2009. Sequencing and analyses of all known human rhinovirus genomes reveal structure and evolution. *Science* 324:55–59.
- Lamson D, Renwick N, Kapoor V, Liu Z, Palacios G, Ju J, Dean A, St George K, Briese T, Lipkin WI. 2006. MassTag polymerase-chain-reaction detection of respiratory pathogens, including a new rhinovirus genotype, that caused influenza-like illness in New York State during 2004–2005. *J. Infect. Dis.* 194:1398–1402.
- Bochkov YA, Gern JE. 2012. Clinical and molecular features of human rhinovirus C. *Microbes Infect.* 14:485–494.
- Simmonds P, McIntyre C, Savolainen-Kopra C, Tapparel C, Mackay IM, Hovi T. 2010. Proposals for the classification of human rhinovirus species C into genotypically assigned types. *J. Gen. Virol.* 91:2409–2419.
- Bochkov YA, Palmenberg AC, Lee W-M, Rathe JA, Amineva SP, Sun X, Pasic TR, Jarjour NN, Liggett SB, Gern JE. 2011. Molecular modeling, organ culture and reverse genetics for a newly identified human rhinovirus C. *Nat. Med.* 17:627–632.
- Hendley JO, Gwaltney JM. 1988. Mechanisms of transmission of rhinovirus infections. *Epidemiol. Rev.* 10:243–258.
- Jennings LC, Dick EC. 1987. Transmission and control of rhinovirus colds. *Eur. J. Epidemiol.* 3:327–335.
- Gwaltney JM, Moskalski PB, Hendley JO. 1978. Hand-to-hand transmission of rhinovirus colds. *Ann. Intern. Med.* 88:463–467.
- D’Alessio D, Peterson J, Dick C, Dick E. 1976. Transmission of experimental rhinovirus colds in volunteer married couples. *J. Infect. Dis.* 133:28–36.
- Hendley J, Wenzel R, Gwaltney JM, Jr. 1973. Transmission of rhinovirus colds by self-inoculation. *N. Engl. J. Med.* 288:1361–1364.
- Dick EC, Jennings LC, Mink KA, Wartgow CD, Inhorn SL. 1987. Aerosol transmission of rhinovirus colds. *J. Infect. Dis.* 156:442–448.
- Winther B, Gwaltney JM, Mygind N, Turner RB, Hendley JO. 1986. Sites of rhinovirus recovery after point inoculation of the upper airway. *JAMA* 256:1763–1767.
- Winther B. 2011. Rhinovirus infections in the upper airway. *Proc. Am. Thorac. Soc.* 8:79–89.
- Arruda E, Boyle TR, Winther B, Pevear DC, Gwaltney JM, Hayden FG. 1995. Localization of human rhinovirus replication in the upper respiratory tract by *in situ* hybridization. *J. Infect. Dis.* 171:1329–1333.
- Winther B, Greve JM, Gwaltney JM, Innes DJ, Eastham JR, McClelland A, Hendley JO. 1997. Surface expression of intercellular adhesion molecule 1 on epithelial cells in the human adenoid. *J. Infect. Dis.* 176:523–525.
- Papi A, Johnston SL. 1999. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF- κ B-mediated transcription. *J. Biol. Chem.* 274:9707–9720.
- Whiteman SC, Bianco A, Knight RA, Spiteri MA. 2003. Human rhinovirus selectively modulates membranous and soluble forms of its intercellular adhesion molecule-1 (ICAM-1) receptor to promote epithelial cell infectivity. *J. Biol. Chem.* 278:11954–11961.
- Winther B, Arruda E, Witek TJ, Marlin SD, Tsianko MM, Innes DJ,

- Hayden FG. 2002. Expression of ICAM-1 in nasal epithelium and levels of soluble ICAM-1 in nasal lavage fluid during human experimental rhinovirus infection. *Arch. Otolaryngol. Head Neck Surg.* 128:131–136.
26. Winther B, Brofeldt S, Christensen B, Mygind N. 1984. Light and scanning electron microscopy of nasal biopsy material from patients with naturally acquired common colds. *Acta Otolaryngol.* 97:309–318.
 27. Turner RB, Hendley JO, Gwaltney JM. 1982. Shedding of infected ciliated epithelial cells in rhinovirus colds. *J. Infect. Dis.* 145:849–853.
 28. Sajjan U, Wang Q, Zhao Y, Gruenert DC, Hershenson MB. 2008. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. *Am. J. Respir. Crit. Care Med.* 178:1271–1281.
 29. Kennedy JL, Turner RB, Braciale T, Heymann PW, Borish L. 2012. Pathogenesis of rhinovirus infection. *Curr. Opin. Virol.* 2:287–293.
 30. Papadopoulos NG, Sanderson G, Hunter J, Johnston SL. 1999. Rhinoviruses replicate effectively at lower airway temperatures. *J. Med. Virol.* 58:100–104.
 31. Papadopoulos NG, Bates PJ, Bardin PG, Papi A, Leir SH, Fraenkel DJ, Meyer J, Lackie PM, Sanderson G, Holgate ST, Johnston SL. 2000. Rhinoviruses infect the lower airways. *J. Infect. Dis.* 181:1875–1884.
 32. Gern JE, Galagan DM, Jarjour NN, Dick EC, Busse WW. 1997. Detection of rhinovirus RNA in lower airway cells during experimentally induced infection. *Am. J. Respir. Crit. Care Med.* 155:1159–1161.
 33. Blair HT, Greenberg SB, Stevens PM, Bilunos PA, Couch RB. 1976. Effects of rhinovirus infection of pulmonary function of healthy human volunteers. *Am. Rev. Respir. Dis.* 114:95–102.
 34. Gutman JA, Peck AJ, Kuypers J, Boeckh M. 2007. Rhinovirus as a cause of fatal lower respiratory tract infection in adult stem cell transplantation patients: a report of two cases. *Bone Marrow Transplant.* 40:809–811.
 35. Ghosh S, Champlin R, Couch R. 1999. Rhinovirus infections in myelo-suppressed adult blood and marrow transplant recipients. *Clin. Infect. Dis.* 29:528–532.
 36. Malcolm E, Arruda E, Hayden FG, Kaiser L. 2001. Clinical features of patients with acute respiratory illness and rhinovirus in their bronchoalveolar lavages. *J. Clin. Virol.* 21:9–16.
 37. Imakita M, Shiraki K, Yutani C, Ishibashi-Ueda H. 2000. Pneumonia caused by rhinovirus. *Clin. Infect. Dis.* 30:611–612.
 38. Triantafyllou K, Vakakis E, Richer EAJ, Evans GL, Villiers JP, Triantafyllou M. 2011. Human rhinovirus recognition in non-immune cells is mediated by Toll-like receptors and MDA5, which trigger a synergistic pro-inflammatory immune response. *Virulence* 2:22–29.
 39. Slater L, Bartlett NW, Haas JJ, Zhu J, Message SD, Walton RP, Sykes A, Dahdaleh S, Clarke DL, Belvisi MG, Kon OM, Fujita T, Jeffery PK, Johnston SL, Edwards MR. 2010. Co-ordinated role of TLR3, RIG-I and MDA5 in the innate response to rhinovirus in bronchial epithelium. *PLoS Pathog.* 6:e1001178. doi:10.1371/journal.ppat.1001178.
 40. Turner RB, Weingand KW, Yeh CH, Leedy DW. 1998. Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds. *Clin. Infect. Dis.* 26:840–846.
 41. Johnston SL, Papi A, Bates PJ, Mastroratte JG, Monick MM, Hunninghake GW. 1998. Low grade rhinovirus infection induces a prolonged release of IL-8 in pulmonary epithelium. *J. Immunol.* 160:6172–6181.
 42. Zhu Z, Tang W, Gwaltney JM, Jr, Wu Y, Elias JA. 1997. Rhinovirus stimulation of interleukin-8 *in vivo* and *in vitro*: role of NF- κ B. *Am. J. Physiol.* 273:L814–L824.
 43. Gentile DA, Villalobos E, Angelini B, Skoner D. 2003. Cytokine levels during symptomatic viral upper respiratory tract infection. *Ann. Allergy Asthma Immunol.* 91:362–367.
 44. Noah TL, Henderson FW, Wortman IA, Devlin RB, Handy J, Koren HS, Becker S. 1995. Nasal cytokine production in viral acute upper respiratory infection of childhood. *J. Infect. Dis.* 171:584–592.
 45. Gentile DA, Doyle WJ, Zeevi A, Howe-Adams J, Kapadia S, Trecki J, Skoner DP. 2003. Cytokine gene polymorphisms moderate illness severity in infants with respiratory syncytial virus infection. *Hum. Immunol.* 64:338–344.
 46. Gentile DA, Doyle WJ, Zeevi A, Piltcher O, Skoner DP. 2003. Responses to respiratory syncytial virus in adults. *Hum. Immunol.* 64:93–98.
 47. Doyle WJ, Casselbrant ML, Li-Korotky H-S, Doyle AP, Lo C-Y, Turner R, Cohen S. 2010. The interleukin 6 – 174 C/C genotype predicts greater rhinovirus illness. *J. Infect. Dis.* 201:199–206.
 48. Naclerio RM, Proud D, Lichtenstein LM, Kagey-Sobotka A, Hendley JO, Sorrentino J, Gwaltney JM. 1988. Kinins are generated during experimental rhinovirus colds. *J. Infect. Dis.* 157:133–142.
 49. Proud D, Naclerio RM, Gwaltney JM, Hendley JO. 1990. Kinins are generated in nasal secretions during natural rhinovirus colds. *J. Infect. Dis.* 161:120–123.
 50. Barclay WS, al-Nakib W, Higgins PG, Tyrrell DA. 1989. The time course of the humoral immune response to rhinovirus infection. *Epidemiol. Infect.* 103:659–669.
 51. Message SD, Johnston SL. 2004. Host defense function of the airway epithelium in health and disease: clinical background. *J. Leukoc. Biol.* 75:5–17.
 52. Alper CM, Doyle WJ, Skoner DP, Buchman CA, Cohen S, Gwaltney JM. 1998. Prechallenge antibodies moderate disease expression in adults experimentally exposed to rhinovirus strain hanks. *Clin. Infect. Dis.* 27:119–128.
 53. Papi A, Contoli M. 2011. Rhinovirus vaccination: the case against. *Eur. Respir. J.* 37:5–7.
 54. Kainulainen L, Vuorinen T, Rantakokko-Jalava K, Osterback R, Ruuskanen O. 2010. Recurrent and persistent respiratory tract viral infections in patients with primary hypogammaglobulinemia. *J. Allergy Clin. Immunol.* 126:120–126.
 55. Fraenkel DJ, Bardin PG, Sanderson G, Lampe F, Johnston SL, Holgate ST. 1995. Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. *Am. J. Respir. Crit. Care Med.* 151:879–886.
 56. Levandowski RA, Ou DW, Jackson GG. 1986. Acute-phase decrease of T lymphocyte subsets in rhinovirus infection. *J. Infect. Dis.* 153:743–748.
 57. Gern JE, Dick EC, Kelly EA, Vrtis R, Klein B. 1997. Rhinovirus-specific T cells recognize both shared and serotype-restricted viral epitopes. *J. Infect. Dis.* 175:1108–1114.
 58. Kelly JT, Busse WW. 2008. Host immune responses to rhinovirus: mechanisms in asthma. *J. Allergy Clin. Immunol.* 122:671–682.
 59. Sperber SJ, Hendley JO, Hayden FG, Riker DK, Sorrentino JV, Gwaltney JM. 1992. Effects of naproxen on experimental rhinovirus colds. *Ann. Intern. Med.* 117:37–41.
 60. Bartlett NW, Walton RP, Edwards MR, Aniscenko J, Caramori G, Zhu J, Glanville N, Choy KJ, Jourdan P, Burnet J, Tuthill TJ, Pedrick MS, Hurle MJ, Plumpton C, Sharp NA, Bussell JN, Swallow DM, Schwarze J, Guy B, Almond JW, Jeffery PK, Lloyd CM, Papi A, Killington RA, Rowlands DJ, Blair ED, Clarke NJ, Johnston SL. 2008. Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. *Nat. Med.* 14:199–204.
 61. Nagarkar DR, Bowman ER, Schneider D, Wang Q, Shim J, Linn MJ, Mchenry CL, Gosangi B, Bentley JK, Wan C, Sajjan US, Lukacs NW, Hershenson MB. 2010. Rhinovirus infection of allergen-sensitized and -challenged mice induces eotaxin release from functionally polarized macrophages. *J. Immunol.* 185:2525–2535.
 62. Rosenthal LA, Szakaly RJ, Amineva SP, Xing Y, Hill MR, Palmenberg AC, Gern JE, Sorkness RL. 2012. Lower respiratory tract infection induced by a genetically modified picornavirus in its natural murine host. *PLoS One* 7:e32061. doi:10.1371/journal.pone.0032061.
 63. Greenberg SB. 2011. Update on rhinovirus and coronavirus infections. *Semin. Respir. Crit. Care Med.* 32:433–446.
 64. Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PAB, Bartlett NW, Keadze T, Mallia P, Stanciu LA, Parker HL, Slater L, Lewis-Antes A, Kon OM, Holgate ST, Davies DE, Kosenko SV, Papi A, Johnston SL. 2006. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat. Med.* 12:1023–1026.
 65. Message SD, Laza-Stanca V, Mallia P, Parker HL, Zhu J, Keadze T, Contoli M, Sanderson G, Kon OM, Papi A, Jeffery PK, Stanciu LA, Johnston SL. 2008. Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc. Natl. Acad. Sci. U. S. A.* 105:13562–13567.
 66. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, Holgate ST, Davies DE. 2005. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J. Exp. Med.* 201:937–947.
 67. Gern J. 2009. Rhinovirus and the initiation of asthma. *Curr. Opin. Allergy Clin. Immunol.* 9:73–78.
 68. Mallia P, Message SD, Gielen V, Contoli M, Gray K, Keadze T, Aniscenko J, Laza-Stanca V, Edwards MR, Slater L, Papi A, Stanciu LA, Kon OM, Johnson M, Johnston SL. 2011. Experimental rhinovirus

- infection as a human model of chronic obstructive pulmonary disease exacerbation. *Am. J. Respir. Crit. Care Med.* 183:734–742.
69. Quint JK, Donaldson GC, Goldring JJP, Baghai-Ravary R, Hurst JR, Wedzicha JA. 2010. Serum IP-10 as a biomarker of human rhinovirus infection at exacerbation of COPD. *Chest* 137:812–822.
 70. Vareille M, Kieninger E, Alves MP, Kopf BS, Möller A, Geiser T, Johnston SL, Edwards MR, Regamey N. 2012. Impaired type I and type III interferon induction and rhinovirus control in human cystic fibrosis airway epithelial cells. *Thorax* 67:517–525.
 71. Chatteraj SS, Ganesan S, Faris A, Comstock A, Lee W-M, Sajjan US. 2011. *Pseudomonas aeruginosa* suppresses interferon response to rhinovirus infection in cystic fibrosis but not in normal bronchial epithelial cells. *Infect. Immun.* 79:4131–4145.
 72. Xu W, Zheng S, Goggans TM, Kiser P, Quinones-Mateu ME, Janocha AJ, Comhair SAA, Slee R, Williams BRG, Erzurum SC. 2006. Cystic fibrosis and normal human airway epithelial cell response to influenza A viral infection. *J. Interferon Cytokine Res.* 26:609–627.
 73. Sutanto E, Kicic A, Foo C, Stevens P, Mullane D, Knight D, Stick S. 2011. Innate inflammatory responses of pediatric cystic fibrosis airway epithelial cells: effects of nonviral and viral stimulation. *Am. J. Respir. Cell Mol. Biol.* 44:761–767.
 74. Kieninger E, Vareille M, Kopf BS, Blank F, Alves MP, Gisler FM, Latzin P, Casaulta C, Geiser T, Johnston SL, Edwards MR, Regamey N. 2012. Lack of an exaggerated inflammatory response on virus infection in cystic fibrosis. *Eur. Respir. J.* 39:297–304.
 75. Gwaltney JM, Hendley JO, Simon G, Jordan WS. 1966. Rhinovirus infections in an industrial population. *N. Engl. J. Med.* 275:1261–1268.
 76. Winther B, Hayden FG, Hendley JO. 2006. Picornavirus infections in children diagnosed by RT-PCR during longitudinal surveillance with weekly sampling: association with symptomatic illness and effect of season. *J. Med. Virol.* 78:644–650.
 77. Miller EK, Lu X, Erdman DD, Poehling KA, Zhu Y, Griffin MR, Hartert TV, Anderson LJ, Weinberg GA, Hall CB, Iwane MK, Edwards KM. 2007. Rhinovirus-associated hospitalizations in young children. *J. Infect. Dis.* 195:773–781.
 78. Vesa S, Kleemola M, Blomqvist S, Takala A, Kilpi T, Hovi T. 2001. Epidemiology of documented viral respiratory infections and acute otitis media in a cohort of children followed from two to twenty-four months of age. *Pediatr. Infect. Dis. J.* 20:574–581.
 79. Renwick N, Schweiger B, Kapoor V, Liu Z, Villari J, Bullmann R, Miething R, Briese T, Lipkin WI. 2007. A recently identified rhinovirus genotype is associated with severe respiratory-tract infection in children in Germany. *J. Infect. Dis.* 196:1754–1760.
 80. Lau SKP, Yip CCY, Tsoi H-W, Lee RA, So L-Y, Lau Y-L, Chan K-H, Woo PCY, Yuen K-Y. 2007. Clinical features and complete genome characterization of a distinct human rhinovirus (HRV) genetic cluster, probably representing a previously undetected HRV species, HRV-C, associated with acute respiratory illness in children. *J. Clin. Microbiol.* 45:3655–3664.
 81. Arakawa M, Okamoto-Nakagawa R, Toda S, Tsukagoshi H, Kobayashi M, Ryo A, Mizuta K, Hasegawa S, Hirano R, Wakiguchi H, Kudo K, Tanaka R, Morita Y, Noda M, Kozawa K, Ichiyama T, Shirabe K, Kimura H. 2012. Molecular epidemiological study of human rhinovirus species A, B and C from patients with acute respiratory illnesses in Japan. *J. Med. Microbiol.* 61:410–419.
 82. Briese T, Renwick N, Venter M, Jarman RG, Ghosh D, Köndgen S, Shrestha SK, Hoegh AM, Casas I, Adjogoua V, Akoua-Koffi C, Myint KS, Williams DT, Chidlow G, van den Berg R, Calvo C, Koch O, Palacios G, Kapoor V, Villari J, Dominguez SR, Holmes KV, Harnett G, Smith D, Mackenzie JS, Ellerbrok H, Schweiger B, Schönnig K, Chadha MS, Leendertz FH, Mishra AC, Gibbons RV, Holmes EC, Lipkin WI. 2008. Global distribution of novel rhinovirus genotype. *Emerg. Infect. Dis.* 14:944–947.
 83. Jin Y, Yuan X-H, Xie Z-P, Gao H-C, Song J-R, Zhang R-F, Xu Z-Q, Zheng L-S, Hou Y-D, Duan Z-J. 2009. Prevalence and clinical characterization of a newly identified human rhinovirus C species in children with acute respiratory tract infections. *J. Clin. Microbiol.* 47:2895–2900.
 84. Lau SKP, Yip CCY, Lin AWC, Lee RA, So L-Y, Lau Y-L, Chan K-H, Woo PCY, Yuen K-Y. 2009. Clinical and molecular epidemiology of human rhinovirus C in children and adults in Hong Kong reveals a possible distinct human rhinovirus C subgroup. *J. Infect. Dis.* 200:1096–1103.
 85. McErlean P, Shackleton LA, Andrews E, Webster DR, Lambert SB, Nissen MD, Sloots TP, Mackay IM. 2008. Distinguishing molecular features and clinical characteristics of a putative new rhinovirus species, human rhinovirus C (HRV C). *PLoS One* 3:e1847. doi:10.1371/journal.pone.0001847.
 86. Lau SKP, Yip CCY, Woo PCY, Yuen K-Y. 2010. Human rhinovirus C: a newly discovered human rhinovirus species. *Emerg. Health Threats J.* 3:e2. doi:10.3134/ehth.10.002.
 87. Singleton RJ, Bulkow LR, Miernyk K, DeByle C, Pruitt L, Hummel KB, Bruden D, Englund JA, Anderson LJ, Lucher L, Holman RC, Hennessy TW. 2010. Viral respiratory infections in hospitalized and community control children in Alaska. *J. Med. Virol.* 82:1282–1290.
 88. Nokso-Koivisto J, Kinnari TJ, Lindahl P, Hovi T, Pitkaranta A. 2002. Human picornavirus and coronavirus RNA in nasopharynx of children without concurrent respiratory symptoms. *J. Med. Virol.* 66:417–420.
 89. van Bente L, Koopman L, Niesters B, Hop W, van Middelkoop B, de Waal L, van Drunen K, Osterhaus A, Neijens H, Fokkens W. 2003. Predominance of rhinovirus in the nose of symptomatic and asymptomatic infants. *Pediatr. Allergy Immunol.* 14:363–370.
 90. Iwane MK, Prill MM, Lu X, Miller EK, Edwards KM, Hall CB, Griffin MR, Staat MA, Anderson LJ, Williams JV, Weinberg GA, Ali A, Szilagyi PG, Zhu Y, Erdman DD. 2011. Human rhinovirus species associated with hospitalizations for acute respiratory illness in young US children. *J. Infect. Dis.* 204:1702–1710.
 91. Fry AM, Lu X, Olsen SJ, Chittaganpitch M, Sawatwong P, Chantira S, Baggett HC, Erdman D. 2011. Human rhinovirus infections in rural Thailand: epidemiological evidence for rhinovirus as both pathogen and bystander. *PLoS One* 6:e17780. doi:10.1371/journal.pone.0017780.
 92. Hennessy TW, Ritter T, Holman RC, Bruden DL, Yorita KL, Bulkow L, Cheek JE, Singleton RJ, Smith J. 2008. The relationship between in-home water service and the risk of respiratory tract, skin, and gastrointestinal tract infections among rural Alaska natives. *Am. J. Public Health* 98:2072–2078.
 93. Graat J, Schouten E, Heijnen M, Kok F, Pallast EGM, de Greeff S, Dorigo-Zetsma J. 2003. A prospective, community-based study on virologic assessment among elderly people with and without symptoms of acute respiratory infection. *J. Clin. Epidemiol.* 56:1218–1223.
 94. Peltola V, Waris M, Osterback R, Susi P, Ruuskanen O, Hyypä T. 2008. Rhinovirus transmission within families with children: incidence of symptomatic and asymptomatic infections. *J. Infect. Dis.* 197:382–389.
 95. Mäkelä MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, Kimpimäki M, Blomqvist S, Hyypä T, Arstila P. 1998. Viruses and bacteria in the etiology of the common cold. *J. Clin. Microbiol.* 36:539–542.
 96. Arruda E, Pitkäranta A, Witek TJ, Doyle CA, Hayden FG. 1997. Frequency and natural history of rhinovirus infections in adults during autumn. *J. Clin. Microbiol.* 35:2864–2868.
 97. Brownlee JW, Turner RB. 2008. New developments in the epidemiology and clinical spectrum of rhinovirus infections. *Curr. Opin. Pediatr.* 20:67–71.
 98. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. 2009. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect. Dis.* 9:291–300.
 99. Gwaltney JM, Jr, Hendley JO, Simon G, Jordan WS, Jr. 1967. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. *JAMA* 202:494–500.
 100. Harris JM, II, Gwaltney JM, Jr. 1996. Incubation periods of experimental rhinovirus infection and illness. *Clin. Infect. Dis.* 23:1287–1290.
 101. Winther B, Alper CM, Mandel EM, Doyle WJ, Hendley JO. 2007. Temporal relationships between colds, upper respiratory viruses detected by polymerase chain reaction, and otitis media in young children followed through a typical cold season. *Pediatrics* 119:1069–1075.
 102. Buchman C, Doyle W, Skoner D. 1994. Otolgic manifestations of experimental rhinovirus infection. *Laryngoscope* 104:1295–1299.
 103. McBride TP, Doyle WJ, Hayden FG, Gwaltney JM. 1989. Alterations of the eustachian tube, middle ear, and nose in rhinovirus infection. *Arch. Otolaryngol. Head Neck Surg.* 115:1054–1059.
 104. Blomqvist S, Roivainen M, Puhakka T, Kleemola M, Hovi T. 2002. Virological and serological analysis of rhinovirus infections during the first two years of life in a cohort of children. *J. Med. Virol.* 66:263–268.
 105. Rihkanen H, Carpen O, Roivainen M, Vaheri A, Pitkäranta A. 2004. Rhinovirus in adenoid tissue. *Int. J. Pediatr. Otorhinolaryngol.* 68:903–908.
 106. Pitkäranta A, Virolainen A, Jero J, Arruda E. 1998. Detection of

- rhinovirus, respiratory syncytial virus, and coronavirus infections in acute otitis media by reverse transcriptase polymerase chain reaction. *Pediatrics* 102:291–295.
107. Ruohola A, Meurman O, Nikkari S, Skottman T, Salmi A, Waris M, Osterback R, Eerola E, Allander T, Niesters H, Heikkinen T, Ruuskanen O. 2006. Microbiology of acute otitis media in children with tympanostomy tubes: prevalences of bacteria and viruses. *Clin. Infect. Dis.* 43:1417–1422.
 108. Pitkäranta A, Roivainen M, Blomgren K, Peltola J, Kajjalainen T, Rätty R, Ziegler T, Rönkkö E, Hatakka K, Korpela R, Poussa T, Leinonen M, Hovi T. 2006. Presence of viral and bacterial pathogens in the nasopharynx of otitis-prone children. A prospective study. *Int. J. Pediatr. Otorhinolaryngol.* 70:647–654.
 109. Gwaltney JM, Phillips CD, Miller RD, Riker DK. 1994. Computed tomographic study of the common cold. *N. Engl. J. Med.* 330:25–30.
 110. Turner BW, Cail WS, Hendley JO, Hayden FG, Doyle WJ, Sorrentino JV, Gwaltney JM. 1992. Physiologic abnormalities in the paranasal sinuses during experimental rhinovirus colds. *J. Allergy Clin. Immunol.* 90:474–478.
 111. Pitkäranta A, Arruda E, Malmberg H, Hayden FG. 1997. Detection of rhinovirus in sinus brushings of patients with acute community-acquired sinusitis by reverse transcription-PCR. *J. Clin. Microbiol.* 35:1791–1793.
 112. Pitkäranta A, Starck M, Savolainen S, Pöyry T, Suomalainen I, Hyypiä T, Carpen O, Vaheri A. 2001. Rhinovirus RNA in the maxillary sinus epithelium of adult patients with acute sinusitis. *Clin. Infect. Dis.* 33:909–911.
 113. Gwaltney JM, Hendley JO, Phillips CD, Bass CR, Mygind N, Winther B. 2000. Nose blowing propels nasal fluid into the paranasal sinuses. *Clin. Infect. Dis.* 30:387–391.
 114. Rihkanen H, Rönkkö E, Nieminen T, Koms K-L, Rätty R, Saxen H, Ziegler T, Roivainen M, Söderlund-Venemo M, Beng AL, Anne L, Hovi T, Pitkäranta A. 2008. Respiratory viruses in laryngeal croup of young children. *J. Pediatr.* 152:661–665.
 115. Henquell C, Mirand A, Deusebis A-L, Regagnon C, Archimbaud C, Chambon M, Bailly J-L, Gourdon F, Hermet E, Dauphin J-B, Labbé A, Peigue-Lafeuille H. 2012. Prospective genotyping of human rhinoviruses in children and adults during the winter of 2009–2010. *J. Clin. Virol.* 53:280–284.
 116. Louie JK, Roy-Burman A, Guardia-Labar L, Boston EJ, Kiang D, Padilla T, Yagi S, Messenger S, Petru AM, Glaser CA, Schnurr DP. 2009. Rhinovirus associated with severe lower respiratory tract infections in children. *Pediatr. Infect. Dis. J.* 28:337–339.
 117. Mansbach JM, Piedra PA, Teach SJ, Sullivan AF, Forgey T, Clark S, Espinola JA, Camargo CA. 2 April 2012. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch. Pediatr. Adolesc. Med.* [Epub ahead of print]. doi:10.1001/archpediatrics.2011.1669.
 118. DeLaMora P, Moscona A. 2 April 2012. Bronchiolitis: too-familiar yet too-mysterious disease of childhood. *Arch. Pediatr. Adolesc. Med.* [Epub ahead of print.] doi:10.1001/archpediatrics.2012.157.
 119. Miller EK, Bugna J, Libster R, Shepherd BE, Scalzo PM, Acosta PL, Hijano D, Reynoso N, Batalle JP, Coviello S, Klein MI, Bauer G, Benitez A, Kleeberger SR, Polack FP. 2012. Human rhinoviruses in severe respiratory disease in very low birth weight infants. *Pediatrics* 129:e60–e67. doi:10.1542/peds.2011-0583.
 120. Midulla F, Pierangeli A, Cangiano G, Bonci E, Salvadei S, Scagnolari C, Moretti C, Antonelli G, Ferro V, Papoff P. 2012. Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur. Respir. J.* 39:396–402.
 121. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. 2003. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J. Allergy Clin. Immunol.* 111:66–71.
 122. Xiang Z, Gonzalez R, Xie Z, Xiao Y, Liu J, Chen L, Liu C, Zhang J, Ren L, Vernet G, Paranhos-Bacalà G, Shen K, Jin Q, Wang J. 2010. Human rhinovirus C infections mirror those of human rhinovirus A in children with community-acquired pneumonia. *J. Clin. Virol.* 49:94–99.
 123. Mermond S, Zurawski V, D'Ortenzio E, Driscoll AJ, Deluca AN, Deloria-Knoll M, Moïsi JC, Murdoch DR, Missotte I, Besson-Leaud L, Chevalier C, Debarnot V, Feray F, Noiretierre S, Duparc B, Fresnais F, O'Connor O, Dupont-Rouzeyrol M, Levine OS. 2012. Lower respiratory infections among hospitalized children in New Caledonia: a pilot study for the Pneumonia Etiology Research for Child Health Project. *Clin. Infect. Dis.* 54(Suppl 2):S180–S189. doi:10.1093/cid/cir1070.
 124. García-García ML, Calvo C, Pozo F, Villadangos PA, Pérez-Breña P, Casas I. 2012. Spectrum of respiratory viruses in children with community acquired pneumonia. *Pediatr. Infect. Dis. J.* 8:808–813.
 125. Broberg E, Niemelä J, Lahti E, Hyypiä T, Ruuskanen O, Waris M. 2011. Human rhinovirus C-associated severe pneumonia in a neonate. *J. Clin. Virol.* 51:79–82.
 126. Lieberman D, Shimoni A, Shemer-Avni Y, Keren-Naos A, Shtainberg R, Lieberman D. 2010. Respiratory viruses in adults with community-acquired pneumonia. *Chest* 138:811–816.
 127. Sangil A, Calbo E, Robles A, Benet S, Viladot ME, Pascual V, Cuchi E, Pérez J, Barreiro B, Sánchez B, Torres J, Canales L, De Marcos JA, Garau J. 2012. Aetiology of community-acquired pneumonia among adults in an H1N1 pandemic year: the role of respiratory viruses. *Eur. J. Clin. Microbiol. Infect. Dis.* 10:2765–2772.
 128. Hicks LA, Shepard CW, Britz PH, Erdman DD, Fischer M, Flannery BL, Peck AJ, Lu X, Thacker WL, Benson RF, Tondella ML, Moll ME, Whitney CG, Anderson LJ, Feikin DR. 2006. Two outbreaks of severe respiratory disease in nursing homes associated with rhinovirus. *J. Am. Geriatr. Soc.* 54:284–289.
 129. Louie JK, Yagi S, Nelson FA, Kiang D, Glaser CA, Rosenberg J, Cahill CK, Schnurr DP. 2005. Rhinovirus outbreak in a long term care facility for elderly persons associated with unusually high mortality. *Clin. Infect. Dis.* 41:262–265.
 130. Murali S, Langston AA, Nolte FS, Banks G, Martin R, Caliendo AM. 2009. Detection of respiratory viruses with a multiplex polymerase chain reaction assay (MultiCode-PLx Respiratory Virus Panel) in patients with hematologic malignancies. *Leuk. Lymphoma* 50:619–624.
 131. Camps Serra M, Cervera C, Pumarola T, Moreno A, Perelló R, Torres A, Jiménez de Anta MT, Marcos MA. 2008. Virological diagnosis in community-acquired pneumonia in immunocompromised patients. *Eur. Respir. J.* 31:618–624.
 132. Kraft CS, Jacob JT, Sears MH, Burd EM, Caliendo AM, Lyon GM. 2012. Severity of human rhinovirus infection in immunocompromised adults is similar to that of 2009 H1N1 influenza. *J. Clin. Microbiol.* 50:1061–1063.
 133. Kaiser L, Aubert J-D, Pache J-C, Deffernez C, Rochat T, Garbino J, Wunderli W, Meylan P, Yerly S, Perrin L, Letovanec J, Nicod L, Tapparel C, Soccac PM. 2006. Chronic rhinoviral infection in lung transplant recipients. *Am. J. Respir. Crit. Care Med.* 174:1392–1399.
 134. Costa C, Bergallo M, Astegiano S, Sidoti F, Terlizzi ME, Gambarino S, Curtioni A, Simeone S, Solidoro P, Cavallo R. 2011. Detection of human rhinoviruses in the lower respiratory tract of lung transplant recipients. *Arch. Virol.* 156:1439–1443.
 135. Liu M, Mallory G, Schecter M. 2010. Long-term impact of respiratory viral infection after pediatric lung transplantation. *Pediatr. Transplant.* 14:431–436.
 136. Liu M, Worley S, Arrigain S, Aurora P, Ballmann M, Boyer D, Conrad C, Eichler I, Elidemir O, Goldfarb S, Mallory GB, Mogayzel PJ, Parakininkas D, Visner G, Sweet S, Faro A, Michaels M, Danziger-Isakov LA. 2009. Respiratory viral infections within one year after pediatric lung transplant. *Transpl. Infect. Dis.* 11:304–312.
 137. Vu D-L, Bridevaux P-O, Aubert J-D, Soccac PM, Kaiser L. 2011. Respiratory viruses in lung transplant recipients: a critical review and pooled analysis of clinical studies. *Am. J. Transplant.* 11:1071–1078.
 138. Ohrmalm L, Wong M, Aust C, Ljungman P, Norbeck O, Broliden K, Tolfvenstam T. 2012. Viral findings in adult hematological patients with neutropenia. *PLoS One* 7:e36543. doi:10.1371/journal.pone.0036543.
 139. Milano F, Campbell AP, Guthrie KA, Kuypers J, Englund JA, Corey L, Boeckh M. 2010. Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. *Blood* 115:2088–2094.
 140. Van Kraaij MGJ, van Elden LJR, van Loon AM, Hendriksen KAW, Laterveer L, Dekker AW, Nijhuis M. 2005. Frequent detection of respiratory viruses in adult recipients of stem cell transplants with the use of real-time polymerase chain reaction, compared with viral culture. *Clin. Infect. Dis.* 40:662–669.
 141. Ison MG, Hayden FG, Kaiser L, Corey L, Boeckh M. 2003. Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. *Clin. Infect. Dis.* 36:1139–1143.
 142. Parody R, Rabella N, Martino R, Otegui M, Cuerpo M, Coll P, Sierra J. 2007. Upper and lower respiratory tract infections by human entero-

- virus and rhinovirus in adult patients with hematological malignancies. *Am. J. Hematol.* 82:807–811.
143. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee W-M, Shult PA, Reisdorf E, Carlson-Dakes KT, Salazar LP, DaSilva DF, Tisler CJ, Gern JE, Lemanske RF. 2008. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am. J. Respir. Crit. Care Med.* 178:667–672.
 144. Gern JE. 2010. The ABCs of rhinoviruses, wheezing, and asthma. *J. Virol.* 84:7418–7426.
 145. Corne JM, Marshall C, Smith S, Schreiber J, Sanderson G, Holgate ST, Johnston SL. 2002. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 359:831–834.
 146. Mak RKY, Tse LY, Lam WY, Wong GWK, Chan PKS, Leung TF. 2011. Clinical spectrum of human rhinovirus infections in hospitalized Hong Kong children. *Pediatr. Infect. Dis. J.* 30:749–753.
 147. Greenberg SB, Allen M, Wilson J, Atmar RL. 2000. Respiratory viral infections in adults with and without chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 162:167–173.
 148. McManus TE, Marley A-M, Baxter N, Christie SN, O'Neill HJ, Elborn JS, Coyle PV, Kidney JC. 2008. Respiratory viral infection in exacerbations of COPD. *Respir. Med.* 102:1575–1580.
 149. Rohde G, Wiethage A, Borg I, Kauth M, Bauer TT, Gillissen A, Bufe A, Schultze-Werninghaus G. 2003. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 58:37–42.
 150. Kherad O, Kaiser L, Bridevaux P-O, Sarasin F, Thomas Y, Janssens J-P, Rutschmann OT. 2010. Upper-respiratory viral infection, biomarkers, and COPD exacerbations. *Chest* 138:896–904.
 151. Seemungal T, Harper-Owen R, Bhowmik A, Moric I, Sanderson G, Message S, Maccallum P, Meade TW, Jeffries DJ, Johnston SL, Wedzicha JA. 2001. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 164:1618–1623.
 152. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. 2000. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 161:1608–1613.
 153. Dimopoulos G, Lerikou M, Tsiodras S, Chranioti A, Perros E, Anagnostopoulou U, Armaganidis A, Karakitsos P. 2012. Viral epidemiology of acute exacerbations of chronic obstructive pulmonary disease. *Pulm. Pharmacol. Ther.* 25:12–18.
 154. Smyth AR, Smyth RL, Tong CY, Hart CA, Heaf DP. 1995. Effect of respiratory virus infections including rhinovirus on clinical status in cystic fibrosis. *Arch. Dis. Child.* 73:117–120.
 155. Olesen HV, Nielsen LP, Schiøtz PO. 2006. Viral and atypical bacterial infections in the outpatient pediatric cystic fibrosis clinic. *Pediatr. Pulmonol.* 41:1197–1204.
 156. De Almeida MB, Zerbinati RM, Tateno AF, Oliveira CM, Romão RM, Rodrigues JC, Pannuti CS, da Silva Filho LVF. 2010. Rhinovirus C and respiratory exacerbations in children with cystic fibrosis. *Emerg. Infect. Dis.* 16:996–999.
 157. Reid AB, Anderson TL, Cooley L, Williamson J, McGregor AR. 2011. An outbreak of human rhinovirus species C infections in a neonatal intensive care unit. *Pediatr. Infect. Dis. J.* 30:1096–1098.
 158. Valenti WM, Clarke TA, Hall CB, Menegus MA, Shapiro DL. 1982. Concurrent outbreaks of rhinovirus and respiratory syncytial virus in an intensive care nursery: epidemiology and associated risk factors. *J. Pediatr.* 100:722–726.
 159. van Piggelen RO, van Loon AM, Krediet TG, Verboon-Macielek MA. 2010. Human rhinovirus causes severe infection in preterm infants. *Pediatr. Infect. Dis. J.* 29:364–365.
 160. Longtin J, Marchand-Austin A, Winter AL, Patel S, Eshaghi A, Jamieson F, Low DE, Gubbay JB. 2010. Rhinovirus outbreaks in long-term care facilities, Ontario, Canada. *Emerg. Infect. Dis.* 16:1463–1465.
 161. Wald TG, Shult P, Krause P, Miller BA, Drinka P, Gravenstein S. 1995. A rhinovirus outbreak among residents of a long-term care facility. *Ann. Intern. Med.* 123:588–593.
 162. Longtin J, Winter AL, Heng D, Marchand-Austin A, Eshaghi A, Patel S, Jamieson F, Weir E, Low DE, Gubbay JB. 2010. Severe human rhinovirus outbreak associated with fatalities in a long-term care facility in Ontario, Canada. *J. Am. Geriatr. Soc.* 58:2036–2038.
 163. Bellei N, Carraro E, Helena A, Perosa S, Benfica D, Paulo S. 2007. Influenza and rhinovirus infections among health-care workers. *Respirology* 12:100–103.
 164. Siegel JD, Rhinehart E, Jackson M, Chiarello L, Health Care Infection Control Practices Advisory Committee. 2007. Guideline for isolation precautions: preventing transmission of infectious agents in health-care settings. *Am. J. Infect. Control* 35(10 Suppl 2):S65–S164. doi:10.1016/j.ajic.2007.10.007.
 165. Miller EK, Edwards KM, Weinberg GA, Iwane MK, Griffin MR, Hall CB, Zhu Y, Szilagyi PG, Morin L-L, Heil LH, Lu X, Williams JV, New Vaccine Surveillance Network. 2009. A novel group of rhinoviruses is associated with asthma hospitalizations. *J. Allergy Clin. Immunol.* 123: 98–104.e1. doi:10.1016/j.jaci.2008.10.007.
 166. Piralla A, Rovida F, Campanini G, Rognoni V, Marchi A, Locatelli F, Gerna G. 2009. Clinical severity and molecular typing of human rhinovirus C strains during a fall outbreak affecting hospitalized patients. *J. Clin. Virol.* 45:311–317.
 167. Tapparel C, L'Huillier AG, Rougemont A-L, Beghetti M, Barazzzone-Argiroffo C, Kaiser L. 2009. Pneumonia and pericarditis in a child with HRV-C infection: a case report. *J. Clin. Virol.* 45:157–160.
 168. Fuji N, Suzuki A, Lupisan S, Sombrero L, Galang H, Kamigaki T, Tamaki R, Saito M, Aniceto R, Olveda R, Oshitani H. 2011. Detection of human rhinovirus C viral genome in blood among children with severe respiratory infections in the Philippines. *PLoS One* 6:e27247. doi:10.1371/journal.pone.0027247.
 169. Linsuwanon P, Payungporn S, Samransamruajkit R, Posuwan N, Makkoch J, Theanboonlers A, Poovorawan Y. 2009. High prevalence of human rhinovirus C infection in Thai children with acute lower respiratory tract disease. *J. Infect.* 59:115–121.
 170. Piralla A, Lilleri D, Sarasini A, Marchi A, Zecca M, Stronati M, Baldanti F, Gerna G. 2012. Human rhinovirus and human respiratory enterovirus (EV68 and EV104) infections in hospitalized patients in Italy, 2008–2009. *Diagn. Microbiol. Infect. Dis.* 73:162–167.
 171. Takeyama A, Hashimoto K, Sato M, Sato T, Kanno S, Takano K, Ito M, Katayose M, Nishimura H, Kawasaki Y, Hosoya M. 2012. Rhinovirus load and disease severity in children with lower respiratory tract infections. *J. Med. Virol.* 84:1135–1142.
 172. Gerna G, Piralla A, Rovida F, Rognoni V, Marchi A, Locatelli F, Meloni F. 2009. Correlation of rhinovirus load in the respiratory tract and clinical symptoms in hospitalized immunocompetent and immunocompromised patients. *J. Med. Virol.* 81:1498–1507.
 173. Ishizuka S, Yamaya M, Suzuki T, Takahashi H, Ida S, Sasaki T, Inoue D, Sekizawa K, Nishimura H, Sasaki H. 2003. Effects of rhinovirus infection on the adherence of *Streptococcus pneumoniae* to cultured human airway epithelial cells. *J. Infect. Dis.* 188:1928–1939.
 174. Wang JH, Kwon HJ, Jang YJ. 2009. Rhinovirus enhances various bacterial adhesions to nasal epithelial cells simultaneously. *Laryngoscope* 119:1406–1411.
 175. Passariello C, Schippa S, Conti C, Russo P, Poggiali F, Garaci E, Palamara AT. 2006. Rhinoviruses promote internalisation of *Staphylococcus aureus* into non-fully permissive cultured pneumocytes. *Microbes Infect.* 8:758–766.
 176. Oliver BGG, Lim S, Wark P, Laza-Stanca V, King N, Black JL, Burgess JK, Roth M, Johnston SL. 2008. Rhinovirus exposure impairs immune responses to bacterial products in human alveolar macrophages. *Thorax* 63:519–525.
 177. Peltola V, Heikkinen T, Ruuskanen O, Jartti T, Hovi T, Kilpi T, Vainionpää R. 2011. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. *Pediatr. Infect. Dis. J.* 30:456–461.
 178. Greer RM, McErlean P, Arden KE, Faux CE, Nitsche A, Lambert SB, Nissen MD, Sloots TP, Mackay IM. 2009. Do rhinoviruses reduce the probability of viral co-detection during acute respiratory tract infections? *J. Clin. Virol.* 45:10–15.
 179. Tanner H, Boxall E, Osman H. 8 June 2012. Respiratory viral infections during the 2009–2010 winter season in central England, UK: incidence and patterns of multiple virus co-infections. *Eur. J. Clin. Microbiol. Infect. Dis.* [Epub ahead of print.] doi:10.1007/s10096-012-1653-3.
 180. Anestad G, Nordbø SA. 2009. Interference between outbreaks of respiratory viruses. *Euro Surveill.* 14(42):pii=19359. <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19359>.
 181. Landry M. 2011. Rhinoviruses, p 1400–1409. In Versalovic J, Carroll KC, Funke G, Jorgensen JH, Landry ML, Warnock DW (ed), *Manual of clinical microbiology*, 10th ed. ASM Press, Washington, DC.

182. Hernes S, Quarsten H, Hagen E, Lyngroth A, Pripp A, Bjorvatn B, Bakke P. 2011. Swabbing for respiratory viral infections in older patients: a comparison of rayon and nylon flocked swabs. *Eur. J. Clin. Microbiol. Infect. Dis.* 30:159–165.
183. Arruda E, Crump C, Rollins B, Ohlin A, Hayden F. 1996. Comparative susceptibilities of human embryonic fibroblasts and HeLa cells for isolation of human rhinoviruses. *J. Clin. Microbiol.* 34:1277–1279.
184. Cate TR, Couch RB, Johnson KM. 1964. Studies with rhinoviruses in volunteers: production of illness, effect of naturally acquired antibody, and demonstration of a protective effect not associated with serum antibody. *J. Clin. Invest.* 43:56–67.
185. Harvala H, McIntyre CL, Mcleish NJ, Kondracka J, Palmer J, Molyneaux P, Gunson R, Bennett S, Templeton K, Simmonds P. 2012. High detection frequency and viral loads of human rhinovirus species A to C in fecal samples; diagnostic and clinical implications. *J. Med. Virol.* 84:536–542.
186. Katpally U, Fu T-M, Freed DC, Casimiro DR, Smith TJ. 2009. Antibodies to the buried N terminus of rhinovirus VP4 exhibit cross-serotypic neutralization. *J. Virol.* 83:7040–7048.
187. Barclay W, Callow K, Sergeant M, al-Nakib W. 1988. Evaluation of an enzyme-linked immunosorbent assay that measures rhinovirus-specific antibodies in human sera and nasal secretions. *J. Med. Microbiol.* 25:475–482.
188. Amineva SP, Aminev AG, Gern JE, Palmenberg AC. 2011. Comparison of rhinovirus A infection in human primary epithelial and HeLa cells. *J. Gen. Virol.* 92:2549–2557.
189. Hendley J. 1999. Clinical virology of rhinoviruses. *Adv. Virus Res.* 54:453–466.
190. Tyrrell D, Bynoe M. 1961. Some further virus isolations from common colds. *Br. Med. J.* i:393–397.
191. Behbehani AM, Lee LH. 1964. Growth, plaque production, and cationic stabilization of rhinovirus type 1 (echovirus 28). *J. Bacteriol.* 88:1608–1611.
192. Price W, Emerson H, Ibler I, Lachaine R, Terrell A. 1959. Studies of the JH and 2060 viruses and their relationship to mild upper respiratory disease in humans. *Am. J. Hyg. (Lond.)* 69:224–249.
193. Holper J, Miller L, Crawford Y, Sylvester J, Marquis G, Jr. 1960. Further studies on multiplication, serology and antigenicity of 2060 and JH viruses. *J. Infect. Dis.* 107:395–401.
194. Tyrrell D, Parsons R. 1960. Some virus isolations from common colds. III. Cytopathic effects in tissue cultures. *Lancet* i:239–242.
195. Olson L, Willhight M, Buescher E. 1972. Recovery and characterization of non-cytopathogenic rhinoviruses. *J. Gen. Virol.* 17:237–240.
196. Leonardi GP, Desormeaux M-L. 2010. A rapid microscopic method for the confirmation of rhinoviruses in cell culture. *Intervirology* 53:426–428.
197. Al-Mulla W, el Mekki A, Al-Nakib W. 1994. Rapid culture-amplified immunofluorescent test for the detection of human rhinoviruses in clinical samples: evidence of a common epitope in culture. *J. Med. Virol.* 42:182–187.
198. Landry ML, Ferguson D. 2000. SimulFluor respiratory screen for rapid detection of multiple respiratory viruses in clinical specimens by immunofluorescence staining. *J. Clin. Microbiol.* 38:708–711.
199. Freymuth F, Vabret A, Rozenberg F, Dina J, Petitjean J, Gouarin S, Legrand L, Corbet S, Brouard J, Lebon P. 2005. Replication of respiratory viruses, particularly influenza virus, rhinovirus, and coronavirus in HuH7 hepatocarcinoma cell line. *J. Med. Virol.* 77:295–301.
200. Hoorn B, Tyrrell D. 1965. On the growth of certain “newer” respiratory viruses in organ cultures. *Br. J. Exp. Pathol.* 46:109–118.
201. Roome AP, Dickinson V, Caul EO. 1971. Simplified organ cultures of human embryo trachea in the diagnosis of viral respiratory disease of children. *J. Clin. Pathol.* 24:487–490.
202. Jang YJ, Lee SH, Kwon H-J, Chung Y-S, Lee B-J. 2005. Development of rhinovirus study model using organ culture of turbinate mucosa. *J. Virol. Methods* 125:41–47.
203. Gama R, Hughes P, Bruce C, Stanway G. 1988. Polymerase chain reaction amplification of rhinovirus nucleic acids from clinical material. *Nucleic Acids Res.* 16:9346. doi:10.1093/nar/16.19.9346.
204. Gama R, Horsnell P, Hughes P, North C, Bruce C, Al-Nakib W, Stanway G. 1989. Amplification of rhinovirus specific nucleic acids from clinical samples using the polymerase chain reaction. *J. Med. Virol.* 28:73–77.
205. Hyypia T, Auvinen P, Maaronen M. 1989. Polymerase chain reaction for human picornaviruses. *J. Gen. Virol.* 70:3261–3268.
206. Torgersen H, Skern T, Blaas D. 1989. Typing of human rhinoviruses based on sequence variations in the 5′ non-coding region. *J. Gen. Virol.* 2:3111–3116.
207. Olive DM, Al-Mufti S, Al-Mulla W, Khan M, Pasca A, Stanway G, Al-Nakib W. 1990. Detection and differentiation of picornaviruses in clinical samples following genomic amplification. *J. Gen. Virol.* 71:2141–2147.
208. Coiras MT, Aguilar JC, García ML, Casas I, Pérez-Breña P. 2004. Simultaneous detection of fourteen respiratory viruses in clinical specimens by two multiplex reverse transcription nested-PCR assays. *J. Med. Virol.* 72:484–495.
209. Mori J, Clewley J. 1994. Polymerase chain reaction and sequencing for typing rhinovirus RNA. *J. Med. Virol.* 44:323–329.
210. Lu X, Holloway B, Dare RK, Kuypers J, Yagi S, Williams JV, Hall CB, Erdman DD. 2008. Real-time reverse transcription-PCR assay for comprehensive detection of human rhinoviruses. *J. Clin. Microbiol.* 46:533–539.
211. Utokaparch S, Marchant D, Gosselink JV, McDonough JE, Thomas EE, Hogg JC, Hegele RG. 2011. The relationship between respiratory viral loads and diagnosis in children presenting to a pediatric hospital emergency department. *Pediatr. Infect. Dis. J.* 30:e18–e23. doi:10.1097/INF.0b013e3181ff2fac.
212. Schibler M, Yerly S, Vieille G, Turin L, Kaiser L, Tapparel C. 2012. Critical analysis of rhinovirus RNA load quantification by real-time reverse transcription-PCR. *J. Clin. Microbiol.* 50:2868–2872.
213. Samuelson A, Westmoreland D, Eccles R, Fox JD. 1998. Development and application of a new method for amplification and detection of human rhinovirus RNA. *J. Virol. Methods* 71:197–209.
214. Loens K, Ieven M, Ursi D, Laat CD, Sillekens P, Oudshoorn P, Goossens H. 2003. Improved detection of rhinoviruses by nucleic acid sequence-based amplification after nucleotide sequence determination of the 5′ noncoding regions of additional rhinovirus strains. *J. Clin. Microbiol.* 41:1971–1976.
215. Loens K, Goossens H, Laat CD, Foolen H, Oudshoorn P, Pattyn S, Sillekens P, Ieven M. 2006. Detection of rhinoviruses by tissue culture and two independent amplification techniques, nucleic acid sequence-based amplification and reverse transcription-PCR, in children with acute respiratory infections during a winter season. *J. Clin. Microbiol.* 44:166–171.
216. Sidoti F, Bergallo M, Terlizzi ME, Piasentin Alessio E, Astegiano S, Gasparini G, Cavallo R. 2012. Development of a quantitative real-time nucleic acid sequence-based amplification assay with an internal control using molecular beacon probes for selective and sensitive detection of human rhinovirus serotypes. *Mol. Biotechnol.* 50:221–228.
217. Mahony JB, Petrich A, Smieja M. 2011. Molecular diagnosis of respiratory virus infections. *Crit. Rev. Clin. Lab. Sci.* 48:217–249.
218. Gern JE, Busse WW. 1999. Association of rhinovirus infections with asthma. *Clin. Microbiol. Rev.* 12:9–18.
219. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O’Toole S, Myint SH, Tyrrell DA, Holgate S. 1995. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 310:1225–1229.
220. Johnston SL, Pattemore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, Cunningham A, Robinson BS, Myint SH, Ward ME, Tyrrell D, Holgate ST. 1996. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am. J. Respir. Crit. Care Med.* 154:654–660.
221. Tapparel C, Cordey S, Junier T, Farinelli L, Van Belle S, Soccal PM, Aubert J-D, Zdobnov E, Kaiser L. 2011. Rhinovirus genome variation during chronic upper and lower respiratory tract infections. *PLoS One* 6:e21163. doi:10.1371/journal.pone.0021163.
222. Taylor-Robinson D, Tyrrell D. 1962. Serotypes of viruses (rhinoviruses) isolated from common colds. *Lancet* i:452–454.
223. Hilleman M. 1967. Present knowledge of the rhinovirus group of viruses. *Curr. Top. Microbiol. Immunol.* 41:1–22.
224. Douglas RJ, Cate T, Couch R. 1966. Growth and cytopathic effect of H type rhinoviruses in monkey kidney tissue culture. *Proc. Soc. Exp. Biol. Med.* 123:238–241.
225. Abraham G, Colonna RJ. 1984. Many rhinovirus serotypes share the same cellular receptor. *J. Virol.* 51:340–345.
226. Andries K, Dewindt B, Snoeks J, Wouters L, Moereels H, Lewi PJ,

- Janssen PA. 1990. Two groups of rhinoviruses revealed by a panel of antiviral compounds present sequence divergence and differential pathogenicity. *J. Virol.* 64:1117–1123.
227. Andries K, Dewindt B, Snoeks J, Willebrords R, Stokbroekx R, Lewi P. 1991. A comparative test of fifteen compounds against all known human rhinovirus serotypes as a basis for a more rational screening program. *Antiviral Res.* 16:213–255.
 228. Palmenberg A, Gern J. Rhinoviruses. In Knipe DM, Howley PM (ed), *Fields virology*, 6th ed, in press. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, PA.
 229. Huang T, Wang W, Bessaud M, Ren P, Sheng J, Yan H, Zhang J, Lin X, Wang Y, Delpeyroux F, Deubel V. 2009. Evidence of recombination and genetic diversity in human rhinoviruses in children with acute respiratory infection. *PLoS One* 4:e6355. doi:10.1371/journal.pone.0006355.
 230. Wisdom A, Kutkowska AE, McWilliam Leitch EC, Gaunt E, Templeton K, Harvala H, Simmonds P. 2009. Genetics, recombination and clinical features of human rhinovirus species C (HRV-C) infections; interactions of HRV-C with other respiratory viruses. *PLoS One* 4:e8518. doi:10.1371/journal.pone.0008518.
 231. Thibaut HJ, De Palma AM, Neyts J. 2012. Combating enterovirus replication: state-of-the-art on antiviral research. *Biochem. Pharmacol.* 83:185–192.
 232. Thibaut HJ, Leyssen P, Puerstinger G, Muigg A, Neyts J, De Palma AM. 2011. Towards the design of combination therapy for the treatment of enterovirus infections. *Antiviral Res.* 90:213–217.
 233. Webster ADB. 2005. Pleconaril—an advance in the treatment of enteroviral infection in immunocompromised patients. *J. Clin. Virol.* 32:1–6.
 234. Rotbart HA, Webster AD. 2001. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin. Infect. Dis.* 32:228–335.
 235. Hayden FG, Herrington DT, Coats TL, Kim K, Cooper EC, Villano SA, Liu S, Hudson S, Pevear DC, Collett M, McKinlay M. 2003. Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. *Clin. Infect. Dis.* 36:1523–1532.
 236. Pevear DC, Hayden FG, Demenczuk TM, Barone LR, Mckinlay MA, Collett MS. 2005. Relationship of pleconaril susceptibility and clinical outcomes in treatment of common colds caused by rhinoviruses. *Antimicrob. Agents Chemother.* 49:4492–4499.
 237. Senior K. 2002. FDA panel rejects common cold treatment. *Lancet Infect. Dis.* 2:264. doi:10.1016/S1473-3099(02)00277-3.
 238. Lambert J. 2011. BTA798 is an orally bioavailable and potent inhibitor of human rhinovirus both *in vitro* and in an experimental challenge virus infection model in healthy volunteers, abstr D-1557. Abstr. 51st Intersci. Conf. Antimicrob. Agents Chemother.
 239. Hayden FG, Hipkind GJ, Woerner DH, Eisen GF, Janssens M, Janssen PA, Andries K. 1995. Intranasal pirodavid (R77,975) treatment of rhinovirus colds. *Antimicrob. Agents Chemother.* 39:290–294.
 240. Hayden FG, Andries K, Janssen PA. 1992. Safety and efficacy of intranasal pirodavid (R77975) in experimental rhinovirus infection. *Antimicrob. Agents Chemother.* 36:727–732.
 241. Patick AK. 2006. Rhinovirus chemotherapy. *Antiviral Res.* 71:391–396.
 242. Hayden FG, Turner RB, Gwaltney JM, Chi-Burris K, Gersten M, Hsyu P, Patick AK, Smith GJ, III, Zalman LS. 2003. Phase II, randomized, double-blind, placebo-controlled studies of rupintrivir nasal spray 2-percent suspension for prevention and treatment of experimentally induced rhinovirus colds in healthy volunteers. *Antimicrob. Agents Chemother.* 47:3907–3916.
 243. Patick AK, Brothers MA, Maldonado F, Binford S, Maldonado O, Fuhrman S, Petersen A, Smith GJ, III, Zalman LS. 2005. *In vitro* antiviral activity and single-dose pharmacokinetics in humans of a novel, orally bioavailable inhibitor of human rhinovirus 3C protease. *Antimicrob. Agents Chemother.* 49:2267–2275.
 244. Anzueto A. 2003. Diagnosis and treatment of rhinovirus respiratory infections. *Chest* 123:1664–1672.
 245. Hayden FG, Gwaltney JM, Jr. 1984. Intranasal Interferon- α_2 treatment of experimental rhinoviral colds infection. *J. Infect. Dis.* 150:174–180.
 246. Hayden FG, Kaiser DL, Albrecht JK. 1988. Intranasal recombinant alpha-2b interferon treatment of naturally occurring common colds. *Antimicrob. Agents Chemother.* 32:224–230.
 247. Barrett B. 2003. Medicinal properties of Echinacea: a critical review. *Phytomedicine* 10:66–86.
 248. Turner R, Bauer R, Woelkart K, Hulsey T, Gangemi JD. 2005. An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections. *N. Engl. J. Med.* 353:341–348.
 249. Goel V, Lovlin R, Barton R, Lyon MR, Bauer R, Lee TDG, Basu TK. 2004. Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. *J. Clin. Pharm. Ther.* 29:75–83.
 250. Taylor JA, Weber W, Standish L, Quinn H, McGann M, Calabrese C. 2003. Efficacy and safety of echinacea in treating upper respiratory tract infections in children. *JAMA* 290:2824–2830.
 251. Barrett BP, Brown RL, Locken K, Maberry R, Bobula JA, Alessio DD. 2002. Treatment of the common cold with unrefined *Echinacea*. *Ann. Intern. Med.* 137:939–946.
 252. Barrett B, Brown R, Rakel D, Marlon M, Bone K, Phyto D, Barlow S, Ewers T. 2010. *Echinacea* for treating the common cold: a randomized trial. *Ann. Intern. Med.* 153:769–777.
 253. Linde K, Barrett B, Bauer R, Melchart D, Woelkart K. 2009. *Echinacea* for preventing and treating the common cold. *Cochrane Database Syst. Rev.* 2009:CD000530. doi:10.1002/14651858.CD000530.pub2.
 254. European Medicines Agency Committee on Herbal Medicine Products. 2009. Assessment report on *Echinacea pallida* (Nutt.) Nutt., radix. Document EMEA/HMPC/332358/2008. European Medicines Agency, London, United Kingdom.
 255. European Medicines Agency Committee on Herbal Medicine Products. 2010. Assessment report on *Echinacea purpurea* (L.) Moench, radix. Document EMA/HMPC/577786/2008. European Medicines Agency, London, United Kingdom.
 256. European Medicines Agency Committee on Herbal Medicine Products. 2008. Assessment report on *Echinacea purpurea* (L.) Moench., herba recens. Document EMEA/HMPC/104918/2006. European Medicines Agency, London, United Kingdom.
 257. Butterworth BE, Korant BD. 1974. Characterization of the large picornaviral polypeptides produced in the presence of zinc ion. *J. Virol.* 14:282–291.
 258. Novick SG, Godfrey JC, Godfrey NJ, Wilder HR. 1996. How does zinc modify the common cold? Clinical observations and implications regarding mechanisms of action. *Med. Hypotheses* 46:295–302.
 259. Korant BD, Butterworth BE. 1976. Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides. *J. Virol.* 18:298–306.
 260. Harisch G, Kretschmer M. 1987. Some aspects of a non-linear effect of zinc ions on the histamine release from rat peritoneal mast cells. *Res. Commun. Chem. Pathol. Pharmacol.* 55:39–48.
 261. Singh M, Das R. 2011. Zinc for the common cold. *Cochrane Database Syst. Rev.* 2011:CD001364. doi:10.1002/14651858.CD001364.pub3.
 262. Science M, Johnstone J, Roth DE, Guyatt G, Loeb M. 2012. Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. *CMAJ* 184:E551–E561. doi:10.1503/cmaj.111990.
 263. Gwaltney JM, Park J, Paul RA, Edelman DA, Connor RRO, Turner RB. 1996. Randomized controlled trial of clemastine fumarate for treatment of experimental rhinovirus colds. *Clin. Infect. Dis.* 22:656–662.
 264. Gwaltney JM, Druce HM. 1997. Efficacy of brompheniramine maleate for the treatment of rhinovirus colds. *Clin. Infect. Dis.* 25:1188–1194.
 265. Sutter AI, Lemiengre M, Campbell H, Mackinnon HF. 2003. Antihistamines for the common cold. *Cochrane Database Syst. Rev.* 2003:CD001267. doi:10.1002/14651858.CD001267.
 266. Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Nair S, Foxlee R, Rivetti A. 2010. Physical interventions to interrupt or reduce the spread of respiratory viruses: a Cochrane review. *Health Technol. Assess.* 14:347–476.
 267. Solomon T, Lewthwaite P, Perera D, Cardoso MJ, McMinn P, Ooi MH. 2010. Virology, epidemiology, pathogenesis, and control of enterovirus 71. *Lancet Infect. Dis.* 10:778–790.
 268. Broderick MP, Hansen CJ, Russell KL. 2008. Exploration of the effectiveness of social distancing on respiratory pathogen transmission implicates environmental contributions. *J. Infect. Dis.* 198:1420–1426.
 269. Kelso JK, Milne GJ, Kelly H. 2009. Simulation suggests that rapid activation of social distancing can arrest epidemic development due to a novel strain of influenza. *BMC Public Health* 9:117. doi:10.1186/1471-2458-9-117.
 270. Glass RJ, Glass LM, Beyeler WE, Min HJ. 2006. Targeted social distancing design for pandemic influenza. *Emerg. Infect. Dis.* 12:1671–1681.

271. Loeb M, Dafoe N, Mahony J, John M, Sarabia A, Glavin V, Chong S, Webb A, Walter SD. 2009. Surgical mask vs N95 respirator among health care workers. *JAMA* 302:1865–1871.
272. Turner RB, Fuls JL, Rodgers ND. 2010. Effectiveness of hand sanitizers with and without organic acids for removal of rhinovirus from hands. *Antimicrob. Agents Chemother.* 54:1363–1364.
273. Turner RB, Fuls JL, Rodgers ND, Goldfarb HB, Lockhart LK, Aust LB. 2012. A randomized trial of the efficacy of hand disinfection for prevention of rhinovirus infection. *Clin. Infect. Dis.* 54:1422–1426.
274. Hayden FG, Albrecht JK, Kaiser DL, Gwaltney JM. 1986. Prevention of natural colds by contact prophylaxis with intranasal α_2 -interferon. *N. Engl. J. Med.* 314:71–75.
275. Farr BM, Gwaltney JM, Adams KF, Hayden FG. 1984. Intranasal interferon- α 2 for prevention of natural rhinovirus colds. *Antimicrob. Agents Chemother.* 26:31–34.
276. Monto AS, Shope TC, Schwartz SA, Albrecht JK. 1986. Intranasal interferon- α_{2b} for seasonal prophylaxis of respiratory infection. *J. Infect. Dis.* 154:128–133.
277. Sperber SJ, Levine PA, Innes DJ, Mills SE, Hayden FG. 1988. Tolerance and efficacy of intranasal administration of recombinant β serine interferon in healthy adults. *J. Infect. Dis.* 158:166–175.
278. Sperber SJ, Levine PA, Sorrentino JV, Riker DK, Hayden FG. 1989. Ineffectiveness of recombinant interferon- β serine nasal drops for prophylaxis of natural colds. *J. Infect. Dis.* 160:700–705.
279. Sperber SJ, Shah LP, Gilbert RD, Ritchey TW, Monto AS. 2004. *Echinacea purpurea* for prevention of experimental rhinovirus colds. *Clin. Infect. Dis.* 38:1367–1371.
280. Turner RB, Riker DK, Gangemi JD. 2000. Ineffectiveness of echinacea for prevention of experimental rhinovirus colds. *Antimicrob. Agents Chemother.* 44:1708–1709.
281. Hemilä H, Chalker E, Douglas B. 2010. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst. Rev.* 2010: CD000980. doi:10.1002/14651858.CD000980.pub3.
282. Rohde GGU. 2011. Rhinovirus vaccination: the case in favour. *Eur. Respir. J.* 37:3–4.
283. Edlmayr J, Niespodziana K, Popow-Kraupp T, Krzyzanek V, Focke-Tejkl M, Blaas D, Grote M, Valenta R. 2011. Antibodies induced with recombinant VP1 from human rhinovirus exhibit cross-neutralization. *Eur. Respir. J.* 37:44–52.
284. Turner R, Wecker M, Pohl G. 1999. Efficacy of tremacamra, a soluble intercellular adhesion molecule 1, for experimental rhinovirus infection. *JAMA* 281:1797–1804.
285. Levandowski RA, Pachucki CT, Rubenis M, Jackson GG. 1982. Topical enviroxime against rhinovirus infection. *Antimicrob. Agents Chemother.* 22:1004–1007.
286. Phillpotts RJ, Wallace J, Tyrrell DA, Tagart VB. 1983. Therapeutic activity of enviroxime against rhinovirus infection in volunteers. *Antimicrob. Agents Chemother.* 23:671–675.
287. Phillpotts R, DeLong D, Wallace J. 1981. The activity of enviroxime against rhinovirus infection in man. *Lancet* i:1342–1344.
288. Miller FD, Monto AS, DeLong DC, Exelby A, Bryan ER, Srivastava S. 1985. Controlled trial of enviroxime against natural rhinovirus infections in a community. *Antimicrob. Agents Chemother.* 27:102–106.
289. Wark PAB, Buchieri F, Johnston SL, Gibson PG, Hamilton L, Mimica J, Zummo G, Holgate ST, Attia J, Thakkestian A, Davies DE. 2007. IFN- γ -induced protein 10 is a novel biomarker of rhinovirus-induced asthma exacerbations. *J. Allergy Clin. Immunol.* 120:586–593.

Samantha E. Jacobs received a B.A. from Cornell University and an M.D. from the University of Pennsylvania. Following an Internal Medicine residency at Mount Sinai Medical Center, she completed a fellowship in Infectious Diseases at New York Presbyterian Hospital/Weill Cornell. During fellowship, she conducted studies on the clinical and molecular epidemiology of human rhinovirus infections in patients with hematologic malignancy and hematopoietic stem cell transplant recipients. In the fall of 2012, Dr. Jacobs joined the faculty of Weill Cornell Medical College as an Instructor in Medicine in the Transplantation-Oncology Infectious Diseases Program in the Division of Infectious Diseases. Dr. Jacobs' current research interests include respiratory viral infections in immunocompromised hosts and infectious disease screening of solid-organ transplantation donors and recipients.



Daryl M. Lamson graduated from the State University of New York at Plattsburg in 1997 with a degree in Medical Technology that included a 1-year clinical internship at Albany Medical Center. After graduation, he worked as a Clinical Laboratory Technologist in the Clinical Chemistry Laboratory and the Molecular Diagnostics Laboratory at Albany Medical Center. For the past 10 years, he has worked as a Research Scientist in the Virology Diseases Laboratory of the Division of Infectious Diseases at the Wadsworth Center in Albany, NY. He participates in viral outbreak investigations and is a major contributor to projects that introduce new molecular technologies and automation into the clinical laboratory. His main research interest over the last 10 years has been molecular strain analysis of a wide variety of viral pathogens obtained from clinical specimens.



Kirsten St. George is in the Division of Infectious Diseases at the Wadsworth Center in Albany, NY. She is a virologist with interests in applied research, infectious disease surveillance, and laboratory regulatory issues. Respiratory viral infections are a major focus for her laboratory, with projects on the investigation of mixed-virus infections, the evolution of antiviral resistance in influenza virus, and the development and validation of new diagnostic assays, including microarrays. Her laboratory is also the New York State reference laboratory for virology. Before moving to Albany in 2004, where Dr. St. George is Director of the Virology Laboratory and Chief of the Laboratory of Viral Diseases, she held positions at the University of Pittsburgh Medical Center (1992 to 2004), the Royal Hobart Hospital in Tasmania (1985 to 1992), the Institute of Medical and Veterinary Science in South Australia (1982 to 1985), and the University of Adelaide (1980 to 1981).



Continued next page

Thomas J. Walsh is Director of the new Transplantation-Oncology Infectious Diseases Program and Professor of Medicine, Pediatrics, and Microbiology and Immunology at Weill Cornell Medical Center. Following graduation from Johns Hopkins University School of Medicine, Dr. Walsh completed 10 postdoctoral years of laboratory investigation, clinical research, and patient care with laboratory expertise in pharmacology, innate host defenses, molecular diagnostics, and medical mycology. Following a distinguished translational research career in the National Cancer Institute's Pediatric Oncology Branch, where he built an internationally recognized program leading to major advances in the diagnosis, treatment, and prevention of invasive fungal infections in children and adults with cancer, Dr. Walsh was recruited to his current position at Weill Cornell Medical Center. The core mission of the Transplantation-Oncology Infectious Diseases Program is to conduct leading translational research, training, and patient care in the diagnosis, treatment, and prevention of life-threatening fungal, bacterial, and viral infections in immunocompromised patients.



HISTORIA CLINICA

RADICADO: 2018-00012-00

RADICADO INTERNO: 2023-06-26-0148



HISTORIA CLINICA 27 FOLIOS

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177

IDANNASOFIA MITCHELL MENA

Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA

Dirección: Teléfono:

Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION

G. etareo: 3
Grupo Sanguineo:



Sede de Atención : 015 BVENTURA CLINICA COMFENALCO

FOLIO 1 FECHA 01/04/2016 08:31:54 TIPO DE ATENCION URGENCIAS

SIGNOS VITALES

Hora Toma: 08:37:14

TAS. mm.Hg.	TAD. mm.Hg.	Media	FC. x Min.	FR. x Min.	Temp. oC	Via Toma Temp.	TALLA cmts	PULSO x Min.	PVC	PESO Kgms	Estado Hidratación	GLUCOME	I.M.C.
0	0	0	228	22	38,80	Axilar	0,00	0	0	7,50	Hidratad	0	0,00
Glasgow	Ramsay	Richmond Rass	Escala dolor	Tipo escala de dolor			Perímetro Cefalico	Perímetro Abdominal		FC. Fetal	Estadio Renal	% Riesgo Cardio.	Cod Profesional
0	0	0	0	MENOR DE EDAD			0,00	0,00		0	0	0	M1296

PIEL: NORMAL

RESPIRATORIO: NORMAL
% SATURACION O.2.: 100

TRIAGE (MOTIVO DE CONSULTA)

TEMPERATURA MAYOR DE 38.5 ASOCIADO A OTROS SINTOMAS -

OBSERVACIONES

PACIENTE MANIFIESTA QUE LA MENOR PRESENTA , FIEBRE, DIARREA EN 2 OCASIONES E INTOLERANCIA A LA VIA ORAL

CLASIFICACION TRIAGE: 3 PRIORIDAD III

Diana Rocio Caicedo R.

DIANA ROCIO CAICEDO RODRIGUEZ

Reg.
ENFERMERIA

Sede de Atención : 015 BVENTURA CLINICA COMFENALCO

FOLIO 2 FECHA 01/04/2016 08:41:07 TIPO DE ATENCION URGENCIAS

MOTIVO DE CONSULTA

"ESTA CON FIEBRE Y DIARREA"

ENFERMEDAD ACTUAL

LACTANTE MENOR CON CUADRO CLINICO DE 1 MES DE EVOLUCION CONSISTENTE EN SINDROME GRIPAL, CON RINORREA HIALINA, ACOMPAÑADO DE TOS NO PRODUCTIVA CON DIFICULTAD RESPIRATORIA. HOY LA TRAE A CONSULTA LA ABUELA POR DEPOSICIONES LIQUIDAS VERDOSA, MODERADA CANTIDAD, CON MOCO, SIN SANGRE DESDE HACE 1 DIA EN MULTIPLES OCASIONES, CONCOMITANTE A ESTO FIEBRE DE 38.5 GRADO.

ANTECEDENTES PERSONALES
PATOLOGICOS: NIEGA
FARMACOLOGICOS: LORATADINA
ALERGIAS: NIEGA
Qx: NIEGA

REVISION X SISTEMAS

CABEZA Y ORAL: NIEGA

EXAMEN FISICO

CABEZA Y ORAL: INGRESA EN BRAZOS DE LA ABUELA, ALERTA, ACTIVA, IRRITABLE, FEBRIL, SIN SIGNOS DE DIFICULTAD RESPIRATORIA

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177

IDANNASOFIA MITCHELL MENA

Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA

Dirección: Teléfono:

Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION

G. etareo: 3
Grupo Sanguineo:



CABEZA: NORMOCEFALA
ORL: ESCLERAS ANICTERICAS, CONJUNTIVAS ROSADAS, MUCOSAS HUMEDAS
CUELLO: MOVIL, NO MASAS NI ADENOPATIAS
C/P: RsCsRs, NO SOPLOS. MV CONSERVADO EN ACP SIN PRESENCIA DE RUIDOS SOBREAGREGADOS
ABD: BLANDO, DEPRESIBLE, NO SIGNOS DE IRRITACION PERITONEAL, NO VISCEROMEGALIAS
G/U: SE OMITE
EXTR: MOVILES, SIMETRICAS, NO EDEMA

DIAGNOSTICO R509 FIEBRE NO ESPECIFICADA Tipo PRINCIPAL

DIAGNOSTICO A09X DIARREA Y GASTROENTERITIS DE PRESUNTO ORIGEN INFECCIOSO Tipo RELACIONADO

FORMULA MEDICA

Cantidad	Dosis	Descripción	Via	Frecuencia	Obs.
1,00	1,00 AMPOLLAS	DIPIRONA 1 GR SLN. INY 33MCG	INTRAVENOSO	Dosis Unica	NUEVO

DILUIR EN 10CC Y PASAR 0.5CC AHORA

ORDENES DE LABORATORIO

Cantidad	Descripción
1	HEMOGRAMA IV
1	COPROLOGICO
1	UROANALISIS CON SEDIMENTO Y DENSIDAD URINARIA

ORDENES DE TERAPIAS

Cantidad	Descripción	Estado
2	NEBULIZACION	
	3CC SSN + 1 GOTA TERBUROT	

WILMAR DALEY PEREA SINISTERRA

Reg.
MEDICINA GENERAL

Sede de Atención : 015 BVENTURA CLINICA COMFENALCO

FOLIO 4 FECHA 01/04/2016 10:07:53 TIPO DE ATENCION URGENCIAS

NOTAS ENFERMERIA

PACIENTE DE 4 MESES EN SU 1 DÍA DE INTERNACIÓN CON LOS SIGUIENTES DIAGNOSTICOS: -FIEBRE NO ESPECIFICADA
-DIARREA Y GASTROENTERITIS DE PRESUNTO ORIGEN INFECCIOSO SE CUMPLEN ORDEN MEDICA A PCTE SIN COMPLICACION
EL MEDICO DE TURNO ORDENA DIPIRONA 1 GRM EV LLEVAR A 10 CC Y APLICAT 0,5 EV + REALIZAR 2 CICLO DE
NEBULIZACION CON 3 CC DE SSN + 1 GOTA DE TERB EN CADA 20 MIN PENDINTE PARA CLINICOS CH PO + COPROLOGICO
SE CUMPLEN ORDEN SIN COMPLICACION

Nota realizada por: ELECENIA BALANTA AMU Fecha: 01/04/16 10:08:36

ELECENIA BALANTA

ELECENIA BALANTA AMU
Reg.
AUXILIAR ENFERMERIA

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177
IDANNASOFIA MITCHELL MENA
Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA
Dirección: Teléfono:
Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION

G. etareo: 3
Grupo Sanguíneo:



Sede de Atención : 015 BVENTURA CLINICA COMFENALCO

FOLIO 5 FECHA 01/04/2016 11:22:28 TIPO DE ATENCION URGENCIAS

ORDENES DE IMAGENES DIAGNOSTICAS

Cantidad	Descripción
1	RADIOGRAFIA DE TORAX (PAO APY LATERAL DECUBITO LATERAL OBLICUAS O LATERAL CON BARIO)

WILMAR DALEY PEREA SINISTERRA
Reg.
MEDICINA GENERAL

Sede de Atención : 015 BVENTURA CLINICA COMFENALCO

FOLIO 6 FECHA 01/04/2016 11:41:10 TIPO DE ATENCION URGENCIAS

EVOLUCION MEDICO

LLEGA REPORTE DE HEMOGRAMA: LEUCOS: 25.060, N: 67.5% L: 20% HGB: 12 PLQ: 457.000
PENDIENTE UROANALISIS, COPROLOGICO Y RX TORAX
PACIENTE MEJORA DIFICULTAD RESPIRATORIA CON NEBULIZACIONES, PERSISTE FEBRIL SE ORDENA DOSIS ORAL DE ACETAMINOFEN
Evolucion realizada por: WILMAR DALEY PEREA SINISTERRA-Fecha: 01/04/16 11:41:28

WILMAR DALEY PEREA SINISTERRA
Reg.
MEDICINA GENERAL

Sede de Atención : 015 BVENTURA CLINICA COMFENALCO

FOLIO 7 FECHA 01/04/2016 12:48:59 TIPO DE ATENCION URGENCIAS

EVOLUCION MEDICO

RX TORAX: NO EVIDENCIO INFILTRADOS, NO ATRAPAMIENTO DE AIRE.
SE OBSERVA COLECCION DE MATERIA FECAL EN INTESTINO
ABDOMEN DOLOROSO A LA PALPACION
PENDIENTE UROANALISIS Y COPROLOGICO PARA DEFINIR CONDUCTA
Evolucion realizada por: WILMAR DALEY PEREA SINISTERRA-Fecha: 01/04/16 12:49:04

WILMAR DALEY PEREA SINISTERRA
Reg.
MEDICINA GENERAL

Sede de Atención : 015 BVENTURA CLINICA COMFENALCO

FOLIO 8 FECHA 01/04/2016 17:40:31 TIPO DE ATENCION URGENCIAS

EVOLUCION MEDICO

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177

IDANNASOFIA MITCHELL MENA

Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA

Dirección: Teléfono:

Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION



LLEGA REPORTE DE PARACLINICOS

COPROLOGICO DIARREICA CAFE FUERTE FLORA BACTERIANA AUMENTADA

SE REVALORA PACIENTE ESTABLE, CON MEJORIA DE SU CUADRO CLINICO DE INGRESO, NO FIEBRE, TOLERA VIA ORAL. SE DECIDE DAR EGRESO CON SIGNOS DE ALARMA PARA RECONSULTAR: INTOLERANCIA A LA VIA ORAL, FIEBRE PERSISTENTE, NO RESPIRA BIEN, DOLOR ABDOMINAL, SI SE PONE MORADO, ETC, EL FAMILIAR REFIERE ENTENDER

Evolucion realizada por: TATIANA ODETH MOSQUERA STOMER Fecha: 01/04/16 17:40:35

Tatiana Odeth Mosquera St

TATIANA ODETH MOSQUERA STOMER

Reg.

MEDICINA GENERAL

Fecha: 06/04/16

Edad: 4 MESES

Sexo: Masculino

G. etareo: 1

Grupo Sanguíneo:

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177

IDANNA SOFIA MITCHELL MENA

Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA

Dirección:

Teléfono:

Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION



Sede de Atención : 015

BVENTURA CLINICA COMFENALCO

FOLIO 1

FECHA: 01/04/2016 08:31:54

TIPO DE ATENCION

URGENCIAS

SIGNOS VITALES

Hora Toma: 08:37:14

TAS. mm.Hg.	TAD. mm.Hg.	Media	FC. x Min.	FR. x Min.	Temp. oC	Via Toma Temp.	TALLA cmts	PULSO x Min.	PVC	PESO Kgms	Estado Hidratación	GLUCOME	I.M.C.
0	0	0	228	22	38,80	Axilar	0,00	0	0	7,50	Hidratad	0	0,00
Glasgow	Ramsay	Richmond Rass	Escala dolor		Tipo escala de dolor		Perímetro Cefalico	Perímetro Abdominal		FC. Fetal	Estadio Renal	% Riesgo	Cod Profesional
0	0	0	0		MENOR DE EDAD		0,00	0,00		0	0	0	M1296

PIEL: NORMAL

RESPIRATORIO: NORMAL

% SATURACION O2.: 100

TRIAGE (MOTIVO DE CONSULTA)

TEMPERATURA MAYOR DE 38.5 ASOCIADO A OTROS SINTOMAS -

OBSERVACIONES

PACIENTE MANIFIESTA QUE LA MENOR PRESENTA, FIEBRE, DIARREA EN 2 OCASIONES E INTOLERANCIA A LA VIA ORAL

CLASIFICACION TRIAGE: 3 PRIORIDAD III

DIANA ROCIO CACEDO RODRIGUEZ

Reg.

ENFERMERIA

Sede de Atención : 015

BVENTURA CLINICA COMFENALCO

FOLIO 2

FECHA: 01/04/2016 08:41:07

TIPO DE ATENCION

URGENCIAS

MOTIVO DE CONSULTA

"ESTA CON FIEBRE Y DIARREA"

ENFERMEDAD ACTUAL

LACTANTE MENOR CON CUADRO CLINICO DE 1 MES DE EVOLUCION CONSISTENTE EN SINDROME GRIPAL, CON RINORREA HIALINA, ACOMPAÑADO DE TOS NO PRODUCTIVA CON DIFICULTAD RESPIRATORIA. HOY LA TRAE A CONSULTA LA ABUELA POR DEPOSICIONES LIQUIDAS VERDOSA, MODERADA CANTIDAD, CON MOCO, SIN SANGRE DESDE HACE 1 DIA EN MULTIPLES OCASIONES, CONCOMITANTE A ESTO FIEBRE DE 38.5 GRADO.

ANTECEDENTES PERSONALES

PATOLOGICOS: NIEGA

FARMACOLOGICOS: LORATADINA

ALERGIAS: NIEGA

Qx: NIEGA

REVISION X SISTEMAS

CABEZAY ORAL: NIEGA

EXAMEN FISICO

CABEZAY ORAL: INGRESA EN BRAZOS DE LA ABUELA, ALERTA, ACTIVA, IRRITABLE, FEBRIL, SIN SIGNOS DE DIFICULTAD RESPIRATORIA

6J.0 *HOSVITAL*

Usuario: 38466049 MERLYN ROSA FANDINO MART

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177

IDANNA SOFIA MITCHELL MENA

Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA

Dirección:

Teléfono:

Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION



CABEZA: NORMOCEFALA

ORL: ESCLERAS ANICTERICAS, CONJUNTIVAS ROSADAS, MUCOSAS HUMEDAS

CUELLO: MOVIL, NO MASAS NI ADENOPATIAS

C/P: RsCsRs, NO SOPLOS. MV CONSERVADO EN ACP SIN PRESENCIA DE RUIDOS SOBREAGREGADOS

ABD: BLANDO, DEPRESIBLE, NO SIGNOS DE IRRITACION PERITONEAL, NO VISCEROMEGALIAS

G/U: SE OMITE

EXTR: MOVILES, SIMETRICAS, NO EDEMA

DIAGNOSTICO R509 FIEBRE NO ESPECIFICADA

Tipo PRINCIPAL

DIAGNOSTICO A09X DIARREA Y GASTROENTERITIS DE PRESUNTO ORIGEN INFECCIOSO

Tipo RELACIONADO

FORMULA MEDICA

Cantidad	Dosis	Descripción	Via	Frecuencia	Obs.
1,00	1,00 AMPOLLAS	DIPIRONA 1 GR SLN. INY 33MCG	INTRAVENOSO	Dosis Unica	NUEVO

DILUIR EN 10CC Y PASAR 0.5CC AHORA

ORDENES DE LABORATORIO

Cantidad	Descripción
1	HEMOGRAMA IV
1	COPROLOGICO
1	UROANALISIS CON SEDIMENTO Y DENSIDAD URINARIA

ORDENES DE TERAPIAS

Cantidad	Descripción	Estado
2	NEBULIZACION	
	3CC SSN + 1 GOTATERBUROT	

WILMAR DALEY PEREA SINISTERRA

Reg.

MEDICINA GENERAL

Sede de Atención : 015

BVENTURACLINICA COMFENALCO

FOLIO 4

FECHA 01/04/2016 10:07:53

TIPO DE ATENCION

URGENCIAS

NOTAS ENFERMERIA

PACIENTE DE 4 MESES EN SU 1 DÍA DE INTERNACIÓN CON LOS SIGUIENTES DIAGNOSTICOS: -FIEBRE NO ESPECIFICADA -DIARREA Y GASTROENTERITIS DE PRESUNTO ORIGEN INFECCIOSO SE CUMPLEN ORDEN MEDICA A PCTE SIN COMPLICACION EL MEDICO DE TURNO ORDENA DIPIRONA 1 GRM EV LLEVAR A 10 CC Y APLICAT 0,5 EV + REALIZAR 2 CICLO DE NEBULIZACION CON 3 CC DE SSN + 1 GOTATERB EN CADA 20 MIN PENDIENTE PARA CLINICOS CH PO + COPROLOGICO SE CUMPLEN ORDEN SIN COMPLICACION

Nota realizada por: ELECENIA BALANTA AMU Fecha: 01/04/16 10:08:36

ELECENIA BALANTA AMU

ELECENIA BALANTA AMU

Reg.

AUXILIAR ENFERMERIA

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177

IDANNA SOFIA MITCHELL MENA

Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA

Dirección: Teléfono:

Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION



Sede de Atención : 015

BVENTURACLINICA COMFENALCO

FOLIO 5

FECHA 01/04/2016 11:22:28

TIPO DE ATENCION

URGENCIAS

ORDENES DE IMAGENES DIAGNOSTICAS

Cantidad

Descripción

1

RADIOGRAFIA DE TORAX (PAO APY LATERAL DECUBITO LATERAL OBLICUAS O LATERAL CON BARIO)

WILMAR DALEY PEREA SINISTERRA

Reg.

MEDICINA GENERAL

Sede de Atención : 015

BVENTURACLINICA COMFENALCO

FOLIO 6

FECHA 01/04/2016 11:41:10

TIPO DE ATENCION

URGENCIAS

EVOLUCION MEDICO

LLEGAREPORTE DE HEMOGRAMA: LEUCOS: 25.060, N: 67.5% L: 20% HGB: 12 PLQ: 457.000

PENDIENTE UROANALISIS, COPROLOGICO Y RX TORAX

PACIENTE MEJORA DIFICULTAD RESPIRATORIA CON NEBULIZACIONES, PERSISTE FEBRIL SE ORDENA DOSIS ORAL DE ACETAMINOFEN

Evolucion realizada por: WILMAR DALEY PEREA SINISTERRA-Fecha: 01/04/16 11:41:28

WILMAR DALEY PEREA SINISTERRA

Reg.

MEDICINA GENERAL

Sede de Atención : 015

BVENTURACLINICA COMFENALCO

FOLIO 7

FECHA 01/04/2016 12:48:59

TIPO DE ATENCION

URGENCIAS

EVOLUCION MEDICO

RX TORAX: NO EVIDENCIO INFILTRADOS, NO ATRAPAMIENTO DE AIRE.

SE OBSERVA COLECCION DE MATERIA FECAL EN INTESTINO

ABDOMEN DOLOROSO A LA PALPACION

PENDIENTE UROANALISIS Y COPROLOGICO PARA DEFINIR CONDUCTA

Evolucion realizada por: WILMAR DALEY PEREA SINISTERRA-Fecha: 01/04/16 12:49:04

WILMAR DALEY PEREA SINISTERRA

Reg.

MEDICINA GENERAL

Sede de Atención : 015

BVENTURACLINICA COMFENALCO

FOLIO 8

FECHA 01/04/2016 17:40:31

TIPO DE ATENCION

URGENCIAS

EVOLUCION MEDICO

No. Doc. Identidad RC 1115461177 No. His. Cli. 1115461177

IDANNA SOFIA MITCHELL MENA

Departamento: 76 VALLE DEL CAUCA Municipio: 109 BUENAVENTURA

Dirección:

Teléfono:

Ocupación: PERSONAS QUE NO HAN DECLARADO OCUPACION



LLEGAREPORTE DE PARACLINICOS

COPROLOGICO DIARREICA CAFE FUERTE FLORA BACTERIANA AUMENTADA

SE REVALORA PACIENTE ESTABLE, CON MEJORIA DE SU CUADRO CLINICO DE INGRESO, NO FIEBRE, TOLERANCIA A LA VIA ORAL. SE
DECIDE DAR EGRESO CON SIGNOS DE ALARMA PARA RECONSULTAR: INTOLERANCIA A LA VIA ORAL, FIEBRE PERSISTENTE,
NO RESPIRA BIEN, DOLOR ABDOMINAL, SI SE PONE MORADO, ETC, EL FAMILIAR REFIERE ENTENDER
Evolucion realizada por: TATIANA ODETH MOSQUERA STOMER-Fecha: 01/04/16 17:40:35

TATIANA ODETH MOSQUERA STOMER

Reg.

MEDICINA GENERAL



HISTORIA CLINICA

7

PACIENTE: HIJA DE MATRA SOFIA MENA ALVAREZ	IDENTIFICACION: MS 316021662	HC: 316021662 - MS
FECHA DE NACIMIENTO: 11/11/2015	EDAD: 0 Años	SEXO: F
RESIDENCIA: BR CENTENARIO	VALLE DEL CAUCA-BUENAVENTURA	TIPO AFILIADO: Beneficiario
OCUPACION:	NOMBRE RESPONSABLE:	TELÉFONO: 3183056738
NOMBRE ACOMPAÑANTE: VLDIMIR MENA	PARENTESCO: Tío(a)	TELÉFONO:
FECHA INGRESO: 1/4/2016 - 11:04:00	FECHA EGRESO: 4/4/2016 - 16:57:40	CAMA: UCIP-301
DEPARTAMENTO: 020107 - UCI PEDIATRICA - SANTA SOFIA	SERVICIO: U.C.I.	
PLAN: EMSSANAR ESS 2015-2016		

Imprimió: ALMA OLIVA GARCIA PALACIOS -alma.garcia

Fecha Impresión : 2016/6/3 - 11:44:02

EVOLUCIONES	
FECHA	EVOLUCIONES
01:01	SERVICIO: URGENCIAS german.sanjuanelo - GERMAN JOSE SANJUANELO CONTRADO ESPECIALIDAD: MEDICO GENERAL BRONQUIOLITIS SOBREINFECTADA PLAN: OBSERVACION NADA VO, DAD, 300 + 5 CC DE KATROL + 7 CC DE NATROL PASAR A 24 CC HORA AMPICILINA SULBACTAM, 300 MG IV CADA 6 HORAS ACETAMINOFEN, 3 CC VO CADA 6 HORAS, TERAPIA RESPIRATORIA CADA 4 HORAS INHALADORES, SS GASES ARTERIALES CSV AC *ANÁLISIS(JUSTIFICACIÓN): SE TRATAD DE LACTANTE MENOR, QUE INGRESA POR PRESENTAR CC DE +- 12 HORAS DE EVOLUCION, CONSISTENTE, EN TOS HUMEDA ASOCIADO A DIFICULTAD RESPIRATORIA, PACIENTE INGRESA EN MALAS CONDICIONES GENERALES POLIPNEICA CON TIRAJES INTERCOSTALES AGREGADOS PULMONARES, SE REvisa RX DE TORAX ENCONTRANDO INFILTRADOS PARA HILIARES, SIN CONSOLIDADOS AEREOS, PACIENTE CON LEVE MEJORIA, PERO PERSISTE CON AGREGADOS PULMONARES, SE DECIDE DEJAR EN OBSERVACION PARA VALROACION POR PEDIATRIA, SE INICIA ANTIBIOTICOTERAPIA, TENIENDO EN CUENTA LEUCOCITGOS INICIALES, DE 25 MIL REPORTADOS, EN 2DO NIVEL. HALLAZGO OBJETIVO: PESO 6 K
04:04	SERVICIO: URGENCIAS mildred.fernandez - MILDRED LUCIA FERNANDEZ QUIRAMA ESPECIALIDAD: MEDICO GENERAL LACTANTE FEMENINA EUTRÓFICA INSUFICIENCIA RESPIRATORIA 2RIA A BRONQUIOLITIS SOBREINFECTADA SOSPECHA SEPSIS DE ORIGEN PULMONAR RIESGO INMINENTE DE FALLA VENTILATORIA PLAN: PESO: 6KG TRASLADÓ A UCIP MONITORIA ELECTRONICA NO INVASIVA CONTINUA OXIGENO POR VENTURY PARA MANTENER SATO2 MAYOR A 95%

S/S GASES ARTERIALES
DEMÁS ORDENES IGUALES

*ANÁLISIS (JUSTIFICACIÓN):

PACIENTE INGRESA A OBSERVACIÓN EN MALAS CONDICIONES GENERALES, TAQUICÁRDICA, CON DISTRES RESPIRATORIO MARCADO A PESAR DE SOPORTE DE OXÍGENO POR VENTURY, SIN DESATURACIÓN, RECIBIÓ A SU INGRESO DOSIS DE ANTIPIRÉTICO ENDOVENOSO PERO PERSISTE CON ALTA TÉRMICA DE 39°C POR LO QUE SUMISTRA DOSIS DE ACETAMINOFEN, POSTERIORMENTE PACIENTE CON MARCADA DISTENSIÓN ABDOMINAL SE INDICA PASO DE SOG OBSERVANDO DRENAJE DE DÉBITO SANGUINOLENTO, SE SOLICITAN GASOMETRIA ARTERIAL PARA EVALUAR NIVEL DE OXIGENACIÓN Y EQUILIBRIO ÁCIDO BASE LOS CUALES NO SE REALIZAN POR NO FUNCIONALIDAD DE LA MÁQUINA DE GASES EN EL MOMENTO, HEMOGRAMA SIN LEUCOCITOSIS, CON ANEMIA MICRO/MICRO SIN REQUERIMIENTO TRANSFUSIONAL, DEMÁS LÍNEAS CELULARES SIN ALTERACIÓN, REACTANTE DE FASE AGUDA SIGNIFICATIVAMENTE AUMENTADA CON RX DE TÓRAX CON HORIZONTALIZACIÓN DE LOS ARCOS COSTALES, SILUETA CARDIOTÍMICA NORMAL, CON INFILTRADOS PARAHILIARES, SIN CONSOLIDADOS NI ATELECTASIAS, A NIVEL ABDOMINAL SE OBSERVA MARCADA DISTENSIÓN DE ASAS, POR EL DETERIORO CLÍNICO DE LA PACIENTE Y EL ALTO RIESGO DE FALLA VENTILATORIA SE COMENTA CON MÉDICO ASISTENCIAL DE LA UNIDAD DE CUIDADOS INTENSIVOS PEDIÁTRICOS QUIEN DA CUPO Y SE PROCEDE PARA SU TRASLADO. SE LE INFORMA A FAMILIARES LA CONDUCTA TOMADA QUIENES ESTÁN DE ACUERDO.

HALLAZGO OBJETIVO:

HALLAZGO SUBJETIVO:

INTERPRETACIÓN APOYO DIAGNÓSTICO:

PROTEÍNA C REACTIVA 149

INTERPRETACIÓN ESTUDIOS IMAGENOLÓGICA:

06:19 SERVICIO: UCI PEDIÁTRICA

ivan.pinto - IVAN ALEXANDER PÍNTO MARTÍNEZ
ESPECIALIDAD: PEDIATRA

- LACTANTE FEMENINA EUTRÓFICA
- INSUFICIENCIA RESPIRATORIA
- HEMORRAGIA ALVEOLAR DIFUSA
- SEPSIS DE ORIGEN PULMONAR
- NEUTROPENIA FEBRIL
- COAGULACIÓN INTRAVASCULAR DISEMINADA DESCOMPENSADA
- PARO CARDIORESPIRATORIO CON REANIMACIÓN FALLIDA

PLAN:

ORDENES MÉDICAS PESO: 6.6 KG

- CUIDADOS INTENSIVOS PEDIÁTRICOS
- CABEZERA A 30°C
- MANTENER EUTERMICO
- NADA VÍA ORAL
- SOG ABIERTA
- VENTILACIÓN MECÁNICA MODO PRESIÓN SIMV TOT 4:5
- LEV: DAD AL 5% 500 CC MÁS SODIO:12.5CC + POTASIO:5CC PASAR A RAZÓN DE 33 CC/HORA (TH 120CC7KG7DIA)
- SSN 0.9% 60 CC PASAR EN 1 HORA
- CEFEPIME 330.MG IV CADA 6 HORAS (DOSIS:200MG/KG/DIA) D0
- AMIKACINA 99 MG IV CADA 24 HORAS (15MG/KG/DIA) D1
- OMEPRAZOL 6.6 MG EV CADA DÍA
- VITAMINA K 5 MG IV AHORA CONTINUAR CADA 12 HORAS
- ADRENALINA 1 MG TOT AHORA
- TRANSFUNDIR 99 CC DE GRE DESLEUCOCITADOS Y COMPATIBLES PASAR EN 3 HORAS
- DIPIRONA 132 MG EV POR RAZÓN NECESARIA EN CASO DE Tº PERSISTENTE MAYOR DE 38,5°C

- MIDAZOLAM 1.9 MG IV AHORA DOSIS 1
- SE SOLICITA RX DE TORAX PORTATIL AHORA
- SE SOLICITA RX DE ABDOMEN SIMPLE AHORA
- SE SOLICITA GASOMETRIA ARTERIAL AHORA
- SS HEMOGRAMA CONTROL, TP, TPT,
- SS CREATININA, BUN, POTASIO, CLORO, SODIO, CALCIO, TGO, TGP, BILIRRUBINAS TOTALES Y DIFERENCIALES, LDH, FOSFATASA ALCALINA, HEMOCULTIVOS X2, UROANALISIS
- SS PROCALCITONINA
- SS DIMERO D, FIBRINOGENO
- SS PANEL VIRAL
- SS ANA, ANCA, ANTI FOSFOLIPIDOS
- MEDIO FISICO POR Tº MAYOR O IGUAL A 38°C
- COLOCACION DE Sonda VESICAL
- CONTROL Estricto de LIQUIDOS ADMINISTRADOS, ELIMINADOS, BALANCE HIDRICO, GASTO URINARIO CADA 6 HORAS
- CONTROL DE GLUCOMETRIAS CADA 12 HORAS
- CUIDADOS DE ENFERMERIA
- MONITOREO CONTINUO
- AVISAR CAMBIOS A MEDICO DE TURNO

2016-04-02

*ANÁLISIS(JUSTIFICACIÓN):

ANALISIS

PCTE DELICADO, QUIEN INGRESA EN MALAS CONDICIONES GENERALES AL SERVICIO DE UCIP, CON COMPROMISO PULMONAR IMPORTANTE 2º A PROCESO INFECCIOSO NEUMONICO MAS SANGRADO ACTIVO POR TOT CONSIDERANDO UNA HEMORRAGIA ALVEOLAR DIFUSA, E IMAGEN RADIOLOGICA CON 9 ESPACIOS INTERCOSTALES CON INFILTRADOS ALGODONOSOS MULTILOBAR RADIOPAVIDAD EN HEMITORAX IZQUIERDO TOT SOBREINSERTADO, POR LO QUE SE INDICA RETIRAR TOT 1 CMS, CARDIACA CONSERVADA, SE DECIDE INICIAR MANEJO ANTIMICROBIANO DE AMPLIO ESPECTRO CON CEFEPIME AMIKACINA, SE INDICA ADOSIS CON FITOMENADIONA Y ADRENALINA POR TOT DANDO SANGRADO ACTIVO, PCTE QUIEN CURSA CON NIVELES DE HB Y HTO EN SENSO ABRUPTO POR LO QUE SE INDICA TRANSFUSION DE GRE DESLEUCOCITADOS Y COMPATIBLES A 15CC/KG, URGENTE ADEMAS CON ALTERACION DE REACTANTE DE FASE AGUDA CON LEUCOPENIA EN ULTIMO HEMOGRAMA Y NEUTROFILIA SE DEJA EN AYUNO CON SOPORTE HIDRICO, SE SOLICITA LABORATORIOS DE FUNCION RENAL FUNCION HEPATICA, TIEMPOS DE COAGULACION CONSIDERANDO UNA CID, HEMOCULTIVOS PARA IDENTIFICACION DE GERME, BAJO VIGILANCIA Estricta ALTO RIESGO DE MORTALIDAD DADO CUADRO CLINICO ACTUAL SE EXPLICA A FAMILIARES CONDICION ACTUAL DEL PCTE Y POSIBLES RIESGOS DEMORTALIDAD DADO POR EL COMPROMISO PULMONAR Y HEMATOLOGICO QUE PRESENTA

PRONOSTICO:RESERVADO

HALLAZGO OBJETIVO:

ACTUALMENTE PCTE DELICADO, CON SANGRADO ACTIVO POR TOT Y Sonda OROGASTRICA, MAL PERFUNDIDO, PALIDO TAQUICARDICO,TAQUIPNEICO,FEBRIL, SATURACIONES OSCILANTES,VARIABLES VITALES: PESO:45 KG TA:128/80 FC:190x min, FR:48 x min, T:37.0°C, SatO2:92% PARAMETROS VENTILATORIOS FIO2: 100% PEEP:7 PIP:20 FR:25% TI:0.4
 CCC: NORMOCEFALA, PUPILAS Miotica MUY POCA RESPUESTA A LA LUZ, CONJUNTIVAS PALIDAS,CUELLO MOVIL SIN ADENOPATIAS
 C/P: TORAX SIMETRICO,EXPANSIBLE BAJO VENTILACION MECANICA CON TIRAJES SUBCOSTALES CON DISMINUCION DE MURMULLO VESICULAR EN BASES PULMONARES,CREPITOS BIBASALES,RSCRS TAQUICARDICOS,SIN SOPLOS
 G/I: ABDOMEN DISTENDIDO POCO DEPRESIBLE, PERISTALSIS DISMINUIDA, IMPRESIONA DOLOR A LA PALPACION,NO MASAS NI MEGALIAS
 G/U: EXTERNAMENTE NORMOCONFIGURADOS PARA SEXO Y EDAD
 EXTREMIDADES: SIMETRICAS SIN EDEMAS, PULSOS DISTALES DE BUEN TONO E INTENSIDAD LLENADO CAPILAR MAS O MENOS 6SEG
 NEUROLOGICO: HIPOACTIVO

HALLAZGO SUBJETIVO:

INGRESO A CUIDADOS INTENSIVO PEDIATRICO
 NOTA RETROSPECTIVA 4.50 AM
 INGRESA PACIENTE DE 4 MESES DE VIDA PROVENIENTE DE SALA DE OBSERVACION DE URGENCIA, QUIEN ES TRAIDA POR LA MADRE POR CUADRO DE MAS O MENOS 33 HORAS DE

EVOLUCION CONSISTENTE EN DETERIORO A NIVEL RESPIRATORIO, DADO POR PATRON TAQUIPNEICO CON TIRAJES SUBCOSTALES MARCADOS, MAS FIEBRE QUE NO MEJORA MANEJADO EN SALA DE URGENCIA CON CORTICOIDES, TERAPIA RESPIRATORIA CON SALBUTAMOL Y SOLUCION HIPERTONICA E INICIO DE DOSIS DE ANTIBIOTICOTERAPIA CON AMPICILINA SULBACTAM, SIN PRESENTAR MEJORIA MOTIVO POR LO QUE COMENTAN A LA UNIDAD DE CUIDADOS INTENSIVOS PEDIATRICOS. PACIENTE QUIEN PRIMERAMENTE FUE LLEVADA A COMFAMAR EN LA MAÑANA DEL 1ERO DE ABRIL DONDE REALIZAN LABORATORIOS QUE MUESTRAN LEUCOCITOSIS CON NEUTROFILIA LEVE TROMBOCITOSIS (12.1/36.4/25060/67.5/20.9/457000) SIN EMBARGO DAN SALIDA CON MANEJO CON SULANP/ENTEROGERMINA/MOXOPPL FLEM/. SE REINTERROGA A LA MADRE QUIEN REFIERE CUADRO DE INICIO 23/03/2016 DADO POR RINORREA HIALINA Y TOS, MANEJADO POR PEDIATRA PARTICULAR CON TERAPIA RESPIRATORIA LA CUAL INICIO EL 28/3/2016, CON POSTERIOR INICIO DE ALTERACION CARACTERISTICAS DE DEPOSICIONES PASTOSAS Y FETIDAS, EL DIA 31/03/2016 INICIA CUADRO FEBRIL CUANTIFICADO EN 38°C CON TIRAJES INTERCOSTALES, TOS E HIPOACTIVA.

ENCUENTRO PACIENTE EN SALA DE OBSERVACION, CON OXIGENO POR CANULA NASAL, CON TIRAJES SUBCOSTALES MARCADOS MAS RETRACCION SUPRACLAVICULAR POLIPNEICO CON RITMO CARDIACO SINUSAL POR MONITOR TAQUICARDIA Y DISTENSION ABDOMINAL, SE TRASLADA A LA UNIDAD DE CUIDADOS INTENSIVOS PEDIATRICOS SE REALIZA INTUBACION OROTRAQUEAL RAPIDA BAJO SEDACION CON TUBO 4.5 FIJADO EN ARCADEA 13, SE EVIDENCIA SANGRADO ACTIVO POR TOT SE PROCEDE A MANEJO MEDICO INTEGRAL EN UCIP.

ANTECEDENTES PRENATALES G2P2, SIN DATOS DE ENFERMEDAD O INFECCION DURANTE EL EMBARAZO, PERFIL INFECCIOSO NEGATIVO SEGUN COMENTA LA MADRE
 ANTECEDENTES PATOLOGICOS: NEGATIVO QUIRURGICOS: NIEGA, TRANSFUSIONES: NIEGA, ZOO: NIEGA COOMBE: NIEGA HOSPITALIZACIONES: NEGATIVO
 VACUNAS COMPLETAS PARA LA EDAD, NO TRAE CARNET ALERGIA: NIEGA ALIMENTACION: LECHE DE FORMULA ETAPA 1

07:28 SERVICIO: UCI PEDIATRICA

Ivan pinto - IVAN ALEXANDER PINTO MARTINEZ
 ESPECIALIDAD: PEDIATRA

- LACTANTE FEMENINA EUTROFICA
- INSUFICIENCIA RESPIRATORIA
- HEMORRAGIA ALVEOLAR DIFUSA
- SEPSIS DE ORIGEN PULMONAR
- NEUTROPENIA FEBRIL
- COAGULACION INTRAVASCULAR DISEMINADA DESCOMPENSADA
- PARO CARDIORESPIRATORIO CON REANIMACION FALLIDA

PLAN:

PLASMA FRECO CONGELADO 66 CADA 12 HORAS
 DOPAMINA 200 MG EN 100 CC SSN 0.9 INICIAR INFUSION A 10 MCG KG MIN
 NOREPINEFRINA 8 MG EN 250 CC DE SSN 0.9 INICIAR INFUSION A 0.05 MG/KGMIN
 HEPARINA REGULAR 792 UNIDADES DILUIDAS EN 48 CC DE DAD 5 EN INFUSION DE 2CC X HORA
 SUIXGXHORA
 ADRENALINA 1.10000 PASAR A 0.3 CC KG DOSIS PARA REANIMACION CARDIOPULMONAR
 SSN 0.9 POR CIENTO 120 CC EN 20 MIN
 ACTA DE DEFUNCION

*ANÁLISIS (JUSTIFICACIÓN):
 NOTA RETROSPECTIVA 6.00 AM

PACIENTE QUIEN REALIZA BRADICARDIA SOSTENIDA CON DESATURACION, SE INICIA MANIOBRAS DE REANIMACION CARDIOPULMONAR AVANZADA CON COMPRESIONES TORAXICAS Y VENTILACION PRESION POSITIVA POR TOT, PACIENTE CON SANGRADO MASIVO POR TOT, SE ENCUENTRA TIEMPOS DE COAGULACION PROLONGADOS SE INDICA COLOCACION DE PLASMA, SE CONSIDERA PACIENTE CON CID DESCOMPENSADA, ADRENALINA A DOSIS DE 0.03MG/KG DOSIS
 RESPUESTA RECIBE 4 DOSIS, BOLO DE SSN 0.9 POR CIENTO 20CC X KG DURACION DE 1ER EVENTO DE PARO CARDIO RESPIRATORIO APROXIMADAMENTE 10 MIN. SE INDICA INICIO DE INOTROPICOS NORADRENALINA/DOPAMINA MAS HEPARINA PARA DISMINUIR ALTERACIONES SECUNDARIA A CID.

6.35

PACIENTE VUELVE A PRESENTAR PARO CARDIORESPIRATORIO SE REANUDA RENIMACION CARDIOPULMONAR AVANZADA, CON PRESION POSTVIA CON AMBUQ POR TOT MAS MEDICAMENTOS, DURANTE ESTE PERIODO SON DOS PAROCARDIORESPIRATORIO QUE REALIZA, CON ABUNDANTE SAÑGRADO POR TOT, SIN EVIDENCIA DE RESPUESTA A MANEJOS INSTAURADOS, SE CONTINUA REANIMACION POR MAS DE 30 MINUTOS, SIN RESPUESTA A LAS 7.05 SE DECLARA PACEINTE FALLECIDO.
SE LE INFORMA A FAMILIAIRES

INTERPRETACIÓN APOYO DIAGNÓSTICO:

TP 35.9 TPT 51.3
LEC 2650 NEU 14.4 LINF 77.7 PTAS 396.000
HB 8.9 HTO 27.2
TIEMPOS PROLONGADOS
LEUCOPENIA NEUTROPENIA
ANEMIA

FECHA	MOTIVOS DE CONSULTA Y ENFERMEDAD ACTUAL	
2016-04-01	23:45	german.sanjuanelo - GERMAN JOSE SANJUANELO CONRADO
		MOTIVO DE CONSULTA : TOS Y DIFICULTAD RESPIRATORIA
		ENFERMEDAD ACTUAL : PACIENTE DE 4 MESES DE EDAD , QUE INGresa EN BRAZOS DE MADRE QUIEN REFIERE CC DE +- 12 HORAS DE EVOLUCION CONSISTENTE ERN FIEBRE NO CUANTIFICADA ASOCIADO A TOS HUMEDA Y DIFICULTAD RESPIRATORIA , ACUDE A COMFAMAR DONDE REALIZAN LABROATORIOS ENCONTRANDO HEMOGRMA CON LEUCOCITOSIS , DAN EGRESO , CON FORMULA MEDICA , INGresa EN MALAS , CONDICIONES GENERALES , POLIPNEICA , CON AGREGADOS PULMONARES . SE DECIDE INGRESAR PARA CUBRIMIENTO , CON CORTICOIDES , INHALADORES , Y TOMA DE NUEVOS LABORATORIOS , PACIENTE FEBRIL ,

ANTECEDENTES PERSONALES		
ANTECEDENTES	OP	DETALLE
ANTECEDENTES	Alergicos	NO NO HAY DATOS EN EL MOMENTO DEL INGRESO

ANTECEDENTES GINECOBISTETRICOS			
ANTECEDENTES	SI	NO	Detalle
GINECOS	menarquia	NO	NO APLICA
	Otros	SI	POR DEFECTO

EXAMEN FISICO222		
PROFESIONAL:		FECHA:2016-04-01
SISTEMA	ESTADO	OBSERVACIONES
Neurologico (1)	NORMAL	CCC PINRAL , MUCOSA ORAL SECA , CP RUIDOS CARDIACOS RITMICOS NO SOPLOS PULMONES CON ESTETORES EN BASES PULMONARES , TIRAJES INTERCOSTALES , ABD BLANDO DEPRESIBLE NO MASAS NI MEGALIAS EXT LLENADO CAPILAR MENOR DE 2 SEG SNC PACIENTE HIPOACTIVA

DIAGNOSTICOS DE INGRESO ASIGNADOS			
CODIGO	DIAGNOSTICO DE INGRESO	ESTADO	OBSERVACION
J219	BRONQUIOLITIS AGUDA, NO ESPECIFICADA		

RESUMEN DEL PLAN TERAPEUTICO	
FECHA	RESUMEN DEL PLAN TERAPEUTICO
23:09	german.sanjuanelo - GERMAN JOSE SANJUANELO CONRADO ESPECIALIDAD: MEDICO GENERAL

2016-04-01	MEDICAMENTO FORMULADO: SALBUTAMOL INH 1 FRASCO Dosis Unica, VIA: INHALADO, DIAS DE TRATAMIENTO: 1 MEDICAMENTO FORMULADO: BECLOMETASONA DIPROPIONATO 1 FRASCO Dosis Unica, VIA: INHALADO, DIAS DE TRATAMIENTO: 1 MEDICAMENTO FORMULADO: METILPREDNISOLONA 12 miligramos Dosis Unica, VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 1 MEDICAMENTO FORMULADO: IPRATROPIO BROMURO 1 FRASCO Dosis Unica, VIA: INHALADO, DIAS DE TRATAMIENTO: 1
00:52	german.sanjuanelo - GERMAN JOSE SANJUANELO CONRADO ESPECIALIDAD: MEDICO GENERAL MEDICAMENTO REFORMULADO: METILPREDNISOLONA 12.00 miligramos Dosis Unica, VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 1 MEDICAMENTO REFORMULADO: METILPREDNISOLONA 3 miligramos Cada 6 Hora(s), VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 5 MEDICAMENTO FORMULADO: ACETAMINOFEN 3 miligramos Cada 6 Hora(s), VIA: ORAL, DIAS DE TRATAMIENTO: 3 MEDICAMENTO REFORMULADO: IPRATROPIO BROMURO 1.00 FRASCO Dosis Unica, VIA: INHALADO, DIAS DE TRATAMIENTO: 1 MEDICAMENTO REFORMULADO: BECLOMETASONA DIPROPIONATO 1.00 FRASCO Dosis Unica, VIA: INHALADO, DIAS DE TRATAMIENTO: 1 MEDICAMENTO FORMULADO: DEXTROSA 1 BOLSA (S) Infusion Continua, VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 3 OBSERVACIONES: 300 CC + 5 CC DE KATROL + 7 CC DE NATROL, PASAR A 24 CC HORA POR BI MEDICAMENTO FORMULADO: CLORURO DE POTASIO 1 AMPOLLA (S) Infusion Continua, VIA: PARENTERAL, DIAS DE TRATAMIENTO: 2 MEDICAMENTO FORMULADO: CLORURO DE SODIO 1 AMPOLLA (S) Infusion Continua, VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 3 MEDICAMENTO FORMULADO: AMPICILINA+SULBACTAM 300 miligramos Cada 6 Hora(s), VIA: PARENTERAL, DIAS DE TRATAMIENTO: 5
2016-04-02	04:41 ivan.pinto - IVAN ALEXANDER PINTO MARTINEZ ESPECIALIDAD: PEDIATRA ORDENES MEDICAS PESO: 6.6 KG HORA 4.50 -CUIDADOS INTENSIVOS PEDIÁTRICOS -CABEZERA A 30°C -MANTENER EUTERMICO -NADA VIA ORAL -SOG ABBIERTA -VENTILACION MECANICA MODO PRESION SIMV TOT 4.5 -LEV: DAD AL 5% 500 CC MAS SODIO:12.5CC + POTASIO:5CC PASAR A RAZON DE 33 CC/HORA (TH 120CC7KG7DIA) -SSN 0.9% 60 CC PASAR EN 1 HORA -CEFEPIME 330 MG IV CADA 6 HORAS (DOSIS:200MG/KG/DIA)D0 -AMIKACINA 99 MG IV CADA 24 HORAS (15MG/KG/DIA) D1 -OMEPRAZOL 6.6 MG EV CADA DIA -VITAMINA K 5 MG IV AHORA CONTINUAR CADA 12 HORAS -ADRENALINA 1 MG TOT AHORA -TRANSFUNDIR 99 CC DE GRE DESLEUCOCITADOS Y COMPATIBLES PASAR EN 3 HORAS -DIPIRONA 132 MG EV POR RAZON NECESARIA EN CASO DE T° PERSISTENTE MAYOR DE 38,5°C -MIDAZOLAM 1.9 MG IV AHORA DOSIS 1 -SE SOLICITA RX DE TORAX PORTATIL AHORA -SE SOLICITA RX DE ABDOMEN SIMPLE AHORA -SE SOLICITA GASOMETRIA ARTERIAL AHORA -SS HEMOGRAMA CONTROL, TP, TPT, -SS GREATININA, BUN, POTASIO, CLORO, SODIO, CALCIO, TGO, TGP, BILIRRUBINAS TOTALES Y DIFERENCIALES, LDH, FOSFATASA ALCALINA, HEMOCULTIVOS X2, UROANALISIS -SS PROCALCITONINA -SS DIMERO D, FIBRINOGENO -SS PANEL VIRAL -SS ANA, ANCA, ANTI FOSFOLIPIDOS -MEDIO FISICO POR T° MAYOR O IGUAL A 38°C -COLOCACION DE Sonda VESICAL -CONTROL Estricto de LIQUIDOS ADMINISTRADOS, ELIMINADOS, BALANCE HIDRICO, GASTO URINARIO CADA 6 HORAS -CONTROL DE GLUCOMETRIAS CADA 12 HORAS -CUIDADOS DE ENFERMERIA -MONITOREO CONTINUO -AVISAR CAMBIOS A MEDICO DE TURNO - MEDICAMENTO FORMULADO: CEFEPIMA 300 miligramos Cada 6 Hora(s), VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 5 - MEDICAMENTO FORMULADO: AMIKACINA 1 AMPOLLA (S) Cada 1 Dia(s), VIA: INTRAMUSCULAR, DIAS DE TRATAMIENTO: 5 - MEDICAMENTO FORMULADO: CLORURO DE SODIO 1 BOLSA (S) Cada 1 Dia(s), VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 1 08:59 ivan.pinto - IVAN ALEXANDER PINTO MARTINEZ ESPECIALIDAD: PEDIATRA MEDICAMENTO FORMULADO: ADRENALINA 1MG/1ML AMPOLLA CAJA X 25 5 AMPOLLA (S) Dosis Unica, VIA: PARENTERAL, DIAS DE TRATAMIENTO: 1 MEDICAMENTO FORMULADO: DOPAMINA 1 AMPOLLA (S) Cada 1 Dia(s), VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 1 MEDICAMENTO FORMULADO: MIDAZOLAM 1 AMPOLLA (S) Cada 1 Dia(s), VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 1

MEDICAMENTO FORMULADO: 1 Cada 1 Día(s), VIA: , DIAS DE TRATAMIENTO: 1
 09:03 ivan.pinto - IVAN ALEXANDER PINTO MARTINEZ
 ESPECIALIDAD: PEDIATRA

MEDICAMENTO FORMULADO: SOLUCION SALINA 1 UNIDAD (ES) Cada 1 Día(s), VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 1
 MEDICAMENTO FORMULADO: SODIO CLORURO 1 BOLSA (S) Cada 1 Día(s), VIA: INTRAVENOSA, DIAS DE TRATAMIENTO: 1

CONSOLIDADO ORDENES MEDICAS DE APOYOS DIAGNOSTICOS

TIPO	CARGO	DESCRIPCION	FECHA/HORA EVOLUCION
BANCO DE SANGRE	911022	PRUEBA DE COMPATIBILIDAD. CRUZADA MAYOR EN TUBO	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911111	PROCESAMIENTO DE LA UNIDAD DE PLASMA FRESCO	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911004	ANTICUERPOS IRREGULARES. DETECCION [RASTREO O RAI] CON CELULAS I Y II. O I. II Y III. EN TUBO	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911016	HEMOCLASIFICACION FACTOR Rh [FACTOR D] EN LAMINA O TUBO	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911107	PROCESAMIENTO DE LA UNIDAD DE GLOBULOS ROJOS O ERITROCITOS LEUCORREDUCIDOS O DELEUCOCITADOS +	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911016	HEMOCLASIFICACION FACTOR Rh [FACTOR D] EN LAMINA O TUBO	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
LABORATORIOS	902212	HEMOCLASIFICACION GRUPO ABO Y FACTOR RH	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos		

Presuntivos			
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911111	PROCESAMIENTO DE LA UNIDAD DE PLASMA FRESCO	2016/4/2 - 08:35:28
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911107	PROCESAMIENTO DE LA UNIDAD DE GLOBULOS ROJOS O ERITROCITOS LEUCORREDUCIDOS O DELEUCOCITADOS +	2016/4/2 - 04:41:50
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
LABORATORIOS	903825L1	CREATININA EN ORINA ESPONTANEA	2016/4/2 - 04:41:50
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
LABORATORIOS	903856	NITROGENO UREICO [BUN]	2016/4/2 - 04:41:50
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
LABORATORIOS	902212	HEMOCLASIFICACION GRUPO ABO Y FACTOR RH	2016/4/2 - 04:41:50
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911022	PRUEBA DE COMPATIBILIDAD. CRUZADA MAYOR EN TUBO	2016/4/2 - 04:41:50
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
BANCO DE SANGRE	911004	ANTICUERPOS IRREGULARES. DETECCION [RASTREO O RAI] CON CELULAS I Y II. O I. II Y III. EN TUBO	2016/4/2 - 04:41:50
	Observacion:		
	Orden Profesional	IVAN ALEXANDER PINTO MARTINEZ	
	Diagnosticos Presuntivos		
PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ CC - 11240018690 T.P 896/2011			
IMAGENOLOGIA RADIOLOGICA	871121	RADIOGRAFIA DE TORAX (P.A. O A.P., LATERAL)	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		

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PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
LABORATORIOS	902024	FIBRINOGENO. COAGULACION	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		
PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
LABORATORIOS	902049	TIEMPO DE TROMBOPLASTINA PARCIAL [PTT]	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		
PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
LABORATORIOS	902045	TIEMPO DE PROTROMBINA [PT]	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		
PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
LABORATORIOS	902210	HEMOGRAMA IV [HEMOGLOBINA. HEMATOCRITO. RECuento DE ERITROCITOS. INDICES ERITROCITARIOS. LEUCOGRAMA. RECuento DE PLAQUETAS. INDICES PLAQUETARIOS Y MORFOLOGIA ELECTRONICA E HISTOGRAMA] METODO AUTOMATICO	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		
PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
LABORATORIOS	902105	DIMERO D POR LATEX	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		
PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
PORTATIL	873501	UTILIZACION DE EQUIPO PORTATIL CONVENCIONAL	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		
PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
PORTATIL	873501	UTILIZACION DE EQUIPO PORTATIL CONVENCIONAL	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		
PROFESIONAL: KATIANA SANTAMARIA VERA CC - 22736831			
IMAGENOLOGIA RADIOLOGICA	872002	RADIOGRAFIA DE ABDOMEN SIMPLE	2016/4/2 - 04:26:37
	Observacion:		
	Orden Profesional	KATIANA SANTAMARIA VERA	
	Diagnosticos Presuntivos		

3/6/2016

Fecha	Usuario	Cantidad	Desechos	Paciente	Observación
02/04/2016 02:42	DIANA YINIBA CUNDUMI TORRES	0 miligramos	488 miligramos	0	

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOA0010244 POS	ACETAMINOFEN 150mg/5ml JARABE	ACETAMINOFEN
FORMULO	GERMAN JOSE SANJUANELO CONRADO	FECHA FORMULACIÓN: 02/04/2016 01:02

VIA DE ADMINISTRACIÓN: ORAL

DOSIS 3.00 miligramos Cada 6 Hora(s)

CANTIDAD 1.00 JARABE

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 02:44	DIANA YINIBA CUNDUMI TORRES	1 miligramos	0 miligramos	0	
02/04/2016 02:46	ELIZABETH MURILLO MONDRAGON	0 miligramos	0.9994 miligramos	0	
02/04/2016 02:46	ELIZABETH MURILLO MONDRAGON	0 miligramos	1797.84 miligramos	0	

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOI0171086 POS	IPRATROPIO BROMURO 0,02 mg/dosis AEROSOL	IPRATROPIO BROMURO
FORMULO	GERMAN JOSE SANJUANELO CONRADO	FECHA FORMULACIÓN: 02/04/2016 01:02

VIA DE ADMINISTRACIÓN: INHALADO

DOSIS 1.00 FRASCO Dosis Unica

CANTIDAD 1.00 AEROSOL

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 02:59	ANDRES CORDOBA IBARGUEN	1 FRASCO	0 FRASCO	0	

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOB0020001 POS	BECLOMETASONA DIPROPIONATO 250MG SOLUCION PARA INHALACION	BECLOMETASONA DIPROPIONATO
FORMULO	GERMAN JOSE SANJUANELO CONRADO	FECHA FORMULACIÓN: 02/04/2016 01:02

VIA DE ADMINISTRACIÓN: INHALADO

DOSIS 1.00 FRASCO Dosis Unica

CANTIDAD 1.00 SOLUCION PARA INHALACION

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOD0102254 POS	DEXTROSA A.D 5% SOLUCION INYECTABLE	DEXTROSA EN AGUA DESTILADA
FORMULO	GERMAN JOSE SANJUANELO CONRADO	FECHA FORMULACIÓN: 02/04/2016 01:03

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS 1.00 BOLSA (S) Infusion Continua

CANTIDAD 1.00 SOLUCION INYECTABLE

OBSERVACIONES E INDICACIONES DE SUMINISTRO 300 CC + 5 CC DE KATROL + 7 CC DE NATROL , PASAR A 24 CC HORA POR BI

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 01:10	CLAUDIA RIASCOS VALENCIA	1 BOLSA (S)	0 BOLSA (S)	0	DEXTROSA AL CINCO PORCIENTE +7CC NATROL +5CC DE K PASAR A 24CCH
02/04/2016 05:00	NEICI CASTRO DELGADO	1 BOLSA (S)	0 BOLSA (S)	0	

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOP0220877 POS	CLORURO DE POTASIO 20MEQ X 10ML SOLUCION INYECTABLE	CLORURO DE POTASIO
FORMULO	GERMAN JOSE SANJUANELO CONRADO	FECHA FORMULACIÓN: 02/04/2016 01:03

VIA DE ADMINISTRACIÓN: PARENTERAL

DOSIS 1.00 AMPOLLA (S) Infusion Continua

CANTIDAD 1.00 SOLUCION INYECTABLE

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 01:10	CLAUDIA RIASCOS VALENCIA	1 AMPOLLA (S)	0 AMPOLLA (S)	0	

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOS0040897 POS	CLORURO DE SODIO 2MEQ/10ML SOLUCION INYECTABLE	CLORURO DE SODIO
FORMULO	GERMAN JOSE SANJUANELO CONRADO	FECHA FORMULACIÓN: 02/04/2016 01:03

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS 1.00 AMPOLLA (S) Infusion Continua

CANTIDAD 1.00 SOLUCION INYECTABLE

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 01:10	CLAUDIA RIASCOS VALENCIA	1 AMPOLLA (S)	0 AMPOLLA (S)	0	

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOA0280517 POS	AMPICILINA+SULBACTAM 1.5G POLVO PARA INYECCION	AMPICILINA+SULBACTAM
FORMULO	GERMAN JOSE SANJUANELO CONRADO	FECHA FORMULACIÓN: 02/04/2016 01:05

VIA DE ADMINISTRACIÓN: PARENTERAL

DOSIS 300.00 miligramos Cada 6 Hora(s)

CANTIDAD 800.00 POLVO PARA INYECCION

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 01:10	CLAUDIA RIASCOS VALENCIA	1 miligramos	0 miligramos		0 SE DILUYE EN 10CC S SN Y SE LE ADMINISTRA 300MG
02/04/2016 02:45	ELIZABETH MURILLO MONDRAGON	0 miligramos	0.49995 miligramos	0	

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOC1050558 POS	CEFEPIMA 1G SOLUCION INYECTABLE	CEFEPIMA
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 06:57

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS 300.00 miligramos Cada 6 Hora(s)

CANTIDAD 2.00 SOLUCION INYECTABLE

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOA0200505 POS	AMIKA CINA 100MG SOLUCION INYECTABLE	AMIKACINA
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 06:57

VIA DE ADMINISTRACIÓN: INTRAMUSCULAR

DOSIS 1.00 AMPOLLA (S) Cada 1 Dia(s)

CANTIDAD 1.00 SOLUCION INYECTABLE

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOS0040590 POS	CLORURO DE SODIO 0.9% SOLUCION INYECTABLE	CLORURO DE SODIO
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 06:58

VIA DE ADMINISTRACIÓN: INTRAVENOSA

<http://dusoft.cosमितel.net/CSSP/cache/JJL34b.html>

3/6/2016

DOSIS

1.00 BOLSA (S) Cada 1 Dia(s)

CANTIDAD

1.00 SOLUCION INYECTABLE

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOA1040495 POS	ADRENALINA 1MG/1ML SOLUCION INYECTABLE	ADRENALINA
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 08:59

VIA DE ADMINISTRACIÓN: PARENTERAL

DOSIS

5.00 AMPOLLA (S) Dosis Unica

CANTIDAD

5.00 SOLUCION INYECTABLE

REGISTRO DE ADMINISTRACIÓN DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 06:30	NEICI CASTRO DELGADO	5 AMPOLLA (S)	0 AMPOLLA (S)		0 PACIENTE PRESENTO CODIGO

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOD0290623 POS	DOPAMINA 200MG/5ML SOLUCION INYECTABLE	DOPAMINA
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 09:00

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS

1.00 AMPOLLA (S) Cada 1 Dia(s)

CANTIDAD

1.00 SOLUCION INYECTABLE

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 06:30	NEICI CASTRO DELGADO	1 AMPOLLA (S)	0 AMPOLLA (S)		0 PACIENTE PRESENTO CODIGO

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOM0230811 POS	MIDAZOLAM 15MG/3ML SOLUCION INYECTABLE	MIDAZOLAM
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 09:01

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS

1.00 AMPOLLA (S) Cada 1 Dia(s)

CANTIDAD

1.00 SOLUCION INYECTABLE

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 06:30	NEICI CASTRO DELGADO	1 AMPOLLA (S)	0 AMPOLLA (S)		0 PACIENTE PRESENTO CODIGO

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFON0360832 NO POS	NOREPINEFRINA 4MG/4ML SOLUCION INYECTABLE	NOREPINEFRINA
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 09:02

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS

1.00 AMPOLLA (S) Cada 1 Dia(s)

CANTIDAD

1.00 SOLUCION INYECTABLE

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 06:30	NEICI CASTRO DELGADO	1 AMPOLLA (S)	0 AMPOLLA (S)		0 PACIENTE PRESENTO CODIGO
02/04/2016 06:30	NEICI CASTRO DELGADO	1 AMPOLLA (S)	0 AMPOLLA (S)		0 PACIENTE PRESENTO CODIGO

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOS0042252 POS	CLORURO DE SODIO 0.9% BOLSA X 500ML SOLUCION INYECTABLE	CLORURO DE SODIO
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 09:03

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS 1.00 UNIDAD (ES) Cada 1 Día(s)

CANTIDAD 1.00 SOLUCION INYECTABLE

CÓDIGO	PRODUCTO	PRINCIPIO ACTIVO
FOFOS0040899 POS	SODIO CLORURO 0.9% SOLUCION INYECTABLE	CLORURO DE SODIO
FORMULO	IVAN ALEXANDER PINTO MARTINEZ	FECHA FORMULACIÓN: 02/04/2016 09:05

VIA DE ADMINISTRACIÓN: INTRAVENOSA

DOSIS 1.00 BOLSA (S) Cada 1 Día(s)

CANTIDAD 1.00 SOLUCION INYECTABLE

REGISTRO DE ADMINISTRACION DE MEDICAMENTOS

Fecha	Usuario	Cantidad	Desechos	Entregas Al Paciente	Observación
02/04/2016 06:30	NEICI CASTRO DELGADO	1 BOLSA (S)	0 BOLSA (S)		0 PACIENTE PRESENTO CODIGO

DIAGNOSTICOS DE EGRESO ASIGNADOS	
CODIGO	DIAGNOSTICO DE EGRESO
J219	BRONQUIOLITIS AGUDA, NO ESPECIFICADA
FECHA	LISTADO DE NOTAS DE ENFERMERIA
2016-04-02	05:10 paola.sanchez - AURA PAOLA SANCHEZ - AUXILIAR DE ENFERMERIA INGRESA PACIENTE AL SERVICIO DE UCI NEONATAL, PROCEDENTE DEL SERVICIO DE URGENCIAS EN MUY MAL ESTADO DE SALUD CONDICIONES EN COMPAÑIA DE AUXILIAR DE ENFERMERIA, MEDICO DE TURNO Y FISIOTERAPEUTA, TOLERANDO OXIGENO POR MASCARILLA AL VENTURY AL 35 POR CIENTO CON DX LACTANTE FEMENINA, INSUFICIENCIA RESPIRATORIA -AL EXAMEN FISICO SE OBSERVA CABEZA NORMOCEFALICA, CON FONTANELAS NORMOTENSAS, OJOS CENTRADOS, PUPILAS NO REACTIVAS, CUELLO MOVIL, TORAX SIMETRICO, ABDOMEN DISTENDIDO, PULMONES VENTILADOS, GENITALES FEMENINOS NORMO CONFIGURADOS, EXTREMIDADES INFERIORES NORMALES QUE SE OBSERVA VENOPUNSION EN MIEMBRO SUPERIOR DERECHO PASANDO LIQUIDOS PACIENTE QUE PESA 3660GR, GLUCOMETRIA DE 75 MG-DL, ES VALORADA X'EL MEDICO DE TURNO QUE ORDENA, COLOCAR LIQUIDOS, SE LE TOMA PARACLINICOS, CREATININA, HEMOGRAMA, BUM, POTASIO CLORO, CALCIO, TGO, TGP, BILIRRUBINAS TOTAL Y DIFERANCIAL, FOSTATASA ALCALINA, SE LE TOMA GASES ARTERIALES, SE LE TOMA DRX DE ABDOMEN SIMPLE Y RX DE TORAX, SE PASA BOLO DE SSN 0.9 X CIENTO PACIENTE QUE ENTRA EN CODIGO AZUL, 05:20 paola.sanchez - AURA PAOLA SANCHEZ - AUXILIAR DE ENFERMERIA PACIENTE QUE SE LE INICIA GOTEIO DE DAD AL 5 X CIENTO MAS ELECTROLITOS, PASANDO A 2.4CC-H, SE LE INICIA NOREPINEFRINA PASANDO A 0.6CC-H, MAS MEDICAMENTOS ORDENADO POR EL MEDICO, 05:22 paola.sanchez - AURA PAOLA SANCHEZ - AUXILIAR DE ENFERMERIA PACIENTE QUE POR ORDEN MEDICA SE INTUBA CON TOT CONECTADO A VENTILACION MECANICA CON FIO2 AL 100 X CIENTO, 07:00 paola.sanchez - AURA PAOLA SANCHEZ - AUXILIAR DE ENFERMERIA PACIENTE QUE PRESENTA BRADICARDIA SOSTENIDA CON DESATURACION SE LE INICIA MANIOBRAS DE REANIMACION CARDIOPULMONAR CON COMPRESION TORAXICAS Y VENTILACION POSITIVA POR TOT PACIENTE QUE PRESENTA SANGRADO POR TOT CON DURACION DEL PRIMER PARO QUE FUE DE 10 MINUTOS, SE LE INICIA INTROPIA VUELVE Y PRESENTA PARO CARDIORESPIRATORIO, SE REANUDA LA REANIMACION CARDIOPULMONAR AVANZADA, CON COMPRESION POSITIVA CON AMBU, MAS MEDICAMENTOS ORDENADOS, DURANTE ESTE PERIODO, SON 2 PARO CARDIORESPIRATORIO, QUE SE OBSERVA EL PACIENTE CON ABUNDANTE SANGRADO POR TOT SIN RESPUESTA, SE CONTINUA LA REANIMACION POR MAS DE 30 MINUTOS, SIN RESPUESTA A LAS 7.05, SE DECLARA FALLECIDA Y EL MEDICO DE TURNO LE INFORMA AL FAMILIAR, SE AREGLA EL CADAVER Y SE BAJA A LA MORGEN Y SE LE HACE ENTREGA DEL ACTA DE DEFUCION AL FAMILIAR.

FECHA	LISTADO DE NOTAS FISIOTERAPEUTAS
2016-04-02	
07:49	ketty.caicedo - KETTY LIZETH CAICEDO BARON
	SE ADMINISTRAN 5 HORAS DE VENTILACION MECANICA.
07:47	ketty.caicedo - KETTY LIZETH CAICEDO BARON
	TERAPIA RESPIRATORIA, PACIENTE CON DIAGNOSTICO DE LACTANTE FEMENINA EUTROFICA -INSUFICIENCIA RESPIRATORIA -HEMORRAGIA ALVEOLAR DIFUSA -SEPSIS DE ORIGEN PULMONAR -NEUTROPENIA FEBRIL -COAGULACION INTRAVASCULAR DISEMINADA DESCOMPENSADA - PARO CARDIORESPIRATORIO CON REANIMACION FALLIDA, PACIENTE QUIEN ONGRESA A LA UNIDAD EN MALAS CONDICIONES GENERALES, CON CUADRO CLINICO DE 24 HORAS CON EVOLUCION TORPIDA, INGRESA EN COMPAÑIA DEL MEDICO, JEFE Y AUXILIAR, CON SOPORTE DE OXIGENO DADO POR MASCARA VENTURY AL 35%, TAQUICARDICA, SATO2 97%, PALIDEZ GENERALIZADA, CON DIBALANCE TORACOABDOMINAL, DESATURACIONES, POR LO QUE SE DECIDE INTUBAR PACIENTE PARA ASEGURAR VIA AEREA, SE INTUBA EN EL PRIMER INTENTO CON TUBO 4.0, FIJO A 11, CON RETORNO SANGUINOLENTO POR TUBO Y POR SONDA OROGASTRICA, SE REALIZA PERMEHABILIZACION OBTENIENDO ABUNDANTE SANGRADO POR TUBO, SE CONECTA A VENTILACION MECANICA EN MODO SIMV+PS10+PC12, CON LOS ISGUIENTES PARAMETROS FIO2 100% TI 0.60, FV 35, PEEP 6, PIP 25, PAW 11.4, PACIENTE EN MALAS CONDICIONES GENERALES, CON

CONTINUO SANGRADO POR TUBO Y BOCA, POR LO QUE SE LE PASA ADRENALINA POR TUBO SIN MEJORIA. PACIENTE QUIEN PRESENTE 3 PARO CARDIORESPIRATORIO LOS CUALES SE ABORDAN CON MANIOBRAS DE REANIMACION AVANZADA, VPP +COMPRESIONES RELACION 15/2, PACIENTE SIN RESPUESTA POSITIVA, CON AUMENTO DE SANGRADO POR VIA AEREA, SE CONTINUA REANIMACION POR 30MIN, SIN RESPUESTAS, ENCONTRADOSE EN ASISTOLIA Y SE DECLARA FALLECIDA A LAS 7:04AM.

21
20

01:57 andres.cordoba - ANDRES CORDOBA IBARGUEN

23.10 TERAPIA RESPIRATORIA. PACIENTE FEMENINA DE 4 MESES DE EDAD, CON DIAGNOSTICO CLINICO DE BRONQUIOLITIS SOBREINFECTADA. INGRESA AL SERVICIO EN BRAZOS DE SU MADRE, DORMIDA, CON SIGNOS DE DIFICULTAD RESPIRATORIA SEVERA, ALETEO NASAL, TIRAJES INFRACOSTALES, SUPRACOSTALES, DISBALANCE TORACOABDOMINAL. SV. FC. 257PPM. SATO2. 0.98. SIN SOPORTE DE OXIGENO, TOLERANDO AIRE AMBIENTE. SE SUMINISTRA OXIGENO POR MASCARA VENTURY AL 0.35. PRESENTA TORAX ESTABLE, NORMAL, BUENA COLORACION, POLIPNEICA, TAQUICARDICA. A LA AUSCULTACION MURMULLO VESICULAR NORMAL CON PRESENCIA DE RUIDOS SOBREGREGADOS CREPITANTES EN AMBOS APEX PULMONARES. SE INICIA ESQUEMA DE RESCATE CON 0.2CC DE SALBUTAMOL + 3CC DE SOLUCION SALINA NORMAL AL 0.9 EN DOS OPORTUNIDADES CADA MEDIA HORA, POSTERIORMENTE SE CONTINUA MANEJO CON ESQUEMA DE NEBULIZACION CON SOLUCION HIPERTONICA CADA 20 MINUTOS DURANTE UNA HORA CONJUNTAMENTE CON ESQUEMA DE INHALOTERAPIA CON BECLOMETASONA Y BROMURO DE IPRATROPIO CADA 10 MINUTOS. SE REALIZAN TECNICAS DE DRENAJE POSTURAL, ACCELERACION DE FLUJO VIBROPERCUSION Y LAVADO NASAL CON FLUJO LIBRE DE OXIGENO OBTENIENDO MODERADA CANTIDAD DE SECRECIONES MUCOIDES. PACIENTE TOLERA PROCEDIMIENTO. SIGNOS VITALES FINALES. FC. 221PPM. SATO2. 0.99. SE DEJA CON SOPORTE DE OXIGENO POR CANULA NASAL AL 0.32. SE COMENTA CON EL MEDICO PARA REVALORACION. PENDIENTE VIGILAR.

LISTADO DE SIGNOS VITALES HC

FECHA	HORA	F.C.F	F.C.	F.R.	PVC	PIC	PESO	TALLA	TENSION	MED.	SITIO T.A.	TEMP.	T.INCU	MANUAL	EVA	SATO ₂	ASC	IMC
2016-04-02	06:00:00	--	42	20	--	--	--	--	27 / 10	15	Miembro Inferior Derecho(NINV)	36.00	--	--	0	31.00	0	0
	PPS	PPD	PPM	PCP	PAM	GC	PPC	SC	IC	IS	IRVS	IRVP	ITVI	ITVD				
	--	--	--	--	15.67	--	--	--	--	--	--	--	--	--	--	--	--	--
2016-04-02	05:00:00	--	51	25	--	--	--	--	32 / 25	27	Miembro Inferior Derecho(NINV)	36.00	--	--	0	76.00	0	0
	PPS	PPD	PPM	PCP	PAM	GC	PPC	SC	IC	IS	IRVS	IRVP	ITVI	ITVD				
	--	--	--	--	27.33	--	--	--	--	--	--	--	--	--	--	--	--	--
2016-04-01	23:46:00	--	160	60	--	--	6,00	--	32 / 25	--	Miembro Inferior Derecho(NINV)	38.50	--	--	0	99.00	0	0

LISTADOS GENERALES DE ASISTENCIA VENTILATORIA

FECHA	HORA	MODOS	FIO ₂	F. RESP.	F. VENT.	ESPONT	TI	REL I:E	PEEP	P PICO	P MESE	PI MED	PAW	To. VIA A	ETCO ₂	TE	PL	PH	SPO ₂	CURVA
2016-04-02	04:04:00	SIMV+PC	FIO2 100%	--	35,0	--	0,6	1.3	6	25	--	--	10,5	--	--	--	--	--	--	--

ESTA HISTORIA AUN NO PRESENTA NOTAS DE OBSERVACION

PROFESIONAL: IVAN ALEXANDER PINTO MARTINEZ

CC - 11240018690 - T.P 896/2011

ESPECIALIDAD - PEDIATRA

Imprimió: ALMA OLIVA GARCIA PALACIOS - alma.garcia

Fecha Impresión : 2016/6/3 - 11:44:05

Laboratorio Clínico
Carrera 47 No. 3 - 53
Barrio Bellavista
Buena Ventura - Colombia
clnicasantasofia@csspmail.net



Paciente:	MENA ALVAREZ HIJA DE MAIRA SOFIA		Orden No.: 2016040250054
Historia:	316021662	Género: Femenino	Fecha y Hora de ingr 2016-04-02 05:04
TELEFONO:		Edad: 205 Días	Fecha de impresión: 03/06/2016 15:43
SERVICIO:	UCI PEDIATRICA SANT	MEDICO:	HABITACION UCIP-301
EMPRESA:	EMSSANAR ESS 2015 2016	MUNICIPIO:	
Fecha de impresión:			

Examen	Resultado	Unidades	Valores de referencia	Validado en
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HEMATOLOGIA

CUADRO HEMATICO

GLOBULOS BLANCOS	2.65	X10 ⁹ /uL	9.40 - 34.00	02/04/2016 05:23
RECuento DE G. ROJOS	3.61	X10 ⁶ / uL	4.00 - 6.60	02/04/2016 05:23
HEMOGLOBINA	8.90	g/dl	14.50 - 22.50	02/04/2016 05:23
HEMATOCRITO	27.20	%	45.00 - 67.00	02/04/2016 05:23
VOLUMEN CORPUSCULAR MEDIO	75.30	fL	95.00 - 121.00	02/04/2016 05:23
HB CORPUSCULAR MEDIA	24.70	pg	31.00 - 37.00	02/04/2016 05:23
CONCENTRACION HB CORPUSCULAR MEDIA	32.70	g/dl	31.00 - 37.00	02/04/2016 05:23
PLAQUETAS	396	10 ⁹ /uL	150 - 450	02/04/2016 05:23
RDW-SD	35.40	fL	35.00 - 55.00	02/04/2016 05:23
RDW-CV	13.40	%	11.00 - 16.00	02/04/2016 05:23
VOLUMEN PLAQUETARIO MEDIO	9.40	fL	9.00 - 13.00	02/04/2016 05:23
CAYADOS	0	%		02/04/2016 05:23
NEUTROFILOS	14.40	%	19.00 - 42.00	02/04/2016 05:23
LINFOCITOS	77.70	%	21.00 - 50.00	02/04/2016 05:23
MONOCITOS	7.50	%	0.00 - 12.00	02/04/2016 05:23
EOSINOFILOS	0.40	%	0.00 - 6.00	02/04/2016 05:23
BASOFILOS	0.00	%	0.00 - 1.00	02/04/2016 05:23
RECuento DE NEUTROFILOS	0.38	X10 ³ /uL	1.30 - 8.30	02/04/2016 05:23
RECuento DE LINFOCITOS	2.06	X10 ³ /uL	2.00 - 17.00	02/04/2016 05:23
RECuento DE MONOCITOS	0.20	X10 ³ /uL	0.01 - 3.50	02/04/2016 05:23
RECuento DE EOSINOFILOS	0.01	X10 ³ /uL		02/04/2016 05:23
RECuento DE BASOFILOS	0	X10 ³ /uL		02/04/2016 05:23
OBSERVACIONES CUADRO HEMATICO	-			02/04/2016 05:23

COAGULACION

TIEMPO DE PROTROMBINA	35.90	seg	02/04/2016 05:43
CONTROL DIARIO TIEMPO DE PROTROMBINA	13.90	seg	02/04/2016 05:43
INR	3.75		02/04/2016 05:43
TIEMPO PARCIAL DE TROMBOPLASTINA	51.30	seg	02/04/2016 05:52
CONTROL DIARIO TIEMPO PARCIAL DE TROMBOPLASTINA (CITROL)	29.80	seg	02/04/2016 05:52
DIMERO D CUANTITATIVO		FEU	03/04/2016 07:10
REMITIDO CLINICA REY DAVID			

Nota: Todos los resultados del Laboratorio deben ser interpretados por el Médico

40250054

Página 2 De 2

Laboratorio Clínico
Carrera 47 No. 3.- 53
Barrio Bellavista
Buena Ventura - Colombia
clnicasantasofia@csspmail.net



Paciente:	MENA ALVAREZ HIJA DE MAIRA SOFIA		Orden No.:	2016040250054	
Historia:	316021662	Género:	Femenino	Fecha y Hora de Ingr	2016-04-02 05:04
TELEFONO:		Edad:	205 Días	Fecha de impresión:	03/06/2016 15:43
SERVICIO:	UCI PEDIATRICA SANT	MEDICO:		HABITACION	UCIP-301
EMPRESA:	EMSSANAR ESS 2015,2016	MUNICIPIO:			
Fecha de impresión:					

Examen	Resultado	Unidades	Valores de referencia	Validado en
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COAGULACION -

Nota: Todos los resultados del Laboratorio deben ser interpretados por el Médico

Laboratorio Clínico
Carrera 47 No. 3 - 53
Barrio Bellavista
Buena Ventura - Colombia
clnicasantasofia@csspmail.net



Paciente:	MENA ALVAREZ HIJA DE MAIRA SOFIA	Orden No.:	2016040250067
Historia:	316021662	Género:	Femenino
TELEFONO:		Edad:	205 Días
SERVICIO:	UCI PEDIATRICA	MEDICO:	HABITACION
EMPRESA:	EMSSANAR ESS SUBSIDIO (CSSP)	MUNICIPIO:	BUENAVENTURA
Fecha de impresión:			

Examen	Resultado	Unidades	Valores de referencia	Validado en
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HÉMATOLOGÍA

HEMOCLASIFICACION	O POSITIVO			02/04/2016 08:35
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BANCO DE SANGRE

ANTICUERPO IRREGULARÉS	NEGATIVO			02/04/2016 08:35
PRUEBA CRUZADA No 1	COMPTIBLE			02/04/2016 08:35
UNIDAD DE GLOBULOS ROJOS POBRES EN LEUCOCITOS #1				02/04/2016 08:35

HEMOCOMPONENTE: GRPL O NEGATIVO

N° UNIDAD: B160013300

N° SELLO DE CALIDAD: B160013300

FECHA DE VENCIMIENTO: 30-04-16

HTLV I Y II: NO REACTIVO

HEMOCLASIFICACION BANCO DE SANGRE	O POSITIVO			02/04/2016 08:35
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Nota: Todos los resultados del Laboratorio deben ser interpretados por el Médico

Laboratorio Clínico
Carrera 47 No. 3 - 53
Barrio Bellavista
Buena Ventura - Colombia
clínicasantasofia@csspmail.net



Paciente:	MENA ALVAREZ HIJA DE MAIRA SOFIA		Orden No.:	2016040250067	
Historia:	316021662	Género:	Femenino	Fecha y Hora de ingr	2016-04-02 08:14
TELEFONO:		Edad:	205 Días	Fecha de impresión:	03/06/2016 15:43
SERVICIO:	UCI PEDIATRICA	MEDICO:	HABITACION		
EMPRESA:	EMSSANAR ESS SUBSIDIO (CSSP)	MUNICIPIO:	BUENAVENTURA		
Fecha de impresión:					

Examen	Resultado	Unidades	Valores de referencia	Validado en
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HEMATOLOGIA

HEMOCLASIFICACION	O POSITIVO			02/04/2016 08:35
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BANCO DE SANGRE

ANTICUERPO IRREGULARES	NEGATIVO			02/04/2016 08:35
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PRUEBA CRUZADA No 1	COMPTIBLE			02/04/2016 08:35
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UNIDAD DE GLOBULOS ROJOS POBRES EN LEUCOCITOS #1				02/04/2016 08:35
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HEMOCOMPONENTE: GRPL O NEGATIVO

N° UNIDAD: B160013300

N° SELLO DE CALIDAD: B160013300

FECHA DE VENCIMIENTO: 30-04-16

HTLV I Y II: NO REACTIVO

HEMOCLASIFICACION BANCO DE SANGRE	O POSITIVO			02/04/2016 08:35
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Nota: Todos los resultados del Laboratorio deben ser interpretados por el Médico

Laboratorio Clínico
Carrera 47 No. 3 - 53
Barrio Bellavista
Buena Ventura - Colombia
clnicasantasofia@csspmail.net



Paciente:	MENA ALVAREZ HIJA DE MAIRA SOFIA		Orden No.:	2016040250068	
Historia:	316021662	Género:	Femenino	Fecha y Hora de ingr	2016-04-02 08:23
TELEFONO:		Edad:	205 Días	Fecha de impresión:	03/06/2016 15:44
SERVICIO:	UCI PEDIATRICA	MEDICO:		HABITACION	
EMPRESA:	EMSSANAR ESS SUBSIDIO (CSSP)	MUNICIPIO:	BUENAVENTURA		
Fecha de Impresión:					

Examen	Resultado	Unidades	Valores de referencia	Validado en
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BANCO DE SANGRE

UNIDAD DE PLASMA FRESCO CONGELADO #1

02/04/2016 08:36

HEMOCOMPONENTE: PLASMA FRESCO CONGELADO O POSITIVO
N° UNIDAD: B160008128
N° SELLO DE CALIDAD: B16000008128
FECHA DE VENCIMIENTO: 18-02-17

Nota: Todos los resultados del Laboratorio deben ser interpretados por el Médico



NIT. 900.973.844-9

NOMBRE DEL PERITO: MARLEN ANABEL ORTIZ BURGOS
ESPECIALIDAD: PEDIATRIA E INFECTOLOGIA PEDIATRICA
C.C. 38.601.255
T/P. RM : 521445

julio 2023

LISTADO DE CASOS EN LOS QUE SE HAN RENDIDO DICTAMENES PERICIALES
A TRAVES DE C&C CORPORACION

	NOMBRE DEL DEMANDANTE	APODERADO	DEMANDADO	JUZGADO/ PROFESIONAL QUE SOLICITA LA PRUEBA	RADICADO
1	SIN INFORMACION	SIN INFORMACION	SIN INFORMACION	PRUEBA ANTICIPADA	R.I.: 2022-09-30-0131 (*)
2	BERNARD EUGENE MITCHEL Y OTRA	SIN INFORMACION	COMFENALCO VALLE DE LA GENTE; CLÍNICA SANTA SOFÍA DEL PACÍFICO. Llamados en garantía: ALLIANZ SEGUROS S.A.; LA PREVISORA S.A.; GRUPO OPERADOR CLÍNICO HOSPITALARIO POR OUTSOURCING S.A.S. (GRUPO OCHOS S.A.S); SEGUROS DEL ESTADO	JUZGADO SEGUNDO CIVIL DEL CIRCUITO DE BUENAVENTURA	2018-00012-00

(*) Los procesos identificados con el radicado R.I. es un mecanismo de control interno que emplea C&C Corporacion para archivar, organizar y dar trazabilidad a la informacion.

HOJA DE VIDA

I. INFORMACION GENERAL

NOMBRE:	MARLEN ANABEL ORTIZ BURGOS
CEDULA DE CIUDADANIA:	38.601.255 de Cali
PROFESIÓN:	Pediatra especialista en Enfermedades Infecciosas

II. FORMACION ACADÉMICA

BÁSICA PRIMARIA:

Colegio Ciudad de Pasto
Pasto – Nariño

BÁSICA SECUNDARIA:

Bachiller Académico

TITULO OBTENIDO:

Universidad Del Valle (Cali)
(2002 – 2009)

ESTUDIOS PREGRADO:

Médico y Cirujano

TITULO OBTENIDO:

Hospital Universitario Del Valle (Cali)
(Noviembre 2008 – Noviembre 2009)

INTERNADO ROTATORIO:

Hospital San Pablo de Ricaurte E.S.E.
Nariño. (Diciembre 2009 – Junio 2010)

SERVICIO SOCIAL OBLIGATORIO:

Instituto Mixto Santa Teresita de
Altaquer Barbacoas – Nariño

Consulta Externa. Urgencias. Promoción y
prevención. Consulta AIEPI.

ESTUDIOS POSGRADO:	Fundación Valle del Lili (Cali) Universidad ICESI (Cali) (2012 – 2015)
TITULO OBTENIDO:	Especialista en Pediatría
ESTUDIOS POSGRADO:	Universidad del Valle (Cali) (2017 – 2020)
TITULO OBTENIDO:	Enfermedades Infecciosas en Pediatría
EXPERIENCIA LABORAL:	Médico General Hospital San Pablo de Ricaurte E.S.E. – Nariño. (Julio – Nov. de 2010)
	Médico General Comfandi. Sede El Prado. Cali. Valle. Enero-Mayo 2011
	Médico General Comfandi. Sede Candelaria. Candelaria. Valle. Junio 2011- Mayo 2012.
	Pediatra de UCI neonatal, hospitalización y urgencias Clínica Los Andes Pasto-Nariño Diciembre 2015 – Diciembre 2017
	Pediatra de UCI neonatal y urgencias Clínica Hispanoamérica Pasto- Nariño. Diciembre 2015 – Diciembre 2017

Pediatra Consulta externa Proinsalud

Pasto – Nariño

Enero 2016 – Febrero 2017

Pediatra Consulta externa

IPS MedFam

Sept 2021 – Junio 2022

Infectóloga Pediatra

Clínica Hispanoamérica y Unidad

Pediátrica Integral Pasto

Marzo 2021 y laborando actualmente

RESOLUCIÓN POR LA QUE SE AUTORIZA EL EJERCICIO PROFESIONAL EN
TODO EL TERRITORIO NACIONAL:

52 – 1445.

Dada en San Juan de Pasto, Nariño, el 01 Julio de 2010.

INSCRIPCIÓN DE REGISTRO MÉDICO EN LA SECRETARÍA DE SALUD DEL
VALLE DEL CAUCA:

Libro N° 9. Inscripción 1195.

Dada en Santiago de Cali, Valle, 01 Diciembre de 2010.

III. OTROS ESTUDIOS REALIZADOS:

- Congreso de Virología ACINVIR – ACIN. Bogotá, Mayo 2022
- Congreso Latinoamericano de Infectología Pediátrica SLIPE 2022.
- XI Simposio Internacional de Resistencia Antimicrobiana, Una Visión Integral, Cali, Colombia, Marzo 2020.
- XVIII Congreso Latinoamericano de Infectología Pediátrica SLIPE 2019 y XIV Congreso Colombiano de Enfermedades Infecciosas, Cartagena, Colombia, Agosto 2019.
- 2do Encuentro nacional de pediatras especialistas en enfermedades infecciosas “Controversias en enfermedades infecciosas en niños”. Bogotá Mayo 2019.
- VIII Simposio Internacional de Infecciones Adquiridas en el Hospital y Uso Prudente de Antimicrobianos. Marzo 2019.
- 31ª Jornadas Pediátricas de Actualización. Cali Marzo 2019
- Curso de reanimación cardiopulmonar básica y avanzada. Universidad del Valle, Noviembre 2019.
- 1r Encuentro Nacional para pediatras especialistas en enfermedades infecciosas. Rio Negro Junio 2018.

IV. PUBLICACIONES Y CONFERENCIAS:

- Caracterización de los pacientes pediátricos con ingestión de cuerpo extraño que ingresaron al servicio de urgencias de una institución de cuarto nivel. Publicación Revista Pediatría. *Pediatr.* 2015;42(1):55-60.www.elsevier.es/revistapediatria.
- Presentación póster factores asociados con eventos adversos en niños con cáncer y fiebre. Congreso SLIPE 2019.
- Neumonía viral vs bacteriana en pediatría. Jornadas Regionales de Pediatría. Sociedad Colombiana de Pediatría, seccional Pasto, Mayo 2019.

- Neumonía en pediatría. Primer simposio de Prevención de Infecciones Asociadas a la atención en Salud. Fundación Hospital San Pedro, San Juan de Pasto, Julio 2019.



MARLEN ANABEL ORTIZ BURGOS

C.C. 38.601.255 de Cali.



República de Colombia
Ministerio de Educación Nacional



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a los 11 días, del mes de Diciembre de 2009


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El Decano

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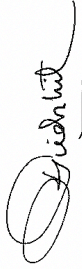
Especialista en Pediatría

A

Marlen Anabel Ortiz Burgos

C.C. 38.601.255 de Cali

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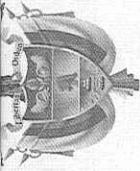
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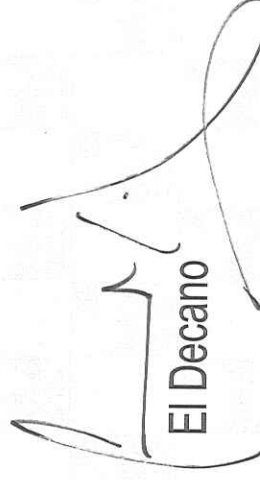
Especialista en Enfermedades Infecciosas en Pediatría

a

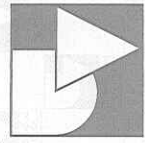
Marlen Anabel Ortiz Burgos

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En testimonio de ello le expide el presente Diploma,
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En la ciudad Santiago de Cali del Departamento del Valle del Cauca, de conformidad con lo dispuesto en la Resolución No 970 emanada de la Rectoría de la Universidad del Valle; el día 29 de Enero de 2021, en nombre de la República de Colombia y por autorización del Ministro de Educación Nacional, confiere el título de:

ESPECIALISTA EN ENFERMEDADES INFECCIOSAS EN PEDIATRÍA

RG 101901 SNIES

a:

MARLEN ANABEL ORTIZ BURGOS

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El diploma correspondiente le será entregado en la fecha prevista en la Resolución No. 970 y anotado en el libro 3 Folio 987 Registro 6 de la Universidad del Valle.

(Fdo) Edgar Varela Barrios

- Rector

(Fdo) Antonio Jose Echeverry Perez

- Secretario General

Se firma en Santiago de Cali, el 29 de Enero de 2021


MARTA SOFIA COTACIO TORRES

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SLIPE

Sociedad Latinoamericana
de Infectología Pediátrica



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La Asociación Colombiana de Infectología - ACIN
y La Sociedad Latinoamericana de Infectología Pediátrica - SLIPE

Certifican que:

MARLEN ANABEL ORTIZ BURGOS

Asistió en calidad de: **PARTICIPANTE** al



Realizado del 21 al 24 de agosto de 2019

Sede: Centro Internacional de Convenciones Las Américas

Cartagena, Colombia

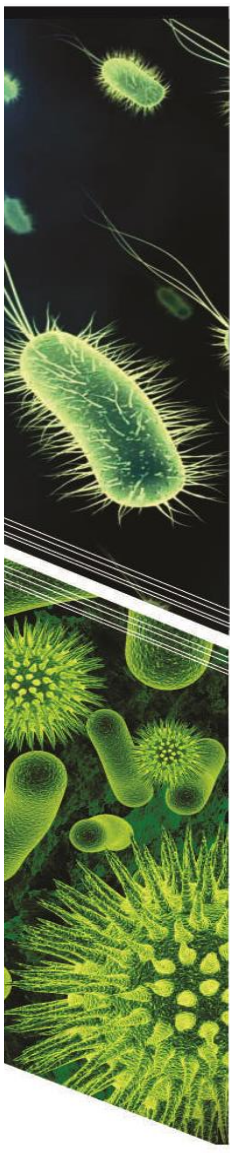
Intensidad horaria: (32 horas)

PIO LÓPEZ LÓPEZ

Presidente ACIN
Presidente Congreso SLIPE 2019

SANDRA VALDERRAMA BELTRÁN

Vicepresidente ACIN
Presidente Congreso ACIN 2019



CERTIFICA QUE:

Marlen Anabel Ortiz Burgos

Identificado(a) con Cedula de Ciudadanía : No.38,601,255

Participo activamente en:

1r Encuentro nacional de pediatras especialistas en enfermedades infecciosas
“Controversias en enfermedades infecciosas en niños”

El evento se realizó en la ciudad de Rionegro-Ant. Los días 15 y 16 de junio de 2018.

Para constancia se firma a los 18 días del mes de Junio del año 2018.



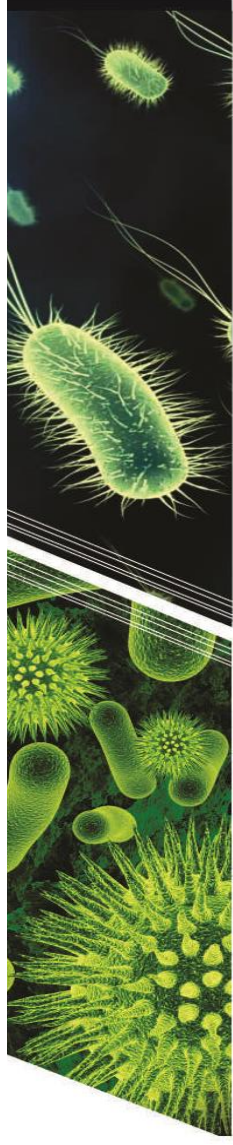
Dr. Carlos Garcés Samudio
Comité Científico Evento



Dra. Claudia Beltrán Arroyave
Comité Científico Evento

Con el apoyo:





CERTIFICA QUE:

MARLEN ANABEL ORTIZ BURGOS

Identificado(a) con Cedula de Ciudadanía No. 38.601.255

Participo activamente en:

2do Encuentro nacional de pediatras especialistas en enfermedades infecciosas
“Controversias en enfermedades infecciosas en niños”

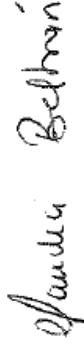
El evento se realizó en la ciudad de Bogotá, El día 11 de Mayo de 2019.

Para constancia se firma a los 13 días del mes de mayo del año 2019.



Dr. Carlos Garcés Samudio
Comité Científico Evento

Con el apoyo:



Dra. Claudia Beltrán Arroyave
Comité Científico Evento

CURSO INTERNACIONAL ACTUALIDAD EN INFECTOLOGÍA PEDIÁTRICA Y VACUNAS

4 y 5 de mayo de 2022



Certificamos que

Anabel Ortiz Burgos

asistió al Curso Internacional Actualidad en Infectología Pediátrica y Vacunas,
realizado los días 4 y 5 de mayo de 2022



Dr. Roberto Debbag
Presidente de SLIPE



Dr. José Brea del Castillo
Presidente, Sociedad Dominicana de Vacunología y
Miembro de la Junta Directiva de SLIPE



**CONGRESO COLOMBIANO
DE VIROLOGÍA CLÍNICA**

ACINVIR 2022

11 al 14 de Mayo Hotel Hilton Bogotá Corterías

La Asociación Colombiana de Infectología - ACIN

Certifica que:

Anabel Ortiz Burgos

Participó en calidad de asistente

En el V Congreso Colombiano de Virología Clínica ACINVIR 2022

Realizado los días 11, 12, 13 y 14 de mayo de 2022

Intensidad horaria 40 horas

ERNESTO MARTÍNEZ BUITRAGO

**Presidente V Congreso Colombiano
de Virología Clínica ACINVIR 2022**

ALFONSO J. RODRÍGUEZ MORALES

**Presidente Asociación
Colombiana de Infectología - ACIN**



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