SEÑOR
**JUEZ QUINCE (15) CIVIL DEL CIRCUITO DE BOGOTÁ**
Ciudad

Demandantes: Tomás Cabra Franco, Dennys Alexandra Franco Salgado, Saimonth Arial Cabra Mancipe, Maritza Mancipe Ortiz.
Demandados: Fundación Santa Fe De Bogotá Y Clínica Marly S.A.
Radicación: 11001310301520190067100
Asunto: Memorial aportando dictamen pericial - Fundación Santa Fé De Bogotá

**ADRIANA GARCÍA GAMA**, mayor de edad, vecina de Bogotá, identificada con cédula de ciudadanía No. 52.867.487 de Bogotá, abogada en ejercicio, portadora de la Tarjeta Profesional No. 144.727 del Consejo Superior de la Judicatura en mi calidad de apoderada judicial de **FUNDACIÓN SANTA FE DE BOGOTÁ** por medio del presente escrito y dentro del término concedido el 9 de octubre de 2024, me permito aportar el **DICTAMEN PERICIAL** rendido por el Doctor **CARLOS EDUARDO OLMOS OLMOS**, médico especialista en inmunología pediátrica.

De acuerdo con lo establecido en el artículo 226 del C.G.P., adjunto los documentos que acreditan la idoneidad del perito y sus datos personales.

Del señor Juez, respetuosamente,

**ADRIANA GARCÍA GAMA**
**C.C. No. 52.867.487 de Bogotá**
**T.P. No. 144.727 del C. S. de la J.**

Bogotá, 18 de julio de 2020

Señores
**JUZGADO QUINCE (15) CIVIL DEL CIRCUITO DE BOGOTÁ**
E. S. D

**Ref:** Proceso verbal de responsabilidad civil médica.

**Demandantes:** Tomás Cabra Franco y otros

**Demandadas:** Fundación Santa Fe de Bogotá y otros.

**Expediente No.** 11001310301520190067100

**Asunto:** Dictamen pericial.

## I. Identificación del Perito

CARLOS EDUARDO OLMOS OLMOS, mayor de edad, natural y residente en la ciudad de Bogotá, médico especialista en inmunología pediátrica egresado de Universidad de Universidad Javeriana en el año de 1882, especialista en Pediatría de la Facultad de Medicina de la Universidad del Rosario en el año de 1987 y subespecialista en Alergología e Inmunología Clínica de Tulane School of Medicine en el año 2000, con más de 20 años de experiencia profesional y habiéndome desempeñado como:

- Cargos más importantes:
  - Jefe, Alergología e Inmunología Clínica, Fundación Cardio Infantil 2004-2012
  - Director, Unidad de Alergia e Inmunología Clínica, CAYRE IPS & Fundación 2008-fecha

- Docencia
  - Universidad del Rosario, Residencia de Pediatría desde 2004-fecha
  - Universidad El Bosque, Subespecializaciones de Reumatología 2012-2018 e Infectología Pediátrica 2013-fecha
  - Docente, Universidad Militar de Colombia, Residencia de ORL en CAYRE, 2015-2018

- Miembro sociedades científicas nacionales y/o internacionales
  - Asociación Colombiana de Alergia, Asma e Inmunología (ACAAI) 2004-fecha
  - Asociación Colombiana de Pediatría 1987-fecha
  - American Academy of Allergy, Asthma, & Immunology (AAAI) 1997-fecha
  - European Academy of Allergy & Clinical Immunology (EAACI) 2010-fecha

- Sociedad Latinoamericana de Inmunodeficiencias Primarias (LASID) 2015-fecha
- Grupo de Inmunodeficiencias Primarias de la Universidad de Antioquia-Nodo CAYRE, Bogotá 2009-Fecha

- Publicaciones más relevantes de los últimos 10 años
  - Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. In: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017.
  - Olivares MM; Alvarez-Olmos MI, Olmos CE et al. Guías Colombiana dde Práctica Clínica para uso de inmunoglobulinas en tratamiento de reposición e inmunomodulación. *Revista Alergia de México. 2017 Vol 64 Suppl.2: s5-s55.*
  - Olmos CE,Gómez C. **Enfoque holístico del paciente con alergia. : ¿qué hay de nuevo?.** *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago). Sociedad Colombiana de Pediatría*
  - Olmos CE, Suárez MA, Gómez C. **Reconociendo Inmunodeficiencias Primarias Mas Allá De Las Señales De Alarma Tradicionales.** *Revista Programa de Educación continuada en Pediatría: Precop* (2015 *Volumen 14 Número 2: 14-31* ). Sociedad Colombiana de Pediatría
  - Olmos CE. **Actualización en alergia al huevo y vacunas. Mitos y realidades** *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago*). Sociedad Colombiana de Pediatría
  - Olmos CE. **Actualización en Vacunas y Alergia.** *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago*). Sociedad Colombiana de Pediatría
  - Olmos CE. **Vacunas y Autoinmunidad.** *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago*). Sociedad Colombiana de Pediatría

- Premios o distinciones[1]
  - Profesor Titular Clínico Universidad del Rosario
  - Docente Universidad El Bosque, División de postgrados
  - Diplomate of The American Board of Allergy and Immunology 2010-Fecha
  - Diplomate of The American Board of Pediatrics 2003

Actualmente hago parte de la Unidad de alergia e inmunología clínica de CAYRE IPS & Fundación, soy miembro activo de las sociedades científicas arriba anotadas y me desempeño como alergólogo e inmunólogo clínico en la práctica privada en el Centro Médico de la Sabana en Bogotá.

[1] Favor diligenciar datos completos de formación profesional

Tal como consta en la hoja de vida y demás anexos que acompañan este dictamen, me permito rendir el siguiente dictamen pericial solicitado por la Fundación Santa Fe de Bogotá con el fin de ser presentado como prueba en el proceso de la referencia que se adelanta en ese Despacho.

## II. Normatividad y Declaraciones

En concordancia con los artículos 226 a 235 - Capítulo VI Titulo Único del Código General del Proceso:

Manifiesto que tengo la experiencia, formación y conocimientos especializados para rendir el dictamen que me ha solicitado la Fundación Santa Fe y que estoy a disposición, si el Juzgado lo considera pertinente, para exponerlo personalmente y absolver los interrogantes y hacer las aclaraciones que se requieran.

Mis datos de contacto son: Dirección: CRA 7 #119-14 Consultorio 418 Centro Médico de La Sabana. Bogotá, DC
Teléfono: 2155619-6121075-6120904-2150120
Celular: 3157734000
Correo electrónico: colmos.8600@gmail.com

Declaro bajo juramento que la información aquí contenida es independiente, profesional y verdadera por quien lo firma. Igualmente, en virtud del numeral 6 del artículo 226 del CGP, manifiesto que no he sido designado en procesos anteriores o en curso por la misma parte o por el mismo apoderado de la parte y que no me encuentro incurso en ninguna causal de inhabilidad de las que trata el artículo 50 del CGP[2], ni tengo conflicto de interés alguno para asumir el presente encargo.

---

[2] *Artículo 50. Exclusión de la lista. El Consejo Superior de la Judicatura excluirá de las listas de auxiliares de la justicia:*
*1. A quienes por sentencia ejecutoriada hayan sido condenados por la comisión de delitos contra la administración de justicia o la Administración Pública o sancionados por la Sala Jurisdiccional Disciplinaria del Consejo Superior de la Judicatura o sus Seccionales.*
*2. A quienes se les haya suspendido o cancelado la matrícula o licencia.*
*3. A quienes hayan entrado a ejercer un cargo oficial.*
*4. A quienes hayan fallecido o se incapaciten física o mentalmente.*
*5. A quienes se ausenten definitivamente del respectivo distrito judicial.*
*6. A las personas jurídicas que se disuelvan.*
*7. A quienes como secuestres, liquidadores o administradores de bienes, no hayan rendido oportunamente cuenta de su gestión, o depositado los dineros habidos a órdenes del despacho judicial, o cubierto el saldo a su cargo, o reintegrado los bienes que se le confiaron, o los hayan utilizado en provecho propio o de terceros, o se les halle responsables de administración negligente.*
*8. A quienes no hayan realizado a cabalidad la actividad encomendada o no hayan cumplido con el encargo en el término otorgado.*
*9. A quienes sin causa justificada rehusaren la aceptación del cargo o no asistieren a la diligencia para la que fueron designados.*
*10. A quienes hayan convenido, solicitado o recibido indebidamente retribución de alguna de las partes.*
*11. A los secuestres cuya garantía de cumplimiento hubiere vencido y no la hubieren renovado oportunamente.*

Igualmente declaro que no me he desempeñado como perito en el pasado.

Por último, en virtud de los numerales 8 y 9 del artículo 226 del CGP, manifiesto que el método utilizado para realizar la experticia encomendada consistió en revisión de la información de la historia clínica, lectura de documentos adicionales, así como respuesta a las preguntas enviadas y declaro que la metodología implementada no varió respecto de la solicitada en las instrucciones enviadas.

## III. Antecedentes Médicos

Para efectos de rendir el presente dictamen he recibido la demanda instaurada por los padres y abuela del paciente Tomás Cabra Franco, la respuesta a la demanda presentada por los apoderados Judiciales de la Fundación Santa Fe, la totalidad de la historia clínica correspondiente al caso en cuestión (3 folios en pdfs: #1 HC eventos 1-11, #2 HC eventos 12-33, #3 Imágenes y laboratorios) y un folio con el dictamen pericial aportado por el parte demandante rendido por la médica general Dra. Diana Paola Álvarez Archila.

Brevemente y antes de proceder con la respuesta al cuestionario que me ha sido planteado, procedo a hacer un breve resumen del cuadro clínico del menor Tomás Cabra Franco:

Se trata de escolar masculino de 9 años con historia de cuadro convulsivo iniciado como síndrome convulsivo facilitado por fiebre desde los 6 meses de edad, sin antecedentes perinatales significativos excepto cesárea por trabajo de parto estacionario, episodio de trauma cráneo-encefálico [TCE] al parecer leves a los 2 años sin evidencia de fracturas ni requerimiento de admisión hospitalaria derivada de los mismos, retraso en desarrollo del lenguaje descrito desde los 2 años y retraso global del neurodesarrollo descrito después de los 3 años, inmunizaciones al día y múltiples consultas a servicios de urgencias (FSB mayoría y algunas en Clínica Universitaria Colombia, EPS Sanitas, Clínica El Country, EMI) por episodios convulsivos febriles asociados a cuadros infecciosos de predominio respiratorio alto de etiología presumiblemente viral, un episodio de laringitis, 3 episodios de OMA en diferentes edades con uno supurativo a los 8 años, faringoamigdalitis estreptocócica a los 5 años, dos episodios de neumonía en diferentes años de manejo ambulatorio uno y otro a los 3 años atribuido a etiología por adenovirus + VRS con sospecha de coinfección bacteriana y dos episodio de gastroenteritis presumiblemente de etiología viral. Terapia antibiótica oral con betalactámicos orales (Amoxicilina-A.Clavulánico principalmente) por episodios de OMA y otras infecciones respiratorias altas, Penicilina Benzatínica para un episodio de amigdalitis estreptocócica y, se menciona en una ocasión IV (Ampicilina-Sulbactam) a los 3 años (2014) durante admisión a UCIP. Indicación de

---

*(...) PARÁGRAFO 3o. No podrá ser designada como perito la persona que haya incurrido en alguna de las causales de exclusión previstas en este artículo.*

broncodilatadores en algunas consultas. Historia de una admisión hospitalaria para estudio de síndrome convulsivo en el 2014 en FSB por neuropediatría y otra en el Instituto Roosevelt el mismo año, este último asociado a depresión/falla respiratoria atribuida a posible efecto de benzodiacepinas para control de status convulsivo que requirió UCIP con descripción de neumonía viral por adenovirus-VSR + coinfección bacteriana (no hay datos de cultivos positivos) complicado con cuadro de "delirium hiperactivo" con manejo multidisciplinario institucional (cuidado intensivo pediátrico, neurología pediátrica, genética, reumatología pediátrica, endocrinología pediátrica, terapia física y del lenguaje, ) e indicación de seguimiento ambulatorio por las mismas. Se encuentra registro con descripciones limitadas de evaluaciones ambulatorias por consulta externa de pediatría (FSB), neurología pediátrica (FSB, Compensar), reumatología pediátrica (después de egreso), medicina homeopática (registros no claros).

Historia de asistencia al jardín infantil en consulta al año (2012) y en otra a los 7 años descrita en consulta en FSB; se menciona contacto en casa con mascotas (perro y dos gatos). No exposición aparente a cigarrillo. No registro de reacciones adversas a vacunas ni de historia de transfusiones sanguíneas.

Historia familiar de malignidad hematológica del lado paterno descrita como leucemia mieloide en la mayoría de los registros, abuelo paterno con leucemia (no se especifica tipo) e historia de diabetes mellitus en abuelo materno. No hay descripción de consanguinidad, muertes tempranas en familiares cercanos por infecciones severas o de autoinmunidad tales como LES, AR, etc.

Desde el punto de vista paraclínico no se evidencian alteraciones hematológicas tipo citopenias (linfopenia, anemia o trombocitopenia) ni alteraciones persistentes elevadas (leucocitosis) excepto coincidiendo con algunos episodios infecciosos; transaminasas normales, niveles de ácido valproico en varias ocasiones dentro de límites normales excepto en una ocasión (aumento de dosis ambulatorio). Cuenta con algunos estudios radiológicos de tórax sin alteraciones crónicas aparentes, se describen hallazgos de procesos bronquiales/neumónicos de algunos episodios clínicamente evaluados en su momento. TAC cerebral con hallazgo incidental de "quiste aracnoideo temporo-parietal derecho". TAC de oídos-mastoides sin evidencia de mastoiditis (2014). Electroencefalogramas descritos como normales. RNM cerebral sin reporte oficial de estancia en Instituto Roosevelt.

## IV. Concepto del Perito Médico

Con base en esta información procedo a responder el cuestionario que me ha sido planteado:

**1. Qué es una inmunodeficiencia primaria?**

**Respuesta**: Las inmunodeficiencias primarias [IDP], denominados recientemente como errores innatos de la inmunidad, comprende un grupo complejo, diverso y heterogéneo de defectos o errores innatos del sistema inmune tanto en su desarrollo como en su función, comprometiendo células y/o componentes del sistema inmune innato o adaptativo que pueden manifestarse con infecciones recurrentes anormales, autoinmunidad, autoinflamación y linfoproliferación principalmente. Aunque han sido consideradas poco frecuentes con frecuencias estimadas de 1:10.000 a 1: 50.000 nacidos vivos, estudios recientes han empezado a mostrar que son más comunes que lo previamente estimado calculándose que pueden llegar al menos a 1:1.000 a 1:5.000 con un impacto importante en la calidad de vida de los afectados. Los avances moleculares recientes han permitido el reconocimiento e identificación de más de 400 defectos en la actualidad con diferentes fenotipos clínicos y compromiso de diferentes sistemas. La mayoría de estas condiciones son enfermedades monogénicas siguiendo una herencia mendeliana simple que se caracterizan por una variabilidad fenotípica debido a diferencias en la penetrancia en la expresión e interacción genética con el ambiente. Sin embargo, los avances en estudios de secuenciación genómica abren un horizonte a nuevos mecanismos, moléculas y genes que están siendo identificados.

**Referencias**


1. Ballow M. Approach to the patient with recurrent infection. In: Middleton's Allergy: Principles and Practices. ELSEVIER Inc. Vol 2. 9th edition. 2020; pp: 1111-1122.
2. Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. In: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; Vol 2.


**2. Qué relación causal hay entre padre con leucemia mieloide y diagnóstico de inmunodeficiencia primaria?**

**Respuesta**: Se ha descrito aumento de susceptibilidad a malignidad, especialmente aquellas anormalidades asociadas a disfunción de las células T o defectos en la reparación del DNA en relación con IDP, tales como canceres linfoides como linfomas, leucemias linfoides, leucemias T cutáneas y, menos frecuentemente, cánceres gástrico y carcinoma de células escamosas. A la luz del conocimiento actual no es posible establecer una relación causal entre el padre con leucemia mieloide e IDP. Sin embargo, siempre debe investigarse la historia familiar de malignidad hematológica T principalmente y consanguinidad en primera línea.

El desarrollo de neoplasias hematológicas, linfomas y tumores sólidos es el resultado de interacciones de múltiples factores tales como el sistema inmune (Inmunodeficiencias, inflamación, autoinmunidad), noxas endógenas y exógenas (Químicos y radiaciones), microbiota (Microbioma, infecciones) y el factor genético del individuo (Mutaciones, variantes comunes, modificadores).

**Referencias**


1. Mayor PC, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the US Immune Deficiency Network Registry. JACI 2018; 141: 1028-35
2. Haas O. Primary immunodeficiency and cancer predisposition revisited: Embedding two closely related concepts into a integrative conceptual framework. Frontiers in Immunol 2019; 2018: 9: 31-36.


**3. Indique si las infecciones que se documentaron en algunos de los ingresos del paciente como otitis y vías respiratorias altas son las esperadas en edad preescolar y escolar? En caso afirmativo, cuál es su prevalencia en esa población?**

**Respuesta:** Las enfermedades infecciosas constituyen una de las principales causas de consultas en la población general, siendo mucho más frecuentes en la población pediátrica, en donde el número de episodios es inversamente proporcional a la edad. Los niños pueden tener muchos episodios infecciosos de tipo repetitivo y autolimitado con respuesta rápida al manejo sintomático y, sin evidencia de secuelas. Estos conocidos como "infección recurrente normal" son debidas a inmadurez del sistema inmune o a la falta de exposición previa. Un niño con adecuado funcionamiento del sistema inmune puede presentar entre 4 a 8 infecciones respiratorias altas al año, siendo mayor la frecuencia en niños que asisten al jardín o que tienen familiares en edad preescolar o escolar o aquellos expuestos al humo del cigarrillo [hasta 10-12 por año]. Esta última causa además puede contribuir al aumento de los síntomas en pacientes alérgicos o asmáticos. Se calcula que el 50% de los niños con infecciones recurrentes se van a encontrar en esta categoría. En general en este grupo, el tipo de infecciones son principalmente respiratorias y de etiología viral, considerándose un episodio de neumonía no severa o hasta dos o más de OMA no complicada en los primeros 3 años de vida. Si tenemos un paciente que presenta 10 episodios en un año, esto implicaría que estaría sintomático casi la mitad el año y continuaría siendo "normal". El desarrollo físico y mental al igual que el examen y los paraclínicos suelen ser normales y responden rápidamente al tratamiento permaneciendo asintomáticos entre un episodio infeccioso y otro o cuando están en vacaciones, por fuera del jardín.

**Referencias**


1. Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. In: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; vol 2.
2. Annamalay A, Le Souëf P. Viral-bacterial interactions in childhood respiratory tract infections. IN: Viral infections in children. Vol 1. R.D. Green (ed.). Springer International Publishing AG 2017.


**4. Es posible establecer algún tipo de relación causal entre el antecedente de leucemia del padre con las convulsiones febriles o las infecciones predominantemente virales**

**Respuesta**: No es posible establecer ningún tipo de relación causal, pero se sabe que la fiebre originada por causas infecciosas, virales o no, pueden facilitar convulsiones febriles.

**5. Episodios de infecciones virales en niños en edad escolar o preescolar son sinónimos o señal de alerta de una posible inmunodeficiencia primaria?**

**Respuesta**: No son sinónimos excepto si se comportan como infecciones diseminadas, complicadas con neumonitis (cuadro severo de compromiso intersticial difuso), meningoencefalitis viral necrotizante o con coinfección bacteriana severa (neumonía con empiema) así como también si son prolongadas o refractarias al tratamiento convencional o antiviral específico.

**Referencias**:


1. Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. En: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; pp.
2. Olmos CE, Suárez MA, Gómez C. Reconociendo inmunodeficiencias primarias: Más allá de las señales tradicionales. PRECOP 2015; 14: 20-31.
3. Tabares-Costa-Tavares V, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014; 34: 10-22.
4. Olmos CE, Lozano M, Quijano C. Infecciones recurrentes y sospecha de inmunodeficiencias primarias. PRECOP 2012; 11: 5-15.

**6. Cuáles fueron los motivos de consulta del menor entre los años 2102 al 2014?**

**Respuesta:** Los motivos de consulta de acerdo con la información aportada fueron múltiples episodios de convulsiones facilitados por fiebre, en su mayor parte asociados a infecciones respiratorias altas de posible etiología viral, otitis media x 3 tratados con terapia antibiótica oral, uno de ellos asociado a neumonía siendo tratado con terapia antibiótica IV con corta estancia hospitalaria, neumonía por adenovirus-VSR con sospecha de infección bacteriana sin aislamiento específico + compromiso neurológico post estatus convulsivo y depresión respiratoria atribuida a efecto de benzodiacepinas para su control. En una de las consultas iniciales en el 2012 se describe trauma facial por caída de 1 metro de altura sin fractura.

**7. ¿Qué diferencias existen desde la clínica, parámetros de laboratorio e imágenes para sospechar inmunodeficiencias primarias cuándo se presentan infecciones bacterianas o virales?**

**Respuesta:** La sospecha de IDP debe combinar presentación clínica, laboratorio, imágenes y antecedentes familiares basados en señales de alerta más allá de las tradicionales, las cuales se ha demostrado tener baja sensibilidad y especificidad.

Desde el punto de vista clínico, la frecuencia y tipo de infecciones varía de acuerdo con la edad, presencia o no de manifestaciones alérgicas, historia exposicional o ambiental siendo más frecuentes y severas en los pacientes con IDP que en los niños sin estas condiciones. Así, las infecciones virales, bacterianas, micobacterianas o fúngicas que requieren admisión hospitalaria, estancia en UCIP, uso frecuente de terapia antibiótica oral o endovenosa, complicaciones tales como empiemas, infección sistémica (sepsis, meningitis, osteomielitis, abscesos en diferentes órganos, entre otros), necesidad de drenajes quirúrgicos, cuadros de mononucleosis severa, dependencia de oxígeno, alteraciones del crecimiento o del neurodesarrollo deben alertar a inmunodeficiencia tanto primaria o secundaria (VIH, desnutrición severa, malignidad, etc.). Otras señales importantes para considerar incluyen diarrea crónica, lesiones cutáneas extensas o recurrentes como moluscos extensos, papilomas cutáneos o piodermitis recurrentes, reacciones adversas a vacunas vivas, caída retardada del muñón umbilical, entre otros.

Desde el punto de vista de laboratorio, existen signos importantes que pueden ser evidenciados en el hemograma como la presencia de citopenias incluyendo leucopenia, neutropenia, linfopenia, anemia, trombocitopenia o combinaciones. Algunas IDP de los fagocitos pueden revelar leucocitosis persistentes con neutrofilia y elevación de reactantes

de fase aguda. En el período neonatal en presencia de cardiopatías congénitas con alteraciones morfológicas, la hipocalcemia es un hallazgo importante.

Desde el punto de vista de imágenes, evidencia de varios episodios de neumonía (2 al año) o neumonía severa y complicada con empiemas (mínimo una al año), demostración de bronquiectasias, presencia de mastoiditis crónica, colecciones o abscesos en tórax, abdomen, SNC o del sistema musculoesquelético, ausencia de timo en el período neonatal, ausencia de bazo, etc.

Referencias


1. Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. En: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; pp.
2. Olmos CE, Suárez MA, Gómez C. Reconociendo inmunodeficiencias primarias: Más allá de las señales tradicionales. PRECOP 2015; 14: 20-31.
3. Tabares-Costa-Tavares V, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014; 34: 10-22.
4. Olmos CE, Lozano M, Quijano C. Infecciones recurrentes y sospecha de inmunodeficiencias primarias. PRECOP 2012; 11: 5-15


**8. ¿Los exámenes, valoraciones e imágenes tomadas al paciente en cada oportunidad que fue visto en la FSB fueron indicadas, pertinentes y coherentes en cada motivo de consulta?**

**Respuesta:** De acuerdo con las descripciones de las historias clínicas de urgencias de la FSB, los estudios de laboratorios e imágenes fueron pertinentes para las consultas específicas.

**9. ¿Las indicaciones de egreso, prescripciones y ordenes de seguimientos por consulta externa con las diferentes especialidades fueron consistentes con diversos motivos de consulta y evolución de su estado clínico?**

**Respuesta:** Las indicaciones de egreso, prescripciones y ordenes de seguimiento por consulta externa fueron consistentes en su mayoría con el motivo específico de consulta especialmente el seguimiento a pediatría, neuropediatría, ORL.

**10. ¿Verificados los diferentes hemo-leucogramas realizados al paciente en la FSB encuentra hallazgos de alteración inmunológica en las diferentes líneas celulares?**

**Respuesta:** No encuentro alteración ien los hemogramas disponibles que sugieran IDP.

**11. ¿De conformidad con la literatura, enuncie cuáles son las señales de alerta para sospechar cuadro de IDP en un infante?**

**Señales:** Por muchos años, desde los años 1990´s, se utilizaron las 10 señales de alarma clásicas de la Jeffrey Modell Foundation. Sin embargo, en la actualidad son de baja sensibilidad (63%) y especificidad (23%), lo cual indica que el 30% de los pacientes con IDP confirmadas no tenían ninguna señal de alarma tradicional para su diagnóstico. Solo si se combinan las siguientes señales: (1) necesidad de uso frecuente de antibióticos endovenosos, (2) historia familiar positiva para IDP específica y (3) falla de medro combinadas identificarían el 96% de IDP de neutrófilos y de complemento, 86% de IDP por déficit de linfocitos T y menos del 60% de IDP por déficit de anticuerpos que son las IDP más frecuentes, lo cual indica la baja sensibilidad de estas señales. Esto es debido en gran parte al aumento del conocimiento y la gran variedad de la expresión clínica de estas enfermedades. Lo ideal es contar con señales más allá de las tradicionales, personalizadas y de acuerdo con la expresión clínica principal.

**Referencias**


1. Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. En: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; pp.
2. Olmos CE, Suárez MA, Gómez C. Reconociendo inmunodeficiencias primarias: Más allá de las señales tradicionales. PRECOP 2015; 14: 20-31.
3. Tabares-Costa-Tavares V, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014; 34: 10-22.


**12. ¿Indique si durante la atención brindada en la FSB, el paciente presentaba dos o más señales de alerta que hicieran sospechar un cuadro de inmunodeficiencia primaria?**

**Respuesta:** La frecuencia de las infecciones respiratorias altas y algunas bajas con uso de terapia antibiótica oral para episodios de OMA y endovenosa en algunos de los episodios por neumonía pudieron alertar a la evaluación inicial ambulatoria con un tamizaje basal y consideración de valoración por inmunología clínica o infectología pediátrica, siendo

importante que se indicara y realizara por parte del pediatra o médico de base desde su servicio de salud básico en la consulta externa ambulatoria cuando realizaron los seguimientos de las evaluaciones después de las atenciones en urgencias. También se podrían haber sugerido dichas valoraciones desde los servicios de urgencias y hospitalarios y desde cualquiera de las diferentes especialidades o subespecialidades que lo evaluaron para realización ambulatoriamente.

Es importante anotar que la asistencia temprana al jardín debe ser considerado como factor contribuyente para aumento de infecciones respiratorias virales en niños con o sin IDP, pudiendo explicar inicialmente la frecuencia de éstas en el paciente y su interpretación por quienes lo atendieron en urgencias.

**13. Revisada la historia clínica de la FSB en consonancia con los laboratorios clínicos practicados y los antecedentes familiares registrados, indíquenos si existe algún soporte clínico o paraclínico, ¿signo o síntoma que hiciera sospechar in cuadro de IDP?**

**Respuesta:** Como se anotó en la pregunta anterior, la frecuencia de los episodios respiratorios y uso de terapia antibiótica pueden ser considerados como señales de alarma, aunque la asistencia a jardín infantil podría haberlas favorecido inicialmente. En cuanto a los paraclínicos, los hemogramas disponibles no muestran alteraciones que sugieran IDP dada la no evidencia de citopenias de ninguna de las líneas ni reacciones leucemoides y los estudios de mastoides tampoco mostraron alteraciones que sugirieran en su momento compromiso crónico o extensión de las OMA. Los antecedentes familiares de leucemia mieloide no alertan para estudio de IDP per se.

Lo que más frecuentemente alerta a IDP en relación con los antecedentes familiares incluyen, entre otros, consanguinidad de primer en los padres, historia de IDP específica [Enfermedad granulomatosa Crónica, Agamaglobulinemia de Bruton] en miembros de la familia, historia de muertes tempranas en familiares cercanos de la familia especialmente en el lado materno si son varones, historia de infecciones severas o abscesos que hayan requerido cirugías o, historia de eczema y sangrado asociado en familiares cercanos, historia de malignidad principalmente de línea T como linfomas, leucemias linfoides, cáncer gástrico e historia de enfermedades autoinmunes endocrinológicas o hematológicas o reumatológicas en miembros cercanos de la familia.

**Referencias**

1. Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. En: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; vol 2.

2. Buttle M, Stiehm ER. Approach to the child with recurrent infections. UpToDate Mar 17, 2020

**14. Las convulsiones febriles relacionadas con infecciones respiratorias son indicativas de un cuadro de IDP?**

**Respuesta:** No son consideradas signos de alarma ni indicativas de PID. Si tendría relevancia si presenta convulsiones secundarias a cuadro de compromiso neurológico de etiología infecciosa directa como meningoencefalitis o abcesos cerebrales.

**15. ¿Indique si las infecciones virales a repetición que se resuelven sin dificultad y el antecedente del papá de leucemia mieloide, indicaban estudiar un cuadro de IDP del infante?**

**Respuesta:** En el escenario que se presenta de infecciones virales a repetición que se resuelven sin dificultad y el antecedente de leucemia mieloide del papá no son indicativas de evaluar para IDP. Véanse respuestas anteriores en relación con historia familiar de malignidad.

**16. Un cuadro de convulsiones febriles a repetición hace sospechar en IDP?**

**Respuesta:** No.

**17. Qué son, ¿cuáles son, ¿cuándo y quién práctica las pruebas para establecer un diagnóstico de IDP?**

**Respuesta:** Los estudios o pruebas para establecer un diagnóstico de IDP dependen de la expresión clínica, señales de acuerdo con la edad de inicio (antes o después de los 6 meses de edad), el tipo, frecuencia, localización, severidad y etiología de procesos infecciosos, manifestaciones en diferentes sistemas (gastrointestinales, respiratorios, cutáneos, etc.), presencia de autoinmunidad, señales al examen físico y señales de laboratorio a nivel hematológico siendo el hemograma (citopenias o leucocitosis persistentes) y el frotis de sangre periférica esenciales.

Las inmunoglobulinas séricas y el estudio para descartar VIH deben estar en la primera línea y pueden ser ordenados por el pediatra u otro especialista que conozca regularmente el paciente con remisión al inmunólogo clínico o en su defecto, al infectólogo pediatra. Estudios de imágenes radiológicas pueden ayudar a evaluar el impacto a nivel respiratorio alto o bajo o evaluar a nivel abdominal ausencia de bazo o aumento de órganos linfoides

(hígado, bazo o adenopatías intraabdominales). En algunas situaciones se requiere estudios para descartar otras condiciones diferentes a IPD como por ejemplo fibrosis quística.

Los estudios más especializados de función de anticuerpos, citometría de flujo para linfocitos T, B, NK con subpoblaciones o para defectos de fagocitos, complemento sérico deben ser orientados por especialistas en inmunología clínica o infectología pediátrica y dependerán de las manifestaciones clínicas y paraclínicas. Los estudios genéticos se orientan de acuerdo con el diagnóstico por estos especialistas y puede requerir el concurso de genetistas, oncohematología, neumología o reumatología pediátricas, entre otros.

**Referencias:**


1. Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. En: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; pp.
2. Buttle M, Stiehm ER. Approach to the child with recurrent infections. UpToDate Mar 17, 2020


**19. ¿En qué fecha de atención se registra por primera vez que el paciente hubiese sufrido una encefalopatía hipóxica?**

**Respuesta:** De acuerdo con el documento disponible parece ser después del evento atendido el 21/11/2014 en la Clínica Marly con descripción de estatus convulsivo que requirió trasladado a la UCIP del Instituto Roosevelt, en donde permaneció hasta el 26/1272014. Sin embargo, es importante tener en cuenta que el paciente tenía estudios previos de TAC cerebral y al parecer se le realizó RNM cerebral constrastada en el Insituto Rooselvet cuyo reporte definitivo no se encuentra claramente descrito en la información disponible para inferior conclusiones.

**20. ¿Cuáles fueron las circunstancias y razones registradas con relación a ese tema?**

**Respuesta** Es muy difícil emitir un juicio de manera retrospectiva, pero de acuerdo con la descripción de los eventos en el folio del demandante, el paciente presentó a los 3 años de edad depresión respiratoria con necesidad de intubación y asistencia ventilatoria que coincidió con infección respiratoria viral por adenovirus + VSR y sospecha de coinfección bacteriana. Tampoco se puede afirmar con certeza que los efectos fueran debidos terapia benzodiazepínica utilizada para lograr el control del estatus convulsivo en un paciente con crisis febriles complejas frecuentes. Adicionalmente con la información disponible, no es posible descartar compromiso viral a nivel cerebral que fuese responsable de la condición

neurológica complicada si el paciente tuviese una IDP no sospechada en ese momento. Considero que este concepto debe ser evaluado con el neurólogo pediatra.

**21. ¿Ocurrió durante una atención brindada en la FSB?**

**Respuesta:** No se encuentra referencia descrita de encefalopatía hipóxica en ninguna de las atenciones por urgencias en FSB.

**22. Se afirma en la demanda que "la FSB incurrió en una omisión al no haber profundizado en una sospecha clínica de una IDP en el menor debido al antecedente de una enfermedad neoplásica de su padre"?**

**Respuesta:** Esta afirmación no es correcta en relación con el tipo de leucemia del padre exclusivamente. El soporte ya está explicado anteriormente en la pregunta relacionada con la historia familiar de malignidad.

**Referencias**


1. Mayor PC, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the US Immune Deficiency Network Registry. JACI 2018; 141: 1028-35
2. Haas O. Primary immunodeficiency and cancer predisposition revisited: Embedding two closely related concepts into a integrative conceptual framework. Frontiers in Immunol 2019; 2018: 9: 31-36.


**23. ¿Qué opinión le merece esta deducción?**

**Respuesta:** Considero que es una deducción que no es razonable ni fundamentada desde el punto de vista del conocimiento científico actual de las IDP cuando se hace referencia exclusivamente al antecedente de la neoplasia del padre. uando las leucemias tienen fondo heredofamiliar, deben ser los oncólogos quienes ecomienden consejería genética y aporten las recomendaciones necesarias al paciente afectado.

**24. ¿Qué soporte y nivel de confianza según la evidencia científica existente en el momento de los hechos, se puede atribuir al examen pericial presentado por la parte demandante?**

**Respuesta:** Los argumentos que pueden apoyar el diagnóstico de IDP no se soportan científicamente basándose en las crisis convulsivas febriles ni en la historia de leucemia mieloide del padre.

Es importante aclarar que ell papel de los médicos de urgencias es resolver la situación y recomendar seguimientos. Es además muy importante recalcar el papel del pediatra o

médico habitual del paciente en la consulta externa, quien debe integrar la información clínica del paciente y definir la necesidad de evaluaciones adicionales. Los estudios para IDP, con excepción del hemograma que se realizó y no evidenció signos de alarma, no se realizan en situaciones de emergencia aunque se puede sugerir para realización ambulatoria.

En mi concepto, no se presenta un soporte robusto y definitivo desde el punto de vista del conocimiento actual de las IDP.

**25. ¿Existe evidencia que soporte las afirmaciones y conclusiones de la pericia?**

**Respuesta**: En relación a mi pericia, soy profesional médico con más de 15 años de experiencia como inmunólogo clínico y alergólogo; realicé desde entrenamiento en la Universidad de Tulane en los Estados Unidos, soy certificado por el Comité Americano de Alergia e Inmunología (American Board of Allergy and Immunology), soy docente de la residencia de Pediatría de la Universidad del Rosario, de residentes de segunda especialidad de la Universidad El Bosque y fui docente de los residentes de ORL del Hospital Militar hasta el 2019. Me he dedicado al campo de las IDP en la práctica clínica desde el 2004 en Colombia. He sido organizador y conferencista en eventos o simposios en IDP en mi país y en congresos internacionales, soy parte del Nodo de IDP CAYRE-Fundación Cardio Infantil, conferencista en el área de IDP y formo parte del comité organizador de las reuniones mensuales en IDP que se realizan en la FCI desde hace más de 10 años. He escrito con varios colaboradores artículos en IDP en el PRECOP, la publicación de educación médica continua de la Sociedad Colombiana de Pediatría, coautor del capítulo de Infección recurrente y sospecha de inmunodeficiencias primarias en el libro Pediatría al día de la Sociedad Colombiana de Pediatría SCP y Panamericana Formas e Impresos SA del 2017 y hice parte del grupo de la guía colombiana del uso de inmunoglobulina endovenosa en el 2017

## V. Fundamento del Estudio

Sustentan las respuestas a este cuestionario las siguientes referencias bibliográficas:


1) Ballow M. Approach to the patient with recurrent infection. In: Middleton´s Allergy: Principles and Practices. ELSEVIER Inc. Vol 2. 9th edition. 2020; pp: 1111-1122.
2) Alvarez MI, Olmos CE, Luengas M. Infección recurrente y sospecha de inmunodeficiencias primarias. In: Pediatría al día. Sociedad Colombiana de Pediatría SCP. Panamericana Formas e Impresos SA. 2017; pp.

3) Mayor PC, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the US Immune Deficiency Network Registry. JACI 2018; 141: 1028-35
4) Haas O. Primary immunodeficiency and cancer predisposition revisited: Embedding two closely related concepts into a integrative conceptual framework. Frontiers in Immunol 2019; 2018: 9: 31-36.
5) Annamalay A, Le Souëf P. Viral-bacterial interactions in childhood respiratory tract infections. IN: Viral infections in children. Vol 1. R.D. Green (ed.). Springer International Publishing AG 2017.
6) Olmos CE, Suárez MA, Gómez C. Reconociendo inmunodeficiencias primarias: Más allá de las señales tradicionales. PECOP 2015; 14: 20-31.
7) Tabares-Costa-Tavares V, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014; 34: 10-22.
8) Olmos CE, Lozano M, Quijano C. Infecciones recurrentes y sospecha de inmunodeficiencias primarias. PRECOP 2012; 11: 5-15

## VI. Anexos

De conformidad con el numeral 3 del Artículo 226 del CGP, acompaño al informe pericial los siguientes anexos que certifican la respectiva formación académica y técnica para rendir la experticia:

1. Curriculum de CARLOS EDUARDO OLMOS O. (1 folio)
2. Copia de la cedula de ciudadanía de CARLOS EDUARDO OLMOS O. (1 folio)
3. Copia de la Tarjeta Médica (2 folios)
4. Copia de acta de grado N° 275 Título Médico Cirujano (1 folio)
5. Copia de acta de grado N° 30069-A Título Especialista en PEDIATRIA 1 folio)
6. Copia de acta de grado N° 3497 Título subespecialista en ALERGIA E INMUNOLOGIA CLINICA (1 folio) Convalidación Título
7. Copia de bibliografía

El anterior informe fue elaborado por

[3]

Nombre completo; CARLOS EDUARDO OLMOS OLMOS
Cédula de Ciudadanía: 9309251 de Corozal, Sucre
Registro médico:

[3] El dictamen debe ir firmado con firma autógrafa por quien lo emite

Carlos E. Olmos, M.D.
Julio 15 del 2020

# CURRICULUM VITAE

## INFORMACION PERSONAL


**NOMBRE:** **Carlos Eduardo Olmos, MD**
**DIRECCION:** Centro Médico "La Sabana", Av. 7a No. 119-14
Consultorio 418
**TELEFONOS:** 6121400- 6121075- 2150120
**E-MAIL:** colmos.8600@gmail.com
**ESTADO CIVIL:** Casado


## ENTRENAMIENTO EDUCATIVO & PROFESIONAL

| | |
|---|---|
| Abril-Mayo 2019 | **Diplomado en liderazgo: being a leader and the effective exercise of leadership.** Asociación Colombiana de Sociedades Científicas. |
| Agosto 2016 | **Diplomado en Autoinmunidad.** Universidad del Rosario |
| Marzo-Mayo, 2009 | **Diplomado en Medicina Basada en la Evidencia** (Virtual). Pontificia Universidad Javeriana |
| Sept. 2007-May 2008 | **Diplomado en Docencia para las Ciencias de la Salud.** Fundación Universitaria de Ciencias de la Salud (FUCS), Bogotá, DC. |
| Oct 2000-Jun 2003 | **Residencia de Pediatría (AAP-USA)** Tulane-Ochsner Pediatrics Residency Program, New Orleans, LA, USA |
| Oct 2001- Oct 2003 | **Subespecialización Clínica en Reumatología Pediátrica.** Tulane University Health Sciences Center. Departamento de Pediatría, Sección de Alergia, Inmunologia y Reumatología Pediátrica. New Orleans, LA |
| Mar 1998- Feb 2000 | **Subepecializacion Clínica (Clinical Fellowship) en Alergia e Inmunología Clínica.** Tulane University Health Sciences Center, New Orleans, LA, USA |
| Ago 1996- Feb 1998 | **Subespecialización en investigación (Research Fellowship) en estudios ambientales en alergia e inmunologia.** Tulane University Medical School, New Orleans, LA, USA |
| Ene 1984- Ene 1987 | **Residencia en Pediatría (Colombia)** Colegio Mayor Nuestra Señora del Rosario-Facultad de Medicina. Hospital Universitario de "San José". Santafe de Bogota, D.C. Colombia |
| Feb. 1976- Enero 1982 | **Doctor en Medicina y Cirugía.** Pontificia Universidad Javeriana- Facultad de Medicina. Santafé de Bogotá, D.C. Colombia |

## LICENCIAS PROFESSIONALES & CERTIFICACIONES

| | |
|---|---|
| 2010-Fecha | Certificación en Inmunología Clínica y Alergia, AAAAI [Comité, Academia Americana de Asma, Alergia e Inmunología- AAP Academia Americana de Pediatría] : Diplomado |
| 2004-Fecha | Res. 3497: Convalidación Título de Especialista en Alergología e Inmunología Ministerio de Educación Nacional de Colombia |
| 2003 | Certificación en Pediatría American Board of Pediatrics AAP: dDplomado |
| 2001-2005 | 14404R: Licencia Médica - Louisiana State Board of Medical Examiners, USA |
| 2004- Fecha | 9309251: Secretaria Distrital de Salud de Bogotá |
| 2003- Fecha | FAAP [Fellow, Academia Americana de Pediatría]: Certificación en Pediatría |
| 1997- Fecha | 0-370-300-6: ECFMG [Certificado de validez indefinida) |
| 1985- Fecha | 9024: Ministerio de Salud de Colombia- Licencia Permanente |

## AREAS DE INTERES

- Educación médica, MBE, profesionalización del alergólogo colombiano
- Salud ambiental, asma y condiciones alérgicas en adultos y niños
- Inmunodeficiencias primarias
- Gastroenteropatia eosinofilica y alergia alimentaria
- Autoinmunidad
- Terapias biológicas
- Dermatitis atópica severa refractaria
- Dermatitis de contacto y Pruebas de parche

## EXPERIENCIA EN INVESTIGACION

| | |
|---|---|
| Feb. 2009-2016 | **Co-investigador**, Universidad del Norte, Universidad Nacional de Colombia. Área/ Temática: Polimorfismos genéticos de nefritis lúpica en Colombia. Proyecto Colciencias 2014. |
| En 2009-2016 | **Co-investigador**, Asociación Colombiana de Reumatología Pediátrica. Área de Investigación Clínica: Prevalencia de las Enfermedades Reumáticas en niños en Colombia |
| Feb. 2009-2014 | **Co-investigador**, Universidad del Norte, Universidad Nacional de Colombia. Área/ Temática: genética de la artritis juvenil en Colombia. Colciencias 2014 |
| Jul- Nov 2003 | **Instructor en Investigación Clínica**, Tulane University Health Sciences Center, New Orleans, LA, USA<br>Área: Programa educacional en salud ambiental en Pediatría |

| | |
|---|---|
| Mar 1998-Feb 2000 | **Co-investigador,** Tulane University Health Sciences Center, Sección de Alergia e Inmunologia Clínica, New Orleans, LA, USA<br>Área: Estudios clínicos en alergia e inmunologia: "Effects of fragrances in asthma", "Mucolitics in COPD", "Seasonal and perennial rhinitis and sinusitis", "Corn allergy" |
| En 1997- 1998 | **Coordinador Clínico,** "Margo Morgan Research Center", New Orleans, LA<br>Área: Estudios Clínicos en Diabetes e Hipertensión |
| Ago 1996-Feb 1998 | **Research Fellow,** Tulane University Health Sciences Center, Section of Allergy and Clinical Immunology.<br>Mentores: Héctor Ortega, MD, PhD, Manuel López, MD<br>Área: Experiencia en técnicas de laboratorio incluyendo RAST; ELISA; Immunoblotting; cultivo celular in-vitro; aerobiologia, retos alimenticios, pruebas cutáneas. |

## EXPERIENCIA LABORAL

| | |
|---|---|
| Ene 2004-Fecha | **Alergia, Inmunología Adultos & Niños, Reumatología Pediátrica.** Práctica privada. Centro Médico de La Sabana, Bogotá, D.C. |
| Mar 2004-Fecha | **Alergia, Inmunología Adultos & Niños, Reumatología Pediátrica**, Director Unidad Alergia-Inmunología CAYRE [Centro de Especialistas], Bogotá, D.C., Colombia. |
| Ene 2004-Nov 2011 | **Alergia, Inmunología Adultos & Niños, Reumatología Pediátrica, Jefe de Área.** Fundación Cardio-Infantil IC. Bogotá, D.C. Colombia. |
| Jun. 2000- Oct 2003 | **Residente 1, 2, 3.** Departamento de Pediatría, Tulane University Health Sciences Center. New Orleans, LA, USA |
| Oct 2001- Oct 2003 | **Fellow, Alergia e Imunologia Clínica, Reumatologia Pediátrica.** Tulane University Health Sciences Center. New Orleans, LA., USA |
| Ago 1990-Ago 1996 | **Pediatra General - Instructor.**<br>Colegio Mayor Nuestra Señora del Rosario-Facultad de Medicina<br>Hospital Universitario de "San José". Departamento de Pediatría<br>Bogotá, DC. Colombia |
| Feb 1989-Jul 1996 | **Pediatra- Práctica Privada**<br>Centro Médico "La Sabana". Cra 7a # 119-14 Consultorio (Office) 418<br>Bogotá, D.C. Colombia |
| Mar 1988- Mar 1993 | **Pediatra. Práctica en Neonatología y Pediatría Ambulatoria**<br>Instituto Colombiano de Seguridad Social (ICSS) Bogotá, DC Colombia |

| | |
|---|---|
| Ene 1987- Ene 1989 | **Pediatra- Servicio Ambulatorio**<br>Instituto de Bienestar Social del SENA. Bogotá, D.C. Colombia<br>Servicio de Salud de Sucre y Vaupes, Colombia |

## EXPERIENCIA DOCENTE

| | |
|---|---|
| Enero 2014-2019 | **Docente, Residencia de ORL** Universidad Militar |
| Julio 2013-fecha | **Docente. Departamento de Postgrados. Programa de Especialización de Infectología Pediátrica.** Universidad El Bosque |
| Julio 2011-fecha | **Docente. Departamento de Postgrados. Programa de Especialización de Reumatología Pediátrica.** Universidad El Bosque |
| Ene. 2012- Fecha | **Docente, Departamento de Pediatría.** Colegio Mayor de Nuestra Señora del Rosario & CAYRE. Experiencia docente en Alergia, Inmunologia & Reumatología Pediatrica a residentes de Pediatría (rotación electiva). |
| Ene. 2004- 2011 | **Docente, Departamento de Pediatría.** Colegio Mayor de Nuestra Señora del Rosario & FCI IC. Experiencia docente en Alergia, Inmunología & Reumatología Pediátrica a estudiantes, internos & residentes de Pediatría (rotación oficial). |
| Julio 2005-Jun 2008 | **Docente, Departamento de Pediatría.** Pontificia Universidad Javeriana & FCI IC. Experiencia docente en pediatría general, Alergia, Inmunologia & Reumatología Pediatrica a estudiantes, internos & residentes de Pediatría (rotación oficial) |
| Oct 2000- Jun 2003 | **Residencia de Pediatría (USA).** Tulane & Ochsner Residency Program. New Orleans, LA, USA. Experiencia docente en pediatría general, alergia, inmunología y reumatología con estudiantes de 1-4o año, residentes y docentes del programa durante las rotaciones clínicas y actividades académicas. |
| Ago 1996- Feb 2000 | **Research & Clinical Fellowship en Alergia, Inmunologia, Reumatología.** Tulane University HSC, New Orleans, LA, USA. Docencia en los aspectos clínicos de la alergia, inmunologia y reumatología a estudiantes de 3-4o año y a residentes de pediatría y medicina interna durante prácticas clínicas ambulatorias y hospitalarias y actividades académicas semanales (club de revistas, discusión de casos especiales, interconsultas, etc.). |
| Ago 1990-Ago 1994 | **Pediatría General- Instructor,** Colegio Mayor Nuestra Señora del Rosario. Facultad de Medicina. Hospital Universitario de "San José", departamento de Pediatria, Bogotá, DC. Colombia |

## HONORES Y RECONOCIMENTOS

| | |
|---|---|
| 2010-Fecha | **Certificación en Inmunología Clínica y Alergia, AAAAI** [Comité, Academia Americana de Asma, Alergia e Inmunología- **AAP** Academia Americana de Pediatría] : Diplomate |
| 2013 | **Certificación en Pediatría** [Comité, AAP Academia Americana de Pediatría] : Diplomate |
| 2009 | **Mejor trabajo en presentación de poster. Congreso Colombiano de Reumatología Pediátrica.** Bogotá, DC. Agosto 16, 2009 |
| 2003 | **2003 "Outstanding Trainee Award":** En reconocimiento al trabajo meritorio a joven investigador Médico. American Federation for Medical Research Southern Section. New Orleans, LA. Feb 2003. |
| 2001 | **Reconocimiento de la Prensa durante la conferencia anual de la Academia Americana de Alergia e Inmunologia (AAAAI) Trabajo:** "New Orleans Vignette anaphylaxis". |
| 1989 | **Reconocimiento y Diploma como profesor.** Facultad de Medicina del Colegio Mayor N. Señora del Rosario. Bogotá, DC. Colombia |

## SOCIEDADES PROFESIONALES

| | |
|---|---|
| 2004-Fecha | **Sociedad Colombiana de Alergia e Inmunología,** Miembro activo |
| 2004-Fecha | **Sociedad Colombiana de Reumatología**, Miembro activo |
| 2004-Fecha | **Sociedad Colombiana de Pediatría**, Miembro activo |
| 2002-2010 | **AAP Environmental Health Nexus,** Miembro-Fellow |
| 2000-2010 | **Academia Americana de Pediatría,** Miembro |
| 1999-2010 | **Southern Research Medical Society,** Miembro |
| 1998-2010 | **Louisiana State Medical Society,** Miembro 124156 |
| 1997-2010 | **Hispano American Medical Association of Louisiana (HAMAL),** Miembro |
| 1997-Fecha | **Colegio Americano de Alergia, Asma e Inmunologia (ACAAI),** Miembro |

## EXPERIENCIA EN SERVICIOS Y COMITES

| | |
|---|---|
| 2009 (Sept.)- Fecha | Grupo de Inmunodeficiencias Primarias. Nodo Bogotá FCI/ CAYRE |
| 2009 (Feb)-2011 | Sociedad Colombiana de Pediatría, Capítulo Central, Vocal |
| 2004 (Jul)- 2010 | Comité de Farmacia & Farmacovigilancia, Fundación Cardioinfantil IC. |
| 2004 -2005 | Comité organizador Congreso Colombiano de Pediatría 2005, Secciones Pediatría ambiental, alergia e Inmunologia pediátrica |
| 2004 (Junio-Agosto) | Asesor Comité de Vacunas Secretaria Salud de Bogota, D.C. |
| 2005 (Enero)- Fecha | Comité organizador Congreso Colombiano de Reumatología Pediatrica 2005 |
| 2005-03-05 | Asesor Grupo de Padres con niños autistas |
| 2005 | Comité desarrollo de Guías Reumatología Pediatrica: Uso de anti-TNF en Pediatría |

## CAPITULOS DE LIBROS

1. Alvarez-Olmos MI, Olmos Olmos CE, Luengas M. **Infección recurrente en Pediatría y sospecha de inmunodeficiencias primarias.** En: Libro de la Sociedad Colombiana de Pediatría. Editorial Médica Panamericana [2017]. Vol. 2.
2. Olmos CE. **Enfoque de las enfermedades reumatológicas en pediatría**. Publicado libro Pediatra Eficiente (2012)
3. Olmos CE. **Inmunoglobulina E e inflamación alérgica.** En edición: Libro de Alergia, Editores: Cardona-Serrano (2010)
4. Olmos CE. **Estrategias Nutricionales en la prevención de alergias.** En edición: Libro de Alergia, Editores: Cardona-Serrano (2010)
5. Alvarez-Olmos MI, Olmos CE. **Resfriado común, resfriado común y asma.** INFECTION Y ALERGIA RESPIRATORIA EN El NIÑO. Reyes, Leal y Aristizabal (Eds). 5a Edición, 2006; Capitulo 24., p.p. 153.
6. Olmos C. **La marcha atópica**. En: Texto de dermatología: 25 años Sociedad de Cirugía de Bogotá Hospital de San José. Editor: Edgar Olmos Olmos. Primera Edición. Fundación Cultural Javeriana de Artes Gráficas. Páginas 213-16; 2006.
7. Alvarez-Olmos MI, Olmos CE. **Resfriado común, resfriado común y asma.** EN: INFECCION Y ALERGIA RESPIRATORIA EN EL NINO. Reyes, Leal y Aristizabal (Eds). 5ª Edición, 2006 p.p.153.
8. López M, Olmos CE. **Asma ocupacional.** En: ASMA BRONQUIAL. De Zubiria. 1ª Edición, 2003
9. López M, Olmos CE: **Neumonitis por hipersensibilidad**. En: INFECCION Y ALERGIA RESPIRATORIA EN El NIÑO. Reyes, Leal y Aristizabal (Eds.); 4th Edición 2001, pp.432-439
10. López M, Olmos CE: **Neumonitis por hipersensibilidad**. En: INFECCION Y ALERGIA RESPIRATORIA EN El NIÑO. Reyes, Leal y Aristizabal (Eds.). 3ª. Edición, 1998, pp. 401-8

## PUBLICACIONES/ JOURNALS

1. Olivares MM; Alvarez-Olmos MI, Olmos CE et al. **Guías Colombiana de Práctica Clínica para uso de inmunoglobulinas en tratamiento de reposición e inmunomodulación.** *Revista Alergia de México. 2017 Vol 64 Suppl.2: s5-s55.*
2. Olmos CE.,Gómez C. **Enfoque holístico del paciente con alergia. : ¿qué hay de nuevo?**. *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago). Sociedad Colombiana de Pediatría*
3. Olmos CE. **Reconociendo Inmunodeficiencias Primarias Mas Allá De Las Señales De Alarma Tradicionales.** *Revista Programa de Educación continuada en Pediatría: Precop* (2015 *Volumen 14 Número 2, Ago* Ago). Sociedad Colombiana de Pediatría
4. Olmos CE. **Actualización en alergia al huevo y vacunas. Mitos y realidades** *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago*). Sociedad Colombiana de Pediatría

5. Olmos CE. **Actualización en Vacunas y Alergia.** *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago*). Sociedad Colombiana de Pediatría
6. Olmos CE. **Vacunas y Autoinmunidad.** *Revista Programa de Educación continuada en Pediatría: Precop* (2015, *Volumen 14 Número 2, Ago*). Sociedad Colombiana de Pediatría
7. Olmos CE. **Fiebre periódica.** *Revista Programa de Educación continuada en Pediatría: Precop* (2011, Nov). ASCOFAME, Sociedad Colombiana de Pediatria
8. Olmos CE. **Lactancia Materna y Desarrollo de alergias.** *Revista Programa de Educación continuada en Pediatría: Precop* (2008, Nov). ASCOFAME, Sociedad Colombiana de Pediatría
9. Olmos CE., Duran MJ. **Dieta Complementaria y Desarrollo de Alergias.** *Revista Programa de Educación continuada en Pediatría: Precop* (2008, Nov). ASCOFAME, Sociedad Colombiana de Pediatría
10. Olmos CE. **Alergia al huevo y a vacunas**. *Revista Programa de Educación continuada en Pediatría: Precop* (2008, Nov). ASCOFAME, Sociedad Colombiana de Pediatría
11. Olmos CE, Quevedo X, Esquivel G. **Esofagitis Eosinofílica.** *Revista Programa de Educación continuada en Pediatría: Precop* (2008, Abril). ASCOFAME, Sociedad Colombiana de Pediatría
12. Olmos CE, Caballero M. **Enfermedades autoinmunes en Pediatría.** *Revista Programa de Educación continuada en Pediatría: Precop* (2008, Abril). ASCOFAME, Sociedad Colombiana de Pediatría
13. Olmos CE. **Marcha atópica**. *Revista Programa de Educación continuada en Pediatría: Precop* (Mayo-Junio, 2007). ASCOFAME, Sociedad Colombiana de Pediatría
14. Olmos CE. **Asma Pediátrica: Qué hay de Nuevo?.** *Revista Programa de Educación continuada en Pediatría: Precop* (Mayo-Junio, 2007). ASCOFAME, Sociedad Colombiana de Pediatría
15. Olmos CE. **Alergia a la Proteína a la leche de vaca**. *Revista Programa de Educación continuada en Pediatría: Precop* (Mayo-Junio, 2007). ASCOFAME, Sociedad Colombiana de Pediatría
16. Alvarez-Olmos MI, Olmos CE**. Probióticos**. *Revista Programa de Educación continuada en Pediatría: Precop* (Mayo-Junio, 2007). ASCOFAME, Sociedad Colombiana de Pediatría.
17. Alvarez-Olmos MI, Olmos CE**. La ontogenia del sistema inmune y su importancia para el pediatra**. *Revista Programa de Educación continuada en Pediatría: Precop* (Mayo-Junio, 2007). ASCOFAME, Sociedad Colombiana de Pediatría.
18. Olmos CE, Alvarez-Olmos MI. **Enfermedad alérgica e infección recurrente.** *Revista Programa de Educación continuada en Pediatría: Precop* (Mayo-Junio, 2007). ASCOFAME, Sociedad Colombiana de Pediatría.
19. Olmos CE, Alvarez-Olmos MI. **Inmunonutrientes e infección recurrente.** *Revista Programa de Educación continuada en Pediatría: Precop* (Mayo-Junio, 2007). ASCOFAME, Sociedad Colombiana de Pediatría.
20. Lopez M, Olmos CE**. Indoor air pollution and Asthma** (Spanish). *Inter-American College of Physicians & Surgeons* 1998; 17 (4): 183-7.
21. Alvarez MI, Olmos CE. Vacuna de Varicela e Inmunodeficiencias Primarias. *Boletin- LAGID: Latin-American Group of Immunodeficiencies* 1998; 2nd issue (www.lagid.com).
22. Alvarez MI, Olmos CE. **Peste Bubónica:"Un enigma filogenético".** *Pediatría: Revista de la Sociedad Colombiana de Pediatría* 1995; 3: 138-44.

## ABSTRACTS/ POSTERS

1. Alvarez-Olmos MI, Medina D, Olmos CE, et al. **Gemelos idénticos con Enfermedad Granulomatosa Crónica ligada a X debutando con colitis de comienzo temprano simulando colitis alérgica.** Día de la Investigación 2018 [Nov]. Fundación Cardio Infantil **[Poster 102]**
2. Hernández Zapata LJ, Velázquez Méndez M, Eraso Garnica R, Alvarez-Olmos M, Guarnizo Zucardi P, Olmos CE, Rivera C, Bautista A and Franco JL [Oct 13, 2015]. **Autoinflammatory Diseases In Five Colombian Patients: Clinical Spectrum and Diagnostic Challenge**. Front. Immunol. Conference Abstract: IMMUNOCOLOMBIA 2015 - 11th Congress of the Latin American Association of Immunology - 10o. Congreso de la Asociación Colombiana de Alergia, Asma e Inmunología. doi: 10.3389/conf.fimmu.2015.05.00034 [Published On-line Sept 2015]
3. Olmos Carlos E[1]; Gómez Catalina. **Quality of life impairment in 20 patients with Hereditary Angioedema in Cayre IPS, Bogota,Colombia. [Poster P0125].** LASID 2015. Argentina, Noviembre 18-21, 2015
4. Olmos Carlos E[1]; Gómez Catalina. **Common Variable Immunodeficiency and autoimmunity in two teenagers brothers in Cayre IPS, Bogota,Colombia. [Poster P070].** LASID 2015. Argentina, Noviembre 18-21, 2015
5. Olivares Margarita; Farfan Rosa; Olmos Carlos E[1]; Gómez Catalina. **Report of Colombian registry for Hereditary Angioedema[Poster P0120].** LASID 2015. Argentina, Noviembre 18-21, 2015
6. Beltrán Juliana; Olmos Carlos E[1]; Gómez Catalina. **Recidivant Acute generalized exanthematous pustulosis (AGEP) induced by macrolide in a pediatric patient. Case report. [Poster].** Inmunocolombia. Medellín Octubre 13-17, 2015
7. Beltrán Juliana; Olmos Carlos E[1]; Gómez Catalina. **Refractory urticaria, bradycardia and contact eczema in patient with nickel hypersensitivity. after atrial septal defect occluder implantation. A case report. [Poster].** Inmunocolombia. Medellín Octubre 13-17, 2015
8. Olmos Carlos E[1]; Gómez Catalina; **Quality of life impairment in 7 patients with Hereditary Angioedema in Cayre IPS, Bogota, Colombia. [Poster].** Inmunocolombia. Medellín Octubre 13-17, 2015
9. Olmos Carlos E[1]; Gómez Catalina. **Common Variable Immunodeficiency and autoimmunity in two teenagers brothers in Cayre IPS, Bogota, Colombia. [Poster P070].** Inmunocolombia. Medellín Octubre 13-17, 2015
10. Olmos Carlos E[1]; Patiño Jaime[2]; Garcés Sandra[3]; Alvarez-Olmos Martha I[2]. **Agamaglobulinemia de Bruton: Experiencia en institución de Cuarto Nivel en Colombia. [Poster].** Plenum Pediátrico Capítulo Central. Bogotá, DC. Noviembre 19, 2011
11. Olmos Carlos E[1]; Patiño Jaime[2]; Garcés Sandra[3]; Alvarez-Olmos Martha I[2]. **Agamaglobulinemia de Bruton: Experiencia en institución de Cuarto Nivel en Colombia. [Poster 51].** 9° Día de la Investigación FUNDACION CARDIONFANTIL IC. Bogotá, DC. Noviembre 11, 2011
12. Olmos CO, Olmos-Alvarez MI. **Autoimmune Lymphoproliferative Syndrome associated to combined immunodeficiency, recurrent macrophage activation syndrome and T-cell skin and lung lymphoma: A pediatric case.** [Poster, Abstract]. First Meeting of the Latin American Society of Primary Immunodeficiencies. Cartagena, Colombia; October 15-19, 2009
13. Alvarez-Olmos MI, Olmos CE. **Chronic Granulomatous Diseases: Two cases.** [Poster, Abstract]. First Meeting of the Latin American Society of Primary Immunodeficiencies. Cartagena, Colombia; October 15-19, 2009

14. Olmos CE, López S, Malagón C. **ARTRITIS IDIOPATICA JUVENIL REFRACTARIA [AIJ]: EXPERIENCIA CON RITUXIMAB.** Congreso Colombiano de Reumatología Pediátrica; Bogotá; Agosto 13-16; 2009 (Poster)
15. Olmos CE, Gutiérrez I, Camargo E, Gastelbondo R, González L, Malagón C. **NEFRITIS LUPICA JUVENIL REFRACTARIA TRATADA CON RITUXIMAB.** Congreso Colombiano de Reumatología Pediátrica; Bogotá; Agosto 13-16; 2009 (Poster- Ganador 2009)
16. Olmos O. C; González CL; Garcés S; Munier J; Salazar AM; Alvarez-Olmos MI. **Síndrome Linfoproliferativo Autoinmune [SLPAI] Asociado a Inmunodeficiencia Mixta, Síndrome de Activación Macrofágica Recurrente, Linfoma T Cutáneo y Pulmonar: A Propósito de un Caso Pediátrico.** Congreso Colombiano de Reumatología Pediátrica; Bogotá; Agosto 13-16; 2009
17. Alvarez-Guevara A; Olmos Olmos CE; Alvarez-Larrañaga MI. **Tuberculosis pleuro-pulmonar en adolescente con Enfermedad de Takayasu en terapia biológica con inhibidor de Factor de Necrosis Tumoral alfa.** Congreso de la Sociedad Latinoamericano de Infectología Pediátrica (SLIPE). Guayaquil, Ecuador; Agosto 12-15, 2009
18. Olmos O CE; P. Durán; AM Salazar. **Poliautoinmunidad en Pediatría.** III Congreso Colombiano de Reumatología Pediátrica. Medellín, Agosto 2007 (Poster)
19. Olmos O CE, Pérez JM, Bernal I. **Arteritis de Takayasu en Pediatría: A propósito de un caso.** III Congreso Colombiano de Reumatología Pediátrica. Medellín, Agosto 2007 (Poster).
20. Alvarez-Olmos MI, Ospina N*, Gastelbondo R, Stapper C, Olmos CE. **Fiebre prolongada, pseudo-síndrome nefrótico y aneurismas coronarios en lactante menor con enfermedad de Kawasaki incompleta.** [Abstracto & Póster]. 24° Congreso Colombiano de Pediatria. Sociedad Colombiana de Pediatria. Cartagena, Junio 2005.
21. Olmos CE, Lagarde DD, Haque S. **Characterization of Eosinophilic Esophagitis in South Louisiana.** ABSTRACT & POSTER presentation, ACAAI, Nov 2003. New Orleans, LA.
22. Olmos CE, Lagarde DD, Haque **S. Eosinophilic Esophagitis in children in Southeast Louisiana.** ABSTRACT & POSTER presentation, ACAAI, Nov 2003. New Orleans, LA.
23. Tanaka L, Olmos C, et al. Corn allergy: **The first double-blind placebo-controlled food challenge** (DBPC). ABSTRACT & POSTER presentation, AAAAI. New Orleans. Mar 2001. Abstract in: *J All Clin Immunol* 2001; 107(2): S189 [#630].
24. Olmos CE, El-Dahr J, et al. **New Orleans beignet anaphylaxis** ABSTRACT & POSTER presentation, AAAAI Meeting. New Orleans, Mar 2001. Abstract in: *J All Clin Immunol* 2001; 107(2): S268 [#878].
25. M. Arecery, C. Olmos, L. Wild. **Sulfasalazine hypersensitivity syndrome presenting as pseudo lymphoma**. ACAAI Annual Meeting. Seattle, Nov 3-8, 2000. ABSTRACT & POSTER P40. Abstract in: *Ann Allergy, Asthma Immunol 2000;*
26. C.E. Olmos, M. Silio, M.I. Alvarez-Olmos, J.El-Dahr. **HIV-1 Negative child with MAC infection, Interferon-γ Defect and Specific Antibody Deficiency**. ABSTRACT & POSTER Presentation. P-124. 2000 ACAAI Annual Meeting. Seattle, Nov 3-8, 2000.
27. Alvarez-Olmos MI, Olmos CE, El-Dahr J, Silio M. **Child with Interferon Gamma Defect and Specific Antibody deficiency.** ABSTRACT & POSTER Presentation, 38th IDSA Meeting 2000, Sept 8-9. New Orleans, LA, USA.

28. Olmos CE, Horner WE, Lopez M. **Airborne fungal spore count in South Louisiana**. ABSTRACT & POSTER, Southern Research Medical Society, New Orleans, LA, Feb 2000. Abstract in: *Allergy Proc.* 2000;
29. Olmos CE, López M, et al. **Mite allergen is not limited to the bedroom.** ABSTRACT & POSTER presentation. ACAAI, San Diego, CA, Nov 1999. Abstract in: *Ann Allergy, Asthma Immunol* 2000.
30. Olmos CE, López M, et al. **Cockroach allergen load in warm humid climate.** ABSTRACT & POSTER presentation, ACAAI, Washington, DC. Abstract in: *Ann Allergy, Asthma Immunol* 1999; 82(1): 116

## EDUCACION MÉDICA CONTINUADA (CME/USA)

1. American College of Allergy, Asthma, Immunology ACAAI. Annual Meeting.2000. Seattle, Nov 3-8, 2000.
2. American Academy of Allergy, Asthma and Immunology AAAAI 57th Annual Meeting. New Orleans, LA 2001.
3. American Academy of Allergy, Asthma and Immunology AAAAI 58th Annual Meeting. New York. Mar 1-6, 2002.
4. American College of Allergy, Asthma and Immunology, Annual Meeting, San Antonio, TX, Nov 2002.
5. American Academy of Pediatrics. Annual Meeting. New Orleáns, LA, USA. Nov 1-5, 2003.
6. American College of Allergy, Asthma and Immunology, Annual Meeting 2003, New Orleans, LA, Nov 6-11, 2003.
7. American Academy of Allergy, Asthma and Immunology AAAAI 60th Annual Meeting. San Antonio, Mar 2-8, 2005.
8. 24o Congreso Colombiano de Pediatria. Cartagena, Junio 2005.
9. Primer Congreso Colombia de Reumatología Pediatria. Bogota, DC. Agosto 2005
10. Congreso Colombiano de Alergia, Asma e Inmunologia. Bogota, D.C. Agosto 2005
11. Congreso Internacional de Infectología e inmunizaciones. Miami, Florida. Octubre 2005
12. American College of Reumatology. San Diego, california, USA. Noviembre 2005.
13. American College of Allergy, Asthma and Immunology, Annual Meeting 2006
14. American College of Allergy, Asthma and Immunology, Annual Meeting 2007
15. American Academy of Allergy, Asthma and Immunology AAAAI 90th Annual Meeting. Philadelphia, VA, USA, Mar 14-17, 2008.
16. European Meeting of Pediatric Rheumatology, London, UK, September 2008.
17. European Meeting of Rheumatology, Copenhagen, Denmark, July 2009
18. American College of Allergy, Asthma and Immunology, Annual Meeting 2010
19. EULAR: European League against Rheumatism. Roma, Italia; Junio 16-19, 2010
20. American College of Rheumatology, USA. Noviembre 2010
21. American Academy of Allergy, Asthma and Immunology AAAAI 67th Annual Meeting; San Francisco, CA; Mar 18-22, 2011.
22. Latin American society of Primary Immunodeficiencies Meeting. Sept 2011; México.
23. American Academy of Allergy, Asthma and Immunology AAAAI 68th Annual Meeting; San Francisco, CA; Mar 18-22, 2012.

24. EULAR Meeting. Jun 2012. Berlin
25. Congeso Latinoamericano de Alergia, Asma e Inmunologia. Octubre 2012. Cartagena.
26. Patch Test Workshop. U Louisville. Nov 2012 y 2013; Phoenix, Arizona
27. Latin American society of Primary Immunodeficiencies Meeting. Oct 2013; Chile.
28. American Academy of Allergy, Asthma and Immunology AAAAI 69th Annual Meeting; Orlando, FL, 2013.
29. American Academy of Allergy, Asthma and Immunology AAAAI 70th Annual Meeting, 2014.
30. American Academy of Allergy, Asthma and Immunology AAAAI 68th Annual Meeting; San Francisco, CA; 2015.
31. Congreso Europeo deAlergia, Asma, Inmunologia. Junio 2015. Barcelona.
32. X Congreso Asociación Colombiana de Alergia, Asma e Inmunología. Medellin, Sept 2015
33. Latin American society of Primary Immunodeficiencies Meeting. Nov 2015; Buenos Aires, 2015.
34. American Academy of Allergy, Asthma and Immunology AAAAI 71th Annual Meeting; Los Angeles, CA; 2016.
35. Congreso Europeo de Alergia, Asma, Inmunologia. Junio 2016. Viena, Austria
36. European society of Primary Immunodeficiencies Meeting. Sept 2016; Barcelona
37. Congreso Europeo de Alergia, Asma, Inmunologia. Junio 2017. Helsinki, Finlandia
38. Latin American Society of Primary Immunodeficiencies Meeting. Oct 2017; Sao Paulo
39. XI Congreso Asociación Colombiana de Alergia, Asma e Inmunología ACAAI. Simposio de World Allergy Organization WAO. Cartagena, Sept. 2017
40. American Academy of Allergy, Asthma and Immunology AAAAI 72th Annual Meeting y WAO meeting; Orlando, Florida; Mar 2-5, 2018
41. Congreso Europeo de Alergia, Asma, Inmunologia. Mayo 2018. Munich
42. American Academy of Allergy, Asthma and Immunology AAAAI 73th Annual Meeting y WAO meeting; San Francisco; Feb 22-25, 2019
43. XII Congreso Asociación Colombiana de Alergia, Asma e Inmunología. Cali, Sept 12-14, 2019

**CONFERENCIAS RECIENTES 2018-2020**

1. WEBINAR. Reunión de Inmunodeficiencias Primarias. FCI. 13/07/2020, 19:00-20:30
   - Modelo holístico del Sistema Inmune en COVID-19: Implicaciones preventivas y terapéuticas
2. WEBINAR. Sociedad Colombiana de Pediatría. 29/04/2020
   - Estrategias potenciales en la prevención de infecciones respiratorias agudas
3. V Simposio de Residentes de Pediatría Universidad del Rosario
   - Inmunodeficiencias Primarias: Un reto para el pediatra
4. Simposio Internacional de Alergología, zona cafetera. Asociación Colombiana de Asma, Alergia e Inmunología. Mayo 17, 2019
   - Omalizumab: Prevención de exacerbaciones de asma y rol en infecciones
   - Asma severa: Qué dicen los algoritmos?

5. CAYRE. SIMPOSIO ANUAL. Bogotá, Marzo 28, 2019
    - Inmunoglobulina Subcutánea: Experiencia en centro de atención
    - Biológicos en asma severa
    - Modelo de atención integral de dermatitis atópica

6. Asociación Colombiana de Probióticos y Prebióticos AcoPyP. Bogotá, Mayo 2018
    - Microbioma, Inmunidad y alergia

2004-2017: A petición

## REFERENCIAS

1. **YEZID MUNOZ, MD.** *Medico director CAYRE [Centro de Artritis & Rehabilitación].* Tel: 5922991 Ext. 402.
2. **JAIME AURELIO CESPEDES LONDOÑO, MD.** *Director, Departamento de Pediatria. Hospital Pediátrico. Fundación Cardio Infantil IC & Colegio Mayor de Nuestra Señora del Rosario.* Bogotá, D.C. Colombia. Tel: 57-1-667 27 27 Ext. 2110. E-mail: jcespedes@cardioinfantil.org
3. **RODOLFO DENNIS, MD, PhD.** *Director Médico. Fundación Cardio Infantil IC & Colegio Mayor de Nuestra Señora del Rosario.* Bogotá, D.C. Colombia. Tel: 57-1-667 27 27. E-mail: rdennis@cardioinfantil.org
4. **ELIZABETH GARCIA, MD.** *Alergóloga y Pediatra, Departamento de Pediatria, Fundación Santafe de Bogota.* Tel: 2152300.
5. **MARTHA CIRO.** *Directora Eduación Médica. CAYRE [Centro de Artritis & Rehabilitación].* Tel: 5922991.
6. **JAIME MORENO.** *Director. Centro Médico de La Sabana.* CRA. 7 #119-14. Tel: 2155619-6121075.

# PONTIFICIA UNIVERSIDAD JAVERIANA

## FACULTAD DE MEDICINA

## ACTA DE GRADO N° 275

En la ciudad de Bogotá el día 22 de Enero de 1982 se llevó a cabo el acto de graduación en el cual la Pontificia Universidad Javeriana, previo el juramento reglamentario, confirió el título de

**MÉDICO Y CIRUJANO**

**A**

**CARLOS EDUARDO OLMOS OLMOS**

identificado(a) con CC N° 9309251 quien cumplió con los requisitos académicos, las exigencias establecidas en los Reglamentos y las normas legales; y le otorgó el Diploma N° 2764 que lo(a) acredita como tal.

La Universidad está autorizada para conferir este título por las normas legales vigentes en Colombia.

Es fiel copia tomada del original, en lo pertinente.

Bogotá, D.C. 04 de Marzo de 2019.

PONTIFICIA UNIVERSIDAD JAVERIANA · COLOMBIA · 1623

**Jairo H. Cifuentes Madrid**
**Secretario General**

Firmada digital y electrónicamente. Según lo dispuesto en la ley colombiana, para su verificación consulte la página web de la Universidad, en Todos Los Servicios, Verificación de Certificados Digitales, código: **A397900055970**

UNIVERSIDAD DEL ROSARIO
Colegio Mayor de Nuestra Señora del Rosario - 1653
Personería Jurídica Res. 58 del 16 de Septiembre de 1895, expedida por el Ministerio de Gobierno

**La Suscrita Secretaria Académica de Posgrados de la escuela de Medicina y Ciencias de la Salud del Colegio Mayor de Nuestra Señora del Rosario**

# HACE CONSTAR

Que en el Libro de Actas del Consejo Directivo de la Facultad de Medicina del Colegio Mayor de Nuestra Señora del Rosario

El día **31** de ***ENERO*** del año **1987**

fue aprobado el Título de Especialista en **PEDIATRÍA**

Al Doctor **CARLOS EDUARDO OLMOS OLMOS**

C.C. **9.309.251** expedida en **COROZAL (SUCRE)**

Con las firmas del Rector, Doctor **ROBERTO ARIAS PÉREZ**

El Decano, Doctor **ANTONIO BECERRA LARA**

El Jefe de Educación Médica, Doctor **EDUARDO CARRIZOSA ALAJMO**

Quien cumplió con los requisitos académicos y reglamentarios y las normas legales; y recibió el diploma registrado bajo el No. 30060-A, del libro No. 44, folio No. 1.

En constancia se firma en la ciudad de Bogotá, D.C., el día ***CINCO*** ***(05)***

del mes de ***JUNIO*** del año de ***DOS MIL DIECINUEVE*** ***(2019)***

**SANDRA CECILIA PULIDO SÁNCHEZ**
**Secretaria Académica**

**CATALINA LLERAS FIGUEROA**
**Secretaria General**

# REPUBLICA DE COLOMBIA

MINISTERIO DE EDUCACION NACIONAL
SECRETARIA GENERAL
Es fiel copia tomada del original
15 OCT 2004

MINISTERIO DE EDUCACION NACIONAL

RESOLUCION NUMERO 3497 DE 20

( 12 OCT 2004 )

Por medio de la cual se resuelve una solicitud de convalidación

**EL DIRECTOR DE CALIDAD PARA LA EDUCACIÓN SUPERIOR**

en ejercicio de sus atribuciones legales y en especial las que le confiere el Decreto 2230 de 2003 y la Resolución No.2763 del 13 noviembre de 2003.

**CONSIDERANDO:**

Que el señor CARLOS EDUARDO OLMOS OLMOS, ciudadano colombiano, identificado con cédula de ciudadanía No.9.309.251 presentó para su convalidación el título de FELLOWSHIP IN ALLERGY AND CLINICAL IMMUNOLOGY otorgado el 28 de febrero de 2000, por The Tulane University of Louisiana - USA, mediante solicitud radicada en el Ministerio de Educación Nacional con el No.21369/04.

Que la solicitud de convalidación fue evaluada por un Par Académico de la Universidad Nacional de Colombia, la cual emitió concepto favorable para su convalidación, señalando que el título obtenido es equivalente al de ESPECIALISTA EN ALERGOLOGÍA E INMUNOLOGÍA.

Que de conformidad con lo dispuesto en el Decreto 2230 de 2003, corresponde al Ministerio de Educación Nacional homologar estudios parciales y convalidar los títulos de educación superior otorgados por instituciones de educación superior extranjeras, de acuerdo con las normas vigentes.

Que con fundamento en las anteriores consideraciones y después de haber estudiado la documentación presentada, se llega a la conclusión que es procedente la convalidación solicitada.

En mérito de lo expuesto,

**RESUELVE:**

**ARTÍCULO PRIMERO.-** Convalidar y reconocer para todos los efectos académicos y legales en Colombia, el título de FELLOWSHIP IN ALLERGY AND CLINICAL IMMUNOLOGY, otorgado el 28 de febrero de 2000, por The Tulane University of Louisiana - USA, al señor CARLOS EDUARDO OLMOS OLMOS, ciudadano colombiano, identificado con la cédula de ciudadanía No. 9.309.251, como equivalente al título de ESPECIALISTA EN ALERGOLOGÍA E INMUNOLOGÍA, que otorgan las instituciones de educación superior colombianas de acuerdo con la Ley 30 de 1992.

**PARÁGRAFO.-** La convalidación que se hace por el presente acto administrativo no exime al profesional beneficiario del cumplimiento de los requisitos exigidos por las normas que regulan el ejercicio de la respectiva profesión.

**ARTÍCULO SEGUNDO.-** La presente Resolución rige a partir de la fecha de su expedición y contra la misma procede el recurso de reposición, que debe ser presentado dentro de los cinco (5) días hábiles siguientes a su notificación de conformidad con el Código Contencioso Administrativo.

NOTIFÍQUESE Y CÚMPLASE

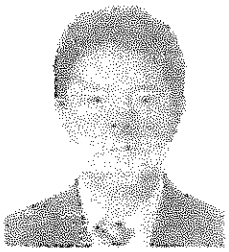
Dada en Bogotá D. C., a los 12 OCT 2004

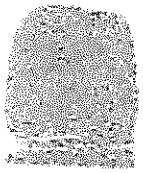
EL DIRECTOR DE CALIDAD PARA LA EDUCACIÓN SUPERIOR

REPUBLICA DE COLOMBIA
IDENTIFICACIÓN PERSONAL

9.309.251
OLMOS OLMOS

CARLOS EDUARDO





12-OCT-1957
COROZAL
(SUCRE)

1.67 O+ M

17-ENE-1976 COROZAL

PROSPERIDAD PARA TODOS

Registro No.

IDENTIFICACIÓN ÚNICA DEL TALENTO HUMANO EN SALUD 11 7869/1993

Profesión u Ocupación

MÉDICO

Nombres y Apellidos

CARLOS EDUARDO OLMOS OLMOS

D.C. o C.E.

8309251

Institución de Educación

UNIV. JAVERIANA

Ciudad

BOGOTÁ, D.C.

Código D55796/11

Fecha de Expedición 27/08/2008

FIRMA

FIRMA
MINISTRO DE SALUD Y PROTECCIÓN SOCIAL O SU DELEGADO

ESTA TARJETA ES DOCUMENTO PÚBLICO Y SE EXPIDE DE CONFORMIDAD CON LA LEY No. 1164 DEL 3 DE OCTUBRE DE 2007. SI ESTA TARJETA ES ENCONTRADA, FAVOR DEVOLVERLA AL MINISTERIO DE SALUD Y PROTECCIÓN SOCIAL.

CON BASE EN LOS DECRETOS 1465 DE 1982 Y 4107 DE 2011, QUE SEÑALAN LAS FUNCIONES DEL CREADO MINISTERIO DE SALUD Y PROTECCIÓN SOCIAL, LEY 1444 DE 2011.

J Clin Immunol (2014) 34:10–22
DOI 10.1007/s10875-013-9954-6

KEY REVIEW ARTICLE

# Attending to Warning Signs of Primary Immunodeficiency Diseases Across the Range of Clinical Practice

**Beatriz Tavares Costa-Carvalho · Anete Sevciovic Grumach · José Luis Franco · Francisco Javier Espinosa-Rosales · Lily E. Leiva · Alejandra King · Oscar Porras · Liliana Bezrodnik · Mathias Oleastro · Ricardo U. Sorensen · Antonio Condino-Neto**

Received: 20 July 2012 / Accepted: 14 October 2013 / Published online: 16 November 2013


**Abstract**
*Purpose* Patients with primary immunodeficiency diseases (PIDD) may present with recurrent infections affecting different organs, organ-specific inflammation/autoimmunity, and also increased cancer risk, particularly hematopoietic malignancies. The diversity of PIDD and the wide age range over which these clinical occurrences become apparent often make the identification of patients difficult for physicians other than immunologists. The aim of this report is to develop a tool for educative programs targeted to specialists and applied by clinical immunologists.
*Methods* Considering the data from national surveys and clinical reports of experiences with specific PIDD patients, an evidence-based list of symptoms, signs, and corresponding laboratory tests were elaborated to help physicians other than immunologists look for PIDD.
*Results* Tables including main clinical manifestations, restricted immunological evaluation, and possible related diagnosis were organized for general practitioners and 5 specialties. Tables include information on specific warning signs of PIDD for pulmonologists, gastroenterologists, dermatologists, hematologists, and infectious disease specialists.
*Conclusions* This report provides clinical immunologists with an instrument they can use to introduce specialists in other areas of medicine to the warning signs of PIDD and increase early diagnosis. Educational programs should be developed attending the needs of each specialty.

Beatriz Tavares Costa-Carvalho and Anete Sevciovic Grumach contributed equally

B. T. Costa-Carvalho (✉)
Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo (UNIFESP-EPM), 725 Otonis Street, São Paulo, SP 04025-002, Brazil
e-mail: beacarvalho@terra.com.br

A. S. Grumach
Department of Pulmonology, Faculty of Medicine ABC, Santo André, SP, Brazil

J. L. Franco
Group of Primary Immunodeficiencies, School of Medicine, University of Antioquia, Medellín, Colombia

F. J. Espinosa-Rosales
Unidad de Investigación en Inmunodeficiencias, Instituto Nacional de Pediatría, México City, Mexico

L. E. Leiva · R. U. Sorensen
Department of Pediatrics and JMF Diagnostic Center for PID, Louisiana State University Health Sciences Center, New Orleans, LA, USA

A. King
Immunology Unit, Luis Calvo Mackenna Hospital, Santiago, Chile

O. Porras
Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera", San José, Costa Rica

L. Bezrodnik
Hospital de Niños "Ricardo Gutiérrez", Buenos Aires, Argentina

M. Oleastro
Hospital Garrahan, Buenos Aires, Argentina

R. U. Sorensen
Faculty of Medicine, University of La Frontera, Temuco, Chile

A. Condino-Neto
Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, SP, Brazil

**Keywords** Primary immunodeficiency · PIDD · recurrent infections · inflammation · autoimmunity · cancer · warning signs

### Abbreviations

| | |
|---|---|
| ALPS | Autoimmune lymphoproliferative syndrome |
| ANA | Antinuclear antibodies |
| AP50 | Alternative pathway of complement system |
| APECED | Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy |
| C1INH | C1 esterase inhibitor |
| CBC | Complete blood count |
| CD40L | CD40 ligand (L) deficiency |
| CGD | Chronic granulomatous disease |
| CSR | Class switch recombination |
| CVID | Common variable immunodeficiency |
| DHR | Dihydrorhodamine |
| EBNA | Epstein-Barr nuclear antigen |
| FHL | Familial hemophagocytic lymphohistiocytosis |
| HAE | Hereditary angioedema |
| HIES | Hyper-IgE syndrome |
| HLH | Hemophagocytic lymphohistiocytosis |
| IPEX | Immunodysregulation, polyendocrinopathy and enteropathy, X-linked |
| OPV | Oral poliovirus vaccine |
| RCP | Reactive C protein |
| SCID | Severe combined immunodeficiency |
| SLE | Systemic lupus erythematosus |
| TSH | Thyroid-stimulating hormone |
| WAS | Wiskott-Aldrich syndrome |
| WHIM | Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome |
| XLA | X-linked agammaglobulinemia |
| XLP | X-linked lymphoproliferative syndrome |

## Introduction

Primary immunodeficiency diseases (PIDD) are a heterogeneous group of more than 150 disorders that result from many different congenital, or even acquired, genetic defects affecting the innate and adaptive immune systems [1, 2]. Despite major advances over the last 20 years in the clinical and molecular characterization of PIDD, many patients remain undiagnosed or have a substantially delayed diagnosis with adverse results on morbidity and mortality.

The diagnosis of PIDD is most often suggested by recurrent or unusual infections and inflammatory or autoimmune conditions. Several lists of warning signs for children or adults are based on these main clinical presentations and, in some cases, family history [3–6]. Arkwright and Gennery concluded that the 10 warning signs promoted by the Jeffrey Modell Foundation have a sensitivity of 56 % and a specificity of 16 % [7]. Subbarayan et al. evaluated 563 children and concluded that the strongest identifier of PIDD is family history. Of secondary relevance were the use of intravenous antibiotics for sepsis, and failure to thrive in children with T lymphocyte primary immunodeficiency disease [8]. Mehra et al. observed that 20 % of hospitalized patients with suspected immune defects would not be included for immunologic investigation according to the 10 warning signs [9].

All currently available lists of warning signs are based on family history and descriptions of infections suggestive of an immunodeficiency. These are general signs that should be known by all physicians. However, there are many specific warning signs that certain specialists need to be aware of. Because of the diversity of immune defects, their respective clinical presentations, and the difficulties in reaching many non-immunology subspecialists with these general warning signs, many signs that should raise suspicion of PIDD are missed by physicians and a large proportion of patients are not properly diagnosed [10–12].

Here, we provide lists of specific warning signs in tables that can be used to familiarize subspecialists with signs and symptoms of PIDD that they are likely to see in patients referred to their practices. The tables will provide quick summaries of the many warning signs and diagnoses encountered by different specialists, with suggestions for appropriate screenings, immunological evaluations, and proper referrals to clinical immunologists.

## Methods

The information offered in this article is based on a review of the pertinent literature and the clinical experience of all authors. Tables I and II list the tests that are recommended for screening of the main immunologic functions, along with histories and infections that all physicians and health care workers need to recognize as warning signs of a possible immunodeficiency. Subsequent tables list special clinical presentations that should alert specific groups of specialists. When presenting information about PIDD from this article, it is important to always include Tables I and II, and the pertinent tables prepared for various specialties.

### General Screening and Evaluation

Table I lists the tests that should be performed according to the main clinical presentations specified in the subsequent tables. In some situations the relevant evaluation is not part of generally available screening tests, and it is preferable to refer the patient directly to an immunologist so that routine and specialized tests can be performed simultaneously. The tables for

specialists will provide data for further laboratory investigation.

## Recurrent, Severe, or Unusual Infections

Our recommendations are similar to those in published lists of warning signs that consider the frequency of various types of infections. However, it is also important to consider the infection type, the circumstances under which infections occur, and which organs and tissues they affect. In our experience, this is a more effective way to identify PIDD than emphasizing exact numbers of different infections or special definitions of severity. When severity is considered, it is important to consider the pathogenicity of an infectious agent; infections with any pathogen of low pathogenicity, such as atypical mycobacteria or toxoplasma, are suggestive of an immune defect even if the infection is not severe. Epidemiological data about infectious agents should be considered as well. For example, paracoccidioidomycosis should be more commonly identified in tropical countries than in European or North American countries (Table II). A general condition that should make any infection suspicious is the concomitant presence of non-infectious complications commonly associated with PIDD, including severe allergy, autoimmunity, unregulated inflammation, or malignancies.

A positive family history definitely suggests a PIDD. However, it is also important to consider certain negative family histories—for example, a family in which only one of 4 siblings has recurrent infections. The fact that the other 3 siblings and parents are healthy rules out environmental factors as the factors predisposing an individual to recurrent infections; it also highlights the immunopathogenic effects of genetic alterations that may have occurred in a single family member.

Recurrent infections are often attributed to the presence of non-immune abnormalities, such as Down syndrome, muscular dystrophy, or various congenital heart defects. Such patients may also have an immunodeficiency, and appropriate recognition and treatment may significantly improve their quality of life.

## Infectious Diseases

Many PIDDs have unique susceptibilities to some pathogens and/or sites of infections that are listed in Table III. Antibody-mediated immunity needs to be evaluated in all severe or unusual infections, in addition to other possible concurring immunological defects. A practical point is to screen for combined immunodeficiencies.

Infectious disease is the hallmark of PIDD, and infectious disease specialists are the physicians most likely to encounter patients with PIDD in their daily practice. The burden of infectious disease is immense even in children with healthy immune systems. Recurrent otitis media is considered to be more than 4 episodes of acute otitis media during the past 12 months with complete resolution of the disease between episodes [13–15].

Any patient with severe or recurrent infections or infection by opportunistic or uncommon microorganisms must be investigated for PIDD after discarding the possibility of infection with human immunodeficiency virus (HIV).

Pyogenic encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*) are frequently associated with infections in patients with antibody or complement deficiencies. Patients with complement deficiencies may also present with meningitis and sepsis associated with pathogens such as *Neisseria* [16].

Agammaglobulinemic patients and, to a lesser extent, patients with common variable immunodeficiency (CVID) have an increased risk of developing bloodstream bacterial infections [17]. A study of 201 patients with X-linked agammaglobulinemia (XLA) indicated that 11 % had at least one episode of meningitis or encephalitis, 10 % had at least one episode of sepsis, and 8 % had at least one episode of septic arthritis [18]. Patients with XLA or CVID are at an increased risk for severe and often fatal infections with enteroviruses,

**Table I** Screening laboratory tests for the non-immunology specialist in order to detect patients with possible PIDD

| Possible PIDD | Screening Tests |
|---|---|
| Antibody mediated immunity (AMI) | • CBC and differential<br>• Serum IgG, IgA, IgM<br>• Antibody titers to protein and polysaccharide vaccines |
| Cellular mediated immunity (CMI) | • CBC and differential<br>• Lymphocytes: CD3, CD4, and CD8; CD19; CD16/56<br>• Chest x-ray |
| Complement (C) | • C4 (if angioedema without urticaria)<br>• CH50 |
| Phagocytosis (P)<br>Neutropenia<br>Neutrophil function | • Neutrophil counts<br>• Oxidative burst by DHR test |
| Autoimmunity | • ANA, RCP |
| Innate immunity (II) | • Specialized tests (consult an immunologist) |

The screening lab tests should be part of any initial immune evaluation. Only the abbreviations in parentheses will be listed as suggested screening tests in all subsequent tables. HIV testing should be a routine test to exclude AIDS

*Abbreviations*: *ANA* antinuclear antibodies, *CBC* complete blood count, *DHR* dihydrorhodamine, *RCP* reactive C protein

**Table II** Infections that are general warning signs of PIDD for all clinicians

**Otitis media***
- Early onset <3–4 months of age
- Recurrence after antibiotic treatment
- Complications: mastoiditis
- Association with invasive infections
- Recurrence after ear tubes
- Change to sinusitis after ear tubes
- Repeated ear tube placement

* The number of otitis episodes that suggest PIDD varies with age: ≥ 3 episodes/year under 5 years; ≥ 2 episodes/year ≥5 years

**Chronic recurrent rhinosinusitis**
- Association with persistent asthma
- Requirement for sinus surgery due to fungal infections

**Pneumonia**

Evaluate after a single pneumonia if the patient has:
- A personal history of recurrent upper respiratory infections (URI) including recurrent otitis media
- A personal history of other immune problems (autoimmunity, chronic diarrhea, periodic fevers, persistent skin rash, etc.)
- Pneumonia that requires hospitalization (any: ICU or regular service)
- Persistent pneumonia after adequate therapy with antibiotics
- Pneumonia requiring IV antibiotics
- Bilateral pneumonias
- Necrotizing pneumonia
- Interstitial pneumonitis

Evaluate patients with 2 or more pneumonias:
- All patients (preferred option)

Or evaluate only if:
- X-ray proven pneumonias in different lung sites
- Positive family history for early death or primary immunodeficiency (PIDD)
- Pneumonia that is complicated by pneumatocele or bronchiectasis

**Uncommon infections or uncommon presentations in HIV-negative patients***

Atypical mycobacteriosis
Tuberculosis resistant infection
Histoplasmosis
Neurocryptococcosis
Aspergilosis
Leishmaniasis
Blastomycosis

* More relevant signs in developed countries or non-endemic countries for these diseases

**Chronic diarrhea or colitis**

Evaluate if the patient has:
Rotavirus
Enteroviruses
*Campylobacter*
*Cryptosporidium*
Persistent *Salmonella*
*Clostridium difficile*
Recurrent giardiasis

**Chronic dermatitis**
Recurrent staphylococcal infections
Recurrent or persistent candidiasis or fungal infections

**Abscesses (liver, lungs, cutaneous)**
*Staphylococcus aureus*

**Infections of central nervous system (CNS)**
Meningococcal meningitis
Herpes encephalitis
Fungal infections

**Complications due to live attenuated vaccines**
Disseminated BCG (*Mycobacterium bovis* Bacillus Calmette-Guérin)
Poliomyelitis due to poliovirus vaccine
Diarrhea due to rotavirus vaccine

See text under "Recurrent, Severe, or Unusual Infections"

For all the common infections listed in this table, evaluation starts with a complete blood count to rule out neutropenia and assessment of antibody mediated immunity

including echoviruses, polioviruses, and coxsackie viruses [17]. The central nervous system is nearly always involved in these infections, and evidence of systemic involvement of muscle, liver, and/or joints is present in about 40 % of patients. These infections are associated with high mortality and morbidity [19].

Other organisms, including *Staphylococcus aureus*, *Pseudomonas* spp, *Mycoplasma* spp, Enterobacteriaceae, *Campylobacter* spp, *Giardia*, and enteroviruses, may be isolated from patients with specific types of PIDD [17]. Infections caused by *Serratia marcessens*, *Nocardia* spp, *Chrombacterium violaceum*, *Granulobacter bethesdensis*, *Burholderia cepacia*, and *gladioli* are strongly suggestive of chronic granulomatous disease (CGD). Evaluation of 259 patients with the X-linked recessive form of CGD indicated that 21 % had a history of either bacteremia or fungemia [20].

Infections caused by mycobacteria, *Salmonella*, *Leishmania*, and *Cryptococcus* suggest defects in the interferon-γ/interleukin-12 axis included in innate immunity (Table III) [21]. As previously mentioned, the incidence of certain infectious agents must be considered according to their endemicity in particular geographical regions. Side effects of Bacillus Calmette-Guérin (BCG) occur in more than 50 % of the severe combined immunodeficiency (SCID) patients in Brazil and more than 17 % of CGD patients in Latin America; this is a relevant warning sign for PIDD [22]. Adverse reactions to other live attenuated viral vaccines such as poliovirus

**Table III** Warning signs of PIDD for infectious disease specialists

| Clinical occurrences | PIDD | Lab screening tests |
|---|---|---|
| Infections from extracellular bacteria | Antibody deficiencies | AMI |
| | Complement deficiencies | C, ANA |
| | Neutropenias | P |
| | IRAK-4, MyD88 | II, RCP |
| Infections due to *Neisseria meningitidis* | Complement deficiency of terminal components (Membrane attack complex) | C + AP50 |
| Infection from *S aureus*, and gram-negative bacterias: *Serratia marcescens*, *Burkholderia cepacia* and *gladioli*,*Nocardia spp*, *Chromobacterium violaceum*, *Granulobacter bethesdensis*. | Chronic granulomatous disease (CGD) | P |
| | Hyper IgE syndrome (HIES)<br>Features: pneumonia from *S aureus*, eczema, fungal infection, joint hypermobility, coarse facial features | Serum IgE, eosinophilia<br>Specific Score[a] |
| Infection from fungi: *Pneumocystis jiroveci*; *Aspergillus and Candida albicans*. | T cell defects | CMI |
| | CD40 ligand (L) deficiency | AMI |
| | HIES | Serum IgE, eosinophilia<br>Specific Score[a] |
| | CGD | P |
| Infection from *Candida albicans* | Chronic mucocutaneous candidiasis | CMI + T lymphocyte proliferation induced by *Candida* |
| Infection by atypical *Mycobacteria*/*Salmonella* and/or Bacillus Calmette-Guérin side effects; *Paracoccidioides sp*, *Leishmania*, *Cryptococcus* | T cell deficiencies | CMI |
| | Severe combined immunodeficiency (SCID) | AMI + CMI |
| | Mendelian susceptibility to mycobacterial diseases | P and/or II |
| Infections from *Herpes* | T and NK cell deficiencies | CMI |
| Fulminant or chronic infection by Epstein-Barr virus | Familial hemophagocytic lymphohistiocytosis (FHL) syndrome<br>X-linked lymphoproliferative (XLP) syndromes, types 1 or 2 | CBC, triglycerides, ferritin, serology EBNA |
| Recurrent or persistent *Cryptosporidium*, *Isospora* | CD40L deficiency | AMI |
| | Common variable immunodeficiency (CVID) | AMI |
| *Giardiasis* | Antibody deficiencies | AMI |
| Complications due to *BCG*, *rotavirus or Varicella* vaccines | SCID, CGD | CMI and/or II and/or P |
| Complications due to oral polio vaccine | Antibody deficiencies | AMI |
| Persistent fever of unknown origin | Autoinflammatory diseases | ANA, RCP, blood smear |

*Abbreviations*: *AMI* antibody mediated immunity, *ANA* antinuclear antibodies, *CBC* complete blood count, *CMI* cellular mediated immunity, *EBNA* Epstein-Barr nuclear antigen, *II* innate immunity, *P* phagocytosis, *RCP* reactive C protein

[a] Score for classical hyper IgE diagnosis [26]

and rotavirus should be carefully observed as well [23]. Several developing countries maintain campaigns with Sabin immunization with the possibility to cause vaccine-derived disease [24].

Although the respiratory and gastrointestinal tracts are the most common systems for presenting illness, the authors observed lymphadenopathy as the most common manifestation in the group of combined T and B cell immunodeficiencies,

and superficial abscesses and lymphadenopathy in the group of congenital defects of phagocyte number and/or function [22, 25, 26] (Table III).

## Otorhinolaryngology and Pulmonology

High percentages of pediatric and adult patients with PIDD have upper and/or lower respiratory tract bacterial infections; thus, they may be referred to otorhinolaryngologists or pulmonologists. Rezaei reported on 930 patients with PIDD, 353 cases of which were identified in the last 5 years. The most common presenting feature of PIDD was pneumonia, which was seen in 20.1 % of patients, followed by diarrhea (13.7 %), sinusitis (10.3 %), and otitis media (9.6 %) [27]. It is important to rule out the existence of cofactors that might be associated with upper respiratory infections (e.g., smoking, day care attendance, gastroesophageal reflux, allergy) before performing extensive immunological evaluation. The most common of these infections are recurrent otitis media, chronic sinusitis, and pneumonia. Recurrent sinus infections have been reported as a presenting occurrence in 19 % to 98 % of patients with PIDD (wide range reflects the variety of PIDD) [28, 29]. An assessment of 103 pediatric and adult patients with a history of recurrent or chronic ear, nose, or throat infections indicated that 16.5 % had defects in antibody-mediated immunity: CVID ($n=2$), IgA deficiency ($n=4$), IgG subclass deficiency ($n=3$), and specific antibody deficiency against polysaccharide antigens ($n=8$) [30]. Warning signs for patients with recurrent otitis include progressive infections leading to mastoiditis; associated abscesses or systemic infections; lack of responsiveness to adequate antibiotic treatment; or occurrence of unusual, severe, or frequently relapsing infections in other sites [31] (Table II).

Pneumonia is a common infectious manifestation of PIDD; one study of patients with CVID indicated that at least two-thirds had one or more pneumonia diagnoses prior to diagnosis of PIDD [32]. According to some registries [33, 34], approximately 50 % of patients with humoral immunodeficiency suffered from upper respiratory tract infections, and 40 % of XLA and CVID patients suffered from recurring pneumonia [27, 35]. Pathogens frequently associated with pneumonia in patients with antibody deficiencies include *S pneumoniae*, *H influenzae* type b, *Haemophilus parainfluenzae*, *Mycoplasma* spp, *Pseudomonas* spp, and *Staphylococcus* spp [17]. Patients with cellular deficiencies such as CD40 Ligand (CD40L) deficiency present with pneumonia that is a result of opportunistic pathogens such as *Pneumocystis*, fungal, or viral infections [36] (Table IV).

Several observational studies have indicated that complications and sequelae of infectious diseases such as bronchiectasis (76 %), recurrent chest infections (21 %), and granulomatous lung disease (5 %) should also raise suspicion of PIDD [37]. A systematic review of the literature conducted by Wood et al. included results from 7 surveys showing that respiratory/chest infections were presenting symptoms for 37 % to 90 % of patients with PIDD [29]. Touw et al. reviewed 26 studies that included 587 patients with CVID and found that up to 73 % developed chronic structural pulmonary complications—most often bronchiectasis and bronchial wall thickening [38]. In another study, pulmonary imaging by chest computed tomography in 30 patients with PIDD revealed abnormalities in 53 %; among these were bronchiectasis (75 %), peribronchial thickening (19 %), air trapping (31 %), lung volume reduction (25 %), atelectasis (12 %), follicular bronchiolitis (12 %), ground-glass abnormality (12 %), and parenchyma nodules (6 %). In this study, pulmonary function testing also indicated abnormalities in 18 patients; these included an obstructive (38.8 %), restrictive (44.4 %), or mixed (16.7 %) pattern of lung function abnormalities [39].

Results from other studies have indicated that *Staphylococcus*-associated pneumonia and bronchial aspergillosis [40] are seen in CGD; lung abscesses represent usual characteristics in hyper IgE syndrome (HIES); and interstitial pneumonia may be observed in patients with SCID [41] (Table IV).

## Gastroenterology

Frequent gastrointestinal manifestations are malabsorption, diarrhea, hepatomegaly, and inflammatory bowel disease (IBD) and all of these are commonly associated with increased morbidity [42–44]. In a systematic review, Wood et al. indicated that GI infections were a presenting symptom in 6 % to 19 % of patients with PIDD [29]. Severe diarrhea can start early in life in patients with SCID or immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX); both of these PIDD are considered pediatric emergencies [45–47]. Rezei et al., in their study of 930 patients with PIDD, indicated that infectious diarrhea occurred in 40.4 % of patients [27]. Recurrent or chronic giardiasis is suggestive of an underlying antibody deficiency [17]. Other pathogens in patients with infectious colitis include rotavirus, *Campylobacter*, enteroviruses, *Cryptosporidium parvum*, *Salmonella* spp, and *Clostridium difficile* [18]. Liver abscesses caused mainly by *S aureus* may also be seen in patients with CGD and HIES (Table V).

Results from a study focusing mainly on pediatric patients with PIDD indicated clinical evidence of liver disease, including hepatomegaly, in 35.5 %; 8 patients (13 %) had clinical and/or laboratory evidence of chronic liver disease. Hepatobiliary infection, sclerosing cholangitis, nodular

**Table IV** Warning signs of PIDD for pulmonologists

| Clinical occurrences | PIDD | Laboratory tests |
|---|---|---|
| Pneumonias due to extracellular bacteria + otitis and sinusitis | Antibody deficiencies | AMI |
| | Complement deficiencies | C, ANA |
| Pulmonary abscess<br>Pneumatocele | Hyper IgE syndrome (HIES)<br>Features: pneumonia by *S aureus*, eczema, fungal infection, joint hypermobility, coarse facial features | Serum IgE, eosinophilia<br>Specific Score[a] |
| Pneumonias due to *Staphylococcus* or fungi | Chronic granulomatous disease (CGD): susceptibility to infections by catalase positive microorganisms. Other infections: adenitis, liver abscess, osteomyelitis | P |
| | Glucose-6-phosphate dehydrogenase (G6PD) deficiency | G6PD activity |
| | Myeloperoxidase deficiency (common in diabetes) | Peroxidase level |
| | HIES | Serum IgE, eosinophilia<br>Specific Score[a] |
| Pneumonia due to *P jiroveci* | T cell deficiencies/$CD4^+$ lymphopenia | CMI, AMI<br>Lymphoproliferation assay |
| | CD40 ligand (L) deficiency | AMI, CMI |
| | Wiskott-Aldrich syndrome (WAS), eczema + thrombocytopenia | CBC including platelet number and size (small sized platelets); CMI, AMI |
| Pneumonia due to *Mycobacteria tuberculosis* or atypical mycobacteria | T cell deficiencies/CD40L deficiency | CMI, AMI |
| | Mendelian susceptibility to mycobacterial diseases | II |

*Abbreviations*: *AMI* antibody mediated immunity, *ANA* antinuclear antibodies, *CBC* complete blood count, *CMI* cellular mediated immunity, *II* innate immunity, *P* phagocytosis

[a] Score for classical Hyper IgE diagnosis [26]

regenerative hyperplasia, and portal hypertension are frequent conditions in CD40L deficiency [48, 49].

## Rheumatology

The risk for autoimmune diseases is elevated in patients with PIDD and is sometimes the only clinical manifestation of their causative condition. Results from a larger study of 248 patients with CVID indicated that 69 (27.8 %) had autoimmune disease. The most common conditions were thrombocytopenia in 18 patients, hemolytic anemia in 12, rheumatoid arthritis in 5, and juvenile rheumatoid arthritis in 4 [50, 51]. Results from another study of 189 patients with systemic lupus erythematosus (SLE) indicated that 6 % had IgA deficiency [52].

Other PIDD are the result of genetic defects that lead to immune dysregulation associated with autoimmune occurrences. Patients with autoimmune lymphoproliferative syndrome (ALPS) develop generalized lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, B cell lymphocytosis, and autoimmune manifestations that commonly include hemolytic anemia, glomerulonephritis, and idiopathic thrombocytopenic purpura [53]. Autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED) are also associated with symptoms of autoimmune disease [54]. Patients with IPEX have mutations in the FOXP3 gene in regulatory T cells, which leads to severe autoimmunity with a high mortality rate [55]. First components of complement deficiency have also been shown to be associated with conditions such as SLE and are likely to prompt referral to a rheumatologist [56]. An important "red flag" for SLE and complement defects is negative serology to double-stranded DNA [57].

Bone and joint abnormalities can occur in patients with PIDD. The most common of these is arthritis, which may be associated with antibody deficiencies, and, less often, with CGD and Wiskott-Aldrich syndrome (WAS) [58, 59]. Importantly, infections with *Ureaplasma urealyticum*, and *Mycoplasma ssp* may lead to erosive arthritis in patients with severe antibody deficiencies. These infections most often result in large-joint monoarthritis involving the knee, shoulder, elbow, or hip joints, and less often in symmetrical polyarthritis [17].

Patients with certain PIDD, such as autoinflammatory syndromes, will present with generalized serositis that might be confused with infectious arthritis. This is often accompanied by a myriad of symptoms, including elevation of acute phase

**Table V** Warning signs of PIDD for gastroenterologists

| Clinical occurrences | PIDD | Laboratory tests |
|---|---|---|
| Chronic diarrhea | Antibody deficiencies | AMI |
| Inflammatory bowel disease | Combined immunodeficiencies (infants) | CMI, AMI |
| Chronic giardiasis | | |
| Autoimmune enteropathy + severe intractable diarrhea. Other diagnoses associated: hypothyroidism, eczema, thrombocytopenia, autoimmune hemolytic anemia, neonatal diabetes | Immunodysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX) | CMI, Coombs, glycemia, and TSH<br>ANA |
| Persistent candidiasis | Combined immunodeficiencies | CMI<br>T cell Lymphoproliferative assay |
| | Chronic mucocutaneous candidiasis | Lymphoproliferation to *Candida* |
| | Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) | Candidin test<br>ANA and endocrine evaluation |
| Severe abdominal pain emulating an acute abdomen | Hereditary angioedema | Dosage and/or functional activity assay of C1INH, C4, C1q |
| Liver abscess mainly due to *S aureus* | Chronic granulomatous disease (CGD) | P |
| | Hyper IgE syndrome (HIES) | Serum IgE, eosinophilia<br>Specific Score[a] |
| Hepatobiliary infection due to *C parvum* | CD40 ligand (L) deficiency | AMI |
| Inflammatory bowel disease in infants | CGD | P |
| | Interleukin-10 (IL-10) or interleukin 10 receptor (IL-10R) deficiencies | II |

*Abbreviations*: *AMI* antibody mediated immunity, *ANA* antinuclear antibodies, *C1INH* C1 esterase inhibitor, *CMI* cellular mediated immunity, *CBC* complete blood count, *II* innate immunity, *P* phagocytosis, *TSH* thyroid stimulating hormone

[a] Score for classical Hyper IgE diagnosis [26]

reactants, rash, deafness, joint deformity, and multifocal osteomyelitis [60].

## Dermatology

Patients with PIDD may have skin conditions including fungal, bacterial, or viral infections; eczematous dermatitis; erythroderma; skin symptoms of autoimmune diseases such as SLE or scleroderma; vasculitis; granuloma formation; and/or problems characteristic of specific immunodeficiency syndromes (e.g., telangiectasia, gray hair, and depigmentation) [61]. An immunological assessment of 382,383 pediatric patients admitted to an outpatient dermatology group indicated that 130 had PIDD. Of these, 69 % had skin infections, 29 % had eczema-dermatitis, and 44 % had other associated cutaneous conditions. In 79 % of this cohort, cutaneous abnormalities preceded and were the basis for the clinical immunologic diagnosis [62], demonstrating the relevance and high frequency of dermatologic manifestations in PIDD patients.

Results from a cross-sectional study of 210 pediatric patients with PIDD (68 with antibody deficiencies, 22 with T cell and combined deficiencies, 57 with phagocytic defects, and 63 with other PIDD) indicated that 67 of the patients (31.9 %) had cutaneous abnormalities preceding the diagnosis of PIDD. Overall, 99 patients had infections and 27 had eczematous dermatitis [63].

Candida infections that may be among the first signs of PIDD include mucocutaneous candidiasis, *Candida paronychia*, granuloma formation, and erythroderma [64]. Patients with phagocytic, cellular, combined, and other PIDD exhibit immune deficits that confer increased susceptibility to fungal infections. Infections associated with *Candida*, *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Paecilomyces*, *Scedosporium*, *Trichosporon*, *Penicillium*, and other fungal organisms have been observed in patients with CGD, SCID, HIES, defects in the interferon-γ/interleukin-12 axis, DiGeorge syndrome/22q deletion syndrome, CD40L deficiency, WAS, and CVID [64]. Patients with Chediak-Higashi or Griscelli syndromes present partial albinism

and gray hair; dermatologists are frequently the first consulted specialists [65]. Prompt diagnosis is established by demonstration of giant intracellular granules in eosinophils, basophils, and monocytes, and are pathognomonic of this disease [66].

Eczema and high serum IgE levels in the first months of life frequently lead to referral to allergists due to suspicion of cow milk protein allergy. However, these occurrences are also present in patients with hypomorphic SCID, IPEX, WAS, DOCK8, and HIES [67]; it has been shown that differential diagnosis is crucial for prognosis [68]. Zhang et al. described DOCK8 mutations in patients with a variant of combined immunodeficiency characterized by unusual susceptibility to cutaneous viral infections and cancers. In addition, DOCK8 deficiency was found in a subgroup of patients who were previously thought to have autosomal recessive HIES with severe allergic manifestations [69]. These syndromes exemplify the need for improved knowledge of PIDD for dermatologists (Table VI). In addition, angioedema without urticaria is often referred to both allergists and dermatologists. Family histories are helpful for such cases, and C4 levels could be a useful screening test [70].

## Hematology/Oncology

Autoimmune hemolytic anemia, thrombocytopenia, and/or neutropenia are also seen in patients with selective IgA deficiency, CVID, and class switch recombination (CSR) defects [50, 71]. In some patients, hematologic abnormalities reflect the underlying pathology responsible for the immunodeficiency. Wiskott-Aldrich syndrome is associated with defects in both B-lymphocyte and T-lymphocyte function, and these patients also have intrinsic platelet abnormalities and significant thrombocytopenia with small platelets [71]. In addition to congenital neutropenia, neutropenia is also associated with XLA, CD40L deficiency, CVID, SCID, and Shwachman-Diamond syndrome [72, 73]. Hemophagocytic lymphohistiocytosis (HLH) is characterized by multisystem inflammation, a reactive process resulting from hyperactivation of macrophages, histiocytes and $CD8^+$ T cells, and abnormalities in the function of natural killer cells (NK cells). The most frequent clinical and laboratorial findings include fever, splenomegaly, cytopenias, hypertriglyceridemia, and elevated ferritin [74]. Both Chediak-Higashi and Griscelli

**Table VI** Warning signs of PIDD for dermatologists

| Clinical occurrences | PIDD | Laboratory test |
|---|---|---|
| Eczema | Wiskott-Aldrich syndrome (WAS) | CBC including platelet number and size (small sized platelets); CMI, AMI |
| | Hyper IgE syndrome (HIES) | Serum IgE, eosinophilia |
| | | Specific Score[a] |
| | Immunodysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX) | CMI, ANA, RCP |
| | | Coombs, glycemia, and TSH |
| | Severe combined immunodeficiency (SCID), erythroderma | CMI |
| Cutaneous lesions by *Mycobacteria* | Combined immunodeficiencies | CMI |
| | Hyper-IgM syndromes | AMI |
| | Mendelian susceptibility to mycobacterial diseases | II |
| | Chronic granulomatous diseases (CGD) | P |
| Partial albinism, gray hair | Chediak-Higashi syndrome<br>Griscelli syndrome | Enlarged cytoplasm granules in blood smear |
| Telangiectasias | Ataxia-telangiectasia | AMI; serum alfa-feto protein |
| Disseminated warts and molluscum<br>Cutaneous herpes infections | Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome<br>Dedicator of cytokinesis 8 (DOCK8) deficiency<br>Idiopathic CD4 lymphopenia | AMI, CMI lymphoproliferation assay |
| Fragile hair, conic teeth | Ectodermal dysplasia | II |

*Abbreviations*: *AMI* antibody mediated immunity, *ANA* antinuclear antibodies, *CBC* complete blood count, *CMI* cellular mediated immunity, *II* innate immunity, *P* phagocytosis, *RCP* reactive C protein, *TSH* thyroid stimulating hormone

[a] Score for classical Hyper IgE diagnosis [26]

**Table VII** Warning signs of PIDD for hematologists

| Clinical occurrences | PIDD | Laboratory tests |
|---|---|---|
| Thrombocytopenia with small-sized platelets | Wiskott-Aldrich syndrome (WAS)<br>Other symptoms: eczema and recurrent infections | CBC including platelet number and size (small sized platelets); CMI, AMI |
| | X-linked thrombocytopenia | |
| Autoimmune cytopenias (autoimmune anemia, thrombocytopenia and neutropenia) | Common variable immunodeficiency<br>Other features: recurrent infections | AMI, ANA |
| Fever, splenomegaly without evidence of malignancy, cytopenias | Hemophagocytic lymphohistiocytosis (HLH) | CBC, triglycerides, ferritin, EBNA |
| Lymphadenopathy + Splenomegaly<br>Excluding neoplasias and infections | Autoimmune lymphoproliferative disease<br>Apoptosis defects | Increased number of alpha beta double-negative T cells (CD3 + CD4-CD8-), ANA, RCP |
| Quantitative and qualitative defects of neutrophils (neutropenia and neutrophilia) | Neutropenias<br>Chronic granulomatous disease (CGD) | P |
| | Leukocyte adhesion deficiency | Leukocytosis, $CD18^{+}$ cells |
| | Partial albinism, Chediak-Higashi or Griscelli syndrome | Enlarged cytoplasm granules |

*Abbreviations*: *AMI* antibody mediated immunity, *ANA* antinuclear antibodies, *CBC* complete blood count, *CMI* cellular mediated immunity, *EBNA* Epstein-Barr nuclear antigen, *P* phagocytosis, *RCP* reactive C protein

syndromes present as hemophagocytic, with an accelerated phase affecting all patients by late childhood. This accelerated phase is characterized by the infiltration of nonmalignant lymphoid and histiocytoid cells into the viscera, usually induced by Epstein-Barr virus. Clinical findings include hepatosplenomegaly, lymphadenopathy, and pancytopenia [75]. Impaired humoral and cellular immune responses, including disturbances in B, T, NK, and dendritic cells, along with chronic inflammatory autoimmune diseases, recurrent bacterial infections, and persistent antigenic stimulation, are speculated to favor carcinogenesis in CVID patients. Lymphoma and gastric cancer are the most frequent neoplasms related to this immunologic defect [76, 77]. The risk of cancer in PIDD patients mainly takes the form of T cell malignancies (70-fold and 250-fold increased risks of leukemia and lymphoma, respectively), and B cell malignancies are high when compared with the general population [78]. The Spanish registry identified that 1.3 % of the 1,069 patients developed cancer; however, the survey was developed within reference hospitals [34].

Non-Hodgkin lymphoma and Hodgkin lymphoma are 2 of the most common PIDD-associated malignancies [79]. A recent large-scale assessment of 1,132 patients in the PIDD registry of the Australasian Society of Clinical Immunology and Allergy indicated that this group had a 1.6-fold excess relative risk of cancer [80]. The relative risk was significantly increased for non-Hodgkin lymphoma, leukemia, and stomach cancer (Table VII).

## Conclusions

During recent years, new PIDD have been identified, including some with susceptibility to specific infectious agents and some diagnosed only in adulthood. Training specialists to recognize PIDD is important in order to identify the diverse PIDD phenotypes. The majority of patients initially present to hospital doctors; therefore, a focus on hospital specialists has been suggested.

Clinical immunologists have an important educational role. Introducing other specialists and health care workers to the relevant warning signs will facilitate the early diagnosis of PIDD in patients, leading to better treatments with less sequelae, or possible cures.

In this review we have addressed the presentations of PIDD that are seen by different medical subspecialists. These warning signs are further influenced by the socioeconomic, climate-related, and living conditions found in different regions of the world. A review of warning signs that are specific to different areas of the world should eventually be undertaken by a worldwide PIDD community of which LASID plays an important part.

**Acknowledgments** The authors would like to acknowledge the Jeffrey Modell Foundation for their support of educational programs in Latin America. We also acknowledge the editorial assistance of BSG Communications, which is supported by Baxter.

**Support** This work was supported by the Latin American Society of Primary Immunodeficiencies through an unrestricted educational grant from Baxter Bioscience.

**Conflicts of interest and funding sources** Dr. Grumach is on the advisory board of Baxter, Shire, and Dyax Pharmaceuticals, has consulted for and received grants, payments, and travel support from Shire, and has received travel expenses from CSL Behring. Dr. Franco is a board member and consultant for and has received payments and travel support from Baxter. Dr. Condino-Neto has received research grants from Fundacao de Amparo a Pesquisa do Estado de São Paulo, Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil, and Baxter Bioscience Research Grants. The other authors had nothing to disclose.



## References

1. Arason GJ, Jorgensen GH, Ludviksson BR. Primary immunodeficiency and autoimmunity: lessons from human diseases. Scand J Immunol. 2010;71:317–28.
2. Al-Herz W, Bousfiha A, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Front Immunol. 2011;2:54.
3. Jeffrey Modell Foundation. 10 Warning Signs [2013-01-30]. Available from: http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=warningsigns. Accessed 22 May 2013.
4. European Society for Immunodeficiencies. 10 Warning Signs of PID-General [2013-01-30]. Available from: http://www.esid.org/clinical-10-warning-signs-of-pid-general-339-0. Accessed 22 May 2013.
5. US Immunodeficiency Network. Disease Registry [1992]. Available from: http://www.usidnet.org/pub/Disease-Registry. Accessed 22 May 2013.
6. Immune Deficiency Foundation. About Primary Immunodeficiency Diseases. Available from: http://primaryimmune.org/about-primary-immunodeficiency-diseases. Accessed 22 May 2013.
7. Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. Ann NY Acad Sci. 2011;1238:7–14.
8. Subbarayan A, Colarusso G, Hughes SM, Gennery AR, Slatter M, Cant AJ, et al. Clinical features that identify children with primary immunodeficiency diseases. Pediatrics. 2011;27:810–6.
9. Mehra A, Sidi P, Doucette J, Rouvelas H, Cunningham-Rundles C. Subspecialty evaluation of chronically ill hospitalized patients with suspected immune defects. Ann Allergy Asthma Immunol. 2007;99:14.
10. Shearer WT, Cunningham-Rundles C, Ochs HD. Primary immunodeficiency: looking backwards, looking forwards. J Allergy Clin Immunol. 2004;113(4):607–9.
11. Buckley RH. Primary immunodeficiency or not? Making the correct diagnosis. J Allergy Clin Immunol. 2006;117(4):756–8.
12. Ballow M, Notarangelo L, Grimbacher B, Cunningham Rundles C, Stein M, Helbert M, et al. Immunodeficiencies. Clin Exp Immunol. 2009;158:14–22.
13. Pichichero ME, Casey JR. Otitis media. Expert Opin Pharmacother. 2002;3:1073–90.
14. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol Head Neck Surg. 2003;129(3 Suppl):S1–32.
15. von Linstow ML, Holst KK, Larsen K, Koch A, Andersen PK, Høgh B. Acute respiratory symptoms and general illness during the first year of life: a population-based birth cohort study. Pediatr Pulmonol. 2008;43(6):584–93.
16. Grimnes G, Beckman H, Lappegård KT, Mollnes TE, Skogen V. Recurrent meningococcal sepsis in a presumptive immunocompetent host shown to be complement C5 deficient—a case report. APMIS. 2011;119:479–84.
17. Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. Clin Microbiol Rev. 2009;22:396–414.
18. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore). 2006;85:193–202.
19. Halliday E, Winkelstein J, Webster AD. Enteroviral infections in primary immunodeficiency (PID): a survey of morbidity and mortality. J Infect. 2003;46:1–8.
20. Winkelstein JA, Marino MC, Johnston Jr RB, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000;79:155–69.
21. de Beaucoudrey L, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, et al. Revisiting human IL-12Rβ1 deficiency: a survey of 141 patients from 30 countries. Medicine (Baltimore). 2010;89:381–402.
22. Mazzucchelli JL, Buzolin M, Vilela MS, Moraes LL, Porto Neto AC, Monteiro FP, et al. Severe combined immunodeficiency in Brazil: a multi-center analysis of demographics; clinical features regarding BCG infection and outcome in 33 patients. J Clin Immunol. 2011;31 Suppl 1:S1–71.
23. Patel MM, Lopez-Collada R, Bulhões MM, De Oliveira LH, Marquez AB, Fannery B, et al. Intussusception risk and benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364:2283–92.
24. Gumede N, Muthambi V, Schoub BD. Immunodeficiency-associated vaccine-derived poliovirus type 3 in infant, South Africa, 2011. Emerg Infect Dis. 2012;18(6):992–4.
25. Condino-Neto A, Oleastro M. Phenotype and genotype spectrum of chronic granulomatous disease in Latin American patients: results from the LASID Registry. J Clin Immunol. 2012;32 Suppl 1:S188.
26. Woellner C, Gertz EM, Schäffer AA, Lagos M, Perro M, Glocker EO, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol. 2010;125(2):424–32.
27. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, et al. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol. 2006;26:519–32.
28. Richtsmeier WJ. Top 10 reasons for endoscopic maxillary sinus surgery failure. Laryngoscope. 2001;111:1952–6.
29. Wood P, Stanworth S, Burton J, Jones A, Peckham DG, Green T, et al. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. Clin Exp Immunol. 2007;149:410–23.
30. Aghamohammadi A, Moin M, Karimi A, Naraghi M, Zandieh F, Isaeian A, et al. Immunologic evaluation of patients with recurrent ear, nose, and throat infections. Am J Otolaryngol. 2008;29:385–92.
31. Urschel S. Otitis media in children with congenital immunodeficiencies. Curr Allergy Asthma Rep. 2010;10:425–33.
32. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34–48.
33. Ryser O, Morell A, Hitzig WH. Primary immunodeficiencies in Switzerland: first report of the national registry in adults and children. J Clin Immunol. 1988;8:479–85.
34. Matamoros Florí N, Mila Llambi J, Español Boren T, Raga Borja S, Fontan CG. Primary immunodeficiency syndrome in Spain: first

report of the National Registry in Children and Adults. J Clin Immunol. 1997;17:333–9.
35. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, et al. Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol. 2002;22:375–80.
36. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore). 2003;82:373–84.
37. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. QJM. 2002;95:655–62.
38. Touw CM, van de Ven AA, de Jong PA, Terheggen-Lagro S, Beek E, Sanders EA, et al. Detection of pulmonary complications in common variable immunodeficiency. Pediatr Allergy Immunol. 2010;21:793–805.
39. Costa-Carvalho BT, Wandalsen GF, Pulici G, Aranda CS, Solé D. Pulmonary complications in patients with antibody deficiency. Allergol Immunopathol (Madr). 2011;39:128–32.
40. Jones LB, McGrogan P, Flood TJ, Gennery AR, Morton L, Thrasher A, et al. Special article: chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. Clin Exp Immunol. 2008;152:211–8.
41. Woodsford MA, Spencer DA, Cant AJ. Immune deficiency and the lung. Paediat Child Health. 2011;21:213–8.
42. Agarwal S, Mayer L. Gastrointestinal manifestations in primary immune disorders. Inflamm Bowel Dis. 2010;16:703–11.
43. Al-Muhsen SZ. Gastrointestinal and hepatic manifestations of primary immune deficiency diseases. Saudi J Gastroenterol. 2010;16:66–74.
44. Guerrerio AL, Frischmeyer-Guerrerio PA, Lederman HM, Oliva-Hemker M. Recognizing gastrointestinal and hepatic manifestations of primary immunodeficiency diseases. J Pediatr Gastroenterol Nutr. 2010;51:548–55.
45. Carneiro-Sampaio M, Jacob CM, Leone CR. A proposal of warning signs for primary immunodeficiencies in the first year of life. Pediatr Allergy Immunol. 2011;22:345–6.
46. Harbuz R, Lespinasse J, Boulet S, Francannet C, Creveaux I, Benkhelifa M, et al. Identification of new FOXP3 mutations and prenatal diagnosis of IPEX syndrome. Prenat Diagn. 2010;30:1072–8.
47. Ozdemir O. Severe combined immune deficiency in an adenosine deaminase deficient patient. Allergy Asthma Proc. 2006;27:172–4.
48. Malamut G, Ziol M, Suarez F, Beaugrand M, Viallard JF, Lascaux AS, et al. Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. J Hepatol. 2008;48(1):74–82.
49. Motamed F, Aghamohammadi A, Soltani M, Mansouri M, Rezaei N, Teimourian S, et al. Evaluation of liver diseases in Iranian patients with primary antibody deficiencies. Ann Hepatol. 2009;8:196–202.
50. Cunningham-Rundles C. Hematologic complications of primary immune deficiencies. Blood Rev. 2002;16:61–4.
51. Michel M, Chanet V, Galicier L, Ruivard M, Levy Y, Hermine O, et al. Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. Medicine (Baltimore). 2004;83:254–63.
52. Mantovani AP, Monclaro MP, Skare TL. Prevalence of IgA deficiency in adult systemic lupus erythematosus and the study of the association with its clinical and autoantibody profiles. Rev Bras Reumatol. 2010;50:273–82.
53. Desai NK, Morkhandikar S, Bajpai S, Pazare AR. Autoimmune lymphoproliferative disorder in an adult patient. J Postgrad Med. 2011;57:131–3.
54. Lankisch TO, Jaeckel E, Strassburg CP. The autoimmune polyendocrinopathycandidiasis-ectodermal dystrophy or autoimmune polyglandular syndrome type 1. Semin Liver Dis. 2009;29:307–14.
55. Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. Nat Rev Endocrinol. 2010;6:270–7.
56. Jesus AA, Liphaus BL, Silva CA, Bando SY, Andrade LE, Coutinho A, et al. Complement and antibody primary immunodeficiency in juvenile systemic lupus erythematosus patients. Lupus. 2011;20:1275–84.
57. American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: an introduction. Arthritis Rheum. 2002;47(4):429–33.
58. Machado P, Santos A, Faria E, Silva J, Malcata A, Chieira C. Arthritis and X linked agammaglobulinemia. Acta Reumatol Port. 2008;33:464–7.
59. Sordet C, Cantagrel A, Schaeverbeke T, Sibilia J. Bone and joint disease associated with primary immune deficiencies. Joint Bone Spine. 2005;72:503–14.
60. Goldbach-Mansky R, Kastner DL. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. J Allergy Clin Immunol. 2009;124:1141–9.
61. Sillevis Smitt JH, Wulffraat NM, Kuijpers TW. The skin in primary immunodeficiency disorders. Eur J Dermatol. 2005;15:425–32.
62. Berron-Ruiz A, Berron-Perez R, Ruiz-Maldonado R. Cutaneous markers of primary immunodeficiency diseases in children. Pediatr Dermatol. 2000;17:91–6.
63. Moin A, Farhoudi A, Moin M, Pourpak Z, Bazargan N. Cutaneous manifestations of primary immunodeficiency diseases in children. Iran J Allergy Asthma Immunol. 2006;5:121–6.
64. Antachopoulos C, Walsh TJ, Roilides E. Fungal infections in primary immunodeficiencies. Eur J Pediatr. 2007;166:1099–117.
65. Valente NYS, Machado MCMR, Boggio P, Alves ACF, Bergonse FN, Casella E, et al. Polarized light microscopy of hair shafts aids in the differential diagnosis of Chédiak-Higashi and Griscelli-Prunieras syndromes. Clinics. 2006;61:327–32.
66. Huizing M, Helip-Wooley A, Westbroek W, Gunay-Aygun M, Gahl WA. Disorders of lysosome-related organelle biogenesis: clinical and molecular genetics. Annu Rev Genomics Hum Genet. 2008;9:359–86.
67. Ozcan E, Notarangelo LD, Geha RS. Primary immune deficiencies with aberrant IgE production. J Allergy Clin Immunol. 2008;122:1054–62.
68. Bezrodnik L, Raccio AC, Canil LM, Rey MA, Carabajal PC, Fossati CA, et al. Hypogammaglobulinaemia secondary to cow-milk allergy in children under 2 years of age. Immunology. 2007;122:140–6.
69. Zhang Q, Davis JC, Ian MPH, Lamborn T, Freeman AF, Jing H, et al. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med. 2009;361:2046–55.
70. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6:24.
71. Immune Deficiencies Foundation of New Zealand. The clinical presentation of the primary immunodeficiency diseases a primer for physicians. In: Immune Deficiencies Foundation of New Zealand;1993. Available from: http://www.idfnz.org.nz/pub/cms/resources__medical/files/GPPRIM1.pdf. Accessed 28 May 2013.
72. Cabral-Marques O, Schimke LF, Pereira PV, Falcai A, de Oliveira JB, Hackett MJ, et al. Expanding the clinical and genetic spectrum of human CD40L deficiency: the occurrence of paracoccidioidomycosis and other unusual infections in Brazilian patients. J Clin Immunol. 2012;32:212–20.
73. Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Moin M, Movahedi M, et al. Neutropenia in Iranian patients with primary immunodeficiency disorders. Haematologica. 2005;90:554–6.
74. Filipovich AH. Hemophagocytic lymphohistiocytosis and related disorders. Curr Opin Allergy Clin Immunol. 2006;6:410–5.

75. Abrams M, Paller A. Genetic immunodeficiency diseases. Adv Dermatol. 2007;23:197–229.
76. Rezaei N, Hedayat M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. J Allergy Clin Immunol. 2011;127:1329–41.
77. Chua I, Quinti I, Grimbacher B. Lymphoma in common variable immunodeficiency: interplay between immune dysregulation, infection and genetics. Curr Opin Hematol. 2008;15:368–74.
78. Regueiro JR, Porras O, Lavin M. Ataxia-telangiectasia. A primary immunodeficiency revisited. Immunol Allergy Clin North Am. 2000;20:177–206.
79. Shapiro RS. Malignancies in the setting of primary immunodeficiency: implications for hematologists/oncologists. Am J Hematol. 2011;86:48–55.
80. Vajdic CM, Mao L, van Leeuwen MT, Kirkpatrick P, Grulich AE, Riminton S. Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? Blood. 2010;116:1228–34.

HHS Public Access

Author manuscript

*J Allergy Clin Immunol*. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

*J Allergy Clin Immunol*. 2018 March ; 141(3): 1028–1035. doi:10.1016/j.jaci.2017.05.024.

# Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry

**Paul C. Mayor, MD**[1], **Kevin H. Eng, PhD**[2], **Kelly L. Singel, BS**[3], **Scott I. Abrams, PhD**[3], **Kunle Odunsi, MD PhD**[1,3], **Kirsten B. Moysich, PhD**[4], **Ramsay Fuleihan, MD**[5], **Elizabeth Garabedian, RN**[6], **Patricia Lugar, MD**[7], **Hans D Ochs, MD**[8], **Francisco A Bonilla, MD PhD**[9], **Rebecca H Buckley, MD**[7], **Kathleen E Sullivan, MD PhD**[10], **Zuhair K Ballas, MD**[11], **Charlotte Cunningham-Rundles, MD PhD**[12], and **Brahm H. Segal, MD**[3,13,14]

[1]Department of Surgery, Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY

[2]Department of Biostatistics and Bioinformatics, Roswell Park Cancer Institute, Buffalo, NY, USA

[3]Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY

[4]Department of Epidemiology and Population Sciences, Roswell Park Cancer Institute, Buffalo, NY

[5]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

[6]National Human Genome Research Institute, Bethesda MD

[7]Duke University Health System, Durham NC

[8]University of Washington and Seattle Children's Research Institute, Seattle WA

[9]Boston Children's Hospital, Boston MA

[10]Children's Hospital of Philadelphia, Philadelphia PA

[11]University of Iowa Carver College of Medicine, Iowa, IA

[12]Mount Sinai School of Medicine, New York City, NY

[13]Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY

[14]Department of Medicine, University at Buffalo Jacobs School of Medicine and Biomedical Sciences

## Abstract

Corresponding Author: Brahm H. Segal, MD, Departments of Medicine and Immunology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, 716-845-5721, Brahm.Segal@RoswellPark.org.



This work was presented at the American Society of Clinical Oncology annual meeting in Chicago, IL June 3-7 2016 as a poster discussion session.

**Background—**We evaluated the overall and site-specific incidence of cancer in subjects with primary immunodeficiency diseases (PIDD) enrolled in the United States Immune Deficiency Network (USIDNET) registry compared with age-adjusted cancer incidence in the Surveillance, Epidemiology and End Results Program (SEER) database. We hypothesized that subjects with PIDD would have an increased incidence of cancer due to impaired immune function.

**Methods—**Overall and site-specific cancer incidence rates were evaluated in subjects with PIDD (n = 3,658) enrolled in the USIDNET registry from 2003–2015, and compared with age-adjusted incidence rates in the SEER database.

**Results—**We observed a 1.42-fold excess relative risk of cancer in subjects with PIDD compared to the age-adjusted SEER population ($p<0.001$). Men with PIDD had a 1.91-fold excess relative risk of cancer compared to the age-adjusted male population ($p<0.001$), while women with PIDD had similar overall cancer rates compared to the age-adjusted female population. Of the four most common malignancies in men and women in SEER (lung, colon, breast, and prostate cancers), we found no significant increase in these diagnoses in subjects with PIDD. Significant increases in lymphoma in both men (10-fold increase, $p<0.001$) and women (8.34-fold increase, $p<0.001$) with PIDD were observed.

**Conclusions—**Excess incidence of cancer occurred in subjects with PIDD. An excess of lymphoma in specific PIDD populations principally drove this increased incidence, while no increased risk of the most common solid tumor malignancies was observed. These data point to a restricted role of the immune system in protecting from specific cancers.

### Keywords

primary immunodeficiency disease; cancer; leukemia; lymphoma; CVID; USIDNET

## Introduction

Cancer immunosurveillance is the concept that the immune system has the ability to recognize and eliminate developing tumors in the absence of external therapy [1]. The most compelling epidemiological evidence for immunosurveillance against tumors is the increased risk of cancers among specific immunocompromised patients, including persons with Acquired Immune Deficiency Syndrome [2–5], hematopoietic stem cell transplant recipients [6, 7], and solid organ transplant recipients [8]. In these secondary immunodeficiencies, multiple factors can influence the risk of cancer including acquired or iatrogenic damage to the immune system or genotoxicity from pharmacotherapy [9].

Primary immunodeficiency diseases (PIDD) are a group of more than 300 single gene defects affecting the immune system [10]. PIDD subjects provide the opportunity to dissect the role of immune protection at the level of specific genes and pathways, allowing us to test the concept of cancer immunosurveillance in subjects with compromised immune systems. An association of PIDD and cancers has been noted for many years [7, 11–20] and has been confirmed by single center studies [17], and from data collected in established registries [12, 14–16, 18–20]. The majority of studies were performed decades ago and involved small sample sizes with limited follow up and no comparison groups [12, 15–19]. In an analysis of the Australasian PIDD data registry involving 1132 subjects, Vajdic et al. [20] observed that

only subjects with common variable immunodeficiency (CVID) and ataxia telangiectasia had an increased risk of cancer and that the spectrum of cancers was narrower than expected. The relative risk in relation to an age-matched general population was increased for non-Hodgkin's lymphoma, leukemia, and gastric cancer. In this analysis, 78% of PIDD subjects had antibody deficiencies, while there was comparatively less representation of PIDDs that do not principally involve an antibody deficiency.

The purpose of our study was to evaluate the overall cancer incidence and site-specific cancer incidence in subjects with PIDD in the United States Immune Deficiency Network (USIDNET) database and compare those incidence rates with age-adjusted data from the general U.S. population. The USIDNET is a research program of the Immune Deficiency Foundation (IDF) formed in 2003 to provide support to investigate important questions in PIDD. One of the main tasks of the USIDNET has been the formation of a longitudinal registry of subject data, so that specific questions regarding the natural history and outcomes of these diseases can be collected over time [11]. To our knowledge, this is the largest population of PIDD subjects analyzed for incidence of cancers.

## Methods

### USIDNET Registry

The USIDNET registry collects a number of variables on subjects with PIDD including clinical, laboratory, and outcome data, which together provide a health survey of this rare group of subjects. The registry data are based on entries from physicians or their designees from 39 academic institutions in the United States who have Institutional Review Board (IRB)-approved protocols and 5 medical offices that use the USIDNET IRB consent protocol. In addition, patients may enroll themselves, also using the USIDNET IRB consent; the data entered is abstracted from submitted released medical records. Physicians are encouraged to offer enrollment to all patients with a confirmed PIDD diagnosis and to not restrict enrollment to patients with a specific PIDD… We surveyed the registry to evaluate cancer incidence among PIDD subjects. Data were extracted using Boolean queries for specific data concerning the demographics and PIDD categories of all subjects with malignancy.

### Surveillance, Epidemiology and End Results Program Estimated Cancer Incidence

The Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute is a coordinated system of population-based cancer registries that collects cancer incidence and survival data from 18 geographic areas throughout the United States that together represent approximately 26% of the U.S. population and includes various diverse ethnic groups [21]. We used SEER data to create an age-adjusted cancer incidence for the general population in 5-year increments. We applied SEER incidence data and adjusted for age to estimate the expected incidence of cancer.

### Statistical Analysis

Demographics of the PIDD database were summarized with descriptive statistics. Statistical analysis was performed using frequency distributions. The $[chi]^2$ test was used for

categorical variables and the t-test was used for continuous variables. We generated age-adjusted cancer incidence using the SEER database and compared to the incidence rates in the USIDNET registry using chi square tests.

## Results

### Cancer Incidence in Subjects with PIDD

As of July 1, 2015, 3,844 subjects with a PIDD diagnosis were included in the USIDNET registry. To be considered for analysis, subjects needed their PIDD diagnosis and age of last follow up to be entered into the database by July 1, 2015. Because subjects in the database did not have the age of cancer diagnosis listed, age at last follow up was used as a surrogate for age of cancer diagnosis. We excluded 186 subjects who did not have the age at last follow up, which left 3,658 subjects in the study. The mean age of subjects in the registry was 47 years, and Caucasian was the most common ethnicity (66.6%) (Table 1). CVID was the most common PIDD diagnosis, with 1,285 (35%) entered subjects (Table 2). Subjects with other immune defects included 483 (13%) with chronic granulomatous disease (CGD), 430 (12%) with DiGeorge syndrome, 248 (7%) with severe combined immunodeficiency (SCID), 227 (7%) with Wiskott-Aldrich syndrome (WAS), 141 (4%) with Hyper IgM syndrome, and 844 (23%) with other diagnosis (Table 2). The registry consisted of 40.6% female vs. 59.4% male subjects (the male predominance reflects the presence of X-linked PIDD). The range of age at last follow up of our cohort was <1 year to 89 years of age.

There were 171 separate cancers reported in the cohort of 3,658 PIDD subjects (4.7%). Ninety-one cancers were diagnosed in women and 80 cancers in men. Of the total cancers diagnosed, 82 (48%) were lymphoma, 25 (15%) were skin cancers, 14 (8%) were genitourinary, 14 (8%) were gastrointestinal cancers, 10 (6%) were breast cancers, 9 (5%) were endocrine cancers, 6 (4%) were cancers of the head and neck, 5 (3%) were lung cancers, 2 (1%) were bone cancers, and 4 (2%) were cancers with unspecified origins (Table 3).

Cancers were noted in only some of the PIDD categories (Table 4). As the most numerous of these, there were 119 (70%) cancers in subjects with CVID. Thirteen (9%) cancers were observed in subjects with hypogammaglobulinema and agammaglobulinemia and 8 (4.6%) cancers were observed in subjects with WAS. Despite the relatively high number of CGD patients in the registry (483), none were diagnosed with cancer. The remaining cancers were diagnosed in subjects with various other PIDD diagnoses (Table 4).

### Comparison to Age-adjusted Cancer Incidence

Figure 1 summarizes the number of expected cancers versus actual cancers found in the PIDD subjects based on gender and their reported age at last follow up. We observed a 1.42-fold excess relative risk of cancer in subjects with PIDD compared to the age-adjusted SEER population ($p<0.001$; Table 5). Men with PIDD were diagnosed with any cancer at a 1.91-fold higher rate than the expected age-adjusted incidence of cancer in men based on SEER data (n=80 versus n=41.8; $p<0.001$). In contrast, women in the USIDNET registry were

diagnosed with cancer at a similar rate compared to the age-adjusted population (n=91 versus n=78.8; p=0.169).

The most common cancer diagnoses in the SEER database were: breast (women only), prostate (men only), lung, and colorectal cancers. We found no significant increase in the incidence of these cancers in subjects with PIDD versus the SEER database (Table 5). No male subjects in the USIDNET registry was diagnosed with prostate cancer compared to the expected rate of cancer diagnosis in the age-adjusted population of 7.8 (p=0.005). Ten female subjects in the USIDENT registry were diagnosed with breast cancer compared to the expected rate of breast cancer diagnosis of 24.6 (p=0.003). There was no significant difference in the rates of lung cancer and colon cancer among PIDD patients versus the age-adjusted population.

Cancers with the highest incidence rates among subjects in the registry were lymphoma, skin cancer and leukemia. There was a significantly higher incidence of lymphoma (n=32 men and n =31 women in the registry) compared to the expected lymphoma incidence of 3.2 in men (p<0.001) and 3.7 in women (p<0.001) in the general population (Table 5). There was also a significantly higher incidence of skin cancer (10 men and 15 women in the USIDNET registry) versus the expected rate of skin cancer of n=2.2 in men, (p<0.001) and n=4.5 in women (p<.001). A limitation in comparing skin cancer rates is that in the USIDNET database, skin cancer was a global category, while in the SEER database, melanoma was the only skin cancer that has reportable population-based data on incidence and death. There was a similar incidence of leukemia in subjects in the registry versus the age-adjusted population. The rate of stomach cancer in the USIDNET subjects was similar to the age adjusted population for men (n=2 in the USIDNET registry vs. n=0.6; p=0.075), and slightly increased in women (n=3 in the USIDNET registry vs n=0.8; p=0.014). Finally, an increase in thyroid cancer occurred in men (4.44-fold increase; p=0.001) but not in women with PIDD compared to the respective age-matched population.

## Cancer Incidence in CVID

While patients with CVID constituted 35% of the total number of PIDD patients in the registry, 70% of the cancer diagnoses occurred in CVID patients. Of the 1285 subjects with CVID, 119 (9.3%) were diagnosed with a cancer (Table 6). Men in the CVID subgroup were diagnosed with a significantly higher rate of cancer than the age-adjusted male population (n=48 versus n=27.5; p<0.001), while women with CVID were diagnosed with cancer at a similar rate as the age-adjusted female population (n=71 versus n=64.3, p=NS). Thirty-seven lymphomas were diagnosed in subjects with CVID, making this the most common cancer diagnosis. Skin cancer (n=23 cases) and breast cancer (n=8 cases) were the next most common cancer diagnoses in the CVID population.

Of the four most common malignancies in men and women in SEER (lung, colon, breast, and prostate cancers), there was no significant increase of these cancers in CVID patients versus the age-adjusted population. No patient with CVID had a diagnosis of prostate cancer compared to the expected rate of prostate cancer diagnosis of n=6.3 (p=0.012). Eight women with CVID had a diagnosis of breast cancer versus the expected incidence rate of 21

(p=0.004). Similar rates of lung and colon cancer were observed in both men and women with CVID versus the expected age-adjusted rates.

The cancers with the highest incidence rates in the subjects with CVID were lymphoma and skin cancer (Table 6). There was a significantly higher incidence of lymphoma (n=16 in men and n=21 in women with CVID) compared to the expected lymphoma incidence of 1.9 in men (p<0.001) and 3 in women (p<.001). There was also a significantly higher incidence of skin cancer (n=9 men and n=14 women with CVID) versus the expected rate of skin cancer (n=1.6 men and n=3.8 women) in the SEER database (p<0.001). Gastric cancer was also more common than expected in the subjects with CVID (n=2 in men and n=3 in women with CVID vs. expected rates of n=0.4 in men (p=0.011) and n=0.7 in women (p=.005)). The incidence of thyroid cancer was higher in men (6.67-fold; p<0.001) but not in women with CVID compared to the age-matched population.

## Discussion

The USIDNET registry is supported by the NIH to enhance the understanding and care of subjects with PIDD. For many years, attempts have been made to evaluate the excess number of malignancy in these subjects. As the USIDNET registry is populated with data on these rare diseases, we undertook an examination of the current registry to gain an up-to-date survey of cancers in PIDD. We observed a 1.42-fold excess relative risk of cancer in subjects with PIDD compared to the age-adjusted population (p<0.001). The greatest increase in cancer incidence in PIDD was observed in lymphoma both in men (10-fold excess relative risk p<0.001) and women (8-fold excess relative risk p<0.001). This excessive lymphoma risk was largely driven by subjects with CVID, the most common PIDD in the registry. In males with PIDD, an increase in skin cancer and thyroid cancer was observed relative to age-matched males in the SEER database, while in females with PIDD, an increase in skin cancer and stomach cancer was observed. Of the most common cancers in the general population (lung, colon, prostate, and breast), no increased incidence was observed in PIDD subjects. These data point to a restricted role of the immune system in protecting from specific cancers.

Non-Hodgkin's lymphoma is the predominant malignancy in a number of PIDD, including CVID, ataxia-telangiectasia, WAS and severe combined immunodeficiency [16]. Since 70% of subjects in the PIDD registry with a cancer diagnosis had CVID, we performed a sub-group analysis of these subjects. Consistent with other studies [14, 18, 22–25], we observed an increased risk of non-Hodgkin lymphoma, gastric cancer, and skin cancer in CVID subjects. In a study of 473 patients with CVID followed over 40 years, lymphoma was diagnosed in 8.2% and other cancers in 7.0% of patients; lymphoma was one of the causes for increased mortality in CVID compared to age- and sex-matched population controls [26]. In an analysis of the Australasian Society of Clinical Immunology and Allergy PIDD Registry of 1132 subjects from 79 centers in Australia, Vajdic et al. [20] reported that only subjects with CVID and ataxia telangiectasia had an increased risk of cancer. A 1.6-fold excess relative risk of cancer was observed for all PIDD combined, and the relative risk in relation to an age-matched general population increased for non-Hodgkin lymphoma, leukemia, and gastric cancer [20]. The increased incidence of gastric cancer in CVID has

been attributed to increased achlorhydria [27] and to *Helicobacter pylori* infection [28]. However, more recently gastric cancer appears rarer in CVID, possibly due to the more common use of antibiotics that would eliminate *H pylori*. (26)

Data from national surveys suggest a US population prevalence of PIDD of 1 in 1200 persons [29]. National surveys of patients with PIDD diagnoses have been performed by the Immune Deficiency Foundation in 1993, 2002 and 2007 to determine the diagnoses rates for different subclasses of PIDD. CVID was the most common PIDD in all three surveys, and made up 63.1% of the PIDD registry in the most recent report [30]. The 2007 survey included 13 possible PIDD diagnoses while the USIDNET registry includes a much broader range of PIDD. Also our cohort reflects a predominantly Caucasian population and minorities such as African Americans, Asians and Hispanics are underrepresented; this observation may reflect underdiagnoses of PIDD among these minorities [31].

PIDD caused by defects in DNA repair are generally associated with other features, such as increased cellular sensitivity to radiation, developmental disorders, and cancers. Ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome, and Nijmegen breakage syndrome have DNA repair defects associated with increased radiation sensitivity [32]. The cancer risk varies among these PIDDs, but, in general, they are at increased risk for lymphoma, leukemia and other cancers [32] because of accumulated DNA damage. In CVID, the increased risk for lymphoma is likely multifactorial, including impaired control of Epstein-Barr virus (EBV)-driven lymphoproliferation and genetic instability of lymphocytes due to sustained activation and proliferation during chronic infections [33–35].

Even with a database as large as USIDNET, some rare PIDD were insufficiently represented or not included. For example, only 3 patients in the registry had GATA2 deficiency, a disorder characterized by immunodeficiency (monocytopenia, B cell, NK cell and $CD4^+$ T cell lymphopenia), neurologic manifestations, pulmonary disease, and susceptibility to myelodysplastic syndrome, acute myeloid leukemia, and solid tumor malignancies principally related to human papilloma virus (HPV)-associated dysplasias and squamous cell cancers [36].

The major strengths of the USIDNET database are its large size, data collection from multiple institutions, prospective reporting, and the broad range of represented PIDD. This study was the largest of its kind to evaluate tumor site-specific cancer incidence in subjects with PIDD and compare those incidences to age-adjusted populations from the SEER database. While registry databases allow collection of rare diseases, there are limitations in that reporting of cases is voluntary, and the diagnoses reported were not independently verified. In addition, the bias of missing data and under-reporting in registries can be substantial. As an example, in the PIDD registry there were no men with the diagnosis of prostate cancer and significantly less women with breast and colon cancer than the expected incidence. This unexpected finding is likely the result of under-reporting of malignancies within the registry. However, if underreporting applied to the entire analysis, the finding of an increased incidence of lymphoma, skin, and gastric cancers may be larger than reported. In addition, the lack of a detailed description of cancer types in the USIDNET database may have led to incorrect classification of cancers and incorrect comparison with age-adjusted

populations from the SEER database. When the age of diagnosis of cancer was not included in the registry, we used age at last follow up as a surrogate for the year of cancer diagnosis, which can falsely increase the age of cancer diagnosis. Finally, our analysis was restricted to incident cancer and was not designed to address the separate question regarding how immunodeficiencies affect cancer prognosis.

Epidemiologic studies in subjects with various immunodeficiencies point to a restricted role of our immune system in protecting against tumors. For example, acquired immune deficiency syndrome (AIDS)-associated malignancies such as Kaposi's sarcoma (caused by human herpesvirus-8), lymphomas (induced by EBV), and cervical and anal cancers (caused by HPV) largely represent defective viral immunosurveillance that predisposes to these cancers. The current study, as well as data from earlier registries, point to two major factors driving increased cancer risk among specific subjects with PIDD: defective DNA repair and failure to provide immune surveillance against chronic viral infections (e.g., EBV and HPV) that cause cancer. However, we did not observe an increased incidence in PIDD patients of the most common solid tumor malignancies seen in the general population (lung, breast, colon, and prostate), an observation that supports a restricted role for immunosurveillance in preventing specific cancers while being less important for others.

## Acknowledgments

**Funding**

This work was supported by Roswell Park Cancer Institute National Cancer Institute (NCI) Cancer Center Support Grant (P30CA016056, 5T32CA108456 [PCM], NLM K01LM012100 [KE], T32CA085183 [KLS], R01CA140622 [SIA], P50 CA159981 [KO], R01CA188900 [BHS and KBM]); and the United State Immunodeficiency Network and Immune Deficiency Foundation (U24AI086037-06).

## Abbreviations

| | |
|---|---|
| **PIDD** | primary immunodeficiency diseases |
| **USIDNET** | United States Immune Deficiency Network |
| **SEER** | Surveillance, Epidemiology and End Results Program |
| **CVID** | common variable immunodeficiency |
| **IRB** | Institutional Review Board |
| **CGD** | chronic granulomatous disease |
| **SCID** | severe combined immunodeficiency |
| **WAS** | Wiskott-Aldrich syndrome |
| **EBV** | Epstein-Barr virus |
| **HPV** | human papilloma virus |
| **AIDS** | Acquired Immune Deficiency Syndrome |

## References


1. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015; 348:69–74. [PubMed: 25838375]
2. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med. 2008; 148:728–736. [PubMed: 18490686]
3. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. Ann Intern Med. 2010; 153:452–460. [PubMed: 20921544]
4. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011; 103:753–762. [PubMed: 21483021]
5. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. Arch Intern Med. 2010; 170:1337–1345. [PubMed: 20696958]
6. Majhail NS. Secondary cancers following allogeneic haematopoietic cell transplantation in adults. Br J Haematol. 2011; 154:301–310. [PubMed: 21615719]
7. Majhail NS, Brazauskas R, Rizzo JD, Sobecks RM, Wang Z, Horowitz MM, et al. Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning. Blood. 2011; 117:316–322. [PubMed: 20926773]
8. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011; 306:1891–1901. [PubMed: 22045767]
9. Olivero OA. Mechanisms of genotoxicity of nucleoside reverse transcriptase inhibitors. Environmental and Molecular Mutagenesis. 2007; 48:215–223. [PubMed: 16395695]
10. Al-Herz W, Bousfiha A, Casanova J-L, Chatila T, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Proceedings of ICI Milan. 2013; 2014:164.
11. Sullivan KE, Puck JM, Notarangelo LD, Fuleihan R, Caulder T, Wang C, et al. USIDNET: a strategy to build a community of clinical immunologists. J Clin Immunol. 2014; 34:428–435. [PubMed: 24711005]
12. Filipovich AH, Heinitz KJ, Robison LL, Frizzera G. The Immunodeficiency Cancer Registry. A research resource. Am J Pediatr Hematol Oncol. 1987; 9:183–184. [PubMed: 3592131]
13. Filipovich AH, Mathur A, Kamat D, Shapiro RS. Primary immunodeficiencies: genetic risk factors for lymphoma. Cancer Res. 1992; 52:5465s–467s. [PubMed: 1327508]
14. Gathmann B, Mahlaoui N, Ceredih, Gerard L, Oksenhendler E, Warnatz K, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014; 134:116–126. [PubMed: 24582312]
15. Hayward AR, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, et al. Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. J Immunol. 1997; 158:977–983. [PubMed: 8993019]
16. Kersey JH, Shapiro RS, Filipovich AH. Relationship of immunodeficiency to lymphoid malignancy. Pediatr Infect Dis J. 1988; 7:S10–S12. [PubMed: 2840629]
17. Kersey JH, Spector BD, Good RA. Cancer in children with primary immunodeficiency diseases. J Pediatr. 1974; 84:263–264. [PubMed: 4359292]
18. Mellemkjaer L, Hammarstrom L, Andersen V, Yuen J, Heilmann C, Barington T, et al. Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. Clin Exp Immunol. 2002; 130:495–500. [PubMed: 12452841]
19. Robison LL, Stoker V, Frizzera G, Heinitz K, Meadows AT, Filipovich AH. Hodgkin's disease in pediatric patients with naturally occurring immunodeficiency. Am J Pediatr Hematol Oncol. 1987; 9:189–192. [PubMed: 3592132]

20. Vajdic CM, Mao L, van Leeuwen MT, Kirkpatrick P, Grulich AE, Riminton S. Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? Blood. 2010; 116:1228–1234. [PubMed: 20466855]
21. National Cancer Institute SEER… as a Research Resource. 2010. Available from http://seer.cancer.gov/about/factsheets/SEER_Research_Brochure.pdf
22. Cunningham-Rundles C, Cooper DL, Duffy TP, Strauchen J. Lymphomas of mucosal-associated lymphoid tissue in common variable immunodeficiency. American Journal of Hematology. 2002; 69:171–178. [PubMed: 11891803]
23. Filipovich AH, Mathur A, Kamat D, Kersey JH, Shapiro RS. Lymphoproliferative disorders and other tumors complicating immunodeficiencies. Immunodeficiency. 1994; 5:91–112. [PubMed: 8032367]
24. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-Term Follow-Up and Outcome of a Large Cohort of Patients with Common Variable Immunodeficiency. J Clin Immunol. 2007; 27:308–316. [PubMed: 17510807]
25. Jonkman-Berk BM, van den Berg JM, ten Berge IJM, Bredius RGM, Driessen GJ, Dalm VASH, et al. Primary immunodeficiencies in the Netherlands: National patient data demonstrate the increased risk of malignancy. Clinical Immunology. 2015; 156:154–162. [PubMed: 25451158]
26. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012; 119:1650–1657. [PubMed: 22180439]
27. Kinlen LJ, Webster AD, Bird AG, Haile R, Peto J, Soothill JF, et al. Prospective study of cancer in patients with hypogammaglobulinaemia. Lancet. 1985; 1:263–266. [PubMed: 2857327]
28. Dhalla F, da Silva SP, Lucas M, Travis S, Chapel H. Review of gastric cancer risk factors in patients with common variable immunodeficiency disorders, resulting in a proposal for a surveillance programme. Clin Exp Immunol. 2011; 165:1–7. [PubMed: 21470209]
29. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007; 27:497–502. [PubMed: 17577648]
30. foundation Id. PRIMARY IMMUNODEFICIENCY DISEASES IN AMERICA: 2007. 2009
31. Foundation ID. PRIMARY IMMUNE DEFICIENCY DISEASES IN AMERICA: 2002. 2002
32. de Miranda NF, Bjorkman A, Pan-Hammarstrom Q. DNA repair: the link between primary immunodeficiency and cancer. Ann N Y Acad Sci. 2011; 1246:50–63. [PubMed: 22236430]
33. Gangemi S, Allegra A, Musolino C. Lymphoproliferative disease and cancer among patients with common variable immunodeficiency. Leukemia Research. 2015; 39:389–396. [PubMed: 25711943]
34. Musolino C, Allegra A, Minciullo PL, Gangemi S. Allergy and risk of hematologic malignancies: Associations and mechanisms. Leukemia Research. 2014; 38:1137–1144. [PubMed: 25171954]
35. Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. Blood. 2006; 107:3034–3044. [PubMed: 16397126]
36. Spinner MA, Sanchez LA, Hsu AP, Shaw PA, Zerbe CS, Calvo KR, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. Blood. 2014; 123:809–821. [PubMed: 24227816]
37. Population estimates. Jul 1.2016 (V2016).

**Key Messages**

These results point to a restricted role of the immune system in protecting from specific cancers and underscore the need for evidence-based approaches for early detection of these cancers in high-risk patients with primary immunodeficiency diseases.

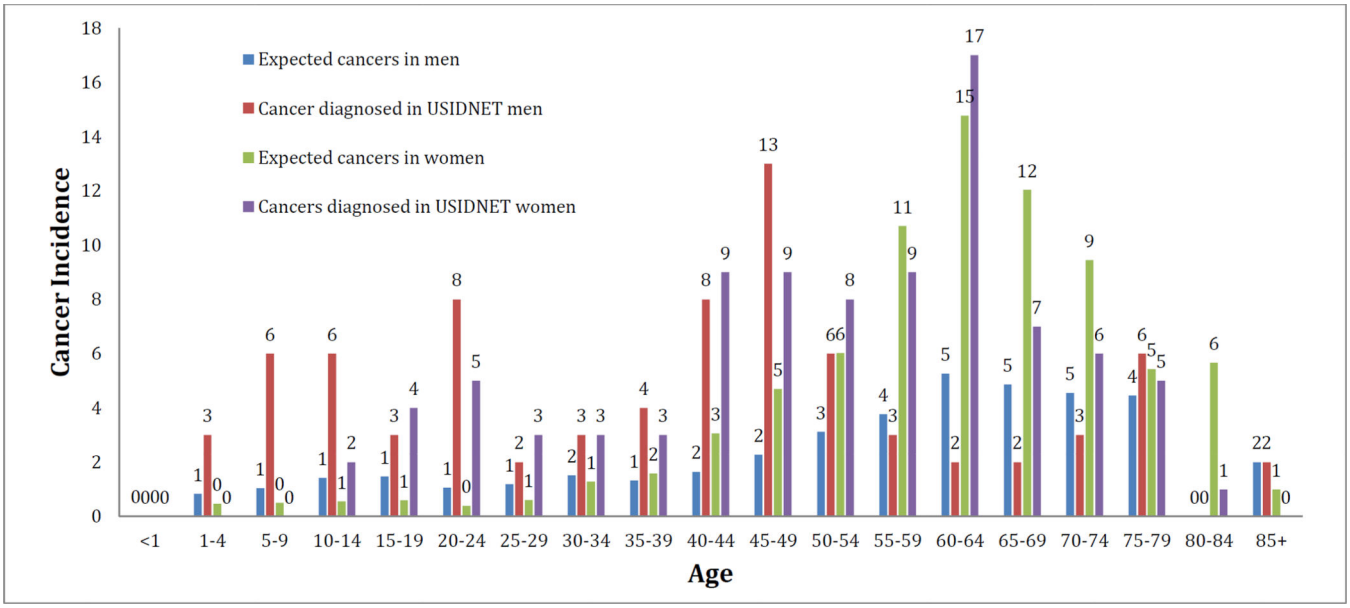



**Figure 1. Actual versus expected cancers diagnosed in men and women in the USIDNET registry**

Cancer incidence in both men and women in the USIDNET registry as well as age adjusted cancer incidence obtained from the SEER database in men and women. We used SEER data to create an age-adjusted cancer incidence for the general population in 5-year increments. We applied SEER incidence data and adjusted for age to estimate the expected incidence of cancer.

*values that appear above the bars represent values rounded to the closest whole number

## Table 1

### Demographics of USIDNET subjects

Demographics of the subjects in the USIDNET registry including, age, race, ethnicity, geographic location, and cancer rates among the different reported races.

| **Demographic** | **No of Patients** | **(%) of USIDNET Cohort** | **(%) of US Population as a whole** * |
|---|---|---|---|
| Average age: 47, Median Age: 29, Age range : <1 to 89 years | | | Median age of the US population : 37.8 |
| **Gender** | | | |
| Male | 2174 | 59.4% | 49.2% |
| Female | 1484 | 40.6% | 50.8% |
| **Race** | | | |
| Caucasian | 2435 | 66.6% | 77.1% |
| African American | 212 | 5.8% | 13.3% |
| Native American | 34 | 0.9% | 1.2% |
| Asian | 62 | 1.7% | 5.6% |
| Multi-racial | 26 | 0.7% | 2.6% |
| None Selected | 889 | 24.3% | N/A |
| **Do you Identify as Hispanic/Latino?** | | | |
| Yes | 280 | 7.7% | 17.6% |
| No | 1309 | 35.8% | N/A |
| Not selected | 2069 | 56.6% | N/A |
| **Cancer and Race** | | **(%) of Cancer Diagnoses in the USIDNET database** | **(%) of Cancer Diagnoses in the US (SEER)** ** |
| Caucasian | 140 | 81.9% | 23.4% |
| African American | 7 | 4.1% | 24.0% |
| Asian | 1 | 0.6% | 16.0% |
| None Selected / Other | 23 | 13.5% | 36.5% |

* [37]

** [21]

## Table 2
### Distribution of primary immunodeficiency in the USIDNET registry

Incidence rates of the different primary immunodeficiency diseases reported in the USIDNET registry. The diagnoses categories represent the classification system published in “Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency” [10].

| PIDD type or subtype | Men | Women | Totals |
|---|---|---|---|
| Common variable immunodeficiency disorders with unknown genetic basis | 556 | 729 | 1285 |
| **Severe combined immunodeficiency** | | | |
| Common gamma-chain deficiencies | 29 | 1 | 30 |
| JAK3 | 4 | 0 | 4 |
| IL7R alpha deficiency | 4 | 4 | 8 |
| CD45 deficiency | 1 | 0 | 1 |
| CD3δ | 1 | 1 | 2 |
| RAG 1 deficiency | 1 | 4 | 5 |
| RAG 2 deficiency | 2 | 0 | 2 |
| DCLRE1C (Artemis) deficiency | 1 | 0 | 1 |
| Reticular dysgenesis, AK2 deficiency | 1 | 0 | 1 |
| Adenosine deaminase (ADA) deficiency | 29 | 24 | 53 |
| SCID unknown type | 88 | 53 | 141 |
| **Other combined immunodeficiencies** | | | |
| CD8 deficiency | 1 | 0 | 1 |
| ZAP70 deficiency | 0 | 1 | 1 |
| MHC class II deficiency | 0 | 1 | 1 |
| Activated PI3K-δ | 0 | 1 | 1 |
| Omenn Syndrome | 4 | 4 | 8 |
| Wiskott–Aldrich Syndrome (WAS) | 225 | 2 | 227 |
| Ataxia telangiectasia | 14 | 7 | 21 |
| Immunodeficiency with centromeric instability and facial anomalies (ICF) | 0 | 1 | 1 |
| DiGeorge anomaly | 85 | 345 | 430 |
| CHARGE syndrome | 0 | 1 | 1 |
| Cartilage hair hypoplasia | 2 | 4 | 6 |
| Hyper IgE syndrome AD STAT3 | 25 | 28 | 53 |
| DOCK 8 | 3 | 3 | 6 |
| Comel– Netherton Syndrome | 1 | 1 | 2 |
| IKAROS deficiency | 1 | 0 | 1 |
| Combined immune deficiency of unknown or unlisted genetic cause | 11 | 19 | 30 |
| **Predominantly antibody deficiencies** | | | |
| Agammaglobulinemia of unknown cause or unlisted gene defect | 9 | 5 | 14 |
| Hypogammaglobulinemia of unknown cause or unlisted gene defect | 44 | 57 | 101 |

| PIDD type or subtype | Men | Women | Totals |
|---|---|---|---|
| BTK deficiency | 378 | 1 | 379 |
| Igα deficiency | 6 | 6 | 12 |
| PI3 kinase deficiency | 1 | 0 | 1 |
| Myelodysplasia with hypogammaglobulinemia | 0 | 1 | 1 |
| Thymoma with immunodeficiency | 1 | 0 | 1 |
| TACI deficiency | 2 | 3 | 5 |
| Warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome | 0 | 1 | 1 |
| Hyper IgM due to uncertain or unlisted cause | 104 | 12 | 116 |
| CD40L deficiency | 21 | 0 | 21 |
| CD40 deficiency | 1 | 0 | 1 |
| AID deficiency | 3 | 0 | 3 |
| Isolated IgG subclass deficiency | 3 | 6 | 9 |
| Selective IgA deficiency | 14 | 14 | 28 |
| Specific antibody deficiency with normal Ig concentrations and normal numbers of B cells | 13 | 28 | 41 |
| Transient hypogammaglobulinemia of infancy with normal numbers of B cells | 4 | 4 | 8 |
| **Diseases of immune dysregulation** | | | |
| UNC13D/Munc13-4 deficiency (FHL3) | 1 | 0 | 1 |
| XIAP deficiency (XLP2) | 1 | 0 | 1 |
| IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked | 4 | 0 | 4 |
| APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy | 6 | 6 | 12 |
| ALPS with unknown or unlisted genetic cause | 3 | 0 | 3 |
| ALPS–FAS | 2 | 0 | 2 |
| ALPS– caspase 8a | 0 | 1 | 1 |
| **Congenital defects of phagocyte number function or both** | | | |
| Neutropenia, due to uncertain or unlisted cause | 1 | 0 | 1 |
| Leukocyte adhesion deficiency with unknown genetic cause | 0 | 1 | 1 |
| Leukocyte adhesion deficiency type 1 (LAD1) | 3 | 2 | 5 |
| CGD, uncertain genetic cause | 87 | 70 | 157 |
| X-linked chronic granulomatous disease (CGD) | 323 | 3 | 326 |
| Autosomal recessive CGD – p22 phox deficiency | 3 | 0 | 3 |
| Autosomal recessive CGD – p47 phox deficiency | 1 | 1 | 2 |
| Autosomal recessive CGD – p67 phox deficiency | 1 | 0 | 1 |
| IFN-γ receptor 1 deficiency | 3 | 0 | 3 |
| STAT1 deficiency (AD form) | 0 | 1 | 1 |
| GATA2 deficiency (Mono MAC syndrome) | 1 | 2 | 3 |
| **Defects in innate immunity** | | | |
| Other defects in innate immunity | 3 | 4 | 7 |
| Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) | 3 | 0 | 3 |
| EDA-ID, X-linked (NEMO deficiency) | 10 | 1 | 11 |

| PIDD type or subtype | Men | Women | Totals |
|---|---|---|---|
| EDA-ID, autosomal dominant | 2 | 0 | 2 |
| IRAK-4 deficiency | 1 | 0 | 1 |
| Chronic mucocutaneous candidiasis of uncertain or unlisted cause | 0 | 1 | 1 |
| STAT1 gain-of-function | 0 | 1 | 1 |
| CD16 deficiency | 1 | 1 | 2 |
| **Autoinflammatory disorders** | | | |
| Autoinflammatory syndrome due to uncertain or unlisted cause | 2 | 0 | 2 |
| Mevalonate kinase deficiency (hyper IgD syndrome) | 0 | 1 | 1 |
| TNF receptor-associated periodic syndrome (TRAPS) | 0 | 1 | 1 |
| **Complement deficiencies** | | | |
| C2 deficiency | 8 | 4 | 12 |
| C3 deficiency | 1 | 0 | 1 |
| C1 inhibitor deficiency | 0 | 3 | 3 |
| Complement deficiency due to uncertain or unlisted cause | 5 | 1 | 6 |
| **Immunodeficiency of unknown or unlisted cause** | | | |
| Immunodeficiency of unknown cause | 4 | 6 | 10 |
| Immune dysregulation with autoimmunity due to uncertain cause | 1 | 1 | 2 |
| Totals | 2174 | 1484 | 3658 |

## Table 3
## Cancer Diagnosis in the USIDNET registry

Incidence rates of cancer site-specific diagnoses made in the USIDNET registry

| Cancers Type | Men | Women | Totals |
|---|---|---|---|
| **Lymphoid cancer** | **41** | **41** | **82** |
| Lymphoma | 32 | 31 | 63 |
| Hematologic tumor NOS * | 3 | 6 | 9 |
| Leukemia | 5 | 3 | 8 |
| Thymus cancer | 0 | 1 | 1 |
| Malignant Histiocytosis | 1 | 0 | 1 |
| **Genitourinary cancer** | **7** | **7** | **14** |
| Bladder cancer | 3 | 0 | 3 |
| Testicular cancer | 3 | N/A | 3 |
| Cervical cancer | N/A | 2 | 2 |
| Renal cancer | 1 | 0 | 1 |
| Uterine cancer | N/A | 2 | 2 |
| Ovarian cancer | N/A | 3 | 3 |
| **Gastrointestinal cancer** | **9** | **5** | **14** |
| Stomach / duodenal cancer | 2 | 3 | 5 |
| Colon cancer | 3 | 1 | 4 |
| Liver cancer | 3 | 0 | 3 |
| Appendiceal cancer | 0 | 1 | 1 |
| Pancreatic cancer | 1 | 0 | 1 |
| **Endocrine cancer** | **4** | **5** | **9** |
| Thyroid cancer | 4 | 3 | 7 |
| Endocrine cancer | 0 | 2 | 2 |
| **ENT cancer** | **5** | **1** | **6** |
| Laryngeal cancer | 2 | 1 | 3 |
| Mouth cancer | 1 | 0 | 1 |
| Eye cancer | 2 | 0 | 2 |
| **Skin (NOS*)** | **10** | **15** | **25** |
| **Lung (NOS*)** | **2** | **3** | **5** |
| **Bone Cancer (NOS*)** | **1** | **1** | **2** |
| **Breast Cancer (NOS*)** | **0** | **10** | **10** |
| **Unspecified Primary** | **1** | **3** | **4** |
| **Totals** | **80** | **91** | **171** |

* Not Otherwise Specified

## Table 4
### Immune Defects and Cancer in the USIDNET registry

Incidence rates of the cancer diagnoses by PIDD type and subtype. NOS represents “Not otherwise specified”

| PIDD Type or Subtype | Cancer in Men | Cancer in Women | Total Number of cancers |
|---|---|---|---|
| CVID | 48 | 71 | 119 |
| **Severe combined immunodeficiency** | | | |
| Common gamma chain deficiency | 2 | 0 | 2 |
| SCID unknown type | 1 | 0 | 1 |
| Adenosine deaminase Deficiency | 1 | 0 | 1 |
| **Other combined immunodeficiencies** | | | |
| Wiskott–Aldrich Syndrome (WAS) | 8 | 0 | 8 |
| Ataxia telangiectasia | 2 | 1 | 3 |
| Hyper IgE AD STAT3 | 1 | 2 | 3 |
| Cartilage hair hypoplasia | 0 | 2 | 2 |
| DOCK8 | 0 | 1 | 1 |
| Activated PI3K-δ | 0 | 1 | 1 |
| Combined immune deficiency with unknown or unlisted genetic cause | 0 | 1 | 1 |
| **Predominantly antibody deficiencies** | | | |
| BTK deficiency | 4 | 0 | 4 |
| Hypogammaglobulinemia | 4 | 5 | 9 |
| Specific antibody deficiency with normal Ig concentrations and normal number of B cells | 0 | 3 | 3 |
| Isolated IgG subclass deficiency | 0 | 2 | 2 |
| CD40 deficiency | 1 | 0 | 1 |
| CD40L deficiency | 1 | 0 | 1 |
| Hyper IgM due to uncertain or unlisted cause | 4 | 1 | 5 |
| Selective IgA deficiency | 0 | 1 | 1 |
| Immunodeficiency of unknown cause | 3 | 0 | 3 |
| Total cancers | 80 | 91 | 171 |

**Table 5**

**Cancer Incidence in the USIDNET registry compared to age-adjusted population**

Comparison of incidence of different cancer site-specific diagnoses made within the registry subjects with the age-adjusted incidence

| USIDNET Registry Subjects | Cancer Type | Number of Cancers Diagnosed | Expected Number of Cancer Diagnosis based on age-adjusted population | p-value | Fold-change in PIDD Cancer Incidence from Expected |
|---|---|---|---|---|---|
| **Men and women combined (n=3658)** | All cancers | 171 | 120.6 | <0.001 | 1.42 |
| **Men (n=2174)** | All cancers | 80 | 41.8 | <0.001 | 1.91 |
| | **Top 3 US cancers** | | | | |
| | Prostate | 0 | 7.8 | 0.005 | N/A |
| | Lung | 2 | 3.2 | 0.502 | 0.62 |
| | Colon | 3 | 3.0 | 1 | 1 |
| | **Cancer Diagnosis Chosen for Comparison to Age-adjusted population** | | | | |
| | Lymphoma | 32 | 3.2 | <0.001 | 10 |
| | Skin | 10 | 2.2 | <0.001 | 4.55 |
| | Leukemia | 5 | 3.5 | 0.422 | 1.43 |
| | Thyroid | 4 | 0.9 | 0.001 | 4.44 |
| | Stomach | 2 | 0.6 | 0.075 | 3.33 |
| | Bladder | 3 | 1.4 | 0.176 | 2.14 |
| | Testicular | 3 | 2.0 | 0.488 | 1.50 |
| | Remaining Cancers | 16 | | | |
| **Women (n=1484)** | All Cancers | 91 | 78.8 | 0.169 | 1.15 |
| | **Top 3 US cancers** | | | | |
| | Breast | 10 | 24.6 | 0.003 | 0.41 |
| | Lung | 3 | 6.3 | 0.189 | 0.48 |
| | Colon | 1 | 5.3 | 0.062 | 0.19 |
| | **Cancer Diagnosis Chosen for Comparison to Age-adjusted population** | | | | |
| | Lymphoma | 31 | 3.7 | <0.001 | 8.34 |
| | Skin | 15 | 4.5 | <0.001 | 3.33 |
| | Leukemia | 3 | 3 | 1 | 1 |

| USIDNET Registry Subjects | Cancer Type | Number of Cancers Diagnosed | Expected Number of Cancer Diagnosis based on age-adjusted population | p-value | Fold-change in PIDD Cancer Incidence from Expected |
|---|---|---|---|---|---|
| | Thyroid | 3 | 6.1 | 0.209 | 0.49 |
| | Stomach | 3 | 0.8 | 0.014 | 3.75 |
| | Ovarian | 3 | 2.4 | 0.699 | 1.25 |
| | Uterine | 2 | 4.9 | 0.190 | 0.41 |
| | Cervix | 2 | 2.2 | 0.893 | 0.91 |
| | Remaining Cancers | 15 | | | |

## Table 6

### Cancer Incidence in Patients with CVID Compared to Age-adjusted Population

Comparison of incidence of different cancer site-specific diagnoses made within the CVID cohort with the age-adjusted incidence

| CVID Subjects | Cancer Type | Number of Cancers Diagnosed | Expected Number of Cancer Diagnosis based on age-adjusted population | P Value | Fold-change in PIDD Cancer Incidence from Expected |
|---|---|---|---|---|---|
| **Men and women combined (n=1285)** | All cancers | 119 | 91.8 | 0.004 | 1.29 |
| **Men (n=556)** | All cancers | 48 | 27.5 | <0.001 | 1.75 |
| | **Top 3 US cancers** | | | | |
| | Prostate | 0 | 6.3 | 0.012 | 0 |
| | Lung | 2 | 2.5 | 0.752 | 0.80 |
| | Colon | 2 | 2.3 | 0.843 | 0.87 |
| | **Cancer Diagnosis Chosen for Comparison to Age-adjusted population** | | | | |
| | Lymphoma | 16 | 1.9 | <0.001 | 8.42 |
| | Skin | 9 | 1.6 | <0.001 | 5.63 |
| | Leukemia | 3 | 1.5 | .221 | 2 |
| | Thyroid | 4 | 0.6 | <0.001 | 6.67 |
| | Stomach | 2 | 0.4 | .011 | 5 |
| | Bladder | 3 | 1.1 | .070 | 2.73 |
| | Testicular | 1 | 1.1 | .924 | .91 |
| | Remaining Cancers | 6 | | | |
| **Women (n=729)** | All Cancers | 71 | 64.3 | 0.403 | 1.10 |
| | **Top 3 US cancers** | | | | |
| | Breast | 8 | 21 | 0.004 | 0.38 |
| | Lung | 2 | 5.4 | 0.143 | 0.37 |
| | Colon | 1 | 4.6 | 0.093 | 0.22 |
| | **Cancer Diagnosis Chosen for Comparison to Age-adjusted population** | | | | |
| | Lymphoma | 21 | 3.0 | <0.001 | 7 |
| | Skin | 14 | 3.8 | <0.001 | 3.68 |
| | Leukemia | 3 | 2.1 | .535 | 1.43 |

| CVID Subjects | Cancer Type | Number of Cancers Diagnosed | Expected Number of Cancer Diagnosis based on age-adjusted population | P Value | Fold-change in PIDD Cancer Incidence from Expected |
|---|---|---|---|---|---|
| | Thyroid | 1 | 5.0 | .073 | .2 |
| | Stomach | 3 | .7 | .005 | 4.29 |
| | Ovarian | 2 | 2.0 | 1 | 1 |
| | Uterine | 2 | 4.2 | .283 | .476 |
| | Cervix | 2 | 1.8 | .881 | 1.11 |
| | Remaining Cancers | 12 | | | |

frontiers in Immunology

REVIEW
published: 12 February 2019
doi: 10.3389/fimmu.2018.03136

# Primary Immunodeficiency and Cancer Predisposition Revisited: Embedding Two Closely Related Concepts Into an Integrative Conceptual Framework

*Oskar A. Haas**

*Department of Clinical Genetics, Children's Cancer Research Institute, Vienna, Austria*

Common understanding suggests that the normal function of a "healthy" immune system safe-guards and protects against the development of malignancies, whereas a genetically impaired one might increase the likelihood of their manifestation. This view is primarily based on and apparently supported by an increased incidence of such diseases in patients with specific forms of immunodeficiencies that are caused by high penetrant gene defects. As I will review and discuss herein, such constellations merely represent the tip of an iceberg. The overall situation is by far more varied and complex, especially if one takes into account the growing difficulties to define what actually constitutes an immunodeficiency and what defines a cancer predisposition. The enormous advances in genome sequencing, in bioinformatic analyses and in the functional *in vitro* and *in vivo* assessment of novel findings together with the availability of large databases provide us with a wealth of information that steadily increases the number of sequence variants that concur with clinically more or less recognizable immunological problems and their consequences. Since many of the newly identified hard-core defects are exceedingly rare, their tumor predisposing effect is difficult to ascertain. The analyses of large data sets, on the other hand, continuously supply us with low penetrant variants that, at least in statistical terms, are clearly tumor predisposing, although their specific relevance for the respective carriers still needs to be carefully assessed on an individual basis. Finally, defects and variants that affect the same gene families and pathways in both a constitutional and somatic setting underscore the fact that immunodeficiencies and cancer predisposition can be viewed as two closely related errors of development. Depending on the particular genetic and/or environmental context as well as the respective stage of development, the same changes can have either a neutral, predisposing and, in some instances, even a protective effect. To understand the interaction between the immune system, be it "normal" or "deficient" and tumor predisposition and development on a systemic level, one therefore needs to focus on the structure and dynamic functional organization of the entire immune system rather than on its isolated individual components alone.

**Keywords: primary immunodeficiency, cancer predisposition, down syndrome, childhood leukemia, immune editing, immune activation, inflammation, microbiome**

OPEN ACCESS

***Edited by:***
*Markus G. Seidel,*
*Medical University of Graz, Austria*

***Reviewed by:***
*Irun R. Cohen,*
*Weizmann Institute of Science, Israel*
*Karl Welte,*
*University of Tubingen, Germany*

***Correspondence:**
*Oskar A. Haas*
*oskar.haas@ccri.at*

***Specialty section:***
*This article was submitted to Primary Immunodeficiencies, a section of the journal Frontiers in Immunology*

***Received:*** *31 October 2018*
***Accepted:*** *19 December 2018*
***Published:*** *12 February 2019*

***Citation:***
*Haas OA (2019) Primary Immunodeficiency and Cancer Predisposition Revisited: Embedding Two Closely Related Concepts Into an Integrative Conceptual Framework. Front. Immunol. 9:3136. doi: 10.3389/fimmu.2018.03136*

## INTRODUCTION

The neoplastic transformation of cells and their subsequent successful clonal expansion and progression into clinically apparent hematologic malignancies and solid tumors is a complex multifactorial process. On the one hand, this process requires changes in the respective cells' genetic program that modify their metabolism and performance and consequently alter their normal differentiation, replicative, and survival capacity. On the other hand, these cells have to learn to adapt themselves and to exploit external deterministic physiological stimuli as well as to flexibly react to a plethora of stochastic environmental challenges (1, 2). This, in turn, defines their capability to achieve successful interactions with and survival strategies within their normal surrounding tissue. With its interactive network of cells, humoral factors, and cytokines, the immune system plays a fundamental role in the recognition of and protection against any internal or external threads, be it abnormal cells, foreign tissues or infections agents. Inborn genetic defects or dysfunctions of the one or the other immune system components may thus unsettle the intricate physiological balance and maintenance of a body's functional homeostasis and thereby diminish its preventive capability or even promote the formation of neoplastic diseases in a proactive manner.

The recent methodological advances in deciphering the composition and structure of the human genome allow us now to identify virtually any DNA sequence alterations in a hitherto unimaginable fast and detailed manner. Various such technologies have in the meantime become invaluable diagnostic mutation screening tools that help to identify clear-cut disease-associated genetic defects in inborn errors of the immune system but also more elusive variants that may participate in the predisposition to malignant diseases in children. These developments are addressed in a large number of original publications as well as in many excellent reviews of these subjects (3–16). Rather than reiterating what has already extensively been written about, I intend to provide a more conceptional framework of this subject and focus my attention on often neglected and less well-appreciated fundamental facts and phenomena, which I consider particular relevant for an in-depth appreciation and understanding of this topic and which I will supplement with some specific examples that illustrate the developments and progress in this field.

To begin with, we first need to (re)define the current view and understanding of "primary immunodeficiency" as well "genetic predisposition and susceptibility."

## PRIMARY IMMUNODEFICIENCY SYNDROMES (PID)

The immune system is composed of highly specialized cells, tissues, organs and soluble factors that interact in a complex way to ensure an organism's immune defense. According to the current definition, PID are thus a group of diseases, which are caused by heritable DNA sequence alterations that impair the quantitative or qualitative function of cellular or humoral components of the adaptive or innate immune system (17). The spectrum of their clinical, often intimately interrelated symptoms includes developmental disorders, autoinflammation, chronic inflammation, autoimmunity, neoplasms as well as serious, recurrent, or unusual infections (18, 19). Initially, the diagnosis of these conditions was based on abnormal laboratory parameters and clinical problems, in particular recurrent, severe or unusual infections that in certain groups of patients occasionally concurred with familial clustering, syndromic features, radiation sensitivity and also a certain propensity to develop particular types of malignancies. With the advent of *in vitro* testing and immunophenotyping technologies, it became possible to better define and differentiate certain categories as well as to characterize even subtle cellular and humoral functional deviances already to a certain extent. In the early days of the molecular genetic era, the respective responsible genes were then identified in cases with highly penetrant genetic traits, which instigated a first, albeit restricted diagnostic mutation screening. With the introduction of more sophisticated sequencing technologies, the discovery of causative genetic defects increased steadily in parallel with the refined dissection, delineation, and definition of such immunodeficiency syndromes. The recent 2017 update of the "Primary Immunodeficiency Committee" of the "International Union of Immunological Societies" thus recognizes 344 genetic defects that define 354 distinct disorders of immunity in nine categories (20, 21). Some of these monogenetic disorders are extremely rare and were so far identified in single families only.

This compilation together with the commonly unconsidered use of the term PID leaves the impression that one indeed knows what the term PID stands for. It is therefore intriguing to note and especially important to point out that there is actually no clear consensus about its definition (22). The reason for this now newly flaring-up debate is the recognition that the perception of immunodeficiency has so far clearly focused only on the most obvious and clinically striking disorders in both adaptive and innate immunity that affect the lympho- and hematopoietic system. With the increasing appreciation that also non-hematopoietic cells and tissues participate in a significant manner in the immune defense this view is currently changing and necessitates an expansion of this concept. For instance, keratinocytes, endothelial cells, and fibroblast secrete as much and as many cytokines as hematopoietic cells do and can thus use their intrinsic pathways for protection against infectious agents also in a similar fashion. Another example are neurons and oligodendrocytes, which are similar essential and sufficient guardians against herpes simplex virus I and probably also other infection agents (22).

Another development that one has to consider in this context are the results that derive from the increasingly sophisticated diagnostic work-up of suspicious cases with technologies that enable nowadays the recognition of even clinically not readily apparent quantitative and qualitative deviations of particular cellular and humoral immune system components. As can be appreciated already in a normal setting, such differences are commonly due to and thus correlate with variations on the sequence level, either in form of single nucleotide

polymorphisms/(SNP) alone or in form of definable haplotypes, which can make it more and more difficult to define a physiological norm and, under particular settings, a clear disease-relevant pathological state (23–32). One of the best documented and therefore most instructive example is the context-dependent implications of the highly variable serum levels of the mannan-binding lectin (MBL), the apparently most common deficiency of a humoral component of the innate immune system (33). The respective gene contains 87 different polymorphic sites with a multitude of possible combinations, of which seven common haplotypes stand out. These haplotypes determine the serum levels as well as the configuration and function of the encoded proteins in a predictable manner, although the possible effects are co-determined by the sex and age of the respective carrier, hormonal changes and immune system activation. Moreover, the frequency of the diverse haplotypes varies world-wide in an ethnicity specific manner. Thus, although the magnitude of particular MBL protein levels are clearly recognizable and determined by genetic factors, the ensuing effects, whether a low or high level becomes detrimental or beneficial or whether it remains irrelevant, are strictly context-dependent and therefore difficult to predict or interpret in a given individual.

Based on an estimate that ∼5% of all genes participate in one or the other way in host defense and immune tolerance, it was predicted that with the new sequencing technologies up to 3,000 PIDs will be identified by the year 2021. Even if one considers only a still monogenic scenario with only two types of alleles per locus (i.e., heterozygous vs. homozygous, loss-of function vs. gain-of-function, hypomorphic vs. amorphic as well as various other variations), it is hardly imaginable that one will be able to functionally evaluate and analyze the magnitude of all the possible outcomes in a reasonable manner to make some sense of the ensuing (patho)physiological effects even in an perhaps otherwise well-defined setting (22, 34).

In the end, these reflections leave us with the question how one actually will define primary immunodeficiencies in the future. When, to which extent and in which form do they need to manifest themselves clinically? Will it be sufficient to just view them as pure monogenic disorders or does one eventually also need to consider the contribution of modifying gene, signaling pathway, and cellular networks in a much stronger way?

## GENETIC PREDISPOSITION AND SUSCEPTIBILITY

The concept of genetic predisposition and susceptibility, which so far was also based primarily on the clinical perception of disease and inheritance patterns, experiences nowadays a similar reinterpretation and paradigm shift as the one of immunodeficiency. The emergence and continuous improvement of fine-scale and cost-efficient targeted, whole exome and whole genome, methylation as well as RNA sequencing approaches, increase the possibilities to investigate the genetic background of heritable and acquired diseases in a previously unprecedented manner (6, 10). Not only has it become much easier to screen all the eligible genes of already well-recognized conditions for causative mutations, it has also become much simpler to identify novel sequence abnormalities in rare, unusual, or merely suspected cases of immunodeficiencies and cancer predisposition. Thus, the special choice of the appropriate mode to search for and ascertain such genetic factors remains nowadays a matter of intention, clinical opportunities and individual demands that, in particular, is based on patient/family-relevant, gene-related, disease-associated, or population-based aspects (30). In a clinical setting, the direct patient-orientated approach is definitely the most important one. The ascertainment of an inborn genetic cause of a particular disease requires not only its appropriate work-up with the best-fitted mutation screening method but also the careful justification of its significance through the assessment of medical records and family history as well as the clinical and laboratory data of an affected patient (7, 13, 14, 34–47). Especially in those cases in which a cancer-prone condition is recognized already before the onset of a malignant disease, securing the specific genetic cause is essential to guide the necessary clinical measures, such as an appropriate treatment and surveillance program together with a suitable genetic counseling (7, 13, 14, 34–47). However, in many instances a potential predisposing germ-line alteration may only be suspected and searched for at the time a malignant disease is diagnosed. Especially if one screens the neoplastic tissue for disease-specific diagnostic alterations, one cannot avoid coming across inborn genetic errors, not only those in already known genes but occasionally also in novel ones. Distinguishing somatic from inherited defects in tumor tissue alone may turn out quite difficult because both types often affect the same genes, a fact that necessitates the verification of the inborn nature of any such changes by analyzing germ line material in addition. Based on such experiences, it is therefore becoming practice to screen for underlying germ-line defects in a more systematic fashion in form of so called "trio analyses," which in addition to a patient's tumor and germ line DNA also requires the parental ones for comparison (4, 13, 34, 35). An increasing number of publications confirm that this approach is particular rewarding, not only for the sake of the patient and her family but also for scientific reasons. In case a particular gene defect is not already clearly indicative of a specific type of predisposing condition, it may be difficult or virtually impossible to decide whether concomitant immune system derangements at diagnosis are actually the cause or the effect of the respective disease. As I will point out later, more subtle predisposing gene alterations that merely modify the function of a gene, such as single nucleotid polymorphisms (SNPs), may not even exert any easily recognizable effects prior to onset of the malignant disease. Predisposing SNPs were originally discovered by large-scale genome wide association studies (GWAS) in regions of the genome, which are linked with particular disease traits. The biological relevance and functional consequences of some of these variants has in the meantime already been established and confirmed with appropriate experiments and test systems (23, 26, 48, 49).

Our current knowledge of the genetic basis of immunodeficiency and tumor predisposition is primarily based on monogenic disorders. We learned to appreciate the

*genetic heterogeneity* of these conditions, meaning that single or similar phenotypes can be generated by different genetic mechanisms. *Polygenic* diseases, on the other hand, are caused by the joint contribution of several independent acting or interacting genes, whose individual contribution might be small or even unnoticeable. GWAS together with WGS studies have now allowed us to extend such analyses to the entire genome in a kind of *omnigenic* approach, which means that we will need to learn to cope with the combinatorial effects of a large number of genetic variants, whose individual contribution is not readily apparent (50). In contrast to Mendelian diseases, which are primarily caused by mutations in the protein-coding part of the genome, complex traits are mainly driven by non-coding variants that presumably affect regulatory elements of genes, such as promoters and enhancers. For instance, risk variants for autoimmune diseases show particular enrichment in active chromatin regions of immune cells (51–53).

The "*omnigenic*" model still accepts that only a modest number of "core genes" or pathways are etiologically important for a specific disease and their dysfunction will still have the strongest impact on the disease process (54). However, in this situation the particular risk will be driven by an accumulation of weak and heterogeneous effects of many modifying gene variants, whose specific configuration might even only become relevant in certain cell types and tissues, whereas in others they might remain completely inconsequential (51). The ultimate and most provocative conclusion and interpretation of this "*omnigenic*" model is of course that virtually any variant with regulatory effects in a given tissue is likely to have some (weak) effects on all diseases that are modulated through this particular tissue (51).

Whereas the identification of risk factors in monogenic diseases requires sequencing of specific genes and the careful functional assessment of any unusual sequence variant that pops up, polygenic risk scores of common diseases are statistically determined likelihoods that are calculated from genome-wide SNP patterns. Given the countless possibilities how defective and normal but functionally dissimilar allele variants of one or multiple genes can be combined and co-inherited, it is therefore astonishing that, as reported recently by Khera et al., the risk scores of such common diseases may under particular circumstances nevertheless reach at least the same magnitude as the ones achieved in monogenic diseases (55). Together with the cell- and tissue-specific utilization of the ensuing gene products, these findings provide a ready explanation for the highly variable penetrance of genuine gene defects and, even more so, for functionally modifying variants and, not least, why it is so difficult to foresee their biological consequences even in monogenic disorders (34). In addition, one has of course also to keep in mind that even in instances with a strong predisposing genetic component, the development of malignancies is always a multifactorial process that not only requires a liable genetic architecture but also some probabilistic elements as well as the participation and interaction of a multitude of other intrinsic and extrinsic factors and mechanisms. In case of hematologic malignancies, such cell-intrinsic defects and abnormalities consist of those that affect (I) (lympho- and hematopoietic stem) cell development, differentiation and apoptosis; (II) lymphocyte signaling, cytoskeleton, cytotoxicity and metabolism and (III) chromosome stability as well as DNA repair (3). Cell-extrinsic factors, on the other hand, comprise chronic inflammation; autoimmune- and autoinflammatory diseases, chronic (viral) infections and an impaired tumor surveillance (**Figure 1**).

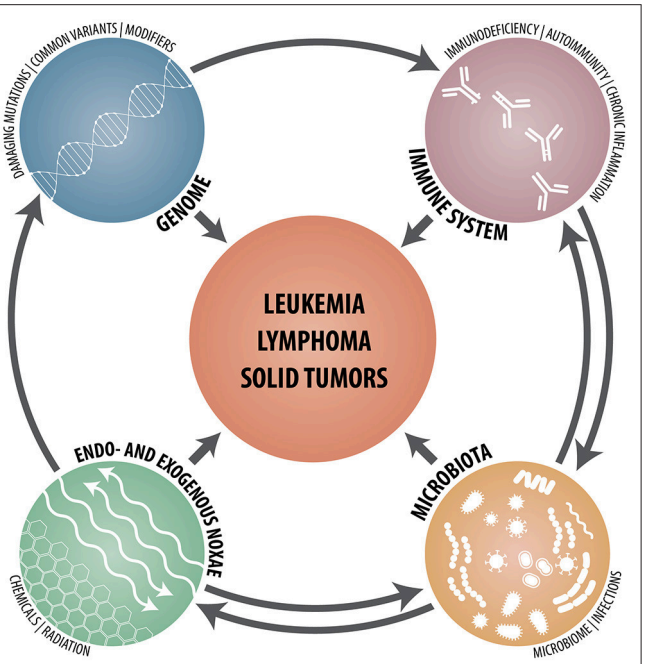



**FIGURE 1 |** Schematic synopsis of the various genetic, immunological, microbial, and environmental constituents that contribute to and participate in the development of hematologic neoplasms, lymphomas and solid tumors.

## SOMATIC MUTATION (SMT) VS. TISSUE ORGANIZATION FIELD (TOFT) THEORY

SMT and TOFT are two apparently competing theories of cancer development. The SMT postulates that cancer is a molecular, gene-based disease that derives from single cells whose autonomous and unrestrained proliferation is driven by the progressive accumulation of accidental and essentially unrelated events (2, 56–58). The TOFT, on the other hand, posits that cancer develops as an adaptive, emergent phenomenon whose fundamental determinants act at the level of tissue and organ homeostasis. In this scenario, inherent genetic constituents as well as a variety of physical, chemical and biological agents, such as cytokines, viruses, chemicals and/or radiation, perturb the functional interaction of diverse cellular modules and subsequently also the organizational state of tissues themselves (58). To a certain extent this process resembles morphogenesis and as such also replicates a tumor's capability to continuously balance novelty with stability and to combine plasticity with robustness (57, 59). The reductionist, bottom-up approach of SMT and the emergentist, top-down approach of TOFT are often considered incompatible because they view the

problem from two different levels of biological complexity. The probably smallest and already generally agreed-upon common centerpiece where these two opinions meet is the tissue micro-environment (57).

Compared to the possibilities of compact tissues, the various closely interconnected humoral and cellular components of the immune system are in a unique situation, because they can exert their action not only in a local microenvironment, but they can also act over and cover the macroenvironment of tissues, organs and even an entire organism in a systemic fashion. Moreover, within a particular context and a respective cellular milieu, components of the immune system can either foster or suppress tumor development. It is thus not surprising that the highly flexible and adaptable immune system, be it normal, impaired, or defective, is one of the major players in the game of tumor predisposition and development (60–64).

The three prevalent and often closely connected complications of PIDs are thus infections, autoimmunity, and malignancies. Nevertheless, it is intriguing to note that except for a few distinct disorders, such as Nijmegen breakage syndrome (NBS), Ataxia telangectasia (AT), and autoimmune lymphoproliferative syndrome (ALPS)-related autoimmune diseases, PIDs do not cluster with malignancies in the human diseaseome network (60, 65). Most of the available information regarding cancer risk derives from specific subtypes that result from defects in genes that regulate DNA repair, cell cycle, apoptosis, bone marrow maturation as well as those that help to protect against virus infections (17, 60). As might be expected, the most common overall hitherto documented forms of malignancies in all these conditions are lymphomas, whereas other neoplasms occur predominantly in a more disorder-typical and -constrained manner (7, 14, 17, 38, 60, 66–72).

## "ENVIRONMENT"

Multicellular organisms are organized in a modular fashion with distinct functional units and compartments. Based on the particular level of organization one can thus distinguish various internal as well as external forms of environment. From the perspective of cells, for instance, such environmental shells may constitute specific niches, tissues, organs and the entire organism. The environment of a developing fetus, on the other hand, is provided by the mother. Following birth, the organism becomes embedded in a milieu of beneficial as well as latent pathogenic microorganism and is then openly exposed to the potentially damaging biological, physical, and chemical agents of the outer world, with which it has then to interact in various ways.

### Fetal-Maternal Immune System Interactions

With regard to immunology, pregnancy is a particular interesting condition because it requires the constructive co-existence of two genetically and immunological distinct individuals within a single body (73, 74). To succeed, this endeavor requires the beneficial cooperation of a fully developed, but during this period dampened, immune system with a just evolving one that still has to mature and achieve its independence. This interaction requires the temporary reorganization and adaptation of the maternal immune system as well as the acceptance of assistance and cooperation of the fetal one. Maternal immune cells therefore help to "teach" those of the fetus to balance the need of self-defense against that of immune tolerance: too much restraint would lead to lethal infections, whereas too little would lead to autoimmunity (75–77). During this especially vulnerable phase this intricate balance can easily be disturbed, in particular by both cell intrinsic (genetic) as well as cell extrinsic biological factors.

Although a fetus expresses genetically foreign paternal antigens, it coexists in harmony inside the mother because it resides in an immune-privileged cocoon (78). Nevertheless, maternal and fetal cells still traffic through the placenta during the entire gestation period. After birth, surviving cells become then the source of a lifelong micro-chimerism in the corresponding opposite bodies, a phenomenon that under particular circumstances may significantly impact the future life of the mother as well as the child in various positive or negative ways (78, 79). Changes in the number, phenotype or distribution of microchimeric cells, for instance, can have an effect on immune surveillance, tissue repair, autoimmune diseases and tumorigenesis. It has thus been suggested that microchimeric cells may modulate health and disease in a similar way as commensal microorganisms control the susceptibility to various immunological and non-immunological disorders (78, 80).

One of the striking pathological consequences of the bidirectional cell trafficking are particular forms of SCID, in which the accumulation of a significant number of maternal T cells can cause a kind of graft-versus-host disease (GVHD) in the immune incompetent child (81, 82). However, even asymptomatic infiltrations of maternal cells are still an independent predictor for the development of GVHD later in life in case of transplantations (82). Conversely, maternal micro-chimerism in cord blood can mediate a graft-versus-leukemia effect in cord blood transplantation (83). Finally, there are also rare instances of maternal-fetal transmissions of malignancies, such as has been reported for lymphoma, leukemia and melanoma (84).

Within the setting of such pre- and postnatal fetal/maternal immune system interactions, the human leukocyte antigen (HLA) system and, in particular, its paternal component plays a particular important role (78). Exposure to inherited paternal antigens as well as non-inherited maternal antigens during pregnancy can lead to either immunization or tolerization, the sequelae of which can have even consequences decades later, not least in form of an alloimmune response in case of transplantation (85).

### HLA System

The HLA system is part of the human major histocompatibility complex (MHC), a region on the short arm of chromosome 6 with some 260 genes that are involved in the immune response. Unsurprisingly, this is also the region of the genome that is associated with the greatest number of diseases with an immune system component, including those "bare lymphocyte" SCID disorders that are caused by deleterious mutations in

certain MHC genes (86–88). As one of the main players in immune system interactions, the HLA system orchestrates the induction, regulation and fine-tuning of immune reactions and, in particular, the selection of the T cell repertoire (89). It is highly polymorphic and comprises more than 15,000 allelic variants (86).

Although specific HLA genotypes do not *per se* predispose to any particular disease in the strict direct sense, they are still highly enriched in and closely associated with distinct forms of inflammatory, autoimmune, and malignant disorders, a fact that not only underlines the central position of this regulatory system in their pathogenesis but also somehow links these otherwise disparate diseases.

HLA genotype patterns are not only associated with distinct sub-types of leukemias and lymphomas, but they can even correlate to some extent with the prognosis and survival of the respective diseases (90, 91). This evidence derived originally from the atypical HLA segregation patterns in leukemic families. They revealed an increase in HLA-identical non-affected sibs, HLA homozygosity, and identical disease-related maternal class II DRB1 haplotypes (90). Together this data is also taken as an indication that ALL is a problem that results from a population level response of HLA to infectious disease. In other words, overrepresented HLA haplotypes can provide some valuable insights into gene environment interactions as well as why and how particular clones are selected that will eventually produce the leukemic cell mass (88, 92–94). According to Greaves, B cell precursor (BCP) ALL evolves in two discrete steps, the *in utero* formation of a preleukemic clone, which is then triggered by a delayed abnormal immune response to common infections, followed by its postnatal conversion to overt leukemia (95–97). In the absence of any direct evidence for a specific causative infectious agent, the respective HLA pattern can thus be used as an indirect proxy measures for a genetically directed immune response and can thereby deliver valuable clues for the involved mechanisms. Based on such investigations, Taylor et al. concluded that BCP ALL is an indirect outcome of a transient auto-immune induced inflammatory molecular mimicry reaction that in turn may also explain why this subtype appears to be associated with delayed infection (88, 92, 93). Other factors that can help tumor cells to escape immune surveillance include somatic mutations that result in structural and functional changes in HLA system components, loss of expression of tumor antigens, lack of co-stimulatory molecules, and production of immunosuppressive cytokines (86). However, even more intriguing is the recent discovery that the HLA class I genotype is also participating in sculpting the entire oncogenic mutation landscape of a neoplasm (98). This is achieved through the continuous elimination of tumor cells with mutations that primarily produce strong antigens, which leads to a selection of cells with mutations that avoid producing such neoantigens (98).

Since the first hit that initiates the formation of the majority of pediatric cancers and leukemias occurs already very early in fetal life, the largest part of their further development still takes place *in utero* (95–97). It is therefore conceivable that fetal/maternal interactions and, in particular, the maternal immune system can influence and modify also the course of the disease in the one or the other way. Because one cannot study these processes directly, one has to rely on the above discussed traces and patterns that remain imprinted especially in the child's immune system after birth and which at least can provide some indirect clues about what had happened prenatally. The essential role of the *in utero* environment is further underlined by the fact that in individuals with a preexistent germline predisposition, secondary leukemia-promoting mutations can only evolve in special niches during distinct stages of organ development. In Down syndrome, for instance, *GATA1* mutations, which emerge exclusively during fetal liver hematopoiesis, cause an accumulation of immature erythro-megakaryocytic precursor cells (99–102). After birth, this pseudo- or preleukemic cell population is usually uncapable to maintain itself any longer and usually collapses within a short period. Although such spontaneous postnatal regressions of embryonic malignancies are quite common, it is not yet clear, whether at all or to which extent this phenomenon can also be attributed, in the strictest or in a broader sense, to the loss of the fetal/maternal interaction or altered activity of the newborns immune system (68, 103).

## Disorders of the DNA Repair System

Embryonic malignancies as well as those associated with PIDs are similar unfortunate byproducts of the complex processes that control normal development (102, 104–106). Environmental triggers such as carcinogenic pollutants and radiation play in general only a subordinate pathogenetic role in the development of childhood malignancies (105, 106). Such factors become primarily relevant only in those PID forms that are due to some types of DNA repair deficiencies (60, 71, 107–112). One of the physiological tasks of this system is to orchestrate processes, such as V(D)J recombination, class switch recombination, and somatic hypermutation, which together generate those lymphocyte-specific reorganizations that provide the basis for the adaptive immune system's genetic diversity (71, 108). Therefore, immune deficient patients with a dysfunctional DNA repair, such as those with an AT, NBS, and Bloom syndrome, are prone to develop lymphomas, whereas those with a dysfunctional DNA repair but without immune deficiency, such as xeroderma pigmentosum, Fanconi anemia, Werner syndrome, and Rothmund–Thomson syndrome, will primarily develop other forms of cancers (71). These occur especially in organs with rapidly dividing cells and/or an increased metabolic activity, including the brain, skin, breast, and the gastrointestinal tract. Since particular DNA repair defects produce characteristic mutation patterns and predispose to specific tumor forms in PID patients, it is in turn even possible to infer already from such indicators which DNA recombination processes are impaired (71).

Patients with constitutional mismatch repair deficiency (CMMRD) are prone to develop gastrointestinal, genitourinary and brain tumors, lymphomas, and leukemias (38, 39, 46, 47, 109, 113–116). They may also develop antibody deficiencies of variable severity, although they are neither a constant nor obligatory feature and usually also have no clinical correlate (107).

Genetic defects that disrupt the normal function of the DNA nucleotide excision repair (NER) complex cause at least eight

overlapping phenotypes, such as xeroderma pigmentosum (XP), Cockayne syndrome (CS), and trichothiodystrophy (TTD) (117, 118). NER is responsible for fixing UV-induced lesions, bulky chemical adducts and some forms of oxidative damage (118). The respective complex comprises at least 30 proteins, three of which (XPB, XPD, and TTDA) are also part of the basal transcription factor TFIIH. The most interesting and intriguing of these proteins is XPD, because, as Lehman pointed out so suitably, it is one gene with two functions (DNA repair and transcription) and three diseases (XP, CS, and TTD) (117). Some of the clinical features of these syndromes are quite similar but some are also markedly different (119). Although all three syndromes have an exceptionally sun-sensitive skin, cancers develop only in patients with XP but not in those with CS and TTD (118). CS and TTD, on the other hand, have neurodevelopmental abnormalities and the latter also ichthyosis and brittle hair. To explain this conflicting and somehow mysterious genotype-phenotype discrepancies, Bootsma and Hoeijmakers proposed already quite some time ago that XP would result, if the defect would concern the DNA repair but not the transcriptional function of the complex, whereas, *vice versa*, the developmental TTD-associated problems would arise, if only the transcriptional part would be affected (120).

DNA repair defects may also impair the formation and production of antibodies, which is the defining feature of CVID (19, 121–127). Patients with such a dysfunctional humoral immunity have an increased probability to develop extra-nodal non-Hodgkin B cell and mucosa-associated lymphomas as well as epithelial tumors of the stomach, breast, bladder, and cervix (70, 128–130). In contrast to most PIDs, CVID-associated lymphomas are more common in older people and usually EBV-negative (70, 128–130). Selective IgA deficiency, in particular, goes along with a 7- to 10-fold increase in gastric adenocarcinomas. This risk is most likely related to an inability to clear *Helicobacter pylori* infections and appears to decrease when these bacteria are eradicated (70, 129, 130).

## Immunoediting

The immune system is in many, apparently paradoxical ways involved in the manifestation and evolution of malignancies. It can facilitate cellular transformation as well as prevent, promote, control and thus shape their development, phenomena that eventually were summarized under the term "cancer immunoediting" (62, 131–137). The concept of immunoediting evolved from the older and more controversial "cancer immune surveillance" one, which was based on the notion that, analogous to the "non-self" of pathogens, our immune system is also able to discriminate between the "malignant self" of pre-cancerous and cancerous cells and the "self" of normal cells (61, 62, 68). To discriminate cancer cells from normal cells, the immune system pursues two main strategies: T and B cells, which belong to the adaptive immune system, recognize altered self-proteins, whereas natural killer (NK) cells, gamma/delta T cells and macrophages, which are part of the innate immune system, take care of stress-induced self-molecules on transformed cells (61). Still, the necessity to establish an effective antitumor response, goes always hand in hand with the formidable challenge to circumvent the destruction of normal cells and to avoid autoimmunity.

Given the tight interaction between the immune system and neoplastic tissues, one naturally expects, and as Corthay put forward in eight arguments, that individuals with PIDs are more prone to develop tumors than the general population (61). At first sight this notion is well-supported by both animal models and clinical observations (61, 68). The best evidence that this is indeed the case derives from experiments with mice that lack key components of the immune system. They have not only an overall higher tumor incidence, but they are also more susceptible to transplanted or chemical carcinogen-induced tumors (64, 138). At second sight, however, all hitherto available data argues against the long-hold notion that potentially dysfunctional immune surveillance mechanisms indeed increase the general tumor risk in all PID patients. If at all, such processes can only play a subordinate and ancillary role.

Reliable information regarding the general and specific tumor risk of individuals with PIDs derives primarily from three large epidemiological studies from the USA, Australia, and the Netherlands (67, 128, 139). Together these studies comprise more than 5,000 patients with around 300 different forms of PIDs. Compared to the general population and previous estimates, these analyses revealed a surprisingly low, only 2-fold increased, overall tumor risk. However, since the respective risk is primarily confined to and therefore significantly higher in the nine most frequent high-penetrant PIDs, it is conversely also much lower or even absent in most of the other PIDs. Distinct genetic PID defects predispose to and concur with special and often unique types of malignancies, the most common of which are non-Hodgkin lymphomas, leukemias, digestive tract as well as virus-induced cancers (67, 68, 70, 128, 129, 139). This particular distribution patterns can already provide some important clues about the underlying defective, disrupted or impaired immune processes that trigger such disease developments. The two major driving forces that are responsible for the 8- to 10-fold excess lymphoma risk in subjects with PIDs, for instance, are a deficient DNA repair and an inadequate response to viral infections (61, 67, 68, 70). The intriguing part of this story is, however, that the incidence of the most frequent cancers, such as breast, lung, and colon, is in the remaining group of PIDs much lower than that in the general population.

## Inadequate Activation and Response of the Immune System

Chronic inflammation, autoinflammation, autoimmunity, and infection-associated overstimulation are closely intertwined derangements of a deficient or compromised immune system (140).

## Chronic Inflammation

Inflammation is a physiological response to tissue stressors such as tissue damage and infectious as well as non-infectious agents that ensures the maintenance of tissue homeostasis (141). Under normal circumstances it mitigates infections, clears damaged cells, and initiates tissue repair (142). If this process is not properly terminated, it can cause substantial

collateral damage and contribute to tumor development (143–145). Chronic inflammation plays not only a pivotal role in different stages of tumorigenesis, but it may also impede the response to therapy (63, 145). Along the route to tumorigenesis, intrinsic genetic factors interact with extrinsic immune system and stromal humoral and cellular components to generate a mixed microenvironment that is composed of tumor-promoting and tumor-suppressive factors, including innate NK and adaptive T cells (62, 63, 145, 146). The fact that, despite their dissimilar etiology and physiology, autoimmune and infectious diseases take advantage of the same immunosuppressive pathways and logistics underlines the global relevance and central position of these particular activities (146).

Infection-provoked chronic inflammatory conditions predispose especially but not exclusively to the development of Hodgkin's, Burkitt's, and mucosa-associated lymphoid tissue (MALT) lymphomas (147–149). The best-known associations are those between *Helicobacter pylori* and gastric lymhomas, Chlamydophila psittaci and ocular adnexal lymphomas as well as *Borrelia burgdorferi* and cutaneous MALT lymphomas, while chronic infections with Epstein-Barr virus (EBV) usually predispose to Burkitt- & Hodgkin lymphomas, those with Hepatitis C virus (HCV) to marginal zone lymphomas and those with Hepatitis B virus (HBV) to hepatocellular carcinoma (147, 148). The pathogenetic role of chronic inflammation remains less clear in case of human papillomavirus-, herpes simplex virus 2-, and cytomegalovirus-triggered malignancies (150).

Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, provoke especially the development of colorectal cancer (151, 152). Crohn's disease, in particular, is a multifactorial disease whose genetic underpinning encompasses 71 so far recognized susceptibility loci (31). Amongst these are the first recognized monogenic causes of such diseases, namely interleukin-10 (IL-10) and IL-10 receptor (IL-10R) loss of function mutations that are the specific cause of a severe, very early onset type of inflammatory bowel disease (153–156). Affected children have an extremely high probability to develop a unique form of monoclonal EBV-negative diffuse large B cell lymphoma, which is characterized by a constitutive activation of the NF-kappaB pathway and a defective local T cell immune response (153). These findings prompted Neven et al. to postulate that not gut inflammation itself but that the defective IL-10 pathway alone was the responsible pathogenetic trigger. Referring to the fact that all these children received azathioprine, which is a well-known lymphoma risk-increasing factor in adults with inflammatory bowel diseases, they suggested that this immunosuppressive treatment was also the final spark that ignited lymphoma development in these children (153).

## Autoimmunity

Autoimmunity is a prominent element in many PIDs, especially in CVIDs, and not least in those, which predispose to malignancies (19, 125, 157–159). Despite their close clinical and genetic interrelationship, autoimmunity, and PIDs were up to now interpreted as two mutually exclusive conditions rather than as two sides of the same coin (157). In consideration of the fact that autoimmunity is the leading symptom in a variety of monogenic disorders that affect T cell development, tolerance, and interferon signaling, complement pathways as well as the resolution of inflammation, this view is changing nowadays (157). The two prototypic examples to illustrate their close interrelationship are the autoimmune lymphoproliferative syndrome (ALPS) and the IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked). In case of ALPS, the respective lymphoproliferation and propensity to develop lymphomas results from apoptosis-impairing germline as well as somatic mutations in the *FAS*, *FASL,* and caspase 10 genes (160–162). Still, mutation carriers have only a <60% chance for disease manifestation (161). The IPEX syndrome, on the other hand, is caused by activating mutations in the *FOXP3* gene (163–165). The encoded transcription factor controls the function of regulatory T cells that are essential for maintaining self-tolerance and immune homeostasis by suppressing aberrant responses such as autoimmunity and allergy (166). Deficiency of cytotoxic T lymphocyte antigen 4 (CTLA-4), which is a crucial inhibitor of T cell response that is also present on regulatory T cells, can therefore generate autoinflammation and autoimmunity in a corresponding fashion (166–169). Moreover, CTLA-4-deficient individuals are at risk to primarily develop EBV-related malignancies (170). Another recently recognized albeit rare cause of autoimmunity are leukemia-predisposing germline mutations in the *IKZF1* gene, which encodes the hematopoietic transcription factor Ikaros (171–175). Finally, one should not forget that autoimmune diseases are also a common problem in one of the most remarkable forms of leukemia-predisposing immunodeficiencies, the Down syndrome (176–178).

## Hyperactivation

The inability of cytotoxic lymphocytes to fend off and kill virus-infected or transformed cells leads to an often uncontrollable hyperactivation of the immune system in form of hemophagocytic lymphohistiocytosis (HLH) (179–181). This distinctive clinical feature is the common denominator of a related group of perforin-deficient hyperinflammatory disorders, so called "perforinopathies," that may either be due to rare congenital gene-disrupting mono- or biallelic mutations or, in less severe form, due to functionally impairing hypomorphic alleles (182–186). Familial hemophagocytic lymphohistiocytosis type 2 (FHL2) is caused by biallelic mutations of the perforin gene (*PRF1*) (179). It shares some of its clinical characteristics with those of anaplastic large cell lymphoma (ALCL), which accounts for ∼10 to 15% of all pediatric non-Hodgkin lymphomas (187–190). About a quarter of these lymphoma patients carry only monoallelic *PRF1* mutations but, remarkably, virtually none in *SH2D1A* or *UNC13D*, genes that are implicated in two other forms of FHL (181, 187, 191–193). Moreover, an otherwise common activity-diminishing *PRF1* gene variant (SNP A91V; rs35947132), is also postulated to predispose to the nasal form of NK/T cell lymphoma in adults, which is the most frequent EBV-related NK/T cell malignancy (188).

## Microbiome

Human beings are holobiontic meta-organisms (194–197). They are composed of host as well as trillions of viral, fungal, bacterial, and eukaryotic microbes that are collectively referred to as the microbiota or microbiome (194–197). This microbiome is acquired and shaped during the first 2 years of life. It co-evolves with its respective host genome and, under physiological conditions, becomes part of a stable, life-long synergistic homoeostasis (194, 195, 197–200). Because of its tight functional link with and profound effects on the host's immune system in health and disease, the microbiome is therefore already regarded as a complex, polygenic trait (200–202). Environmental, and host-related perturbations of this microbial ecosystem reduce almost invariably its diversity. This is a common finding in many multifactorial inflammatory, autoimmune, metabolic, neoplastic, and neurodegenerative diseases, although it is rarely known whether such a dysbiosis is indeed the cause or the effect of the underlying ailment (197, 203). Nevertheless, the host's immune system is certainly the most important force that shapes the configuration of the normal and dysbiotic microbiome, which, in turn, may of course be a significant cofounding factor in immune-mediated and immune-associated diseases (197). A healthy or dysbiotic microbiota can influence the host innate immune system and it is therefore no surprise that microorganisms are also implicated in the pathogenesis of at least 20% of all human malignancies (204). In a dysbiotic state, alterations in the signature of microbial molecules that are sensed by the host can lead to a different activation state of the immune system. These changes may alter the balance of host cell proliferation and death, guide immune system function and influence metabolism of host-produced factors, ingested food and pharmaceuticals (205). Moreover, they may also drive transformation by affecting genomic stability, resistance to cell death and proliferative signaling (205). Both chronic high-grade as well as lower-grade smoldering inflammatory disorders drive a tumor-permissive milieu, a problem that was extensively studied and confirmed in mice that were deficient in various immunologically relevant genes (199, 205, 206). It is worth noting that such a cancer susceptibility can even be transferred to healthy mice by cohousing, fostering or fecal transplants (195, 199, 207). Since polymorphisms in immunologically relevant genes affect human microbiota composition and cancer predisposition, this observation is therefore also highly relevant for such human diseases (201, 202, 208, 209).

Based on these results, Dzutsev et al. therefore suggested that malignancies can be viewed as systemic diseases that alter the physiological homeostatic interaction of the entire meta-organism (143, 195). Mostly because of its effects on metabolism, cellular proliferation, inflammation, and immunity, the microbiome would interact with their development at virtually every level, including predisposing conditions, initiation, genetic instability, susceptibility to host immune response, progression, comorbidity and, not least, response to therapy (143, 195, 205). In support of this notion, Yamamoto et al reported, for instance, that variation in intestinal microbes between different animal facilities or as a consequence of experimental perturbations profoundly affected the incidence of lymphoma and survival of Atm (ataxia telangiectasia mutated)-deficient mice (210). Another very intriguing and instructive example of how we will one day perhaps be able to exploit particular constituents of the microbiome for medical and therapeutic purposes was recently provided by Bromberg et al. (211). They showed that with the delivery of stool samples from pregnant mice or gavage with isolated B. pseudolongum species to those with cardiac allografts they were able to improve their long-term survival as well as to prevent inflammation and fibrosis in this respective organ (211).

## *Bona Fide* Infections

The IARC classifies 10 microbial agents (7 viruses, 2 parasites, and 1 bacterium) as group 1 human carcinogens (195, 204). Over 90% of all infection-attributed cancers are attributed to *Helicobacter pylori*, HBV and HCV, and human papillomaviruses (HPV) (204). Except for HCV, all human oncogenic viruses encode at least one oncogene and may therefore directly induce neoplastic transformation, although, as alluded to above, infection-associated inflammation and dysbiosis most likely play a likewise significant role in this context. Thus, Plottel et al. distinguish three classes of microbe-induced human malignancies, the first is defined as involving immunologic tissues, the second requires direct microbial interactions with parenchymal cells and the third involves distant effects from local interactions (212).

The likelihood to be either protected or to become infected as well as the infection outcome depends primarily on the diverse conditions that guide the interactions between the respective pathogen and its potential host. These include their specific genetic set-up and functional fitness to invade or defend themselves, as well as on a variety of other factors, such as concomitant infections as well as the age and microbial constitution of the respective host (213–220). To invade host cells, pathogens exploit and hijack particular cell surface proteins. Amongst the docking receptors that were identified so far in case of the Malaria parasite plasmodium falciparum, for instance, are CD55 and structural variants of the GYPA and GYPB genes (220–224). CD55-null erythrocytes, in particular, are refractory to invasion by all isolates of plasmodium falciparum (222). The second example is *CCR5*, which encodes a coreceptor for HIV entry. Consequently, carriers of an otherwise phenotypically and functionally completely inconsequential homozygous 32-bp deletion are resistant to HIV infection (225). Although HIV infections are indisputably the cause of the "acquired" immune deficiency, one can still argue that all these infection-related problems are nevertheless due to a genetically primed primary albeit clinically inapparent susceptibility. The point I want to stress here is that what one currently perceives as a "normal" wild-type or a "defective" susceptible gene variant is merely a matter of choice, frequency, common habit, and/or subjective interpretation. Since the functional consequences of any such variant will always remain context-dependent, one therefore needs to keep in mind that the distinction between "protective" and "defective" can never be an absolute dogma, but always lies in the eyes of the beholder.

Epstein-Barr virus (EBV) is a ubiquitous virus that infects virtually all humans and obligatory leads to a usually

asymptomatic symbiotic lifelong latent persistence (214, 226). Although this EBV latency may provide an evolutionary mutualistic benefit to its hosts as an immune adjuvant that apparently protects against lethal Listeria monocytogenes and *Yersinia pestis* infections (227, 228), the many EBV-associated problems have nowadays become clinically far more relevant and interesting. At present, the literature distinguishes more than 25 EBV-related disease entities, including those that are associated with various forms of immunodeficiencies and those that concur with a high propensity to develop diverse hematopoietic, epithelial, and mesenchymal malignancies (66, 226, 229–234). These disease forms can be roughly divided into reactive EBV-associated lymphoid and histiocytic/dendritic proliferations (including reactive lesions with or without diverse malignant potential), B cell proliferations (including Hodgkin lymphoma and plasma cell neoplasms), T/NK cell proliferations, immunodeficiency-related lymphoid proliferations and histiocytic/dendritic proliferations (66, 226, 229, 231–236). Taken together, EBV contributes to about 1.5% of all cases of human cancer worldwide (229, 237).

The type and incidence of EBV associated diseases varies significantly in different parts of the world, an observation that can be attributed to the different distribution of genetic susceptibility factors, including individual-, HLA-, and ethnicity-specific ones, to environmental- and geographic-specific co-founding influences but also to the existence of particular EBV strains that may produce different disease patterns (27, 66, 153, 213, 214, 217, 218, 229, 230, 232–234, 236, 238–240).

In contrast to the above-mentioned HIV infection, which significantly increases the risk for malignant diseases and especially lymphomas, such a risk is, if at all, by far not as pronounced in case of Malaria (241–243). The only notable exception concerns the concomitant early and sustained infection of Plasmodium falciparum and EBV, which together are the essential pathogenetic ingredients in the endemic form of Burkitt lymphoma in Africa (217–219, 236, 238, 244–246). In this particular combination, the Plasmodium infection destabilizes the genome of rapidly dividing EBV-infested germinal center B cells by eliciting the protracted expression of the activation-induced cytidine deaminase, a mutation-aggravating enzyme (238, 245).

At one point in their life, virtually all humans become infected with EBV, most of them without any acute, severe or lasting health problems. However, in those who do, one can often identify an underlying disease-associated, more or less pronounced genetic susceptibility, which begs for the question whether EBV-associated disease processes indeed afflict also "immunocompetent" individuals, or put the other way around, what in the end will define such an "immune (in)competence" (235).

## PREDISPOSITION TO HEMATOLOGIC NEOPLASMS IN CHILDREN

The role of predisposing germline mutations and sequence variants in children and adults with various types of hematologic malignancies was hitherto largely underappreciated, because not all of them concur with nor create any easily recognizable clinical stigmata or suspicious family history. Especially if one screens neoplastic tissues for disease- and/or therapy relevant somatic mutations, it becomes of critical importance to distinguish those from germline ones, because the latter may also have a profound clinical impact as regards choice of therapy, donor selection in case of transplantations, evaluation of comorbidities as well as surveillance strategies (8, 173).

A recent paper by Duan et al. provides an excellent and very comprehensive overview about all the primary immunodeficiencies that in particular predispose to the development of various types of lymphomas and hematologic malignancies (3). The authors compiled more than 60 conditions, which comprised all subgroups of syndromic and non-syndromic cellular and humoral PID as well as defects in phagocytes and innate immunity.

To pack some of the underlying principles and problems into a practical and newsworthy perspective, I will now briefly turn to recent findings in three categories of childhood leukemia.

### Constitutional Trisomy 21

Trisomy 21 is not only the most common chromosome abnormality in liveborns but in many aspects also one of the most outstanding and fascinating examples of an immune system disorder, although for a long time the precise nature of the respective immunological derangements remained elusive (178). Since it is not a monogenic ailment, it is also hardly ever viewed as a primary immunodeficiency, although it clearly concurs with multiple distinct immunological and developmental defects that affect the myeloid but also the early and committed B-lymphoid progenitor compartments in second trimester fetal liver (247). I chose this most intriguing and highly instructive example to explain in which way the predisposing risk score of a kind of "polygenic" disposition can easily reach at least the same magnitude as the one that is otherwise only achievable in a monogenic setting (55).The ensuing variable and clinically often inapparent immunological alterations in Down individuals comprise a mild to moderate decrease in T and B cells, impaired mitogen-induced T cell proliferation, reduced specific antibody responses to immunizations as well as defects of neutrophil chemotaxis (248). Affected individuals suffer from various types of autoimmune and autoinflammation diseases, whereas it is still a matter of debate whether they are also more prone to experience more or severer infections than non-Down individuals (176, 178, 248, 249). The first clues that helped to resolve the functional consequences of this immunological conundrum derived from recent transcriptome and proteome analyses. They revealed that the presence of an extra chromosome 21 leads, amongst others, to an overexpression of the four chromosome 21-encoded interferon receptors and, therefore, place this syndrome into the class of interferonopathies. Interferons are normally produced by cells in response to viral or bacterial infections, regulate genes in neighboring cells and shut down the production of proteins, which activate the immune system and thereby prevent the spread of the infection (250, 251). In line with interferonopathies and autoinflammatory conditions, individuals

with Down syndrome display higher levels of many pro-inflammatory cytokines (including IL-6, IL-22, TNF-α, and MCP-1) as well as complement consumption, a state that indicates that the immune system is constantly fighting viral infections that are in fact not there (250). Whether and to which extent such a faulty overreaction may also participate in promoting the development of hematologic neoplasms perhaps in a similar fashion as in genuine virus infection-triggered malignancies, remains to be elucidated.

Individuals with an inborn trisomy 21 have also an extraordinary risk to acquire special forms of hematologic neoplasms in early life, whereas they are otherwise exquisitely protected against the development of any other malignancies (252, 253). Compared to normal age-matched children, the self-limiting transient myeloproliferative disorder (TMD) together with the acute megakaryoblastic leukemia (AML-M7), is ∼150 times and the B cell precursor ALL ∼33 times more common (99, 101, 102, 253, 254). Of particular note are also the absence of infant ALL, the rarity of T-ALL and, compared to normal children, the different distribution pattern of genetic B-ALL subtypes (255).

The occurrence of specific mutations in the receptive precursor cells determine which form of leukemia will eventually develop. In case of TMD, the perturbation of megakaryocyte-erythroid precursor cell differentiation fosters the appearance of a highly specific truncating mutation in exon 2 of the hematopoietic transcription factor GATA1. This in turn provides the receptive cellular and molecular environment for the occurrence of further mutations, primarily in the JAK and RAS signaling pathways as well as in epigenetic regulators and multiple cohesion components, which then facilitate the further progression into AML (99, 101, 104, 254). A reduced lymphoid gene expression in fetal liver hematopoietic precursor cells impairs B-lymphoid development in a similar fashion. The ensuing maturation arrest leads to an ∼10-fold reduction in B cells. The concomitant accumulation of pro-B progenitors (247), on the other hand, increases the likelihood for illegitimate V(D)J recombination-mediated chromosomal rearrangements, in particular *CRLF2* gene fusions, that can be found in approximately half of all Down syndrome BCP ALL cases (99, 104). To explore the potential contribution of chromosome 21-encoded and overexpressed genes, a set of 31 triplicated orthologous human genes were tested in germline mouse models (256). Their presence induced progenitor B cell self-renewal *in vitro*, maturation defects *in vivo* and the development of especially *CRLF2*-rearranged and *JAK2* pathway-activated BCP ALL. Out of these 31 genes, the nucleosome-remodeling protein high mobility group nucleosome-binding domain- containing protein 1 (*HMGN1*), whose protein product suppresses H3K27me3, turned out to be the most relevant candidate. Together with secondary alterations in the *CRLF2*, *JAK2*, *NRAS,* or *KRAS* genes, it promotes both B cell proliferation *in vitro* and the development of B ALL in mice *in vivo* (256).

Given the extraordinary susceptibility and the high incidence of leukemias, one would intuitively expect that both myeloid and lymphoid forms should occasionally occur together by pure chance alone. However, such a coincidence has so far never been reported. On the one hand, this lack of co-occurrence might indicate that the development of a specific type of leukemia requires and is subject to very individual-specific predisposing conditions. On the other hand, it is also in keeping with the fact that these patients virtually never suffer from secondary neoplasms and that they are in a unique and matchless way also protected against the development of any other types of neoplasms (252, 253).

This protective effect also has been put down to a copy number-dependent gene dosage but also context-dependent effect of specific chromosome 21-encoded genes. The presence of three *ETS2* copies, for instance, act as tumor repressor in the ApcMin intestinal cancer mouse model, whereas in the PyMT breast cancer mouse model it functions as tumor promoter, albeit within the non-cancerous stromal cells, where it regulates the expression of genes that produce the extracellular matrix, an essential component for tumor growth and metastasis (257–260). Two other relevant genes are the Down's syndrome candidate region-1 (*DSCR1*), which encodes a suppressor of the vascular endothelial growth factor (VEGF)-mediated angiogenic signaling by the calcineurin pathway, and *DYRK1A*, which encodes a regulator of cell proliferation (261). In mice, the presence of a single extra copy of Dscr1 is sufficient to diminish tumor growth by suppressing the calcineurin pathway and therefore also angiogenesis, an effect that is significantly enhanced by an extra copy of Dyrk1a. For the sake of completeness, one needs to take at least also note of several other trisomic chromosome21-encoded genes whose presence in the stromal compartment helps to reduce tumor angiogenesis, namely the angiogenic inhibitor *ADAMTS1*, the transcription regulator *ERG* and, finally, the endothelial cell-specific genes *JAMB* and *PTTG1IP* (257).

## Bone Marrow Failure (BMF), Myelodysplastic Syndromes (MDS), and Myeloid Leukemias

**Table 1** provides a comprehensive summary of the various disease entities together with their causative genetic background. For a more in-depth overview I refer the interested reader to recent publications that deal with these individual subjects in detail (8, 60, 158, 264, 265, 268, 269, 272, 275, 283, 299, 300). Herein, I merely select a few instructive examples to highlight some of the intriguing phenomena that are particularly pertinent for the topic discussed herein.

Fanconi Anemia (FA) is not only the most common inherited BMF disorder but, with a 500- to 700-fold higher incidence of head and neck squamous cell carcinomas in older patients, also a highly penetrant cancer susceptibility syndrome (301). Except for the X-linked *FANCB* gene, it is due to bi-allelic mutations that can affect one of 21 genes, which encode various components of the evolutionarily conserved FA/BRCA repair complex. Five of these (*BRCA2, PALB2, RAD51C, SLX4,* and *BACH1*) specifically predispose also to breast cancer. The encoded proteins participate in biochemical pathways that safeguard not only against the effects of alkylating agents and radiation but, probably even more relevant, also against those of endogenous aldehydes, oxidative stress, inflammation,

**TABLE 1 |** Immunodeficiency syndromes that predispose to the development of bone marrow failure, myelodysplasia and myeloid leukemias.

| Disease/Syndrome | Defective genes | Malignancy risk | Remarks | References |
|---|---|---|---|---|
| Fanconi Anemia (FA) | *FANCA, FANCB, FANCC, FANCD1/BRCA2, FAND2, FANCE, FANCF, FANCG/XRCC9, FANCI/KIAA1794, FANCJ/BRIP1/BACH1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANCQ/ERCC4, FANCR/RAD51, FANCS/BRCA1, FANCT/UBE2T, FANCU/XRCC2, FANCV/REV7/MAD2L2* | MDS, AML, T-ALL, squamous cell carcinomas (head & neck, genitourinary tract), breast cancer | Currently 21 known genes that encode members of the FA/BRCA repair complex | (8, 262–265) |
| **RIBOSOMOPATHIES** | | | | |
| Diamond_Blackfan anemia (DBA) | *RPL3, RPL5, RPL10, RPL10A, RPL11, RPL15, RPL18, RPL19, RPL26, RPL27, RPL31, RPL34, RPL35, RPL35A, RPS7, RPS10, RPS11, RPS15A RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, RPLP0, TSR2, GATA1, CECR1* | 25% life-long overall risk of 5.4 odds ratio<br><br>MDS, AML, colon cancer, osteogenic sarcoma, and genital cancer | 26 ribosomal genes, 6% phenocopies in non-ribosomal genes, 22% unidentified | (265–269) |
| Dyskeratosis Congenita (DC) | *ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RTEL1, TERC, TERT, TINF2, WRAP53, STN1/OBFC1* | MDS, AML, squamous cell cancers of the head, neck & anogenital region | Telomere-associated ribonucleoprotein (RNP) and shelterin complexes | (265, 269–272) |
| Shwachman-Diamond-Bodian Syndrome (SDBS), | *SBDS, DNAJC21/HSP40, EFL1* | 5% leukemia risk (AML, CML, ALL) | Defective processing of rRNA into ribosome assembly, majority unidentified | (265, 269, 273) |
| Cartilage hair hypoplasia (CHH) | R*MPR* | Non-Hodgkin lymphoma, basal cell carcinoma | RNA component of RNAse MPR, one single Finnish founder mutation | (265, 269, 274) |
| Aplastic anemia/ pancytopenia | *MECOM, ERCC6L2* | MDS | | (275) |
| **PLATELET DISORDERS** | | | | |
| Amegakaryocytic thrombocytopenia | Mostly *MPL* (thrombopoietin receptor), *RUNX1, ANKRD26, MYH9, PTPN1* | Pancytopenia, leukemia | | (265, 276) |
| Thrombocytopenia absent radius (TAR) syndrome | del(1q21.1) & *RBM8A* SNP | Leukemia (rare) | | (265, 277) |
| Familial thrombocytopenia | *ETV6, RUNX1, DDX41, ANKRD26* | MDS, leukemias | | (8) |
| Congenital neutropenia | *CSF3R, ELANE, G6PC3, GFI1, HAX1, JAGN1, VPS45, WAS* | G-CSF treatment, dose-dependent MDS/AML risk | | (264, 278, 279) |
| *GATA2* deficiency (Emberger & Monomac syndrome) | *GATA2* | MDS, AML (monosomy 7) | | (275, 280–286) |
| Mirage & ataxia-pancytopenia syndrome | *SAMD9, SAMD9L* | MDS, AML (monosomy 7) | | (273, 287–294) |
| Rasopathies | *NF1, PTPN11, CBL, NRAS, KRAS* | JMML, ALL | | (295–298) |

*Apart of being present in the germ line, somatic mutations of most of these genes can be commonly encountered in sporadic forms of analogous malignancies.*

mitophagy, and virophagy (263, 265, 302, 303). All these factors damage DNA in form of distinct inter-strand DNA crosslinks. The inability to repair these damages is the primary driver of the various biological and clinical problems that define this disease category.

Small aldehydes, such as acetaldehyde and formaldehyde, are not only ubiquitously present in the environment, but also potentially toxic byproducts of the normal cellular metabolism and especially de-methylation reactions (304–306). Given that they provide already a rich source for endogenous inter-strand DNA and protein cross links, one can envisage that the pathogenic manifestations and consequences of FA mutations may also be strongly influenced and modified by the functional capability of aldehyde detoxifying enzymes, such as aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 5 (ADH5) (306, 307). In line with this notion, Japanese FA children that carried a functionally deficient ALDH2E504K allele were shown to progress more rapidly to aplastic anemia but not to MDS or AML (307–309). Moreover, malformations were only more severe in two of three homozygous carriers, which indicates that a deficient maternal genetic background might contribute to this outcome (310). Maternal-produced aldehydes diffuse indeed across the placenta and can thus damage the developing embryo's DNA, whereas embryo-derived ones can in turn be detoxified by the maternal organism. An inappropriate *in utero* exposure, such as an excessive maternal ethanol consumption during gestation, would therefore aggravate not only the formation of congenital abnormalities in FA but it provides also an intriguing etiological link to analogous phenotypic changes that define the alcohol embryopathy (308). Whether a disturbed aldehyde detoxifying system might also be causatively involved in the *in utero* initiation of childhood leukemias remains currently a matter of speculation (307).

In addition to stalling and destabilizing DNA replication forks directly, formaldehyde also selectively depletes BRCA2 via proteasomal degradation, a circumstance that poses a special risk for heterozygous *BRCA2* mutation carriers. In these, formaldehyde-induced degradation can decrease the respective protein levels below the otherwise protective one of normal wild-type individuals and thereby potentiate their mutagenic vulnerability (311).

Taken together, these observations have significant implications for risk awareness and avoidance as well as the clinical management of FA patients. On the positive side, they offer new treatment opportunities, for instance in form of ALDH2 agonists and the widely used diabetes drug metformin, which acts as aldehyde scavenger. At least in mouse models, both of them are able to delay the onset of BMF and malignancies as well as improve hematopoiesis (263, 312, 313).

One remarkable feature of many heritable diseases is that somatic mutations can occasionally autocorrect the particular inherited gene defect in the respective cells (314). Such reverting mutations transform a homozygous or combined heterozygous state again back into a heterozygous functionally compensated state, either through somatic recombination, gene conversion or a compensatory mutation (314, 315). Although this phenomenon is well-known in immunodeficiencies, its effects are most probably still underappreciated. In BMF syndromes such an autocorrection can spontaneously improve or even resolve the specific underlying hematopoietic problem. Amongst others, such spontaneous remissions have repeatedly been documented in FA, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome and, more recently, in the *SAMD9*- and *SAMD9L*-associated Mirage and ataxia-pancytopenia syndromes, respectively (273, 287–293, 301, 316). Heterozygous *SAMD9L* gain-of-function mutations decrease cell proliferation. The loss of the mutation-carrying chromosome 7 in bone marrow cells therefore leads to the development of MDS and acute myeloid leukemias, whereas a compensating duplication of the normal allele in form of an uniparental disomy (UPD) 7 or 7q is able to resolve the cytopenias (287–293).

The somatic appearance of a complete or partial UPD always draws attention to regions that are usually highly relevant for specific disease processes (317, 318). Such UPDs may either contain duplicated gain of function mutations or, as alluded to in the example above, eliminate them (317, 318). A similar important consequence is the mere transformation of a heterozygous to a homozygous state. In case of the HLA-containing region on the short arm of chromosome 6, for instance, it is clearly exerted through a selective pressure, since the loss of one HLA haplotype is an important immune-escape mechanism. It protects neoplastic cells from the immune surveillance machinery and therefore also plays a crucial role for disease recurrence after haploidentical stem cell transplantations (319, 320). Contrariwise, such a haplotype loss is able to shield hematopoietic cells from the destructive effects of autoimmunity, as has been demonstrated in case of aplastic anemia (321). The practical problems that arise from such a hematopoietic revertant mosaicism is that it may lead to an ascertainment bias and cause difficulties in identifying underlying disease-relevant mutations (322).

The formation of such well-adapted clones might suggest that such compensatory mechanisms are rare events. However, there is ample evidence that this is definitely not the case. Rather than being a life-long stable system the genome is a highly dynamic one that is continuously modified and shaped by ongoing mutational processes, which eventually promote the appearance of cell clones and populations with an increased survival fitness. The formation of somatic mosaicism is therefore the rule rather than the exception, as exemplified by Davis et al., who observed a remarkable clonal heterogeneity and diversity of lymphocytes in a patient with a Wiskott-Aldrich syndrome (323). The continuous generation of such cellular variants and the selective pressures they are exposed to is thus not only a characteristic of the exceptional dynamics of neoplastic but also of normal cells populations (324).

## B-Cell Precursor Acute Lymphoblastic Leukemia (BCP ALL)

Germline lesions that predispose to BCP ALL in children comprise not only those which cause various cancer prone and chromosomal syndromes but also other genuine gene disrupting defects as well as high and low risk variants. The majority of these

**TABLE 2 |** Chromosomal locations of GWAS-verified SNPs or genuine germline gene defects that predispose to the development of particular types of childhood ALL.

| Chromosome region | Candidate genes | Type | Function | All subset | References |
|---|---|---|---|---|---|
| 2(q22.3) | Not specified | SNP | – | *ETV6–RUNX1* | (24) |
| 3(q28) | *TP63* | SNP | P53 family of transcription factors | *ETV6-RUNX1* | (325) |
| 7(p12.2) | *IKZF1* | SNP, gene defects | Ikaros family of Zinc finger transcription factors | Not specified | (32, 172, 326, 327) |
| 8(q24.1) | MYC? | SNP | Proto-oncogene, BHLH transcription factor | Not specified | (24, 25) |
| 9(p12) | *PAX5* | Gene defects | Paired box transcription factor | Not specified | (48, 328) |
| 9(p21.3) | *CDKN2A & CDKN2B* | SNP | Cyclin-dependent kinase Inhibitors | Not specified | (329–331) |
| 9(p24.1) | *JAK2* | SNP | Tyrosine kinase | *BCR-ABL1*-like | (49) |
| 10(p12.2) | *PIP4K2A* | SNP | Kinase | Not specified | (329, 332) |
| 10(p14) | *GATA3* | SNP | GATA family of transcription factors | *BCR-ABL1*-like | (332, 333) |
| 10(q21.2) | *ARID5B* | SNP | Transcription coactivator | Hyperdiploid | (26, 32, 326, 327) |
| 10(q26.13) | *LHPP* | SNP | Phosphatase | Not specified | (28) |
| 11(p11.2) | *PTPRJ* | SNP | Family of protein tyrosine phosphatases | *ETV6-RUNX1* | (325) |
| 12(p13.2) | *ETV6* | Gene defects | Proto-oncogene, ETS domain family of transcription factor | Hyperdiploid | (334–338) |
| 12(q23.1) | *ELK3* | SNP | ETS domain family of transcription factor | Not specified | (28) |
| 12(q24.1) | *PTPN11* | Gene defects* | Family of protein tyrosine phosphatases | Hyperdiploid | (297) |
| 14(q11.2) | *CEBPE* | SNP | bZIP transcription factor | Hyperdiploid | (23, 25, 32, 327) |
| 16(p13.3) | *CREBBP* | Gene defects** | Histone acetyltransferase | Hyperdiploid | Haas, unpublished observation |
| 17(p13.1) | *TP53* | Gene defects*** | Tumor-suppressor, transcription factor | Hypodiploid | (339–341) |
| 17(q12) | *IKZF3* | SNP | Ikaros family of Zinc finger transcription factors | Not specified | (25) |
| 17(q21.2) | *STAT3* | SNP | Signal transducer and transcription activator | *BCR-ABL1*-like | (49) |

*For a more general overview about ALL predisposition syndromes and ALL predisposing RASopathies see Kratz et al. and Cave et al., respectively (62, 243). *Noonan syndromes, Rasopathy, **Rubinstein-Taybi syndrome, ***Li-Fraumeni syndrome.*

affect genes that encode B-cell development and transcription factors as well as components of various signal transduction pathways (**Table 2**) (42, 297, 342).

The development of B lymphocytes, in particular, is coordinated by specific regulatory transcription networks that activate the respective B-lymphoid program and at the same time oppress alternate cell fates (343). Somatic mutations in several of these key regulators, such as *IKZF1*, *TCF3*, *EBF1,* and *PAX5*, induce leukemic transformation by blocking normal B cell differentiation, which then leads to the accumulation of leukemic B-cell precursors. Although their role in leukemogenesis has been known and explored already for quite some time, the awareness that otherwise apparently inconsequential germline variants may also exert a predisposing effect is quite new. The biological relevance and functional consequences of some of these variants has been confirmed in the meantime with appropriate *in vitro* and *in vivo* experiments and test systems (23–26, 28, 332, 333).

Take for instance *PAX5,* a member of the "paired box" family of transcription factors, which encodes the B cell lineage specific activator protein that is expressed at early but not late stages of B-cell differentiation (195). Out of the three up to now reported families with highly penetrant germline variants, 13 carriers developed ALL (48, 328). In the two families, in which the respective information was provided, all unaffected carriers as well as those with ALL had normal immunoglobulin levels and no evidence of an impaired B cell function at diagnosis (328). Moreover, in line with Greaves two step model, leukemia developed in mice only after exposure to common pathogens and the acquisition of second hits in the IL7R/JAK3/STAT5 signaling axis (344).

Another revealing example is *IKZF1*, which encodes IKAROS, a member of a hematopoietic zinc-finger transcription factor family (345–347). The mutational spectrum of human IKZF1-associated diseases ranges from somatic to germline and from haploinsufficient to dominant negative forms (171). Somatic mutations occur in overall 15% of BCP-ALL and especially in prognostic adverse genetic subtypes (348, 349). Heterozygous germline mutations cause two different forms of immunodeficiency. The haploinsufficient, autosomal dominant late onset form of common variable immunodeficiency (CVID)

has an incomplete penetrance, is clinically mild and concurs with a marked decrease in B-cell numbers and immunoglobulin levels as well as autoimmunity (175, 350, 351). The early-onset dominant negative CVID, on the other hand, is characterized by innate and adaptive immune defects of the B, T and myeloid cell lineage (171). Notably, 2/29 of patients with the late onset form developed B-ALL and 1/7 patients as well as another independently reported one with the early onset form developed T-ALL (171, 346, 351). Based on these observations, Churchman and colleagues screened remission samples from 4,963 childhood ALL cases, identified a total of 28 unique *IKZF1* variants in 43 and succeeded to prove a functional consequence in 22 of them (172, 173). Evans et al. even attempted to elucidate the influence of a parental environmental exposure on such leukemia-predisposing risk alleles (352). They found some preliminary albeit hitherto unexplainable evidence that the *IKZF1* risk genotype might have a stronger effect if the mother took folic acid or if the father did not smoke prior to pregnancy (352).

Finally, Auer et al reported a first intriguing example of a "double-hit one-pathway" scenario, in which the biparental inherited combination of two rare germline variants, JAK2 (G571S) and STAT3 (K370R), whose products synergistically interact in the same disease-relevant JAK/STAT signal transduction pathway, is obviously sufficient to induce a Ph-like BCP-ALL (49).

## CONCLUDING REMARKS

During their entire development and ongoing existence, both the immune system as well as malignant diseases need to adapt themselves to highly variable and continuously fluctuating environmental conditions, which requires a high flexibility that is largely driven by a combination of interacting antagonistic as well as synergistic deterministic events and regulatory probabilities. "Immunodeficiency" and "tumor susceptibility" are thus two closely intertwined concepts, whose original understanding was based on easily explicable clinical symptoms as well as certain genetic norms. As long as these were based on such more or less simple phenotypic and genotypic features, one did not require any further explanatory definitions. However, the switch from phenotypic to genetic ascertainment programs include now much less obvious disease categories, healthy carriers as well as only vaguely defined potentially predisposed individuals. Although this approach enables of course unprecedented insights into the fine-scale structural and regulatory organization of biological system, the boundaries of classification standards get increasingly blurred, which goes hand in hand with the awareness that it becomes increasingly difficult and virtually impossible to define either of these terms in an unambiguous manner anymore. The more closely one looks, the harder it gets to find genes that are not in one or the other way part of this game.

In his highly recommendable and readable book "Tending Adam's garden," Irun Cohen portrays the immune system as a cognitive system (353). Like its prototypic equivalent, the brain, it learns through individual experience and thereby forms a functionally highly efficient, flexible, and to some extent also redundant interactive structure. As Cohen pointed out, a particular gene may only become essential once the system has organized itself around it so that thereafter the system becomes dependent on it. In case this particular gene is already defective at the beginning, the system often can compensate for this loss and organize itself around an alternative gene, which then becomes the essential one.

Thus, organizational entities depend not only on distinct features of particular sub-units but even more so on their functional interactions. In case of the immune system, such multi-component, self-emergent networks comprise a variety of distinct cellular as well as humoral host constituents, but also a manifold of environmental factors, such as the maternal immune system, the microbiome, infectious agents, as well as physical and chemical agents, that co-govern and modulate, but often also interfere and disrupt its normal development during different stages.

Thus, organizational entities depend perhaps less on the appropriate function of particular genetic sub-units alone but much more on the successful interaction of their cellular and humoral products, an observation that is readily evident in case of genetically determined developmental disorders that can cause both immune system deficiencies as well as malignant diseases.

The essential implication of Cohens' model is that we only may become more successful in curing such disease when we begin to understand the decision-making processes of the immune system rather than that of the effects of individual components alone.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

## ACKNOWLEDGMENTS

This paper is dedicated to my late friend and colleague Andreas Heitger, a devoted immunologist, with whom it was always fun to discuss the philosophical part of the activity and behavioral pro and cons of the immune system.

I acknowledge the networking support by the COST Action CA16223 LEukaemia GENe Discovery by data sharing, mining and collaboration (LEGEND) as well as by the IBFM Leukemia & Lymphoma Genetic Predisposition Committee, the Österreichische Kinderkrebsforschung for the continuous funding of my research work and Fikret Rifatbegovic's invaluable help in designing and drawing the Figure.

## REFERENCES

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* (2011) 144:64674. doi: 10.1016/j.cell.2011.02.013

2. Sonnenschein C, Soto AM. Theories of carcinogenesis: an emerging perspective. *Semin Cancer Biol.* (2008) 18:372–77. doi: 10.1016/j.semcancer.2008.03.012

3. Duan L, Grunebaum E. Hematological malignancies associated with primary immunodeficiency disorders. *Clin Immunol*. (2018) 194:46–59. doi: 10.1016/j.clim.2018.06.011
4. Gröbner SN, Worst BC, Weischenfeldt J, Buchhalter I, Kleinheinz K, Rudneva VA, et al. The landscape of genomic alterations across childhood cancers. *Nature* (2018) 555:321–7. doi: 10.1038/nature25480
5. Kager L, Jimenez Heredia R, Hirschmugl T, Dmytrus J, Krolo A, Müller H, et al. Targeted mutation screening of 292 candidate genes in 38 children with inborn haematological cytopenias efficiently identifies novel disease-causing mutations. *Br J Haematol*. (2018) 182:251–8. doi: 10.1111/bjh.15389
6. Ochs HD, Petroni D. From clinical observations and molecular dissection to novel therapeutic strategies for primary immunodeficiency disorders. *Am J Med Genet A* (2018) 176:784–803. doi: 10.1002/ajmg.a.38480
7. Desai AV, Perpich M, Godley LA. Clinical assessment and diagnosis of germline predisposition to hematopoietic malignancies: the university of chicago experience. *Front Pediatry* (2017) 5:252. doi: 10.3389/fped.2017.00252
8. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. *Blood* (2017) 130:424–32. doi: 10.1182/blood-2017-02-735290$
9. Seleman M, Hoyos-Bachiloglu R, Geha RS, Chou J. Uses of next-generation sequencing technologies for the diagnosis of primary immunodeficiencies. *Front Immunol*. (2017) 8:847. doi: 10.3389/fimmu.2017.00847
10. Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, et al. Primary immunodeficiency diseases: genomic approaches delineate heterogeneous Mendelian disorders. *J Allergy Clin Immunol*. (2017) 139:232–45. doi: 10.1016/j.jaci.2016.05.042
11. Al-Mousa H, Abouelhoda M, Monies DM, Al-Tassan N, Al-Ghonaium A, Al-Saud B, et al. Unbiased targeted next-generation sequencing molecular approach for primary immunodeficiency diseases. *J Allergy Clin Immunol*. (2016) 137:1780–7. doi: 10.1016/j.jaci.2015.12.1310
12. Gallo V, Dotta L, Giardino G, Cirillo E, Lougaris V, D'Assante R, et al. Diagnostics of primary immunodeficiencies through next-generation sequencing. *Front Immunol*. (2016) 7:466. doi: 10.3389/fimmu.2016.00466
13. Kuhlen M, Borkhardt A. Cancer susceptibility syndromes in children in the area of broad clinical use of massive parallel sequencing. *Eur J Pediatry* (2015) 174:987–97. doi: 10.1007/s00431-015-2565-x
14. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. *N Engl J Med*. (2015) 373:2336–46. doi: 10.1056/NEJMoa1508054
15. Nijman IJ, van Montfrans JM, Hoogstraat M, Boes ML, van de Corput L, Renner ED, et al. Targeted next-generation sequencing: a novel diagnostic tool for primary immunodeficiencies. *J Allergy Clin Immunol*. (2014) 133:529–34. doi: 10.1016/j.jaci.2013.08.032
16. Raje N, Soden S, Swanson D, Ciaccio CE, Kingsmore SF, Dinwiddie DL. Utility of next generation sequencing in clinical primary immunodeficiencies. *Curr Allergy Asthma Rep*. (2014) 14:468. doi: 10.1007/s11882-014-0468-y
17. Raje N, Soden S, Swanson D, Ciaccio CE, Kingsmore SF, Dinwiddie DL. *Primary Immunodeficiency Diseases*. Berlin Heidelberg: Springer (2016).
18. Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. *Ann NY Acad Sci*. (2011) 1238:7–14. doi: 10.1111/j.1749-6632.2011.06206.x
19. Cunningham-Rundles C. The many faces of common variable immunodeficiency. *Hematol Am Soc Hematol Educ Program* (2012) 2012:301–5. doi: 10.1182/asheducation-2012.1.301$
20. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W, et al. The 2017 IUIS phenotypic classification for primary immunodeficiencies. *J Clin Immunol*. (2018) 38:129–43. doi: 10.1007/s10875-017-0465-8
21. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. *J Clin Immunol*. (2018) 38:96–128. doi: 10.1007/s10875-017-0464-9
22. Conley ME, Notarangelo LD, Casanova JL. Definition of primary immunodeficiency in 2011: a "trialogue" among friends. *Ann N Y Acad Sci*. (2011) 1238:1–6. doi: 10.1111/j.1749-6632.2011.06212.x
23. Studd JB, Yang M, Li Z, Vijayakrishnan J, Vijayakrishnan J, Lu Y, et al. Genetic predisposition to B-cell acute lymphoblastic leukemia at 14q11.2 is mediated by a CEBPE promoter polymorphism. *Leukemia* (2018) 100:347. doi: 10.1038/s41375-018-0184-z
24. Vijayakrishnan J, Studd J, Broderick P, Kinnersley B, Holroyd A, Law PJ, et al. Genome-wide association study identifies susceptibility loci for B-cell childhood acute lymphoblastic leukemia. *Nat Commun*. (2018) 9:1340. doi: 10.1038/s41467-018-03178-z
25. Wiemels JL, Walsh KM, de Smith AJ, Metayer C, Gonseth S, Hansen HM, et al. GWAS in childhood acute lymphoblastic leukemia reveals novel genetic associations at chromosomes 17q12 and 8q24.21. *Nat Commun*. (2018) 9:286. doi: 10.1038/s41467-017-02596-9
26. Studd JB, Vijayakrishnan J, Yang M, Migliorini G, Paulsson K, Houlston RS. Genetic and regulatory mechanism of susceptibility to high-hyperdiploid acute lymphoblastic leukaemia at 10p21.2. *Nat Commun*. (2017) 8:14616. doi: 10.1038/ncomms14616
27. Sud A, Thomsen H, Law PJ, Försti A, Filho MIDS, Holroyd A, et al. Genome-wide association study of classical Hodgkin lymphoma identifies key regulators of disease susceptibility. *Nat Commun*. (2017) 8:1892. doi: 10.1038/s41467-017-00320-1
28. Vijayakrishnan J, Kumar R, Henrion MY, Moorman AV, Rachakonda PS, Hosen I, et al. A genome-wide association study identifies risk loci for childhood acute lymphoblastic leukemia at 10q26.13 and 12q23.1. *Leukemia* (2017) 31:573–9. doi: 10.1038/leu.2016.271
29. odil N, Langlais D, Gros P. Primary immunodeficiencies and inflammatory disease: a growing genetic intersection. *Trends Immunol*. (2016) 37:126–40. doi: 10.1016/j.it.2015.12.006
30. Cerhan JR, Slager SL. Familial predisposition and genetic risk factors for lymphoma. *Blood* (2015) 126:2265–73. doi: 10.1182/blood-2015-04-537498
31. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet*. (2010) 42:1118–25. doi: 10.1038/ng.717
32. Papaemmanuil E, Hosking FJ, Vijayakrishnan J, Price A, Olver B, Sheridan E, et al. Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia. *Nat Genet*. (2009) 41:1006–10. doi: 10.1038/ng.430
33. Heitzeneder S, Seidel M, Forster-Waldl E, Heitger A. Mannan-binding lectin deficiency - Good news, bad news, doesn't matter? *Clin Immunol*. (2012) 143:22–38. doi: 10.1016/j.clim.2011.11.002
34. Taeubner J, Wieczorek D, Yasin L, Brozou T, Borkhardt A, Kuhlen M. Penetrance and expressivity in inherited cancer predisposing syndromes. *Trends Cancer* (2018) 4:718–28. doi: 10.1016/j.trecan.2018.09.002
35. Kuhlen M, Borkhardt A. Trio sequencing in pediatric cancer and clinical implications. *EMBO Mol Med*. (2018) 10:e8641–7. doi: 10.15252/emmm.201708641
36. Kratz CP, Achatz MI, Brugières L, Frebourg T, Garber JE, Greer MC, et al. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. *Clin Cancer Res*. (2017) 23:e38–45. doi: 10.1158/1078-0432.CCR-17-0408
37. Porter CC, Druley TE, Erez A, Kuiper RP, Onel K, Schiffman JD, et al. Recommendations for surveillance for children with leukemia-predisposing conditions. *Clin Cancer Res*. (2017) 23:e14–22. doi: 10.1158/1078-0432.CCR-17-0428
38. Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, et al. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am J Med Genet A* (2017) 173:1017–37. doi: 10.1002/ajmg.a.38142
39. Tabori U, Hansford JR, Achatz MI, Kratz CP, Plon SE, Frebourg T, et al. Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood. *Clin Cancer Res*. (2017) 23:e32–7. doi: 10.1158/1078-0432.CCR-17-0574
40. Walsh MF, Chang VY, Kohlmann WK, Scott HS, Cunniff C, Bourdeaut F, et al. Recommendations for childhood cancer screening and surveillance in DNA repair disorders. *Clin Cancer Res*. (2017) 23:e23–31. doi: 10.1158/1078-0432.CCR-17-0465
41. Jongmans MC, Loeffen JL, Waanders E, Hoogerbrugge PM, Ligtenberg MJ, Kuiper RP, et al. Recognition of genetic predisposition in pediatric cancer

patients: an easy-to-use selection tool. *Eur J Med Genet*. (2016) 59:116–25. doi: 10.1016/j.ejmg.2016.01.008
42. Kratz CP, Stanulla M, Cave H. Genetic predisposition to acute lymphoblastic leukemia: overview on behalf of the I-BFM ALL Host Genetic Variation Working Group. *Eur J Med Genet*. (2016) 59:111–5. doi: 10.1016/j.ejmg.2015.10.003
43. Similuk M, Rao VK, Churpek J, Lenardo M. Predispositions to lymphoma: a practical review for genetic counselors. *J Genet Couns*. (2016) 25:1157–70. doi: 10.1007/s10897-016-9979-0
44. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL, Guideline Development Group, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. (2015) 17:70–87. doi: 10.1038/gim.2014.147
45. Schneider M, Chandler K, Tischkowitz M, Meyer S. Fanconi anaemia: genetics, molecular biology, and cancer - implications for clinical management in children and adults. *Clin Genet*. (2015) 88:13–24. doi: 10.1111/cge.12517
46. Vasen HF, Ghorbanoghli Z, Bourdeaut F, Cabaret O, Caron O, Duval A, et al. Guidelines for surveillance of individuals with constitutional mismatch repair-deficiency proposed by the European Consortium "Care for CMMR-D" (C4CMMR-D). *J Med Genet*. (2014) 51:283–93. doi: 10.1136/jmedgenet-2013-102238
47. Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). *J Med Genet*. (2014) 51:355–65. doi: 10.1136/jmedgenet-2014-102284
48. Auer F, Rüschendorf F, Gombert M, Husemann P, Ginzel S, Izraeli S, et al. Inherited susceptibility to pre B-ALL caused by germline transmission of PAX5 c.547G> A. *Leukemia* (2014) 28:1136–8. doi: 10.1038/leu.2013.363
49. Auer F, Lin M, Nebral K, Gertzen CGW, Haas OA, Kuhlen M, et al. Novel recurrent germline JAK2 G571S variant in childhood acute B-lymphoblastic leukemia: a double hit one pathway scenario. *Blood* (2018) 132:387. doi: 10.1182/blood-2018-99-115293
50. Mitchell KJ. What is complex about complex disorders? *Genome Biol*. (2012) 13:237. doi: 10.1186/gb-2012-13-1-237
51. Boyle EA, Li YI, Pritchard JK. An expanded view of complex traits: from polygenic to omnigenic. *Cell* (2017) 169:1177–86. doi: 10.1016/j.cell.2017.05.038
52. Farh KK, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* (2015) 518:337–43. doi: 10.1038/nature13835
53. Maurano MT, Haugen E, Sandstrom R, Vierstra J, Shafer A, Kaul R, et al. Large-scale identification of sequence variants influencing human transcription factor occupancy *in vivo*. *Nat Genet*. (2015) 47:1393–401. doi: 10.1038/ng.3432
54. Wray NR, Wijmenga C, Sullivan PF, Yang J, Visscher PM. Common disease is more complex than implied by the core gene omnigenic model. *Cell* (2018) 173:1573–80. doi: 10.1016/j.cell.2018.05.051
55. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. (2018) 50:1219–24. doi: 10.1038/s41588-018-0183-z
56. Sonnenschein C, Soto AM. Carcinogenesis explained within the context of a theory of organisms. *Prog Biophys Mol Biol*. (2016) 122:70–6. doi: 10.1016/j.pbiomolbio.2016.07.004
57. Soto AM, Sonnenschein C. The somatic mutation theory of cancer: growing problems with the paradigm? *Bioessays* (2004) 26:1097–107. doi: 10.1002/bies.20087
58. Laconi E, Sonnenschein C. Cancer development at tissue level. *Semin Cancer Biol*. (2008) 18:303–4. doi: 10.1016/j.semcancer.2008.03.002
59. Longo G, Montevil M, Sonnenschein C, Soto AM. In search of principles for a theory of organisms. *J Biosci*. (2015) 40:955–68. doi: 10.1007/s12038-015-9574-9
60. Hauck F, Voss R, Urban C, Seidel MG. Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. *J Allergy Clin Immunol*. (2018) 141:59–68.e4. doi: 10.1016/j.jaci.2017.06.009
61. Corthay A. Does the immune system naturally protect against cancer? *Front Immunol*. (2014) 5:197. doi: 10.3389/fimmu.2014.00197
62. Chow MT, Moller A, Smyth MJ. Inflammation and immune surveillance in cancer. *Semin Cancer Biol*. (2012) 22:23–32. doi: 10.1016/j.semcancer.2011.12.004
63. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* (2010) 140:883–99. doi: 10.1016/j.cell.2010.01.025
64. Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest*. (2007) 117:1137–46. doi: 10.1172/JCI31405
65. Goh KI, Cusick ME, Valle D, Childs B, Vidal M, Barabási AL. The human disease network. *Proc Natl Acad Sci USA*. (2007) 104:8685–90. doi: 10.1073/pnas.0701361104
66. Latour S, Winter S. Inherited immunodeficiencies with high predisposition to epstein-barr virus-driven lymphoproliferative diseases. *Front Immunol*. (2018) 9:1103. doi: 10.3389/fimmu.2018.01103
67. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the United States Immune Deficiency Network Registry. *J Allergy Clin Immunol*. (2018) 141:1028–35. doi: 10.1016/j.jaci.2017.05.024
68. Satge D. A tumor profile in primary immune deficiencies challenges the cancer immune surveillance concept. *Front Immunol*. (2018) 9:1149. doi: 10.3389/fimmu.2018.01149
69. Verhoeven D, Stoppelenburg AJ, Meyer-Wentrup F, Boes M. Increased risk of hematologic malignancies in primary immunodeficiency disorders: opportunities for immunotherapy. *Clin Immunol*. (2018) 190:22–31. doi: 10.1016/j.clim.2018.02.007
70. Mortaz E, Tabarsi P, Mansouri D, Khosravi A, Garssen J, Velayati A, et al. Cancers related to immunodeficiencies: update and perspectives. *Front Immunol*. (2016) 7:365. doi: 10.3389/fimmu.2016.00365
71. de Miranda NF, Björkman A, Pan-Hammarström Q. DNA repair: the link between primary immunodeficiency and cancer. *Ann N Y Acad Sci*. (2011) 1246:50–63. doi: 10.1111/j.1749-6632.2011.06322.x
72. Shapiro RS. Malignancies in the setting of primary immunodeficiency: implications for hematologists/oncologists. *Am J Hematol*. (2011) 86:48–55. doi: 10.1002/ajh.21903
73. Racicot K, Kwon JY, Aldo P, Silasi M, Mor G. Understanding the complexity of the immune system during pregnancy. *Am J Reprod Immunol*. (2014) 72:107–116. doi: 10.1111/aji.12289
74. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol*. (2010) 63:425–33. doi: 10.1111/j.1600-0897.2010.00836.x
75. Burlingham WJ. A lesson in tolerance–maternal instruction to fetal cells. *N Engl J Med*. (2009) 360:1355–7. doi: 10.1056/NEJMcibr0810752
76. Mold JE, Michaëlsson J, Burt TD, Muench MO, Beckerman KP, Busch MP, et al. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells *in utero*. *Science* (2008) 322:1562–5. doi: 10.1126/science.1164511
77. Trowsdale J, Betz AG. Mother's little helpers: mechanisms of maternal-fetal tolerance. *Nat Immunol*. (2006) 7:241–6. doi: 10.1038/ni1317
78. Kinder JM, Stelzer IA, Arck PC, Way SS. Immunological implications of pregnancy-induced microchimerism. *Nat Rev Immunol*. (2017) 17:483–94. doi: 10.1038/nri.2017.38
79. Cismaru CA, Pop L, Berindan-Neagoe I. Incognito: are microchimeric fetal stem cells that cross placental barrier real emissaries of peace? *Stem Cell Rev*. (2018) 14:632–41. doi: 10.1007/s12015-018-9834-9
80. Jeanty C, Derderian SC, Mackenzie TC. Maternal-fetal cellular trafficking: clinical implications and consequences. *Curr Opin Pediatr*. (2014) 26:377–82. doi: 10.1097/MOP.0000000000000087
81. Müller SM, Ege M, Pottharst A, Schulz AS, Schwarz K, Friedrich W. Transplacentally acquired maternal T lymphocytes in severe combined immunodeficiency: a study of 121 patients. *Blood* (2001) 98:1847–851.
82. Wahlstrom J, Patel K, Eckhert E, Kong D, Horn B, Cowan MJ, et al. Transplacental maternal engraftment and posttransplantation graft-versus-host disease in children with severe combined immunodeficiency. *J Allergy Clin Immunol*. (2017) 139:628–33.e10. doi: 10.1016/j.jaci.2016.04.049
83. van Rood JJ, Scaradavou A, Stevens CE. Indirect evidence that maternal microchimerism in cord blood mediates a graft-versus-leukemia effect in

cord blood transplantation. *Proc Natl Acad Sci USA*. (2012) 109:2509–14. doi: 10.1073/pnas.1119541109
84. Isoda T, Ford AM, Tomizawa D, van Delft FW, De Castro DG, Mitsuiki N, et al. Immunologically silent cancer clone transmission from mother to offspring. *Proc Natl Acad Sci USA*. (2009) 106:17882–5. doi: 10.1073/pnas.0904658106
85. van den Boogaardt DE, van Rood JJ, Roelen DL, Claas FH. The influence of inherited and noninherited parental antigens on outcome after transplantation. *Transpl Int*. (2006) 19:360–71. doi: 10.1111/j.1432-2277.2006.00304.x
86. Dendrou CA, Petersen J, Rossjohn J, Fugger L. HLA variation and disease. *Nat Rev Immunol*. (2018) 18:325–39. doi: 10.1038/nri.2017.143
87. Trowsdale J, Knight JC. Major histocompatibility complex genomics and human disease. *Annu Rev Genomics Hum Genet*. (2013) 14:301–23. doi: 10.1146/annurev-genom-091212-153455
88. Taylor M, Hussain A, Urayama K, Chokkalingam A, Thompson P, Trachtenberg E, et al. The human major histocompatibility complex and childhood leukemia: an etiological hypothesis based on molecular mimicry. *Blood Cells Mol Dis*. (2009) 42:129–35. doi: 10.1016/j.bcmd.2008.10.009
89. Mosaad YM. Clinical role of human leukocyte antigen in health and disease. *Scand J Immunol*. (2015) 82:283–306. doi: 10.1111/sji.12329
90. Klitz W, Gragert L, Trachtenberg E. Spectrum of HLA associations: the case of medically refractory pediatric acute lymphoblastic leukemia. *Immunogenetics* (2012) 64:409–19. doi: 10.1007/s00251-012-0605-5
91. Masucci GV, Andersson E, Villabona L, Helgadottir H. Survival of the fittest or best adapted: HLA-dependent tumor development. *J Nucleic Acids Investig.* (2010) doi: 10.4081/jnai.2010.1654
92. Taylor GM, Dearden S, Ravetto P, Ayres M, Watson P, Hussain A, et al. Genetic susceptibility to childhood common acute lymphoblastic leukaemia is associated with polymorphic peptide-binding pocket profiles in HLA-DPB1*0201. *Hum Mol Genet*. (2002) 11:1585–97.
93. Taylor GM, Hussain A, Lightfoot TJ, Birch JM, Eden TO, Greaves MF. HLA-associated susceptibility to childhood B-cell precursor ALL: definition and role of HLA-DPB1 supertypes. *Br J Cancer* (2008) 98:1125–31. doi: 10.1038/sj.bjc.6604257
94. Taylor M, Harrison C, Eden T, Birch J, Greaves M, Lightfoot T, et al. HLA-DPB1 supertype-associated protection from childhood leukaemia: relationship to leukaemia karyotype and implications for prevention. *Cancer Immunol Immunother*. (2008) 57:53–61. doi: 10.1007/s00262-007-0349-5
95. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer* (2018) 18:471–84. doi: 10.1038/s41568-018-0015-6
96. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer* (2006) 6:193–203. doi: 10.1038/nrc1816
97. Greaves M. *In utero* origins of childhood leukaemia. *Early Hum Dev*. (2005) 81:123–9. doi: 10.1016/j.earlhumdev.2004.10.004
98. Marty R, Kaabinejadian S, Rossell D, Slifker MJ, van de Haar J, Engin HB, et al. MHC-I genotype restricts the oncogenic mutational landscape. *Cell* (2017) 171:1272–1283.e15. doi: 10.1016/j.cell.2017.09.050
99. Roberts I, Izraeli S. Haematopoietic development and leukaemia in Down syndrome. *Br J Haematol*. (2014) 167:587–99. doi: 10.1111/bjh.13096
100. Yoshida K, Toki T, Okuno Y, Kanezaki R, Shiraishi Y, Sato-Otsubo A, et al. The landscape of somatic mutations in Down syndrome-related myeloid disorders. *Nat Genet* (2013) 45:1293–1299. doi: 10.1038/ng.2759
101. Malinge S, Izraeli S, Crispino JD. Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome. *Blood* (2009) 113:2619–28. doi: 10.1182/blood-2008-11-163501
102. Izraeli S. Down's syndrome as a model of a pre-leukemic condition. *Haematologica* (2006) 91:1448–52.
103. Raciborska A, Bilska K, Wecławek-Tompol J, Ussowicz M, Pogorzała M, Janowska J, et al. Solid cancers in the premature and the newborn: report of three national referral centers. *Pediatr Neonatol.* (2016) 57:295–301. doi: 10.1016/j.pedneo.2015.08.007
104. Roberts I, Fordham NJ, Rao A, Bain BJ. Neonatal leukaemia. *Br J Haematol*. (2018) 182:170–84. doi: 10.1111/bjh.15246
105. Maris JM, Denny CT. Focus on embryonal malignancies. *Cancer Cell* (2002) 2:447–50.
106. Perera FP. Environment and cancer: who are susceptible? *Science* (1997) 278:1068–73. doi: 10.1126/science.278.5340.1068
107. Tesch VK, IJspeert H, Raicht A, Rueda D, Dominguez-Pinilla N, Allende LM, et al. No overt clinical immunodeficiency despite immune biological abnormalities in patients with constitutional mismatch repair deficiency. *Front Immunol.* (2018) 9:1506. doi: 10.3389/fimmu.2018.01506
108. Prochazkova J, Loizou JI. Programmed DNA breaks in lymphoid cells: repair mechanisms and consequences in human disease. *Immunology* (2016) 147:11–20. doi: 10.1111/imm.12547
109. Lavoine N, Colas C, Muleris M, Bodo S, Duval A, Entz-Werle N, et al. Constitutional mismatch repair deficiency syndrome: clinical description in a French cohort. *J Med Genet.* (2015) 52:770–8. doi: 10.1136/jmedgenet-2015-103299
110. Chrzanowska KH, Gregorek H, Dembowska-Baginska B, Kalina MA, Digweed M. Nijmegen breakage syndrome (NBS). *Orphanet J Rare Dis.* (2012) 7:13. doi: 10.1186/1750-1172-7-13
111. Moraes MC, Neto JB, Menck CF. DNA repair mechanisms protect our genome from carcinogenesis. *Front Biosci.* (2012) 17:1362–88.
112. Slatter MA, Gennery AR. Primary immunodeficiencies associated with DNA-repair disorders. *Expert Rev Mol Med*. (2010) 12:e9. doi: 10.1017/S1462399410001419
113. Durno CA, Sherman PM, Aronson M, Malkin D, Hawkins C, Bakry D, et al. Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome. *Eur J Cancer* (2015) 51:977–83. doi: 10.1016/j.ejca.2015.02.008
114. Bakry D, Aronson M, Durno C, Rimawi H, Farah R, Alharbi QK, et al. Genetic and clinical determinants of constitutional mismatch repair deficiency syndrome: report from the constitutional mismatch repair deficiency consortium. *Eur J Cancer* (2014) 50:987–96. doi: 10.1016/j.ejca.2013.12.005
115. Wimmer K, Kratz CP. Constitutional mismatch repair-deficiency syndrome. *Haematologica* (2010) 95:699–701. doi: 10.3324/haematol.2009.021626
116. Thoms KM, Kuschal C, Emmert S. Lessons learned from DNA repair defective syndromes. *Exp Dermatol.* (2007) 16:532–44. doi: 10.1111/j.1600-0625.2007.00559.x
117. Lehmann AR. The xeroderma pigmentosum group D (XPD) gene: one gene, two functions, three diseases. *Genes Dev.* (2001) 15:15–23.
118. de Boer J, Hoeijmakers JH. Nucleotide excision repair and human syndromes. *Carcinogenesis* (2000) 21:453–60.
119. Kraemer KH, Patronas NJ, Schiffmann R, Brooks BP, Tamura D, DiGiovanna JJ. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. *Neuroscience* (2007) 145:1388–96. doi: 10.1016/j.neuroscience.2006.12.020
120. Bootsma D, Hoeijmakers JH. Repair DNA. Engagement with transcription. *Nature* (1993) 363:114–5. doi: 10.1038/363114a0
121. Bogaert DJ, Dullaers M, Lambrecht BN, Vermaelen KY, et al. Genes associated with common variable immunodeficiency: one diagnosis to rule them all? *J Med Genet.* (2016) 53:575–90. doi: 10.1136/jmedgenet-2015-103690
122. Maffucci P, Filion CA, Boisson B, Itan Y, Shang L, Casanova JL, et al. Genetic diagnosis using whole exome sequencing in common variable immunodeficiency. *Front Immunol.* (2016) 7:220. doi: 10.3389/fimmu.2016.00220
123. Abbott JK, Gelfand EW. Common variable immunodeficiency: diagnosis, management, and treatment. *Immunol Allergy Clin North Am.* (2015) 35:637–58. doi: 10.1016/j.iac.2015.07.009
124. Gangemi S, Allegra A, Musolino C. Lymphoproliferative disease and cancer among patients with common variable immunodeficiency. *Leuk Res.* (2015) 39:389–96. doi: 10.1016/j.leukres.2015.02.002
125. Ameratunga R, Brewerton M, Slade C, Jordan A, Gillis D, Steele R, et al. Comparison of diagnostic criteria for common variable immunodeficiency disorder. *Front Immunol*. (2014) 5:415. doi: 10.3389/fimmu.2014.00415
126. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol.* (2014) 134:116–26. doi: 10.1016/j.jaci.2013.12.1077

127. Park JH, Resnick ES, Cunningham-Rundles C. Perspectives on common variable immune deficiency. *Ann N Y Acad Sci.* (2011) 1246:41–9. doi: 10.1111/j.1749-6632.2011.06338.x
128. Vajdic CM, Mao L, van Leeuwen MT, Kirkpatrick P, Grulich AE, Riminton S. Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? *Blood* (2010) 116:1228–34. doi: 10.1182/blood-2010-03-272351
129. Salavoura K, Kolialexi A, Tsangaris G, Mavrou A. Development of cancer in patients with primary immunodeficiencies. *Anticancer Res.* (2008) 28:1263–9.
130. Mellemkjaer L, Hammarstrom L, Andersen V, Yuen J, Heilmann C, Barington T, et al. Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. *Clin Exp Immunol.* (2002) 130:495–500.
131. Teng MW, Galon J, Fridman WH, Smyth MJ. From mice to humans: developments in cancer immunoediting. *J Clin Investig.* (2015) 125:3338–46. doi: 10.1172/JCI80004
132. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases–elimination, equilibrium and escape. *Curr Opin Immunol.* (2014) 27:16–25. doi: 10.1016/j.coi.2014.01.004
133. Gross E, Sunwoo JB, Bui JD. Cancer immunosurveillance and immunoediting by natural killer cells. *Cancer J.* (2013) 19:483–9. doi: 10.1097/PPO.0000000000000005
134. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* (2011) 331:1565–70. doi: 10.1126/science.1203486
135. Zamarron BF, Chen W. Dual roles of immune cells and their factors in cancer development and progression. *Int J Biol Sci.* (2011) 7:651–8.
136. Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. *Immunology* (2007) 121:1–14. doi: 10.1111/j.1365-2567.2007.02587.x
137. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity* (2004) 21:137–48. doi: 10.1016/j.immuni.2004.07.017
138. Ribatti D. The concept of immune surveillance against tumors. The first theories. *Oncotarget* (2017) 8:7175–80. doi: 10.18632/oncotarget.12739
139. Jonkman-Berk BM, van den Berg JM, Ten Berge IJ, Bredius RG, Driessen GJ, Dalm VA, et al. Primary immunodeficiencies in the Netherlands: national patient data demonstrate the increased risk of malignancy. *Clinical Immunol.* (2015) 156:154–62. doi: 10.1016/j.clim.2014.10.003
140. McGonagle D, Aziz A, Dickie LJ, McDermott MF. An integrated classification of pediatric inflammatory diseases, based on the concepts of autoinflammation and the immunological disease continuum. *Pediatr Res.* (2009) 65:38R−45R. doi: 10.1203/PDR.0b013e31819dbd0a
141. Medzhitov R. Origin and physiological roles of inflammation. *Nature* (2008) 454:428–35. doi: 10.1038/nature07201
142. Karin M, Clevers H. Reparative inflammation takes charge of tissue regeneration. *Nature* (2016) 529:307–15. doi: 10.1038/nature17039
143. Dzutsev A, Goldszmid RS, Viaud S, Zitvogel L, Trinchieri G. The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. *Eur J Immunol.* (2015) 45:17–31. doi: 10.1002/eji.201444972
144. Shalapour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J Clin Invest.* (2015) 125:3347–55. doi: 10.1172/JCI80007
145. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* (2008) 454:436–44. doi: 10.1038/nature07205
146. Baniyash M, Sade-Feldman M, Kanterman J. Chronic inflammation and cancer: suppressing the suppressors. *Cancer Immunol Immunother* (2014) 63:11–20. doi: 10.1007/s00262-013-1468-9
147. Ferreri AJ, Govi S, Ponzoni M. Marginal zone lymphomas and infectious agents. *Semin Cancer Biol.* (2013) 23:431–40. doi: 10.1016/j.semcancer.2013.09.004
148. Thieblemont C, Bertoni F, Copie-Bergman C, Ferreri AJ, Ponzoni M. Chronic inflammation and extra-nodal marginal-zone lymphomas of MALT-type. *Semin Cancer Biol.* (2014) 24:33–42. doi: 10.1016/j.semcancer.2013.11.005
149. Valente AL, Schroeder B, Shriver CD, Henning JD, et al. Chronic inflammation in cancer: the role of human viruses. *Adv Tumor Virol.* (2015) 5:1–11. doi: 10.4137/atv.S19779
150. Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology* (2002) 16:217–26.
151. Boyapati R, Satsangi J, Ho GT. Pathogenesis of Crohn's disease. *F1000Prime Rep*. (2015) 7:44. doi: 10.12703/P7-44
152. Schreiber S, Rosenstiel P, Albrecht M, Hampe J, Krawczak M. Genetics of Crohn disease, an archetypal inflammatory barrier disease. *Nat Rev Genet*. (2005) 6:376–88. doi: 10.1038/nrg1607
153. Neven B, Mamessier E, Bruneau J, Kaltenbach S, Kotlarz D, Suarez F, et al. A Mendelian predisposition to B-cell lymphoma caused by IL-10deficiency R. *Blood* (2013) 122:3713–3722. doi: 10.1182/blood-2013-06-508267
154. Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K,et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. *Gastroenterology* (2012) 143:347–55. doi: 10.1053/j.gastro.2012.04.045
155. Glocker EO, Kotlarz D, Klein C, Shah N, Grimbacher B. IL-10 and IL-10 receptor defects in humans. *Ann N Y Acad Sci.* (2011) 1246:102–7. doi: 10.1111/j.1749-6632.2011.06339.x
156. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med.* (2009) 361:2033–45. doi: 10.1056/NEJMoa0907206
157. Schmidt RE, Grimbacher B, Witte T. Autoimmunity and primary immunodeficiency: two sides of the same coin? *Nat Rev Rheumatol*. (2017) 14:7–18. doi: 10.1038/nrrheum.2017.198
158. Seidel MG. Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment. *Blood* (2014) 124:2337–44. doi: 10.1182/blood-2014-06-583260
159. Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. *Blood* (2002) 99:2694–702.
160. Rieux-Laucat F, Magerus-Chatinet A, Neven B. The autoimmune lymphoproliferative syndrome with defective FAS or FAS-ligand functions. *J Clin Immunol*. (2018) 38:558–68. doi: 10.1007/s10875-018-0523-x
161. Price S, Shaw PA, Seitz A, Joshi G, Davis J, Niemela JE, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. *Blood* (2014) 123:1989–99. doi: 10.1182/blood-2013-10-535393
162. Straus SE, Jaffe ES, Puck JM, Dale JK, Elkon KB, Rösen-Wolff A, et al. The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. *Blood* (2001) 98:194–200.
163. Barzaghi F, Amaya Hernandez LC, Neven B, Ricci S, Kucuk ZY, Bleesing JJ, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: an international multicenter retrospective study. *J Allergy Clin Immunol*. (2018) 141:1036–49 e1035. doi: 10.1016/j.jaci.2017.10.041
164. Gambineri E, Perroni L, Passerini L, Bianchi L, Doglioni C, Meschi F, et al. Clinical and molecular profile of a new series of patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome: inconsistent correlation between forkhead box protein 3 expression and disease severity. *J Allergy Clin Immunol*. (2008) 122:1105–1112.e1. doi: 10.1016/j.jaci.2008.09.027
165. Bacchetta R, Passerini L, Gambineri E, Dai M, Allan SE, Perroni L, et al. Defective regulatory and effector T cell functions in patients with FOXP3 mutations. *J Clin Invest*. (2006) 116:1713–22. doi: 10.1172/JCI25112
166. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, et al. CTLA-4 control over Foxp3+ regulatory T cell function. *Science* (2008) 322:271–5. doi: 10.1126/science.1160062
167. Schubert D, Bode C, Kenefeck R, Hou TZ, Wing JB, Kennedy A, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. *Nat Med*. (2014) 20:1410–6. doi: 10.1038/nm.3746
168. Rudd CE. The reverse stop-signal model for CTLA4 function. *Nat Rev Immunol*. (2008) 8:153–60. doi: 10.1038/nri2253
169. Gough SC, Walker LS, Sansom DM. CTLA4 gene polymorphism and autoimmunity. *Immunol Rev.* (2005) 204:102–15. doi: 10.1111/j.0105-2896.2005.00249.x

170. Egg D, Schwab C, Gabrysch A, Arkwright PD, Cheesman E, Giulino-Roth L, et al. Increased risk for malignancies in 131 affected CTLA4 mutation carriers. *Front Immunol*. (2018) 9:2012. doi: 10.3389/fimmu.2018.02012
171. Boutboul D, Kuehn HS, Van de Wyngaert Z, Niemela JE, Callebaut I, Stoddard J, et al. Dominant-negative IKZF1 mutations cause a T, B, and myeloid cell combined immunodeficiency. *J Clin Invest*. (2018) 128:3071–87. doi: 10.1172/JCI98164
172. Churchman ML, Qian M, Te Kronnie G, Zhang R, Yang W, Zhang H, et al. Germline genetic IKZF1 variation and predisposition to childhood acute lymphoblastic leukemia. *Cancer Cell* (2018) 33:937–948.e8. doi: 10.1016/j.ccell.2018.03.021
173. Kamihara J, Shimamura A. It's ALL in the family: IKZF1 and hereditary leukemia. *Cancer Cell* (2018) 33:798–800. doi: 10.1016/j.ccell.2018.04.008
174. Van Nieuwenhove E, Garcia-Perez JE, Helsen C, Rodriguez PD, van Schouwenburg PA, Dooley J, et al. A kindred with mutant IKAROS, autoimmunity. *J Allergy Clin Immunol.* (2018) 142:699–702.e2. doi: 10.1016/j.jaci.2018.04.008
175. Hoshino A, Okada S, Yoshida K, Nishida N, Okuno Y, Ueno H, et al. Abnormal hematopoiesis and autoimmunity in human subjects with germline IKZF1 mutations. *J Allergy Clin Immunol*. (2017) 140:223–31. doi: 10.1016/j.jaci.2016.09.029
176. Pellegrini FP, Marinoni M, Frangione V, Tedeschi A, Gandini V, Ciglia F, et al. Down syndrome, autoimmunity and T regulatory cells. *Clin Exp Immunol*. (2012) 169:238–43. doi: 10.1111/j.1365-2249.2012.04610.x
177. Chistiakov D. Down syndrome and coexistent autoimmune diseases. *J Appl Biomed*. (2007) 5:71–76.
178. Cuadrado E, Barrena MJ. Immune dysfunction in Down's syndrome: primary immune deficiency or early senescence of the immune system? *Clin Immunol Immunopathol*. (1996) 78:209–14.
179. Cetica V, Sieni E, Pende D, Danesino C, De Fusco C, Locatelli F, et al. Genetic predisposition to hemophagocytic lymphohistiocytosis: report on 500 patients from the Italian registry. *J Allergy Clin Immunol*. (2016) 137:188–96.e4. doi: 10.1016/j.jaci.2015.06.048
180. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol*. (2015) 90:220–24. doi: 10.1002/ajh.23911
181. Arico M, Imashuku S, Clementi R, Hibi S, Teramura T, Danesino C, et al. Hemophagocytic lymphohistiocytosis due to germline mutations in SH2D1A, the X-linked lymphoproliferative disease gene. *Blood* (2001) 97:1131–3.
182. Chaudhry MS, Gilmour KC, House IG, Layton M, Panoskaltsis N, Sohal M, et al. Missense mutations in the perforin (PRF1) gene as a cause of hereditary cancer predisposition. *Oncoimmunology* (2016) 5:e1179415. doi: 10.1080/2162402X.2016.1179415
183. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. *Nat Rev Immunol*. (2015) 15:388–400. doi: 10.1038/nri3839
184. Osinska I, Popko K, Demkow U. Perforin: an important player in immune response. *Cent Eur J Immunol*. (2014) 39:109–15. doi: 10.5114/ceji.2014.42135
185. Trapani JA, Thia KY, Andrews M, Davis ID, Gedye C, Parente P, et al. Human perforin mutations and susceptibility to multiple primary cancers. *Oncoimmunology* (2013) 2:e24185. doi: 10.4161/onci.24185
186. Voskoboinik I, Trapani JA. Perforinopathy: a spectrum of human immune disease caused by defective perforin delivery or function. *Front Immunol*. (2013) 4:441. doi: 10.3389/fimmu.2013.00441
187. Ciambotti B, Mussolin L, d'Amore ES, Pillon M, Sieni E, Coniglio ML, et al. Monoallelic mutations of the perforin gene may represent a predisposing factor to childhood anaplastic large cell lymphoma. *J Pediatr Hematol Oncol*. (2014) 36:e359–65. doi: 10.1097/MPH.0000000000000073
188. Manso R, Rodríguez-Pinilla SM, Lombardia L, Ruiz de Garibay G, Del Mar López M, Requena L, et al. An A91V SNP in the perforin gene is frequently found in NK/T-cell lymphomas. *PLoS ONE* (2014) 9:e91521. doi: 10.1371/journal.pone.0091521
189. Cannella S, Santoro A, Bruno G, Pillon M, Mussolin L, Mangili G, et al. Germline mutations of the perforin gene are a frequent occurrence in childhood anaplastic large cell lymphoma. *Cancer* (2007) 109:2566–71. doi: 10.1002/cncr.22718
190. Clementi R, Locatelli F, Dupré L, Garaventa A, Emmi L, Bregni M, et al. A proportion of patients with lymphoma may harbor mutations of the perforin gene. *Blood* (2005) 105:4424–8. doi: 10.1182/blood-2004-04-1477
191. Aricò M, Mussolin L, Carraro E, Buffardi S, Santoro N, D'Angelo P, et al. Non-Hodgkin lymphoma in children with an associated inherited condition: a retrospective analysis of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). *Pediatr Blood Cancer* (2015) 62:1782–9. doi: 10.1002/pbc.25565
192. Booth C, Gilmour KC, Veys P, Gennery AR, Slatter MA, Chapel H, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. *Blood* (2011) 117:53–62. doi: 10.1182/blood-2010-06-284935
193. Filipovich AH, Zhang K, Snow AL, Marsh RA. X-linked lymphoproliferative syndromes: brothers or distant cousins? *Blood* (2010) 116:3398–408. doi: 10.1182/blood-2010-03-275909
194. Round JL, Palm NW. Causal effects of the microbiota on immune-mediated diseases. *Sci Immunol*. (2018) 3:eaao1603. doi: 10.1126/sciimmunol.aao1603
195. Dzutsev A, Badger JH, Perez-Chanona E, Roy S, Salcedo R, Smith CK, et al. Microbes and cancer. *Annu Rev Immunol*. (2017) 35:199–228. doi: 10.1146/annurev-immunol-051116-052133
196. Kundu P, Blacher E, Elinav E, Pettersson S. Our gut microbiome: the evolving inner self. *Cell* (2017) 171:1481–93. doi: 10.1016/j.cell.2017.11.024
197. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. *Nat Rev Immunol*. (2017) 17:219–32. doi: 10.1038/nri.2017.7
198. Tamburini S, Shen N, Wu HC, Clemente JC. The microbiome in early life: implications for health outcomes. *Nat Med*. (2016) 22:713–22. doi: 10.1038/nm.4142
199. Garrett WS, Gordon JI, Glimcher LH. Homeostasis and inflammation in the intestine. *Cell* (2010) 140:859–70. doi: 10.1016/j.cell.2010.01.023
200. Khachatryan ZA, Ktsoyan ZA, Manukyan GP, Kelly D, Ghazaryan KA, Aminov RI. Predominant role of host genetics in controlling the composition of gut microbiota. *PLoS ONE* (2008) 3:e3064. doi: 10.1371/journal.pone.0003064
201. Benson AK. Host genetic architecture and the landscape of microbiome composition: humans weigh in. *Genome Biol.* (2015) 16:203. doi: 10.1186/s13059-015-0775-1
202. Benson AK, Kelly SA, Legge R, Ma F, Low SJ, Kim J, et al. Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. *Proc Natl Acad Sci USA*. (2010) 107:18933–8. doi: 10.1073/pnas.1007028107
203. Fulde M, Sommer F, Chassaing B, van Vorst K, Dupont A, Hensel M, et al. Neonatal selection by Toll-like receptor 5 influences long-term gut microbiota composition. *Nature* (2018) 560:489–93. doi: 10.1038/s41586-018-0395-5
204. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol.* (2012) 13:607–15. doi: 10.1016/S1470-2045(12)70137-7
205. Garrett WS. Cancerand the microbiota. *Science* (2015) 348:80–6. doi: 10.1126/science.aaa4972
206. Gagliani N, Hu B, Huber S, Elinav E, Flavell RA. The fire within: microbes inflame tumors. *Cell* (2014) 157:776–83. doi: 10.1016/j.cell.2014.03.006
207. Garrett WS, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, et al. Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell* (2007) 131:33–45. doi: 10.1016/j.cell.2007.08.017
208. Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, et al. Environment dominates over host genetics in shaping human gut microbiota. *Nature* (2018) 555:210–5. doi: 10.1038/nature25973
209. Blekhman R, Goodrich JK, Huang K, Sun Q, Bukowski R, Bell JT, et al. Host genetic variation impacts microbiome composition across human body sites. *Genome Biol.* (2015) 16:191. doi: 10.1186/s13059-015-0759-1
210. Yamamoto ML, Maier I, Dang AT, Berry D, Liu J, Ruegger PM, et al. Intestinal bacteria modify lymphoma incidence and latency by affecting systemic inflammatory state, oxidative stress, and leukocyte genotoxicity. *Cancer Res.* (2013) 73:4222-4232. doi: 10.1158/0008-5472.CAN-13-0022

211. Bromberg JS, Hittle L, Xiong Y, Saxena V, Smyth EM, Li L, et al. Gut microbiota-dependent modulation of innate immunity and lymph node remodeling affects cardiac allograft outcomes. *JCI Insight* (2018) 3:121045. doi: 10.1172/jci.insight.121045
212. Plottel CS, Blaser MJ. Microbiome and malignancy. *Cell Host Microbe* (2011) 10:324–35. doi: 10.1016/j.chom.2011.10.003
213. Correia S, Bridges R, Wegner F, Venturini C, Palser A, Middeldorp JM, et al. Sequence variation of Epstein-Barr virus: viral types, geography, codon usage and diseases. *J Virol.* (2018) 92:e01132–18 .doi: 10.1128/JVI.01132–18
214. Young LS, Yap LF, Murray PG. Epstein-Barr virus: more than 50 years old and still providing surprises. *Nat Rev Cancer* (2016) 16:789–802. doi: 10.1038/nrc.2016.92
215. Yilmaz B, Portugal S, Tran TM, Gozzelino R, Ramos S, Gomes J, et al. Gut microbiota elicits a protective immune response against malaria transmission. *Cell* (2014) 159:1277–89. doi: 10.1016/j.cell.2014.10.053
216. Arvey A, Tempera I, Tsai K, Chen HS, Tikhmyanova N, Klichinsky M, et al. An atlas of the Epstein-Barr virus transcriptome and epigenome reveals host-virus regulatory interactions. *Cell Host Microbe* (2012) 12:233–45. doi: 10.1016/j.chom.2012.06.008
217. Magrath I. Epidemiology: clues to the pathogenesis of Burkitt lymphoma. *Br J Haematol.* (2012) 156:744–56. doi: 10.1111/j.1365-2141.2011.09013.x
218. Mutalima N, Molyneux E, Jaffe H, Kamiza S, Borgstein E, Mkandawire N, et al. Associations between Burkitt Lymphoma among Children in Malawi and Infection with HIV, EBV and Malaria: results from a case-control study. *PLoS ONE* (2008) 3:e2505. doi: 10.1371/journal.pone.0002505.t005
219. Thorley-Lawson DA, Allday MJ. The curious case of the tumour virus: 50 years of Burkitt's lymphoma. *Nat Rev Microbiol.* (2008) 6:913–24. doi: 10.1038/nrmicro2015
220. Kwiatkowski DP. How malaria has affected the human genome and what human genetics can teach us about malaria. *Am J Hum Genet.* (2005) 77:171–92. doi: 10.1086/432519
221. Leffler EM, Band G, Busby GBJ, Kivinen K, Le QS, Clarke GM, et al. Resistance to malaria through structural variation of red blood cell invasion receptors. *Science* (2017) 356: eaam6393. doi: 10.1126/science.aam6393
222. Egan ES, Jiang RH, Moechtar MA, Barteneva NS, Weekes MP, Nobre LV, et al. Malaria. A forward genetic screen identifies erythrocyte CD55 as essential for *Plasmodium falciparum* invasion. *Science* (2015) 348:711–4. doi: 10.1126/science.aaa3526
223. Williams TN. Human red blood cell polymorphisms and malaria. *Curr Opin Microbiol.* (2006) 9:388–94. doi: 10.1016/j.mib.2006.06.009
224. Hadley TJ, Peiper SC. From malaria to chemokine receptor: the emerging physiologic role of the Duffy blood group antigen. *Blood* (1997) 89:3077–91.
225. Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* (1996) 86:367–77.
226. Rezk SA, Zhao X, Weiss LM. Epstein-Barr virus (EBV)-associated lymphoid proliferations, a 2018 update. *Hum Pathol.* (2018) 79:18–41. doi: 10.1016/j.humpath.2018.05.020
227. Barton ES, White DW, Cathelyn JS, Brett-McClellan KA, Engle M, Diamond MS, et al. Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature* (2007) 447:326–9. doi: 10.1038/nature05762
228. White DW, Keppel CR, Schneider SE, Reese TA, Coder J, Payton JE, et al. Latent herpesvirus infection arms cells NK. *Blood* (2010) 115:4377–83. doi: 10.1182/blood-2009-09-245464
229. Farrell PJ. Epstein-Barr virus and cancer. *Annu Rev Pathol.* (2018) doi: 10.1146/annurev-pathmechdis-012418-013023
230. Iwatsuki K, Xu Z, Ohtsuka M, Kaneko F. Overview of EBV-associated T/NK-cell lymphoproliferative diseases. (2018) 1–17.
231. Grywalska E, Rolinski J. Epstein-Barr virus-associated lymphomas. *Semin Oncol.* (2015) 42:291–303. doi: 10.1053/j.seminoncol.2014.12.030
232. Palendira U, Rickinson AB. Primary immunodeficiencies and the control of Epstein-Barr virus infection. *Ann N Y Acad Sci.* (2015) 1356:22–44. doi: 10.1111/nyas.12937
233. Kushekhar K, van den Berg A, Nolte I, Hepkema B, Visser L, Diepstra A. Genetic associations in classical hodgkin lymphoma: a systematic review and insights into susceptibility mechanisms. *Cancer Epidemiol Biomarkers Prev.* (2014) 23:2737–47. doi: 10.1158/1055-9965.EPI-14-0683
234. Parvaneh N, Filipovich AH, Borkhardt A. Primary immunodeficiencies predisposed to Epstein-Barr virus-driven haematological diseases. *Br J Haematol.* (2013) 162:573–86. doi: 10.1111/bjh.12422
235. Worth AJ, Houldcroft CJ, Booth C. Severe Epstein-Barr virus infection in primary immunodeficiency and the normal host. *Br J Haematol.* (2016) 175:559–76. doi: 10.1111/bjh.14339
236. Vockerodt M, Yap LF, Shannon-Lowe C, Curley H, Wei W, Vrzalikova K, et al. The Epstein-Barr virus and the pathogenesis of lymphoma. *J Pathol.* (2015) 235:312–22. doi: 10.1002/path.4459
237. Khan G, Hashim MJ. Global burden of deaths from Epstein-Barr virus attributable malignancies 1990-2010. *Infect Agent Cancer* (2014) 9:38. doi: 10.1186/1750-9378-9-38
238. Robbiani DF, Deroubaix S, Feldhahn N, Oliveira TY, Callen E, Wang Q, et al. Plasmodium infection promotes genomic instability and AID-dependent B Cell lymphoma. *Cell* (2015) 162:727–37. doi: 10.1016/j.cell.2015.07.019
239. Quintanilla-Martinez L, Ridaura C, Nagl F, Sáez-de-Ocariz M, Durán-McKinster C, Ruiz-Maldonado R, et al. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. *Blood* (2013) 122:3101–10. doi: 10.1182/blood-2013-05-502203
240. Tang M, Zeng Y, Poisson A, Marti D, Guan L, Zheng Y, et al. Haplotype-dependent HLA susceptibility to nasopharyngeal carcinoma in a Southern Chinese population. *Genes Immun.* (2010) 11:334–42. doi: 10.1038/gene.2009.109
241. Qin L, Chen C, Chen L, Xue R, Ou-Yang M, Zhou C, et al. Worldwide malaria incidence and cancer mortality are inversely associated. *Infect Agent Cancer* (2017) 12:14. doi: 10.1186/s13027-017-0117-x
242. Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the global burden of disease study 2013. *Lancet* (2014) 384:1005–70. doi: 10.1016/S0140-6736(14)60844-8
243. Lehrer S. Association between malaria incidence and all cancer mortality in fifty U.S. States, and the District of Columbia. *Anticancer Res.* (2010) 30:1371–3.
244. Chene A, Donati D, Orem J, Mbidde ER, Kironde F, Wahlgren M, et al. Endemic Burkitt's lymphoma as a polymicrobial disease: new insights on the interaction between *Plasmodium falciparum* and Epstein-Barr virus. *Semin Cancer Biol.* (2009) 19:411–20. doi: 10.1016/j.semcancer.2009.10.002
245. Robbiani DF, Bothmer A, Callen E, B Reina-San-Martin, Dorsett Y, Difilippantonio S, et al. AID is required for the chromosomal breaks in c-myc that lead to c-myc/IgH translocations. *Cell* (2008) 135:1028–38. doi: 10.1016/j.cell.2008.09.062
246. Rochford R, Cannon MJ, Moormann AM. Endemic Burkitt's lymphoma: a polymicrobial disease? *Nat Rev Microbiol.* (2005) 3:182–7. doi: 10.1038/nrmicro1089
247. Roy A, Cowan G, Mead AJ, Filippi S, Bohn G, Chaidos A, et al. Perturbation of fetal liver hematopoietic stem and progenitor cell development by trisomy 21. *Proc Natl Acad Sci USA.* (2012) 109:17579–84. doi: 10.1073/pnas.1211405109
248. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. *Clin Exp Immunol.* (2011) 164:9–16. doi: 10.1111/j.1365-2249.2011.04335.x
249. Giménez-Barcons M, Casteràs A, Armengol Mdel P, Porta E, Correa PA, Marín A, et al. Autoimmune predisposition in Down syndrome may result from a partial central tolerance failure due to insufficient intrathymic expression of AIRE, peripheral antigens. *J Immunol.* (2014) 193:3872–9. doi: 10.4049/jimmunol.1400223
250. Sullivan KD, Evans D, Pandey A, Hraha TH, Smith KP, Markham N, et al. Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation. *Sci Rep.* (2017) 7:14818. doi: 10.1038/s41598-017-13858-3
251. Sullivan KD, Lewis HC, Hill AA, Pandey A, Jackson LP, Cabral JM, et al. Trisomy 21 consistently activates the interferon response. *Elife* (2016) 5:1709. doi: 10.7554/eLife.16220
252. Hasle H. Pattern of malignant disorders in individuals with Down's syndrome. *Lancet Oncol.* (2001) 2:429–36. doi: 10.1016/S1470-2045(00)00435-6

253. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. *Lancet* (2000) 355:165–9. doi: 10.1016/S0140-6736(99)05264-2
254. Izraeli S. Leukaemia – a developmental perspective. *Br J Haematol.* (2004) 126:3–10. doi: 10.1111/j.1365-2141.2004.04986.x
255. Izraeli S. Similar yet different. *Blood* (2010) 116:1019–20. doi: 10.1182/blood-2010-05-285197
256. Lane AA, Chapuy B, Lin CY, Tivey T, Li H, Townsend EC, et al. Triplication of a 21q22 region contributes to B cell transformation through HMGN1 overexpression and loss of histone H3 Lys27 trimethylation. *Nat Genet.* (2014) 46:618–23. doi: 10.1038/ng.2949
257. Reynolds LE, Watson AR, Baker M, Jones TA, D'Amico G, Robinson SD, et al. Tumour angiogenesis is reduced in the Tc1 mouse model of Down's syndrome. *Nature* (2010) 465:813–7. doi: 10.1038/nature09106
258. Rabin KR, Whitlock JA. Malignancy in children with trisomy 21. *Oncologist* (2009) 14:164–73. doi: 10.1634/theoncologist.2008-0217
259. Sussan TE, Yang A, Li F, Ostrowski MC, Reeves RH. Trisomy represses Apc(Min)-mediated tumours in mouse models of Down's syndrome. *Nature* (2008) 451:73–5. doi: 10.1038/nature06446
260. Threadgill DW. Down's syndrome: paradox of a tumour repressor. *Nature* (2008) 451:21–2. doi: 10.1038/451021a
261. Baek KH, Zaslavsky A, Lynch RC, Britt C, Okada Y, Siarey RJ, et al. Down's syndrome suppression of tumour growth and the role of the calcineurin inhibitor DSCR1. *Nature* (2009) 459:1126–30. doi: 10.1038/nature08062
262. Suliman A, Smith FO, Kupfer GM. Fanconi anemia: a pathway of hematopoiesis and cancer predisposition. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure.* Cham: Springer International Publishing (2018).p. 81–97. doi: 10.1007/978-3-319-61421-2_4
263. Cheung RS, Taniguchi T. Recent insights into the molecular basis of Fanconi anemia: genes, modifiers, and drivers. *Int J Hematol.* (2017) 106:335–44. doi: 10.1007/s12185-017-2283-4
264. West AH, Churpek JE. Old and new tools in the clinical diagnosis of inherited bone marrow failure syndromes. *Hematol Am Soc Hematol Educ Program* (2017) 2017:79–87. doi: 10.1182/asheducation-2017.1.79
265. Chirnomas SD, Kupfer GM. The inherited bone marrow failure syndromes. *Pediatr Clin North Am.* (2013) 60:1291–310. doi: 10.1016/j.pcl.2013.09.007
266. Aspesi A, Ellis SR. Ribosomopathies through a diamond lens. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure. Pediatric Oncology.* Cham: Springer International Publishing (2018).
267. Hattangadi SM, Lipton JM. Diamond-blackfan anemia. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure.* Cham: Springer International Publishing (2018) doi: 10.1007/978-3-319-61421-2_7
268. Ulirsch JC, Verboon JM, Kazerounian S, Guo MH, Yuan D, Ludwig LS, et al. The genetic landscape of diamond-blackfan anemia. *Am J Hum Genet.* (2018) 103:930–47. doi: 10.1016/j.ajhg.2018.10.027
269. Narla A, Ebert BL. Ribosomopathies: human disorders of ribosome dysfunction. *Blood* (2010) 115:3196–205. doi: 10.1182/blood-2009-10-178129
270. Dodson L, Bertuch AA. Dyskeratosis Congenita and the Telomere Biology Disorders. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure,* Cham: Springer International Publishing (2018) doi: 10.1007/978-3-319-61421-2_6
271. Savage SA. Beginning at the ends: telomeres and human disease. *F1000Res* (2018) 7: F1000 Faculty Rev-524. doi: 10.12688/f1000research.14068.1
272. Townsley DM, Dumitriu B, Young NS. Bone marrow failure and the telomeropathies. *Blood* (2014) 124:2775–83. doi: 10.1182/blood-2014-05-526285
273. Myers KC, Shimamura A. Shwachman-Diamond Syndrome. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure,* Cham: Springer International Publishing (2018) doi: 10.1007/978-3-319-61421-2_8
274. Kostjukovits S, Klemetti P, Valta H, Martelius T, Notarangelo LD, Seppänen M, et al. Analysis of clinical and immunologic phenotype in a large cohort of children and adults with cartilage-hair hypoplasia. *J Allergy Clin Immunol.* (2017) 140:612–4 e615. doi: 10.1016/j.jaci.2017.02.016
275. Bluteau O, Sebert M, Leblanc T, Peffault de Latour R, Quentin S, Lainey E, et al. A landscape of germ line mutations in a cohort of inherited bone marrow failure patients. *Blood* (2018) 131:717–32. doi: 10.1182/blood-2017-09-806489
276. Nakano T, Di Paola J. Inherited Thrombocytopenias. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure,* Cham: Springer International Publishing (2018) doi: 10.1007/978-3-319-61421-2_11
277. Albers CA, Paul DS, Schulze H, Freson K, Stephens JC, Smethurst PA, et al. Compound inheritance of a low-frequency regulatory SNP, a rare null mutation in exon-junction complex subunit RBM8A causes syndrome TAR. *Nat Genet.* (2012) 44:435–439, S431–432. doi: 10.1038/ng.1083
278. Mehta HM, Corey SJ. Inherited Neutropenias and Their Insights into Cellular and Developmental Biology. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure,* Cham: Springer International Publishing, (2018) doi: 10.1007/978-3-319-61421-2_10
279. Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. *Nat Rev Dis Prim.* (2017) 3:17032. doi: 10.1038/nrdp.2017.32
280. Hirabayashi S, Wlodarski MW, Kozyra E, Niemeyer CM. Heterogeneity of GATA2-related myeloid neoplasms. *Int J Hematol.* (2017) 106:175–82. doi: 10.1007/s12185-017-2285-2
281. Wlodarski MW, Collin M, Horwitz MS. GATA2 deficiency and related myeloid neoplasms. *Semin Hematol.* (2017) 54:81–6. doi: 10.1053/j.seminhematol.2017.05.002
282. Wlodarski MW, Hirabayashi S, Pastor V, Starý J, Hasle H, Masetti R, et al. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. *Blood* (2016) 127:1387–97; quiz 1518. doi: 10.1182/blood-2015-09-669937
283. Churpek JE, Pyrtel K, Kanchi KL, Shao J, Koboldt D, Miller CA, et al. Genomic analysis of germ line and somatic variants in familial myelodysplasia/acute myeloid leukemia. *Blood* (2015) 126:2484–90. doi: 10.1182/blood-2015-04-641100
284. Collin M, Dickinson R, Bigley V. Haematopoietic and immune defects associated with GATA2 mutation. *Br J Haematol.* (2015) 169:173–87. doi: 10.1111/bjh.13317
285. Ganapathi KA, Townsley DM, Hsu AP, Arthur DC, Zerbe CS, Cuellar-Rodriguez J, et al. GATA2 deficiency-associated bone marrow disorder differs from idiopathic aplastic anemia. *Blood* (2015) 125:56–70. doi: 10.1182/blood-2014-06-580340
286. Mir MA, Kochuparambil ST, Abraham RS, Rodriguez V, Howard M, Hsu AP, et al. Spectrum of myeloid neoplasms and immune deficiency associated with germline GATA2 mutations. *Cancer Med.* (2015) 4:490–9. doi: 10.1002/cam4.384
287. Davidsson J, Puschmann A, Tedgård U, Bryder D, Nilsson L, Cammenga J. SAMD9 and SAMD9L in inherited predisposition to ataxia, pancytopenia, and myeloid malignancies. *Leukemia* (2018) 32:1106–15. doi: 10.1038/s41375-018-0074-4
288. Pastor VB, Sahoo SS, Boklan J, Schwabe GC, Saribeyoglu E, Strahm B, et al. Constitutional SAMD9L mutations cause familial myelodysplastic syndrome and transient monosomy 7. *Haematologica* (2018) 103:427–37. doi: 10.3324/haematol.2017.180778
289. Shima H, Koehler K, Nomura Y, Sugimoto K, Satoh A, Ogata T, et al. Two patients with MIRAGE syndrome lacking haematological features: role of somatic second-site reversion SAMD9 mutations. *J Med Genet.* (2018) 55:81–5. doi: 10.1136/jmedgenet-2017-105020
290. Wong JC, Bryant V, Lamprecht T, Ma J, Walsh M, Schwartz J, et al. Germline SAMD9 and SAMD9L mutations are associated with extensive genetic evolution and diverse hematologic outcomes. *JCI Insight* (2018) 3: 121086. doi: 10.1172/jci.insight.121086
291. Buonocore F, Kühnen P, Suntharalingham JP, Del Valle I, Digweed M, Stachelscheid H, et al. Somatic mutations and progressive monosomy modify SAMD9-related phenotypes in humans. *J Clin Invest.* (2017) 127:1700–13. doi: 10.1172/JCI91913
292. Collin M. I am SAMD9L: 7q regulator am I. *Blood* (2017) 129:2210–2. doi: 10.1182/blood-2017-03-770198
293. Tesi B, Davidsson J, Voss M, Rahikkala E, Holmes TD, Chiang SCC, et al. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. *Blood* (2017) 129:2266–79. doi: 10.1182/blood-2016-10-743302
294. Narumi S, Amano N, Ishii T, Katsumata N, Muroya K, Adachi M, et al. SAMD9 mutations cause a novel multisystem disorder, syndrome MIRAGE,

and are associated with loss of chromosome 7. *Nat Genet.* (2016) 48:792–7. doi: 10.1038/ng.3569
295. Murakami N, Okuno Y, Yoshida K, Shiraishi Y, Nagae G, Suzuki K, et al. Integrated molecular profiling of juvenile myelomonocytic leukemia. *Blood* (2018) 131:1576–86. doi: 10.1182/blood-2017-07-798157
296. Niemeyer CM. JMML genomics and decisions. *Hematology Am Soc Hematol Educ Program.* (2018) 2018:307–12. doi: 10.1182/asheducation-2018.1.307
297. Cavé H, Caye A, Strullu M, Aladjidi N, Vignal C, Ferster A, et al. Acute lymphoblastic leukemia in the context of RASopathies. *Eur J Med Genet.* (2016) 59:173–8. doi: 10.1016/j.ejmg.2016.01.003
298. Stieglitz E, Taylor-Weiner AN, Chang TY, Gelston LC, Wang YD, Mazor T, et al. The genomic landscape of juvenile myelomonocytic leukemia. *Nat Genet.* (2015) 47:1326–33. doi: 10.1038/ng.3400
299. Hofmann I. Pediatric Myelodysplastic Syndromes. In: Kupfer G, Reaman G, Smith F, editors. *Bone Marrow Failure,* Cham: Springer International Publishing (2018) doi: 10.1007/978-3-319-61421-2_3
300. Wegman-Ostrosky T, Savage SA. The genomics of inherited bone marrow failure: from mechanism to the clinic. *Br J Haematol.* (2017) 177:526–42. doi: 10.1111/bjh.14535
301. Auerbach AD. Fanconi anemia and its diagnosis. *Mutat Res.* (2009) 668:4–10. doi: 10.1016/j.mrfmmm.2009.01.013
302. Bagby, G. Recent advances in understanding hematopoiesis in Fanconi Anemia. *F1000Res* (2018) 7:105. doi: 10.12688/f1000research.13213.1
303. Garaycoechea JI, Patel KJ. Why does the bone marrow fail in Fanconi anemia? *Blood* (2014) 123:26–34. doi: 10.1182/blood-2013-09-4 27740
304. Pontel LB, Rosado IV, Burgos-Barragan G, Garaycoechea JI, Yu R, Arends MJ, et al. Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen. *Mol Cell* (2015) 60:177–88. doi: 10.1016/j.molcel.2015.08.020
305. Parmar K, D'Andrea AD. Stressed out: endogenous aldehydes damage hematopoietic stem cells. *Cell Stem Cell* (2012) 11:583–4. doi: 10.1016/j.stem.2012.10.007
306. Rosado IV, Langevin F, Crossan GP, Takata M, Patel KJ. Formaldehyde catabolism is essential in cells deficient for the Fanconi anemia DNA-repair pathway. *Nat Struct Mol Biol.* (2011) 18:1432–4. doi: 10.1038/nsmb.2173
307. Oberbeck N, Langevin F, King G, de Wind N, Crossan GP, Patel KJ. Maternal aldehyde elimination during pregnancy preserves the fetal genome. *Mol Cell* (2014) 55:807–17. doi: 10.1016/j.molcel.2014.07.010
308. Van Wassenhove LD, Mochly-Rosen D, Weinberg KI. Aldehyde dehydrogenase 2 in aplastic anemia, Fanconi anemia and hematopoietic stem cells. *Mol Genet Metab.* (2016) 119:28–36. doi: 10.1016/j.ymgme.2016.07.004
309. Hira A, Yabe H, Yoshida K, Okuno Y, Shiraishi Y, Chiba K, et al. Variant ALDH2 is associated with accelerated progression of bone marrow failure in Japanese Fanconi anemia patients. *Blood* (2013) 122:3206–9. doi: 10.1182/blood-2013-06-507962
310. Ruiz S, Fernandez-Capetillo O. The maternal side of Fanconi Anemia. *Mol Cell* (2014) 55:803–4. doi: 10.1016/j.molcel.2014.08.029
311. Tan SLW, Chadha S, Liu Y, Gabasova E, Perera D, Ahmed K, et al. A class of environmental and endogenous toxins induces BRCA2 haploinsufficiency and genome instability. *Cell* (2017) 169:1105–18.e5. doi: 10.1016/j.cell.2017.05.010
312. Zhang QS, Tang W, Deater M, Phan N, Marcogliese AN, Li H, et al. Metformin improves defective hematopoiesis and delays tumor formation in Fanconi anemia mice. *Blood* (2016) 128:2774–84. doi: 10.1182/blood-2015-11-683490
313. Chen CH, Ferreira JC, Gross ER, Mochly-Rosen D. Targeting aldehyde dehydrogenase 2: new therapeutic opportunities. *Physiol Rev.* (2014) 94:1–34. doi: 10.1152/physrev.00017.2013
314. Jonkman MF. Revertant mosaicism in human genetic disorders. *Am J Med Genet.* (1999) 85:361–64.
315. Youssoufian H, Pyeritz RE. Mechanisms and consequences of somatic mosaicism in humans. *Nat Rev Genet.* (2002) 3:748–58. doi: 10.1038/nrg906
316. Venugopal P, Moore S, Lawrence DM, George AJ, Hannan RD, Bray SC, et al. Self-reverting mutations partially correct the blood phenotype in a Diamond Blackfan anemia patient. *Haematologica* (2017) 102:e506–9. doi: 10.3324/haematol.2017.166678
317. Makishima H, Maciejewski JP. Pathogenesis and consequences of uniparental disomy in cancer. *Clin Cancer Res.* (2011) 17:3913–23. doi: 10.1158/1078-0432.CCR-10-2900
318. O'Keefe C, McDevitt MA, Maciejewski JP. Copy neutral loss of heterozygosity: a novel chromosomal lesion in myeloid malignancies. *Blood* (2010) 115:2731–9. doi: 10.1182/blood-2009-10-201848
319. Vago L, Perna SK, Zanussi M, Mazzi B, Barlassina C, Stanghellini MT, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. *N Engl J Med.* (2009) 361:478–88. doi: 10.1056/NEJMoa0811036
320. Villalobos IB, Takahashi Y, Akatsuka Y, Muramatsu H, Nishio N, Hama A, et al. Relapse of leukemia with loss of mismatched HLA resulting from uniparental disomy after haploidentical hematopoietic stem cell transplantation. *Blood* (2010) 115:3158–61. doi: 10.1182/blood-2009-11-254284
321. Katagiri T, Sato-Otsubo A, Kashiwase K, Morishima S, Sato Y, Mori Y, et al. Frequent loss of HLA alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia. *Blood* (2011) 118:6601–9. doi: 10.1182/blood-2011-07-365189
322. Asur RS, Kimble DC, Lach FP, Jung M, Donovan FX, Kamat A, et al. Somatic mosaicism of an intragenic FANCB duplication in both fibroblast and peripheral blood cells observed in a Fanconi anemia patient leads to milder phenotype. *Mol Genet Genomic Med.* (2018) 6:77–91. doi: 10.1002/mgg3.350
323. Davis BR, Dicola MJ, Prokopishyn NL, Rosenberg JB, Moratto D, Muul LM, et al. Unprecedented diversity of genotypic revertants in lymphocytes of a patient with Wiskott-Aldrich syndrome. *Blood* (2008) 111:5064–7. doi: 10.1182/blood-2007-06-095299
324. Fernández LC, Torres M, Real FX. Somatic mosaicism: on the road to cancer. *Nat Rev Cancer* (2016) 16:43–55. doi: 10.1038/nrc.2015.1
325. Ellinghaus E, Stanulla M, Richter G, Ellinghaus D, te Kronnie G, Cario G, et al. Identification of germline susceptibility loci in ETV6-RUNX1-rearranged childhood acute lymphoblastic leukemia. *Leukemia* (2012) 26:902–9. doi: 10.1038/leu.2011.302
326. Treviño LR, Yang W, French D, Hunger SP, Carroll WL, Devidas M, et al. Germline genomic variants associated with childhood acute lymphoblastic leukemia. *Nat Genet.* (2009) 41:1001–5. doi: 10.1038/ng.432
327. Prasad RB, Hosking FJ, Vijayakrishnan J, Papaemmanuil E, Koehler R, Greaves M, et al. Verification of the susceptibility loci on 7p12.2, 10q21.2, and 14q11.2 in precursor B-cell acute lymphoblastic leukemia of childhood. *Blood* (2010) 115:1765–7. doi: 10.1182/blood-2009-09-241513
328. Shah S, Schrader KA, Waanders E, Timms AE, Vijai J, Miething C, et al. A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia. *Nat Genet.* (2013) 45:1226–31. doi: 10.1038/ng.2754
329. Xu H, Zhang H, Yang W, Yadav R, Morrison AC, Qian M, et al. Inherited coding variants at the CDKN2A locus influence susceptibility to acute lymphoblastic leukaemia in children. *Nat Commun.* (2015) 6:7553. doi: 10.1038/ncomms8553
330. Hungate EA, Vora SR, Gamazon ER, Moriyama T, Best T, Hulur I, et al. A variant at 9p21.3 functionally implicates CDKN2B in paediatric B-cell precursor acute lymphoblastic leukaemia aetiology. *Nat Commun.* (2016) 7:10635. doi: 10.1038/ncomms10635
331. Vijayakrishnan J, Henrion M, Moorman AV, Fiege B, Kumar R, da Silva Filho MI, et al. The 9p21.3 risk of childhood acute lymphoblastic leukaemia is explained by a rare high-impact variant in CDKN2. *Sci Rep A* (2015) 5:15065. doi: 10.1038/srep15065
332. Migliorini G, Fiege B, Hosking FJ, Ma Y, Kumar R, Sherborne AL, et al. Variation at 10p12.2 and 10p14 influences risk of childhood B-cell acute lymphoblastic leukemia and phenotype. *Blood* (2013) 122:3298–307. doi: 10.1182/blood-2013-03-491316
333. Perez-Andreu V, Roberts KG, Xu H, Smith C, Zhang H, Yang W, et al. A genome-wide association study of susceptibility to acute lymphoblastic leukemia in adolescents and young adults. *Blood* (2015) 125:680–6. doi: 10.1182/blood-2014-09-595744
334. Zhang MY, Churpek JE, Keel SB, Walsh T, Lee MK, Loeb KR, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. *Nat Genet.* (2015) 47:180–5. doi: 10.1038/ng.3177
335. Noetzli L, Lo RW, Lee-Sherick AB, Callaghan M, Noris P, Savoia A, et al. Germline mutations in ETV6 are associated with thrombocytopenia, red

cell macrocytosis and predisposition to lymphoblastic leukemia. *Nat Genet*. (2015) 47:535–8. doi: 10.1038/ng.3253
336. Topka S, Vijai J, Walsh MF, Jacobs L, Maria A, Villano D, et al. Germline ETV6 mutations confer susceptibility to acute lymphoblastic leukemia and thrombocytopenia. *PLoS Genet*. (2015) 11:e1005262. doi: 10.1371/journal.pgen.1005262
337. Moriyama T, Metzger ML, Wu G, Nishii R, Qian M, Devidas M, et al. Germline genetic variation in ETV6 and risk of childhood acute lymphoblastic leukaemia: a systematic genetic study. *Lancet Oncol*. (2015) 16:1659–66. doi: 10.1016/s1470-2045(15)00369-1
338. Duployez N, Abou Chahla W, Lejeune S, Marceau-Renaut A, Letizia G, Boyer T, et al. Detection of a new heterozygous germline ETV6 mutation in a case with hyperdiploid acute lymphoblastic leukemia. *Eur J Haematol*. (2018) 100:104–7. doi: 10.1111/ejh.12981
339. Qian M, Cao X, Devidas M, Yang W, Cheng C, Dai Y, et al. TP53 germline variations influence the predisposition and prognosis of B-Cell acute lymphoblastic leukemia in children. *J Clin Oncol*. (2018) 36:591–9. doi: 10.1200/JCO.2017.75.5215
340. Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Ding L, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet*. (2013) 45:242–52. doi: 10.1038/ng.2532
341. Safavi S, Olsson L, Biloglav A, Veerla S, Blendberg M, Tayebwa J, et al. Genetic and epigenetic characterization of hypodiploid acute lymphoblastic leukemia. *Oncotarget* (2015) 6:427 93–802. doi: 10.18632/oncotarget.6000
342. Furutani E, Shimamura A. Germline genetic predisposition to hematologic malignancy. *J Clin Oncol*. (2017) 35:1018–28. doi: 10.1200/JCO.2016.70.8644
343. Somasundaram R, Prasad MA, Ungerbäck J, Sigvardsson M. Transcription factor networks in B-cell differentiation link development to acute lymphoid leukemia. *Blood* (2015) 126:144–52. doi: 10.1182/blood-2014-12-575688
344. Martín-Lorenzo A, Hauer J, Vicente-Dueñas C, Auer F, González-Herrero I, García-Ramírez I, et al. Infection exposure is a causal factor in B-cell precursor acute lymphoblastic leukemia as a result of Pax5-inherited susceptibility. *Cancer Discov*. (2015) 5:1328–43. doi: 10.1158/2159-8290.CD-15-0892
345. John LB, Ward AC. The Ikaros gene family: transcriptional regulators of hematopoiesis and immunity. *Mol Immunol*. (2011) 48:1272–8. doi: 10.1016/j.molimm.2011.03.006
346. Heizmann B, Kastner P, Chan S. The Ikaros family in lymphocyte development. *Curr Opin Immunol*. (2018) 51:14–23. doi: 10.1016/j.coi.2017.11.005
347. Fan Y, Lu D. The Ikaros family of zinc-finger proteins. *Acta Pharm Sin B* (2016) 6:513–21. doi: 10.1016/j.apsb.2016.06.002
348. Marke R, van Leeuwen FN, Scheijen B. The many faces of IKZF1 in B-cell precursor acute lymphoblastic leukemia. *Haematologica* (2018) 103:565–74. doi: 10.3324/haematol.2017.185603
349. Stanulla M, Dagdan E, Zaliova M, Moricke A, Palmi C, Cazzaniga G, et al. IKZF1(plus) defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-Cell precursor acute lymphoblastic leukemia. *J Clin Oncol*. (2018) 36:1240–9. doi: 10.1200/JCO.2017.74.3617
350. Bogaert DJ, Kuehn HS, Bonroy C, Calvo KR, Dehoorne J, Vanlander AV, et al. A novel IKAROS haploinsufficiency kindred with unexpectedly late and variable B-cell maturation defects. *J Allergy Clin Immunol*. (2018) 141:432–5.e437. doi: 10.1016/j.jaci.2017.08.019
351. Kuehn HS, Boisson B, Cunningham-Rundles C, Reichenbach J, Stray-Pedersen A, Gelfand EW, et al. Loss of B cells in patients with heterozygous mutations in IKAROS. *N Engl J Med*. (2016) 374:1032–43. doi: 10.1056/NEJMoa1512234
352. Evans TJ, Milne E, Anderson D, de Klerk NH, Jamieson SE, Talseth-Palmer BA, et al. Confirmation of childhood acute lymphoblastic leukemia variants, ARID5B and IKZF1, and interaction with parental environmental exposures. *PLoS ONE* (2014) 9:e110255. doi: 10.1371/journal.pone.0110255
353. Cohen IR. *Tending Adam's Garden*. Elsevier (2000).

**Conflict of Interest Statement:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# primarias más allá de las señales de alarma tradicionales

primarias más allá de las señales de alarma tradicionales

Carlos E. Olmos Olmos, MD, MPH
Especialista en Alergia e Inmunología
Director Unidad de Alergia e Inmunología, Cayre IPS y Fundación
Profesor titular de pediatría, Universidad del Rosario/Militar

Catalina Gómez Parada, MD
Médica de investigación en la Unidad de Alergia e Inmunología, Cayre IPS y Fundación

María Alejandra Suárez Fuentes, MD
*Fellow* de Infectología Pediátrica, Universidad El Bosque
Pediatra FUCS

## Objetivo principal

Actualizar las señales de reconocimiento y diagnóstico de inmunodeficiencias primarias.

## Objetivos específicos

- Describir las nuevas estrategias para la identificación temprana de inmunodeficiencias primarias más allá de las señales de alerta convencionales conocidas.
- Redefinir y desarrollar nuevas señales de alarma para diagnosticar estas enfermedades tempranamente.
- Ampliar el espectro clínico de las inmunodeficiencias, permitiendo a los médicos y especialistas su sospecha.

## Resumen

En resumen, las IDP son un grupo complejo, diverso y heterogéneo de enfermedades que se presentan no solo a través de infecciones inusuales y recurrentes, sino también con manifestaciones autoinmunes y oncológicas. El objetivo primordial de establecer nuevas señales de alerta es tener una mejor oportunidad en la sospecha precoz de las IDP que nos permita llegar a su diagnóstico prontamente, ofrecer un manejo temprano y así reducir el impacto de estas patologías sobre los órganos blanco, disminuyendo su morbimortalidad.

Las 10 señales de alerta diseñadas a inicios de los 90 se hicieron con base a no más de

100 inmunodeficiencias diagnosticadas hasta ese entonces; estas, a la luz de las más de 200 patologías existentes hoy en día, estarían obsoletas, presentando una baja sensibilidad y especificidad, en donde más o menos 1 de cada 4 pacientes con inmunodeficiencias no tendría ninguna de estas señales.

Se requiere entonces la incorporación de nuevos signos clínicos/señales que sean más personalizadas y específicas de acuerdo con los diferentes compromisos del paciente, teniendo en cuenta los muchos escenarios de trabajo y el diverso personal médico que puede captar a estos niños, con el objetivo primordial de hacer un reconocimiento y una sospecha temprana de los pacientes con IDP, disminuyendo así sus comorbilidades y mejorando su calidad de vida.

## Introducción

Las inmunodeficiencias primarias (IDP) son enfermedades raras pero de gran impacto en la calidad de vida de los pacientes que las padecen, por lo que se requiere de un alto sentido de sospecha para su reconocimiento temprano y para mejorar así su pronóstico. En Colombia, se estima una frecuencia de 1:300.000, según reportes para 2006.

Las IDP han sido identificadas ya hace más de 60 años; a finales de 2000, se habían descrito 100 tipos, sin embargo, en los últimos 20 años los avances moleculares han permitido que el número de estas se hayan duplicado a más de 200 y crezca rápidamente año tras año.

A principios de los 90, se publicaron las 10 señales de alarma para identificar las, que hoy, 20 años después, son insuficientes y menos efectivas para su diagnóstico, debido al aumento del espectro y la gran variedad clínica de estas enfermedades, incluyendo compromiso neurológico, respiratorio, cutáneo, gastrointestinal, autoinmune, neoplásico, entre otros por lo que se requiere evolución de estos signos a unos más personalizados, incluyentes y específicos, que ayuden a reconocer más pacientes durante la práctica clínica.

La idea es desarrollar señales que vayan más allá de las tradicionalesde acuerdo con el grupo de especialidad, para mejorar el diagnóstico temprano y ofrecer tratamiento que modifique el curso de la enfermedad. A continuación, se detallarán nuevos signos que pueden ser de utilidad para el pediatra moderno colombiano y los subespecialistas pediátricos.

## Inmunodeficiencias actuales y las señales convencionales, la necesidad de redefinir y desarrollar nuevos signos

En un estudio reciente realizado en Inglaterra en 141 niños hospitalizados para estudiar inmunodeficiencias, el 23% fue finalmente diagnosticado con ellas y, de estos, 105 tenían al menos una señal tradicional. En estos pacientes, la especificidad de las señales convencionales no sobrepasó el 23% y la sensibilidad, el 63%. El 30% de los pacientes con IDP no tenía ninguna señal de alarma tradicional.

En otro estudio inglés, compararon a 430 niños con inmunodeficiencia primaria versus 133 niños que presentaban infecciones recurrentes no usuales pero sin inmunodeficiencias; se encontró que el predictor más importante y fuerte fue la historia familiar positiva para inmunodeficiencia (18 veces más común en pacientes con inmunodeficiencias), seguido del uso de antibióticos o necesidad de antibióticos endovenosos y, por último, la falla de medro.

La combinación de estas tres señales (historia familiar de IDP, uso de antibióticos y falla de medro) identifica el 96% de pacientes con inmunodeficiencias de neutrófilos y complemento, el 86% de inmunodeficiencias por déficit de linfocitos T y menos del 60% de los déficits de anticuerpos, que son las inmunodeficiencias más frecuentes. Esto indica la baja sensibilidad

de las señales de alarma tradicionales para diagnosticar estas enfermedades hoy en día.

Se deben considerar unas señales más personalizadas, donde se defina el propósito y la audiencia blanco, su grupo etario, el escenario de trabajo de los médicos (consulta externa, urgencias, hospitalización general o cuidado intensivo) y su especialidad.

También es necesario clasificar las guías de alerta según hallazgos clínicos (neurológicos, respiratorios, cutáneos, gastrointestinales, autoinmunes, neoplásicos) y paraclínicos, como hemograma e inmunoglobulinas.

## ¿Cómo se clasifican las inmunodeficiencias actualmente?

Las IDP se clasifican según el defecto del sistema inmune (SI) subyacente o por combinaciones de ellos, ya sea por alteración en la cantidad o calidad de sus componentes. El funcionamiento del SI ya fue revisado en un *Precop* anterior (vol. 11, N° 1, pp. 5-61), por lo que invitamos a los lectores a consultar este texto.

Existen cinco categorías principales (figura 1):

1. Déficit predominantemente de anticuerpos (SAD), que es la más frecuente 60-65%.
2. Déficit de linfocitos T y B (inmunodeficiencias combinadas).
3. Déficit del sistema inmune innato (fagocitos, complemento).
4. Déficit de síndromes de inmunodeficiencias en síndromes bien definidos.
5. Déficits producidos por la alteración en el SI regulatorio o enfermedades autoinflamatorias.

Teniendo en cuenta estas categorías, se describirán señales específicas considerando las diferentes edades en la etapa pediátrica, el sistema involucrado, signos infecciosos, autoinmunes, hematológicos, oncológicos, historia familiar, hallazgos al examen físico, etc.

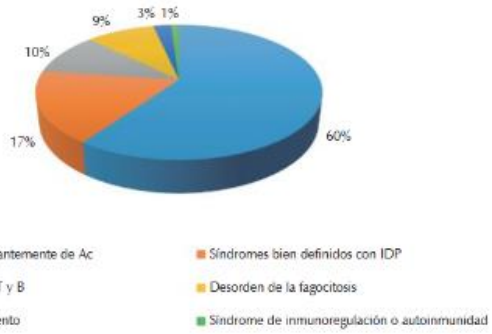
## 1. Señales según grupo etario

### Neonatales

Varias inmunodeficiencias primarias se presentan en esta etapa y de su reconocimiento temprano depende el pronóstico de ellas. Las características principales:

- Candidiasis oral.

**Figura 1.** Distribución de inmunodeficiencias primarias




Fuente: http://esid.org/Working-Parties/Registry/ESID-Database-Statistics

- Diarrea crónica.
- Neumonitis que no desaparece.
- Lesiones extensas de piel.
- Eritrodermia.
- Falla de medro en los primeros meses de vida.
- Caída tardía del cordón umbilical (más de 30 días).
- Hepatoesplenomegalia y linfadenopatías.
- Ausencia de timo por radiografía.
- Infecciones recurrentes por bacterias oportunistas.
- Enfermedad cardíaca congénita (defectos conotruncales).
- Hipocalcemia.
- Hipogammaglobulinemia (IgM menor de 20, IgA menor de 5).
- Linfopenia (menor de 2.000 linfocitos totales, linfopenia T menor de 2.500).
- Historia familiar de inmunodeficiencias o muerte de familiares en la infancia por causa desconocida.

Como el medio intrauterino es estéril, las inmunodeficiencias no son fatales embriológicamente; después del nacimiento, el neonato es expuesto a un sinnúmero de organismos y este solo cuenta con un sistema inmune innato primitivo y un sistema inmune adaptativo primario que depende en gran medida de la protección transplacentaria, la cual es predominantemente humoral, pasiva y temporal.

A mayor severidad más temprana es la presentación de las inmunodeficiencias; los niños con ausencia de linfocitos T y B sufren de infecciones severas con organismos triviales, como rotavirus y virus sincitial respiratorio (VSR). Hay que sospechar en estos casos inmunodeficiencia severa combinada (SCID) y síndromes como el de DiGeorge.

La separación tardía del cordón (15 a 30 días) es sugestiva de deficiencia de adhesión leucocitaria y la eritrodermia neonatal con *rash* intenso nos puede guiar hacia un síndrome de hiper-IgE.

### Entre 6 meses y 5 años

Esta etapa es conocida como el nadir de protección, ya que los anticuerpos maternos desaparecen en su mayoría a los seis meses. Si hay ausencia de linfocitos B o anormalidades en los anticuerpos, como en la agammaglobulinemia de Bruton, un 50% de los pacientes inician con neumonías en esta edad o con otitis tempranas antes del año, y el 88% antes de tres años[4]. También aparecen enfermedades como las granulomatosas crónicas, manifestadas por infecciones cutáneas o abscesos.

### Mayores de 5 años

En esta edad, el sistema inmune ha madurado considerablemente y ya no depende tanto del sistema inmune innato; si persisten infecciones recurrentes inusuales en esa época, como las respiratorias, hay sospecha de déficit de anticuerpos, como el síndrome variable común (CVID, por su sigla en inglés) y el déficit de complemento.

## 2. Señales por sistemas

### Señales dermatológicas

Un 30% de las inmunodeficiencias se caracteriza por lesiones en piel, como molusco contagioso, verrugas y eczemas extensos o eritrodermia[4,10]. Si estas lesiones son suficientemente extensas, siempre se debe sospechar inmunodeficiencia combinada, síndrome de hiper-IgE o defectos DOCH8.

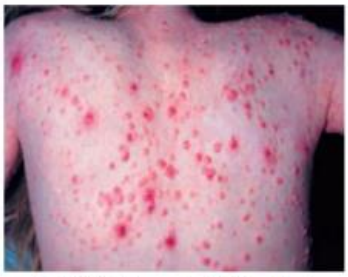
Cuando existe eczema petequial o sangrado, hay que sospechar síndrome de Wiskott-Aldrich, que se asocia además con trombocitopenia.

Recordar que el síndrome de hiper-IgE se caracteriza por eczema, moluscos extensos (figura 2), papilomas virales cutáneos, alergia a alimentos, infecciones piodérmicas por estafilococo y/o *Candida*.

### Señales gastroenterológicas

La diarrea crónica con o sin malabsorción sin una causa aparente debe hacer sospechar SAD y amerita estudio con inmunoglobulinas séricas.

**Figura 2.** Molusco contagioso extenso



Fuente: The Paediatric Immunology Unit, Great North Children's Hospital, Newcastle upon Tyne.

Niños con clínica de enfermedad inflamatoria intestinal de aparición temprana antes de los cinco años pueden tener la manifestación inicial de una enfermedad granulomatosa crónica, sobre todo si se relacionan con neumonías, abscesos perineales o cutáneos, linfadenopatías y diarrea, que puede ser con o sin sangre asociada a pérdida de peso.

Cuando se encuentra en estos pacientes *Cryptosporidium*, giardias, enterovirus, rotavirus o norovirus persistentemente, obliga a descartar IDP.

Niños con transaminasas elevadas y colangitis esclerosante sugieren síndrome de hiper-IgM, debido a una deficiencia de CD40 ligando estos pacientes se infectan específicamente con *Cryptosporidimum parvum*. Los abscesos hepáticos múltiples recurrentes son característicos de la enfermedad granulomatosa crónica y un agente causal frecuente es el *Staphilococcus aureus*.

## Señales respiratorias

El niño sano tiene usualmente infecciones respiratorias que aumentan en frecuencia dependiendo de ciertos factores, como exposición a cigarrillo, asistencia al jardín o enfermedad alérgica, de difícil diferenciación con las causadas por IDP, en especial el grupo de los preescolares.

Existen señales respiratorias que incluyen, además de los signos de alerta tradicionales (tabla 1), enfermedades o condiciones comunes con curso no común, por ejemplo, infecciones por VSR que no mejoran después de 7 a 10 días o niños con bronquiolitis persistentes.

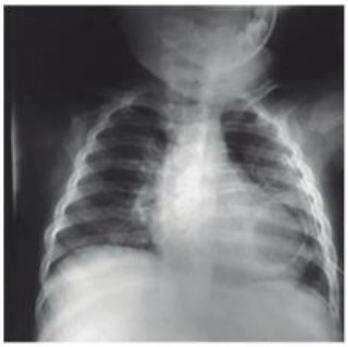
**Tabla 1. Inmunodeficiencias y neumonías**

- Infecciones a repetición, incluyendo otitis.
- Historia de fiebres, diarreas, brotes.
- Hospitalización por neumonía.
- Complicaciones, ya sean neumonía bilaterales, necrosantes, intersticiales.
- Necesidad de antibióticos para tratamiento.
- Historia familiar de inmunodeficiencias.
- Aislamiento de gérmenes, como *Staphilococcus*, hongos, *Pneumocystis jiroveci*, *Aspergillus*, micobacterias.

Fuente: elaborada por los autores.

La presencia de afecciones respiratorias inusuales, como neumatoceles (figura 3), debe hacer sospechar síndrome de hiper-IgE y más si está asociada a eczema y eosinofilia. Las bronquiectasias son otro hallazgo característico y, aunque la patología más relacionada es la fibrosis quística, siempre debe sospecharse inmunodeficiencia primaria.

**Figura 3.** Neumatoceles en radiografía de tórax



Fuente: The Paediatric Immunology Unit, Great North Children's Hospital, Newcastle upon Tyne.

En infecciones recurrentes de un solo sitio, además de alteraciones anatómicas, se debe descartar siempre inmunodeficiencia. Estas se presentan principalmente en la agammaglobulinemia de Bruton, SAD o CVID.

Se debe sospechar enfermedad granulomatosa crónica en paciente con neumonías por *Aspergillus*.

En un estudio reciente de 103 pacientes, entre niños y adultos, con inmunodeficiencia, se encontró historia de infección recurrente en oídos, nariz, garganta y senos paranasales en un 16,5%, asociándose a defectos en la inmunidad humoral principalmente10. En la tabla 2, se pueden observar las situaciones relacionadas con otitis media aguda, que nos deben hacer sospechar inmunodeficiencias.

**Tabla 2. Inmunodeficiencias y otitis media**

- Antes de los seis meses.
- Refractariedad a manejo antibiótico.
- Extensión a otomastoiditis.
- Infección invasiva asociada.
- Recurrencia después de timpanostomía.
- Colocación de tubos a repetición.
- Más de tres por año antes de los cinco años, más de dos después de los cinco años.

Fuente: elaborada por los autores.

El 50% de los pacientes con inmunodeficiencia humoral por SAD tiene historia de neumonías a repetición por patógenos comunes, como *Streptococcus pneumoniae, Haemophilus influenzae* tipo b, *Mycoplasma* y *Staphilococcus*. Sin embargo, en neumonías por gérmenes oportunistas, como *Pneumocystis*, hongos y virus, se debe sospechar síndrome de hiper-IgE, enfermedad granulomatosa crónica o SCID.

Otros estudios han demostrado que los pacientes con CVID desarrollan además bronquiectasias, granulomas, nódulos y enfermedad pulmonar intersticial.

## Señales infecciosas

Las inmunodeficiencias se reconocen principalmente por el aumento en la susceptibilidad a infecciones, sobre todo infecciones por microbios poco comunes.

*Hongos:* la presencia de infección invasiva por hongos es poco usual en niños inmunocompetentes, el *Pneumocystis jiroveci* es el agente infeccioso más frecuente en infecciones en SCID y son manifestaciones muy tempranas en la vida, e, incluso, con neumonías severas que llevan a falla respiratoria.

Los pacientes con enfermedad granulomatosa crónica tienen defectos en el mecanismo de muerte intracelular y son susceptibles a infecciones por hongos, muchas veces son infecciones indolentes y recurrentes, principalmente por *Aspergillus*. La *Candida* hace parte de la flora normal y en niños normales no causa mayores problemas, sin embargo, en inmunodeficientes esta produce enfermedades significativas, como candidiasis mucocutánea e infecciones invasivas.

*Bacterias:* el neumococo, por su cápsula, es de difícil procesamiento, requiere, por lo tanto, para su opsonificación, de un sistema de anticuerpos bien conformados y, si esto no existe, se presentan neumonías invasivas, como en el caso de la asplenia. En la infección por meningococo, se requiere del SI del complemento, el cual debe estar íntegro; estas inmunodeficiencias, aunque raras en nuestro medio, hay que pensarlas cuando la infección por meningococo es recurrente, o por ciertos serotipos, o en historia familiar de meningitis o inmunodeficiencias.

El *Staphilococcus aureus* es frecuente como colonizador en dermatitis atópica, pero es cuando se asocia a infección que es muy usual en pacientes con enfermedad granulomatosa crónica, sobre todo cuando hace parte de adenitis supurativa, abscesos periamigdalinos o hepáticos.

*Micobacterias:* efectos secundarios a la vacuna BCG pueden orientar hacia una inmunodeficiencia; hay que tener en cuenta que una reacción local o el compromiso de un solo ganglio (BCGitis) puede ser normal, pero múltiples adenopatías o diseminación (BCGosis) es una manifestación de SCID, enfermedad granulomatosa o defectos del eje interferón gammaglobulina.

*Virus:* fallas en la respuesta adecuada a los virus son una señal de inmunodeficiencia. El grupo del herpes virus humano, como el virus de la varicela, generalmente produce enfermedad leve que solo requiere manejo sintomático, sin embargo, la aparición de complicaciones serias, como neumonía o sepsis, requiere estudios para defectos de linfocitos T.

El virus de Epstein-Barr (VEB) afecta a todos los niños inmunocompetentes de manera asintomática o pueden desarrollar mononucleosis infecciosa autolimitada. Cuando estas infecciones son severas, pueden producir enfermedades linfoproliferativas, linfomas, hipogammaglobulimenia o anemia aplásica, y es imprescindible descartar inmunodeficiencia.

## Señales oncológicas

Las neoplasias son la manifestación más frecuente de las inmunodeficiencias primarias después de las infecciones y la autoinmunidad. Los pacientes con IDP tienen un mayor riesgo de linfoma, siendo esta la segunda causa de muerte luego de las infecciones; en los más jóvenes, predominan los linfomas de linfocitos B, los cuales son más difusos, con compromiso extranodal, implicando al SNC, pulmón y sistema gastrointestinal; generalmente se asocian con presencia crónica de VEB y virus del herpes; todas estas manifestaciones son más usuales en la CVID.

El cáncer gástrico es otra neoplasia frecuente en inmunodeficiencia, sobre todo en la CVID, cuando se asocia con *H. pylori*, anemia perniciosa y aclorhidria.

El pronóstico de los pacientes con cáncer asociado a IDP es peor comparado con inmunocompetentes.

Las inmunodeficiencias más relacionadas con neoplasias son del tipo déficit de linfocitos T o combinadas.

## Señales autoinmunes

La autoinmunidad, después de infecciones, es la manifestación más común de las inmunodeficiencias. El riego de enfermedades autoinmunes es elevado en estos pacientes y algunas veces es la única manifestación clínica. Uno de cada 4 pacientes con CVID tiene asociado trombocitopenia, anemia hemolítica o artritis idiopática juvenil. El 6% de los pacientes con LES diseminado tiene déficit de IgA.

Inmunodeficiencias por déficit de los mecanismos de apoptosis, como el síndrome linfoproliferativo autoinmune, compuesto por hepatoesplenomegalia, linfoadenopatías, hipergammaglobulinemia y linfocitosis, se reconocen por las manifestaciones autoinmunes, como anemia hemolítica, púrpura trombocitopenia inmunológica y glomerulonefritis.

Enfermedades autoinmunes asociadas a patologías endocrinas, infecciones por *Candida* y distrofia ectodérmica deben hacer pensar en inmunodeficiencias relacionadas con endocrinopatías (Apeced, por su sigla en inglés); en varones se llama IPEX. Todas tienen características de inmunodeficiencias de tipo autoinmune por alteraciones en el sistema inmune regulatorio.

Los defectos del complemento también se manifiestan de manera autoinmune, en especial cuando hay defectos de las primeras porciones del complemento, muchos de ellos tienen LES clínico pero seronegativo.

Poliartritis severas, como se ve en AIJ, que no responden fácilmente al tratamiento deben hacer sospechar SAD, sobre todo cuando

son producidas por *Ureaplasma urealyticum* y *Mycoplasma*.

## 3. Señales de la historia familiar

La historia familiar de inmunodeficiencias es considerada una de las tres señales de alerta tradicionales con mayor potencial diagnóstico para inmunodeficiencias. El problema es que con frecuencia no se sabe o no se entiende la importancia de esto.

Se recomienda hacer las siguientes preguntas en formas puntuales y en diferentes ocasiones:

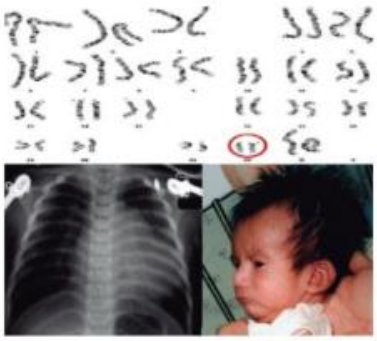
1) Preguntar por consanguinidad (si los padres son primos en primer grado o lejanos).
2) Historia de muerte temprana o no explicada en la familia, más si son varones.
3) Historia de infecciones severas o recurrentes en otros miembros de la familia.
4) Historia de abscesos únicos o recurrentes que sobre todo hayan requerido cirugía.
5) Historia de cáncer, principalmente linfomas o cáncer gástrico en la familia.
6) Historia de enfermedades autoinmunes, como lupus eritematoso sistémico (LES).
7) Enfermedades hematológicas autoinmunes.
8) Historia de eczema y sangrado asociados.

La positividad en alguno de estos aspectos debería hacer sospechar una inmunodeficiencia, especialmente de SCID, enfermedad granulomatosa crónica o agammaglobulinemia.

## 4. Señales al examen físico

*Facies:* pacientes con nariz en botón, filtrum no desarrollado, orejas pequeñas, paladar ojival o hendido deben orientar hacia la sospecha de síndrome de DiGeorge (figura 4), que se caracteriza por una inmunodeficiencia T principalmente. Aquellos con cara asimétrica, frente prominente, orejas bajas, hipertelorismo, paladar ojival, eczema, infecciones cutáneas por *S. aureus* y neumonías deben hacer sospechar síndrome de hiper-IgE.

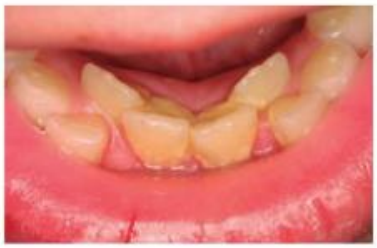
**Figura 4.** Síndrome de DiGeorge



Fuentes: primaryimmune.org y Expert Consult.

- *Dentición:* en pacientes con retardo o ausencia en la aparición de dientes de leche o retardo en la caída con persistencia de la dentición primaria y coincidencia de doble línea de dientes, se debe sospechar la presencia de síndrome de hiper-IgE (figura 5). Incisivos cónicos y ausencia de dientes orientan hacia defectos de inmunodeficiencia primaria mixtos, como el tipo NEMO (NF-ĸB *essential modulator deficiency*). Gingivoestomatitis y aftas recurrentes severas se ven frecuentemente en pacientes con enfermedad granulomatosa crónica, síndrome de Wiskott-Aldrich, inmunodeficiencia de Chédiak-Higashi y neutropenias, además de síndrome de hiper-IgM e hiper-IgE.

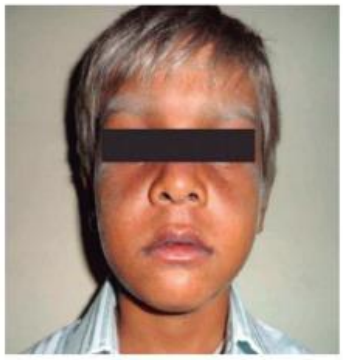
**Figura 5.** Doble línea de dientes típicos en síndrome de hiper-IgE



Fuente: The Paediatric Immunology Unit, Great North Children's Hospital, Newcastle upon Tyne.

- *Piel:* el albinismo oculocutáneo parcial se ve exclusivamente en inmunodeficiencia tipo Chédiak-Higashi.

**Figura 6.** Cabello color plata de síndrome de Chédiak-Higashi



Fuente: Sahana M, Sacchidanand S, Hiremagalore R, Asha G. Silvery grey hair: clue to diagnose immunodeficiency. Int J Trichology 2012;4(2):83-5.

- *Talla:* estatura baja desproporcionada, con displasia esquelética e infecciones debe hacer sospechar defectos de linfocitos T; también se ven asociados a síndrome nefrótico y retardo mental, por ejemplo, hipoplasia de cabello y cartílago (displasia inmunoósea), espondilocondrodisplasia e inmunodeficiencia. Estatura corta relacionada con microcefalia, sensibilidad al sol dada por telangiectasias y manchas café con leche se observan en inmunodeficiencias de linfocitos T, ejemplos de esto serían los síndromes de Nijmegen[8] y de Bloom.

## 5. Señales hematológicas

Las IDP usualmente no requieren investigaciones complicadas, el cuadro hemático completo debe ser entonces evaluado con detalle.

- *Leucocitos:* 2 conteos diferentes de linfocitos absolutos totales por debajo de 3.000 en menores de tres meses deben hacer sospechar SCID. En niños mayores de un año, estas cifras ya son diferentes y valores debajo del anotado pueden ser normales; se sospecha inmunodeficiencia en aquellos niños que tengan menos de 1.500 linfocitos absolutos, como en el adulto; en ambas situaciones, los leucocitos totales pueden ser normales.
- *Neutrófilos:* una cuenta absoluta de neutrófilos por debajo de 1.500/mm3 debe hacer sospechar neutropenia cíclica o inmunodeficiencia por defecto del CD40 ligando o también llamado síndrome de hiper-IgM.
- *Eritrocitos:* la presencia de eritrofagocitosis en el frotis periférico o anemia aplásica predominan en el síndrome linfoproliferativo ligado al sexo.
- *Plaquetas:* trombocitopenia menor de 100.000 con tamaño y volumen disminuidos están presentes en el síndrome de Wiskott-Aldrich.

Es importante tener en cuenta las tablas de referencia de cada laboratorio y compararlas con tablas estandarizadas, como, por ejemplo, las de Harriet Lane, para no generar un sobrediagnóstico o subdiagnóstico.

## Lecturas recomendadas


1. Olmos C, Lozano M, Quijano C. Infecciones recurrentes y sospecha de inmunodeficiencias primarias. Precop, 11(1):5-14.
2. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Front Immunol 2014;5:162.
3. Modell V, Gee B, Lewis B, Orange JS, Roifman CM, Routes JM, et al. Global study of primary immunodeficiency diseases (PI)--diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation. Immunol Res 2011;51(1):61-70.
4. Cant A, Battersby A. When to think of immunodeficiency? In: Curtis N, Finn A, Pollard AJ. Hot topics in infection and immunity in children IX. New York, USA: Springer; 2013. p. 167-77.
5. MacGinnitie A, Aloi F, Mishra S. Clinical characteristics of pediatric patients evaluated for primary immunodeficiency. Pediatr Allergy Immunol 2011;22(7):671-5.
6. Subbarayan A, Colarusso G, Hughes SM, Gennery AR, Slatter M, Cant AJ, et al. Clinical features that identify children with primary immunodeficiency diseases. Pediatrics 2011; 127(5):810-6.
7. Rezai N, Debries E, et al. Common presentations and diagnostic apologize. In: Sullivan KE, Styehm, ER. Stiehm's immune deficiencies. Angeles, CA: Elsevier; 2014.
8. Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. In: Casanova JL, Conley ME, Notarangelo L, editors. The year in human and medical genetics: inborn errors of immunity I. Ann. N.Y. Acad. Sci.; 2011. p. 7-14.
9. O'Sullivan MD, Cant AJ. The 10 warning signs: a time for a change? Curr Opin Allergy Clin Immunol 2012;12(6):588-94.
10. Costa-Carvalho BT, Grumach AS, Franco JL, Espinosa-Rosales FJ, Leiva LE, King A, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol 2014;34(1):10-22.
11. Leiva LE, Bezrodnik L, Oleastro M, Condino-Neto A, Costa-Carvalho BT, Grumach AS, et al. Primary immunodeficiency diseases in Latin America: proceedings of the Second Latin American Society for Immunodeficiencies (LASID) Advisory Board. Allergol Immunopathol (Madr) 2011;39(2):106-10.

examen consultado

6. ¿Cuándo sospechar inmunodeficiencias primarias?

A. si hay otitis media antes de los seis meses de difícil manejo
B. si se presenta una sola neumonía complicada
C. si se manifiesta dermatitis atópica más moluscos extensos
D. si hay diarrea en el lactante alimentado con leche materna que no gana peso
E. todas las anteriores

7. ¿Cuál de estas señales no hacen sospechar inmunodeficiencia primaria?

A. niños con retardo o ausencia en la aparición o desaparición de dientes
B. diarrea y vómito persistente
C. historia de consanguinidad en los padres
D. presencia de abscesos periamigdalinos y de adenopatías supurativas cervicales
E. infecciones por hongo sistémicas sin inmunosupresión previa

8. ¿Cuál de las siguientes son señales convencionales y nuevas para sospechar inmunodeficiencia?

A. paciente pediátrico con PTI recurrente y anemia hemolítica autoinmune
B. historia recurrente o refractaria a tratamiento de *H. pylori*
C. adolescentes con lupus *like* con serología negativa
D. talla baja más displasia esquelética e infecciones
E. talla corta más microcefalia
F. todas las anteriores

# Viral-Bacterial Interactions in Childhood Respiratory Tract Infections

8

Alicia Annamalay and Peter Le Souëf

**Abstract**

Acute respiratory infection (ARI) is an important cause of childhood morbidity and mortality worldwide. ARIs are caused primarily by viruses and bacteria that are often co-detected in respiratory specimens. Although viral-bacterial co-infections are frequently reported in children with ARI, their clinical significance and the mechanisms leading to ARI are not well understood. The respiratory tract is a reservoir of a diverse community of microorganisms, including both commensals and potential pathogens and there is growing evidence that the interactions between viruses and bacteria play a key role in the development of ARI. A better understanding of the interactions between viruses and bacteria in the respiratory tract may enhance insight into the pathogenesis of ARI, and potentially reveal new prevention and treatment strategies. This chapter summarizes the current knowledge on viruses, bacteria and viral-bacterial interactions in childhood ARI and the possible mechanisms by which these interactions may lead to disease.

## 8.1 Introduction

Acute respiratory infection (ARI), both upper and lower, is a significant cause of childhood morbidity and mortality worldwide. Lower respiratory infection (LRI), including pneumonia, is among the leading causes of childhood mortality worldwide, accounting for close to a million deaths in children under 5 years of age in 2013 [1]. Viruses and bacteria can be detected in most children with ARI. However, both are also frequently detected in asymptomatic children, and hence, the clinical

A. Annamalay (✉) • P. Le Souëf
School of Paediatrics and Child Health, University of Western Australia,
Perth, WA 6840, Australia
e-mail: alicia.annamalay@uwa.edu.au



R.J. Green (ed.), *Viral Infections in Children, Volume I*,
DOI 10.1007/978-3-319-54033-7_8

significance of their detection has long been debated. Furthermore, a wide range of prevalence rates are reported for the detection of viruses and bacteria, most likely due to differences in case definitions, diagnostic tools and methodologies used between studies and hence, the epidemiology and etiology of ARI are still not clear. Viruses and bacteria are often co-detected in respiratory samples from children with ARI and their interaction is likely to play a key role in the development of disease. However, the clinical significance of viral-bacterial co-infections and the mechanisms leading to ARI are not well understood.

Viruses are identified more frequently than bacteria in children with ARI [2]. Respiratory syncytial virus (RSV) has long been believed to be the most important viral cause of childhood ARI, particularly bronchiolitis, accounting for at least three million hospitalizations and up to 200,000 deaths each year [3]. Human rhinovirus (RV) is the leading cause of upper respiratory infections (URI), but is also an important cause of LRI including pneumonia and bronchiolitis, and accounts for the majority of asthma attacks in children [4, 5]. Advances in molecular methods such as polymerase chain reaction (PCR) in recent years have led to the identification of new viruses and viral species, and the importance of other viruses is now widely acknowledged. Adenovirus, influenza virus, parainfluenza virus, human metapnuemovirus, coronavirus and bocavirus are among other commonly identified respiratory viruses known to contribute to the burden of childhood ARI.

Although less frequently detected than viruses, bacteria were traditionally believed to be the cause of more severe ARI-associated morbidity and mortality, particularly in developing countries [6, 7]. However, traditional diagnostic methods such as blood culture, which are still considered the gold standard in most settings, lack sensitivity and hence, the disease burden attributable to specific bacteria is not well understood. The recent advent of sequencing technologies such as 16S rRNA gene sequencing have led to the discovery of far more diverse respiratory microbial communities than previously recognized [8]. However, advanced diagnostics are largely limited to countries with the most resources and studies detecting a comprehensive range of pathogens remain scarce or non-existent. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are acknowledged as the most common and important bacterial pathogens in childhood ARI, although more recent studies have reported substantial reductions of ARIs due to pneumococcus and *Haemophilus influenzae type B* (Hib), most likely owing to the widespread introduction of conjugate vaccines [9].

The respiratory tract is a reservoir of a diverse community of microorganisms, both commensals and potential pathogens [10]. There is growing evidence that synergistic and antagonistic interactions between viruses and bacteria play a key role in the development of ARI. A better understanding of the interactions between viruses and bacteria in the respiratory tract may provide improved insight into the pathogenesis of ARI, and potentially reveal new prevention and treatment strategies. This chapter summarizes the current knowledge on viruses, bacteria and viral-bacterial interactions in childhood ARI and the possible mechanisms by which these interactions may lead to disease.

## 8.2 Respiratory Viruses

Respiratory viruses are an important cause of both upper and lower ARI. The burden of viral respiratory infections is greatest in children, with infants and preschool children experiencing an estimated 6–10 viral infections annually [11]. The role of viruses in URI is well established, with 90% of URI caused by viruses compared with only 10% caused by bacteria [12]. Respiratory viruses are also commonly identified in children with LRI, and although their role in LRI is acknowledged, evidence for the clinical significance of respiratory viruses in LRI is still debated. Lung aspiration is considered the gold–standard for sampling since it is obtained directly from the site of infection and would indicate etiological significance for LRI, but is limited due to its invasive nature and rate of complications [11]. Upper respiratory tract samples such as nasopharyngeal aspirates are easily obtained and hence, more frequently used in etiological studies. However, it is argued that viruses identified in the nasopharynx represent only colonization and are not indicative of LRI. Nonetheless, viruses of the upper respiratory tract are more commonly identified in children with LRI than in asymptomatic, healthy children. A 2015 systematic review and meta–analysis of case-control studies of children with and without LRI found evidence for causal attribution of RSV, influenza, parainfluenza virus, human metapnuemovirus and RV in children presenting with LRI compared to asymptomatic or healthy children [13]. However, there was no significant difference in the detection of adenovirus, bocavirus or coronavirus between cases and controls.

While RSV and RV are widely acknowledge to be the most common and important viral causes of ARI in children, recent advances in molecular methods have highlighted the significance of other respiratory viruses.

### 8.2.1 Common Respiratory Viruses

#### 8.2.1.1 Respiratory Syncytial Virus

RSV has been considered the most important viral cause of ARI in children, although its contribution is variable [14, 15]. RSV is a seasonal virus that peaks in the cold season in temperate climates and in the rainy season in tropical climates [15]. It affects about 90% of infants and young children by the age of 2 years, with peak rates occurring in infants 6 weeks to 6 months of age [15]. There are two subtypes of RSV, A and B, which circulate concurrently, although some studies have suggested that RSV-A may be more virulent than RSV-B [16–18]. In 2005, there were an estimated 33.8 million new episodes of RSV-associated ARI worldwide in children less than 5 years of age, with at least 3.4 million RSV-associated ARI hospitalizations, and an estimated 66,000–199,000 deaths, 99% of which occurred in developing countries [3]. Hence, RSV is justifiably seen to be the most important cause of childhood ARI and a major cause of ARI-associated hospital admission [3]. Although RSV has been associated with higher rates of hospitalization than other respiratory viruses in several studies, estimates of RSV-associated ARI

incidence and hospitalization are highly variable between and within regions, likely due to methodological differences [15].

#### 8.2.1.2 Human Rhinovirus

RV is the most commonly identified respiratory virus in both adults and children and was found to be responsible for approximately two-thirds of cases of the common cold [19]. Hence, it is frequently referred to as the "common cold" virus. However, there is now abundant evidence from experimental and observational studies to support the role of RV as a lower respiratory tract pathogen. Early experiment studies with RV suggested that viral replication was optimal at 33 °C (91.4 °F) and was reduced at 37 °C (98.6 °F) and 39 °C (102.2 °F) [20, 21]. However, more recent studies have shown minimal differences in replication capacities at 33 °C (91.4 °F) and 37 °C (98.6 °F) for eight different RV strains, including when viruses were cultured and titrated at the same temperature [22]. Hence, RV is now recognised as an important cause of LRI including pneumonia and bronchiolitis and importantly, accounts for the majority of asthma attacks in children [4, 5]. Several studies worldwide have reported RV as the most common virus identified in children with LRI, with identification rates of up to 63% in some populations [23].

RV was first isolated and associated with respiratory clinical disease in human in 1956 [24] and by the 1980s, one hundred and one RV-A and RV-B serotypes, known as the reference or prototype had been preserved and distributed by the American Type Culture Collection (ATCC). The retrospective discovery of the third RV species, RV-C, reported in 2006 [25, 26], led to several new investigations of the prevalence of RV. The majority of these studies in children hospitalized with ARI found that RV-C was the most prevalent RV species and was often associated with more severe illness [5, 25–31].

#### 8.2.1.3 Adenovirus

Adenovirus is another common viral cause of ARI. Adenoviruses are classified into seven species, A to G, and different serotypes have been implicated in different clinical syndromes [32]. While the majority of adenovirus infections present as a mild URI, adenovirus is also known to cause LRI including pneumonia, bronchiolitis and bronchitis [32, 33]. Adenoviruses can also cause gastrointestinal, ophthalmologic, genitourinary and neurological infections. Adenovirus infections are most common during infancy and early childhood and is prevalent in up to 17% of children hospitalized with ARI [32]. Adenovirus is often associated episodes of recurrent wheezing, fever, hypoxia and lengthy hospitalizations [32].

#### 8.2.1.4 Influenza Virus

Influenza virus is an important cause of ARI morbidity and mortality, with the highest burden among children less than 5 years of age and adults over 65 years of age [34, 35]. The two main subtypes of influenza virus, A and B, routinely circulate and are responsible for seasonal flu epidemics each year. In the first study to estimate the global incidence of influenza-associated ALRI in children less than 5 years of age, there were an estimated 90 million new cases of influenza episodes, 20 million cases

of influenza-associated ARI and one million cases of influenza-associated severe ARI causing 28,000–111,500 deaths worldwide in 2008 [36]. In a more recent systematic analysis of the burden of influenza in paediatric respiratory hospitalizations between 1982 and 2012, influenza was associated with an estimated 870,000 hospitalizations in children less than 5 years of age annually [37].

#### 8.2.1.5 Human Parainfluenza Virus

Human parainfluenza virus (HPIV), first discovered in the late 1950s, is an important cause of ARI in children, accounting for 2–17% of hospitalized cases [38–40]. There are four types of HPIV, HPIV 1–4. HPIV-1 to HPIV-3 are common causes of ARI in infants and young children, while HPIV-4 is less commonly associated with respiratory illness [41]. Serologic studies have demonstrated that almost all children between 6 and 10 years of age have evidence of past infection, suggesting mild or asymptomatic primary infections [42].

#### 8.2.1.6 Human Metapnuemovirus

Human metapneumovirus (hMPV) was first isolated from young children with respiratory tract disease the Netherlands in 2001 [43]. Although hMPV was only recently discovered, phylogenetic analysis showed that hMPV has been circulating in humans for at least 50 years [44]. Clinical symptoms of hMPV are similar to those caused by RSV, ranging from URI to severe bronchiolitis and pneumonia [43, 45]. In a study evaluating the burden of hMPV infections in children in the USA, hMPV was detected in 6% of children hospitalized with ARI, 7% of children in outpatient clinics and 7% of children examined in emergency departments, with the greatest burden in children less than 1 year of age [46]. Other studies of hMPV in children hospitalized with ARI have reported prevalences as high as11–25% [47–50].

#### 8.2.1.7 Human Coronavirus

Human coronavirus is often associated in respiratory illness. Four human coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1) are endemic in most populations and are associated with mild, self-limiting respiratory illnesses. Another two human coronaviruses, SARS-CoV and MERS-CoV cause severe respiratory syndromes and present a significant threat with their high fatality rates. The four non-severe human coronaviruses are implicated in both URI and LRI, with reported prevalence of approximately 10% in children hospitalized with ARI [51].

#### 8.2.1.8 Human Bocavirus

Human bocavirus 1 (hBoV1) was first discovered in 2005 from patients with LRI in Sweden and was the first virus to be discovered by molecular virus screening [52]. Since then, three additional species of HboV, hBoV2, hBoV3 and hBoV4 have been discovered, [53–55] although these species are found in the gastrointestinal tract and have been associated with gastroenteritis [53–55]. In contrast, HboV1 is associated with respiratory illness, and more specifically childhood ARI, with reported prevalence ranging from 1.5 to 19% [56]. As with other respiratory viruses, diagnosis of hBoV1 infection is not possible by clinical presentation and for URI common

symptoms include common cold-like symptoms and wheezing and for LRI clinical scenarios include pneumonia and bronchiolitis [57].

### 8.2.2 Viral Co-infections

The advent of improved molecular methods in recent years has increased the sensitivity in identifying viruses in children with ARI [58]. As a result, identification of multiple viruses in respiratory specimens from children with ARI is frequently reported [59, 60], with co-infection rates as high as 40–50% [23, 61]. However, the relationship between viral co-infections and severity of ARI in children is not conclusive. Some studies have reported increased risk of ARI hospitalization, increased length of hospital stay and worse clinical outcomes in children with viral co-infections [60, 62–65]. In contrast, recent systematic reviews and meta-analysis evaluating the relationships between respiratory viral co-infections in children have concluded that viral-coinfections were not associated with ARI severity [66–69].

To date, experimental studies of respiratory co-infections are scarce. An *in-vitro* study examining interactions between RSV and influenza virus demonstrated that growth of RSV was blocked by competitive infection with influenza A virus [70]. In the study by Shinjoh et al., RSV infection produced a higher peak viral load in single infections than in co-infections with influenza virus, if the infections were initiated at the same time [70]. However, if the influenza co-infection was initiated after the RSV infection, influenza growth was suppressed by RSV [70]. The study also demonstrated suppression of the growth of RSV by influenza A infection at the level of viral protein synthesis [70]. Indirect immunofluorescence revealed that a large proportion of infected cells synthesized both RSV and influenza A virus antigens, while scanning electron microscopy demonstrated that influenza A and RSV virions possessing surface antigens specific for each virus were selectively released from dually-infected cells [70].

In a mathematical model study investigating the dynamics of respiratory viral co-infections, Pinky et al. found that during co-infections, one virus could block another virus by being the first to infect the available host cells and that viral interference through immune response interaction was unlikely [71]. Interestingly, the study found that viral growth rate determines which virus will dominate a simultaneous infection [71]. For example, RV, the fastest-growing virus, reduced replication of the remaining viruses during a co-infection, while parainfluenza virus, the slowest-growing virus is suppressed in the presence of other viruses [71]. The authors of the study suggest that the blocking of one virus infection by the presence of another could be explained through resource competition and this finding has been supported by clinical studies of children with ARI [72, 73]. Canducci et al. found that co-infection of RSV and metapneumovirus in infants with ARI was a protective factor for length of hospital stay and hypoxia, when compared with RSV infection alone [72]. Marguet et al. also found shorter length of hospitalization in infants with RSV and RV co-infection comparing with single RSV infection [73].

Several other explanations for why identification of multiple viruses do not increase ARI severity have been suggested. One suggestion is that identification of a virus in a respiratory specimen using molecular methods may represent early detection of an infection, asymptomatic carriage, low-virulent infection or prolonged shedding [65]. Therefore, some cases of co-infection may simply be a subject of co-detection. It is also possible that the clinical outcome of viral co-infections is dependent on specific viral combinations, and this may explain the lack of consensus in the literature regarding whether viral co-infections is associated with an increased ARI severity. Many viral co-infection combinations have been reported, as reviewed by Scotta et al., with RSV and RV being the most frequently detected co-infection, although many studies do not even specify the viruses involved in viral co-infections [66].

## 8.3 Respiratory Bacteria

Although less frequently detected than viruses, bacteria are also acknowledged to be an important cause of ARI-associated morbidity and mortality. Traditional diagnostic methods such as blood culture, which are still considered the gold standard in most settings, lack sensitivity, and hence the disease burden attributable to specific bacteria is not well understood. Given the absence of a reference standard for the detection of bacterial pathogens, the prevalence of bacteria in ARI is likely to be higher than often reported. *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus* are acknowledged as the most common and important bacterial pathogens in childhood ARI, although more recent studies have reported substantial reductions of pneumococcal and Hib disease, most likely owing to the widespread introduction of conjugate vaccines [9]. Culture-independent techniques have also demonstrated that the human microbiome is far greater in extent than previously recognised [74] and that only 1% of all bacteria can be cultured using standard diagnostic methods [8]. However, advanced diagnostics are still rare in most clinical settings and studies detecting a comprehensive range of pathogens remain scarce or non-existent.

The lower respiratory tract and lungs were traditionally believed to be sterile and free from bacteria. However, it is now widely accepted that the lungs are constantly exposed to diverse communities of bacteria from the upper respiratory tract and this has been confirmed with the use of culture-independent techniques such as the 16S rRNA gene sequencing. In one of the first studies in the field, Hilty et al. challenged the dogma that the lower respiratory tract is sterile by showing that bronchial tree contains a characteristic microbial flora that differs between health and disease [75].

The human respiratory tract is home to a diverse community of both commensal and potential pathogenic bacteria that cause respiratory disease. The term "microbiome" was first proposed in 2001 by Joshua Lederberg and is used to describe this "ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space." [76] In a balanced state, the respiratory microbiome is believed to play a beneficial role for the human host [77]. However, imbalances in the respiratory microbiome can contribute to the acquisition of new

pathogens, carriage of multiple pathogens or interactions among pathogens that lead to respiratory disease. In order to cause respiratory disease, bacterial pathogens must first colonize the nasopharynx. Since the nasopharynx lies between the nose, sinuses, ears, larynx, and the lower respiratory tract, pathogens of the nasopharynx can be the source for both upper and lower respiratory tract infections and hence, plays an important role in both the development of disease and the spread of pathogens [78]. Colonization is believed to be a dynamic and complex microbial process involving acquisition and elimination of species, interactions among microbes and between microbes and the host, and interference by environmental factors [10]. Given these bacteria often co-exist in the same ecological niche; it is likely that highly evolved relationships exist between these bacteria and their interactions with each other play a critical role in the pathogenesis of disease [79]. Furthermore, it is also likely that these species interact with one another even during healthy states [10].

### 8.3.1 Common Respiratory Bacteria

#### 8.3.1.1 *Streptococcus pneumoniae*

*Streptococcus pneumoniae,* or pneumococcus*,* is a Gram-positive, alpha-hemolytic (under aerobic conditions) or beta-hemolytic (under anaerobic conditions), facultative anaerobic member of the Streptococcaceae family [80]. It is responsible for a range of illnesses including pneumonia, meningitis, bacteremia, otitis media and sinusitis [81] and is the most commonly isolated organism in patients with community-acquired pneumonia [82]. *S. pneumoniae* colonizes the upper respiratory tract and is part of the normal flora of healthy individuals, particularly children. Although there are over 90 different serotypes, most cases of disease are caused by relatively few serotypes, with the ten most common serotypes accounting for 62% of invasive pneumococcal disease [83]. Since its isolation in 1881, there have been great efforts to treat and prevent *S. pneumoniae.* Antibiotic treatment for invasive pneumococcal infections typically includes broad-spectrum antibiotics until results of antibiotic sensitivity testing are available. However, emerging antibiotic resistance is a growing concern because of its potential negative impact on the outcome of patients who receive standard antibiotic therapy. Pneumococcal vaccines such as the pneumococcal conjugate vaccine or pneumococcal polysaccharide vaccine are now commonly administered to children globally.

#### 8.3.1.2 *Haemophilus influenzae*

*Haemophilus Influenzae* is a Gram-negative, coccobacillary, facultative anaerobic pathogenic bacterium belonging to the Pasteurellaceae family [84]. It was first described in 1892 during an influenza pandemic and was mistakenly considered to be the cause of influenza until 1933 when the viral cause of influenza was known [85]. *H. influenzae* is commonly found in the upper and lower respiratory tract as a commensal but also causes a variety of both invasive infections, such as bacteremia, facial cellulitis, septic arthritis, and meningitis primarily in non-immune children

under age 4 years of age, and respiratory tract infections such as pneumonia, acute otitis media, bronchitis, epiglottitis and sinusitis in children and adults [86]. There are six different *H. influenzae* capsular serotypes, a through f, in addition to nonencapsulated or nontypeable strains. The two most important human pathogens are the capsular serotype b strains and the nontypeable strains which are nonencapsulated. Non-typeable *H. influenzae* (NTHi) live exclusively in the pharynges of humans and are increasingly recognized as pathogens that cause both localized infections of the respiratory tract (middle ear spaces, sinuses, and bronchi) and systemic infections such as bacteremia and pneumonia [86].

#### 8.3.1.3 *Moraxella catarrhalis*

*Moraxella catarrhalis* is a Gram-negative, aerobic, oxidase-positive diplococcus belonging to the Moracellaceae family that was first described in 1896 [87]. For most of the past century, *M. catarrhalis* was regarded as an upper respiratory tract commensal organism. However since the late 1970s, *M. catarrhalis* has been recognized as an important and common human respiratory tract pathogen [88]. Nasopharyngeal colonization is more prevalent among infants compared with adults, with colonization rates varying between 33 and 100% in infants from different parts of the world [89–91]. *M. catarrhalis* is also a common cause of otitis media in infants and children, causing 15–20% of acute otitis media episodes [88].

#### 8.3.1.4 *Staphylococcus aureus*

*Staphylococcus aureus,* a Gram-positive coccal bacterium belonging to the Staphylococcaceae family, frequently colonizes the nasopharynx, respiratory tract and skin [92]. It is both a commensal bacterium and a human pathogen, with colonization rates of approximately 30% in the general population, although higher rates are observed in young children and the elderly [92, 93]. *S. aureus* is also a leading cause of bacteremia and infective endocarditis as well as osteoarticular, skin and soft tissue, pleuropulmonary, and device-related infections [93].

### 8.3.2 Bacterial Interactions

Several studies have investigated interactions between bacteria, although mostly in experimental and mathematical model studies. In an *in-vivo* study where *H. influenzae* was introduced into the nasopharynx of neonatal rats that had or had not been pre-colonized by *S. pneumoniae,* Margolis et al. reported that *H. influenzae* density increased when *S. pneumoniae* was present, suggesting synergism between these bacterial species [94]. However, when these two species were inoculated in the reverse order, inhibition was observed, indicating competition between both species [94]. Another *in-vivo* study by Lysenko et al. found that both *S. pneumoniae* and *H. influenzae* successfully colonized mice when each bacteria species was injected separately [95]. However, when *S. pneumoniae* was co-colonized with an *H. influenzae* strain, the density of *S. pneumoniae* was lower than when inoculated alone, and this was later proved to be fully dependent on complement- and

neutrophil-mediated killing of pneumococci [96]. These findings were supported by a large epidemiological study of the 9-valent pneumococcal conjugate vaccine and prevalence of bacterial colonization in HIV-uninfected and HIV-infected children in South Africa that reported inverse associations between *S. pneumoniae* and *S. aureus* and between *S. aureus* and *H. influenzae* in HIV-uninfected children but not HIV-infected children [97].

Mathematical models investigating bacterial interactions have produced conflicting results. Using a multivariate random effects model for longitudinal data, Jacoby et al. found a positive association between *S. pneumoniae* and *H. influenzae* colonization among Aboriginal and non-Aboriginal children in Australia [98]. In contrast, Pettigrew et al. modeled bacterial colonization in children and reported *S. pneumoniae* colonization to be negatively associated with colonization by *H. influenzae* [99]. The study also reported negative associations between *S. pneumoniae* and *S. aureus* and between *H. influenzae* and *S. aureus*, but interestingly, when *H. influenzae* was present with *M. catarrhalis*, the odds of *S. pneumoniae* colonization increased by more than two-fold [99]. These studies suggest that interactions between bacteria are complex and may shift from negative to positive when additional bacteria species are present.

## 8.4 Epidemiology of Viral-Bacterial Co-infections

### 8.4.1 Historical Context

Viral-bacterial co-infections are frequently detected in children with respiratory illness, and there is strong evidence for enhanced ARI severity in children during co-infections compared with single infections [100]. While most studies report viral-bacterial co-infection rates ranging from 20 to 50%, rates as high as 66–77% have been observed [70–72]. The clinical significance of viral-bacterial co-infections and mechanisms that drive these interactions are not well understood. It is difficult to determine the relative importance of individual viruses and bacteria involved in co-infections since both viruses and bacteria can be carried commensally in the respiratory tract and their detection may reflect colonization, rather than infection. Furthermore, it is not possible to distinguish between primary and secondary infections in clinical studies, making it difficult to elucidate the interactions between viruses and bacteria in co-infections.

The earliest suggestion that viral infections predispose to secondary bacterial infections has been attributed to French physician R. T. H. Laennec, who observed that the prevalence of pneumonia increased following an influenza epidemic in 1803 [69]. In 1947, British epidemiologist, William Farr, coined the term “excess mortality” to describe the increase in number of deaths during the influenza season that were not caused by influenza itself, and developed the methodology used today to quantitate mortality in influenza epidemics [70]. The association between influenza and secondary bacterial infections came into particular influenza pandemics during the twentieth century, as well as subsequent observational and experimental

studies, provided further evidence that viral infections predispose to secondary bacterial infections.

During the 1918 "Spanish flu" pandemic, over 50 million deaths occurred, most of which were not caused directly by influenza alone but rather as a result of secondary bacterial pneumonia [71]. The most frequently identified organisms in sputum, lung and blood samples of infected patients were *S. pneumoniae, H. influenzae, Streptococcus pyogenes* and *S. aureus*, and it was believed that the influenza virus acted synergistically with pathogenic bacteria resulting in increased incidence of disease and death [71]. These findings were supported by data from the 1957 "Asian flu" and 1968 "Hong Kong flu" pandemics showing that increased mortality was associated with increased incidence of bacterial pneumonia [72, 73]. The availability of antibiotics effective for secondary bacterial infections was believed to be a key factor for the lower number of deaths during the 1957 and 1968 pandemics compared with 1918. During the 2009 "swine flu" pandemic involving the H1N1 influenza virus, bacterial co-infection was frequently reported in fatal pneumonia cases, with *S. pneumoniae* being the most frequent bacteria identified [74, 75].

### 8.4.2 Clinical Evidence of Viral-Bacterial Co-infections in Children

The best and most studied example of respiratory viral-bacterial co-infections involves influenza virus, and influenza virus-bacterial co-infections has been well described in both adults and children, with clear associations with increased disease severity [101–103]. However, with the exception of outbreaks, influenza virus is a relatively infrequent viral pathogen compared to other respiratory viruses including RV and RSV.

RSV is commonly implicated in viral-bacterial co-infections with reported co-infection rates of up to 17.5–44% in RSV-infected children [104–108]. In children with severe bronchiolitis studied by Thorburn et al., bacteria were isolated from 42% of lower airway secretions from infants with RSV using culture methods [107]. *H. influenzae* and *S. aureus* were the most common bacteria identified and furthermore, the study reported that children with bacterial co-infection were at increased risk for bacterial pneumonia [107]. In serological study of children with community-acquired pneumonia, 39% of children had viral-bacterial co-infections, of which RSV and *S. pneumoniae* was the most common combination, accounting for 33% of cases [109]. Like influenza, both RSV and *S. pneumoniae* infection peaks during the winter months [110] and RSV has also been linked to seasonal increases in *S. pneumoniae* [111]. In a case-control study by Benet et al., co-infection of RSV and *S. pneumoniae* was more common in cases than in controls but co-infection of RV and *S. pneumoniae* was not different between cases and controls [112]. RSV-bacterial co-infection has also been associated with increased disease severity compared with RSV alone including longer hospital stays and more frequent admission to pediatric intensive care unit [108] and longer ventilator support [105, 107]. However, associations identified in clinical studies are often weak and only

occasionally reach statistical significance. Additionally, some studies have reported bacterial co-infection rates below 2% in children with RSV [113–116]. In a study of infants hospitalized with RSV, bacterial co-infection was found in only 0.6% of children hospitalized for RSV-associated LRI [116].

RV is also commonly implicated in viral-bacterial co-infections. In a study of children with invasive pneumococcal disease by Techasaensiri et al. 34% of children had a viral co-infection, of which 25% were influenza, and 21% were RV [117]. The study reported that children with viral-coinfections were admitted to the pediatric intensive care unit more frequently and had longer hospital stays than children without viral-coinfections [117]. In a study of children with community-acquired pneumonia by Honkinen et al., viral-bacterial coinfection was identified in 66% of children, of which RV and *S. pneumoniae* was the most common combination, accounting for approximately 7% of cases [118]. Furthermore, the study reported that all cases of treatment failure had a viral-bacterial co-infection. Lauinger et al. found that among RV-infected children, bacterial co-infections, identified in 8% of children, were associated with increased admission to ICU [119].

Other respiratory viruses have also been implicated in bacterial co-infections in children, but to a lesser degree. It has been suggested that the pathogenesis of hMPV infection is strongly affected by bacterial co-infection with *S. pneumoniae*. In a study of children hospitalized with LRI in South Africa, Madhi et al. found that administration of conjugate pneumococcal vaccine reduced the incidence of hMPV infection and the incidence of clinical pneumonia in both HIV positive and negative patients [120]. These findings suggest that a significant proportion of hMPV-associated hospitalizations may be prevented by vaccination with pneumococcal conjugate vaccine. Adenovirus co-infection was identified in 21% of children with invasive pneumococcal disease [117]. Some studies have found associations between overall respiratory virus incidence and bacterial incidence, without distinguishing the specific pathogens involved [110]. While clinical studies confirm that viral-bacterial co-infections are common in children with ALRI, the absence of a control population in most studies makes it difficult to elucidate the clinical significance of co-infections.

## 8.5 Mechanisms for Viral-Bacterial Interactions

The historical context of viral-bacterial co-infections during influenza pandemics have led to a predominantly unidirectional view that primary viral infections increase the development of secondary bacterial infections leading to LRI. Viral-bacterial co-infections in children have been described in many clinical studies, with some associations with disease severity. However, in clinical studies, it is difficult to differentiate primary from secondary infections and to elucidate the clinical significance of co-infections. However, several *in-vivo* and *in-vitro* experimental model studies have proposed mechanisms to explain interactions between viruses and bacteria. Most mechanisms involve viral facilitation of secondary bacterial infections, for example through disruption of the respiratory epithelium or

modulation of innate and adaptive immune responses to decrease bacterial clearance or increase bacterial adherence. However, there is also growing evidence that bacterial infections may promote secondary viral infections, though direct interactions, bacterial interference with antiviral immunity or by synergism or complementation by virulence factors that have similar functions.

### 8.5.1 Viral Promotion of Secondary Bacterial Infections

#### 8.5.1.1 Decreased Bacterial Clearance

The respiratory epithelium is the primary site of host-pathogen encounter in the respiratory tract and the first line of defence against infection [121, 122]. The respiratory epithelium restricts bacterial attachment through mucociliary clearance and maintenance of cell-cell junctions, which restricts access to bacterial receptors [123]. There is evidence that primary viral infections disrupt the respiratory epithelium leading to decreased bacterial clearance. *In-vitro* studies have shown that cells infected with RV, RSV, adenovirus and influenza led to impairment of mucociliary function and consequent decreased clearance of bacteria including *S. pneumoniae* and *H. influenzae* [124–127].

Modulation of innate immune cells following a viral-infection is also believed to decrease bacterial clearance in the respiratory tract. Among host innate immune responses, alveolar macrophages are the major cell population in the normal airway and form the first line of defence against respiratory pathogens. A deficiency in alveolar macrophage-mediated phagocytosis following influenza has been reported in several studies. Using a murine-model, Ghoneim et al. showed that influenza infection depleted and induced cell death of alveolar macrophages leading to impaired clearance of *S. pneumoniae* [128]. Influenza and *S. pneumoniae* co-infection in mice has been also been shown to result in synergistic stimulation of type 1 interferons (IFNs) leading to impaired recruitment of macrophages and subsequently, increased bacterial colonization [129]. Another murine-model study by Jamieson et al. showed that influenza infection resulted in decreased production of inflammatory cytokines and chemokines through virus-induced glucocorticoid production, reduced recruitment of innate immune cells to the infection site and consequently, a dramatic increase in bacterial burden [130].

#### 8.5.1.2 Increased Bacterial Adherence

Viral infections of respiratory epithelial cells can also promote bacterial adherence to host cells. In an experimental mouse model study, Hament et al. found that *S. pneumoniae* adherence to epithelial cells was enhanced by a preceding RSV infection [131] and it was later shown through *in-vitro* and *in-vivo* studies that RSV was capable of direct binding to *S. pneumoniae* [132]. Similarly, Avadhanula et al. showed that respiratory viruses including RSV, HPIV, and influenza virus enhanced adhesion of *H. influenzae* and *S. pneumoniae* to primary immortalized cell lines but only RSV and HPIV increased receptor expression for bacteria by primary bronchial epithelial cells and A549 cells [133]. Other studies have shown that RSV

virions can bind directly to *S. pneumoniae and H. influenzae* acting as a direct coupling particle between bacteria and epithelial cells and thereby increasing colonization by, and enhancing, invasiveness of bacteria [124, 134]. There is also evidence that during RSV infection, viral glycoproteins at the host cell surface, act as additional receptions for bacteria adherence [132, 134]. Respiratory viruses can also increase expression of host surface proteins to which bacteria can bind [133, 135, 136]. Host cell receptors for bacterial adherence have also been found to be exposed by viral neuraminidase activities in studies of influenza virus and *S. pneumoniae* [137, 138]. There is also evidence that viral-mediated epithelia damage can lead to exposure of the basement membrane and additional receptors for bacterial adherence [139, 140].

Although the majority of evidence for enhanced bacterial adherence during viral respiratory infection comes from studies of influenza virus or RSV, there is growing evidence for the role of RV in bacterial adhesion. In an *in-vitro* study by Wang et al., nasal epithelial cells were infected with RV, and then *S. aureus*, *S. pneumoniae*, or *H. influenzae* were added to the culture [140]. Compared with RV-uninfected control cells, the adhesion of *S. aureus*, *S. pneumoniae*, and *H. influenzae* increased significantly in RV-infected nasal epithelial cells. In another *in-vitro* study on the effects of RV infection on the adherence of S. *pneumoniae* to tracheal epithelial cells, the number of *S. pneumoniae* adhering to epithelial cells increased after RV infection [141].

### 8.5.2 Bacterial Promotion of Secondary Viral Infections

The historical emphasis on influenza—*S. pneumoniae* co-infections in adults and the unidirectional view that viral infections increase bacterial growth may be less relevant for children. While *S. pneumoniae* carriage rates are approximately 4% in adults, carriage rates are over 50% in children [142] and up to 80% in children under 5 in developing countries [143]. This supports growing evidence that bacterial infections may promote secondary viral infections, rather than vice versa. In a large, double-blind placebo-controlled trial in infants in South Africa, the 9-valent pneumococcal conjugate vaccine was shown to prevent 31% of pneumonias associated with respiratory viruses in children in hospital, leading to the suggestion that viruses contribute to the pathogenesis of bacterial pneumonia [144]. In another study of healthy children under 2 years of age, Verkaik et al. found that higher seroconversion rates to hMPV were associated with increased nasopharyngeal carriage of *S. pneumoniae* [145]. Furthermore, well-differentiated normal human bronchial epithelial cells pre-incubated *in-vitro* with *S. pneumoniae* resulted in increased susceptibility to infection with HMPV-enhanced green fluorescent protein, suggesting that *S. pneumoniae* can modulate HMPV infection [145].

Experimental models often show an increase in influenza virus titres following a bacterial challenge. In one study, influenza viral titres in mice were shown to increase when *S. pneumoniae* was present [146]. Subsequent mathematical modelling by Smith et al. established that the influenza infection reduced the bacterial clearance ability of alveolar macrophages and that the secondary *S. pneumoniae* infection enhanced viral release from infected cells [146]. In contrast, in another mouse model

study by McCullers et al., influenza infection preceding a pneumococcal challenge primed for pneumonia led to 100% mortality [147]. Interestingly, this effect was specific for viral infection preceding bacterial infection, and reversal of the order of administration led to protection from influenza and improved survival [147].

Further evidence of bacterial promotion of viral infections has been demonstrated by enhanced RSV and hMPV infection of primary epithelial cells with the addition of bacterial lipopeptides, suggesting that bacteria facilitated viral attachment to host cells [148]. *H. influenzae* has also been shown to increase airway epithelial cell ICAM-1 and TLR3 expression, leading to enhanced binding of RV and a potentiation of RV-induced chemokine release [149].

It has also been suggested that viruses might be capable of using their microbial environment to escape immune clearance, highlighting the importance of commensal microbiota in viral infections [150].

## 8.6 Conclusion

Although viral-bacterial co-infections are common, the clinical significance of co-infections and the mechanisms leading to ARI are yet to be fully clarified. Complex synergistic and antagonistic interactions between viruses and bacteria most likely play a key role in the development of ARI. Viruses and bacteria of the respiratory microbiome may each influence the pathogenicity and consecutive development of infections of the other. Improving knowledge of the interactions between viruses and bacteria may lead to a better understanding of the pathogenesis of ARI and eventually to new prevention and treatment strategies.

## References

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430–40.
2. Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Coordinated Data Group of BOSTID Researchers. Rev Infect Dis. 1990;12(Suppl 8):870–88.
3. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, 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(9725):1545–55.
4. Hayden FG. Rhinovirus and the lower respiratory tract. Rev Med Virol. 2004;14(1):17–31.
5. Bizzintino JA, Lee WM, Laing IA, Vang F, Pappas T, Zhang G, et al. Association between human rhinovirus C and severity of acute asthma in children. Eur Respir J. 2011;37(5):1037–42.
6. Forgie IM, O'Neil KP, Lloyd EN, Leinonen M, Campbell H, Whittle HC, et al. Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infections in infants presenting at the hospital. Pediatr Infect Dis J. 1991;10(1):33–41.
7. Forgie IM, O'Neil KP, Lloyd EN, Leinonen M, Campbell H, Whittle HC, et al. Etiology of acute lower respiratory tract infections in Gambian children: II. Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital. Pediatr Infect Dis J. 1991;10(1):42–7.

8. Staley JT, Konopka A. Measurement of in situ activities of nonphotosynthetic microrganisms in aquatic and terrestrial habitats. Annu Rev Microbiol. 1985;39:321–46.
9. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. Children. N Engl J Med. 2015;372(9):835–45.
10. Bosch AATM, Biesbroek G, Trzcinski K, Sanders EAM, Bogaert D. Viral and bacterial interactions in the upper respiratory tract. PLoS Pathog. 2013;9(1):e1003057.
11. Glezen WP, Denny FW. Epidemiology of acute lower respiratory disease in children. N Engl J Med. 1973;288(10):498–505.
12. Fahey T, Stocks N, Thomas T. Systematic review of the treatment of upper respiratory tract infection. Arch Dis Child. 1998;79(3):225–30.
13. Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: a systematic review and meta–analysis. J Glob Health. 2015;5(1):010408.
14. Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. Trop Med Int Health. 1998;3(4):268–80.
15. Simoes EAF. Respiratory syncytial virus infection. Lancet. 1999;354(9181):847.
16. Jafri H, Wu X, Makari D, Henrickson KJ. Distribution of respiratory syncytial virus subtypes A and B among infants presenting to the emergency department with lower respiratory tract infection or apnea. Pediatr Infect Dis J. 2013;32(4):335–40.
17. Martinello RA, Chen MD, Weibel C, Kahn JS. Correlation between respiratory syncytial virus genotype and severity of illness. J Infect Dis. 2002;186(6):839–42.
18. Walsh EE, McConnochie KM, Long CE, Hall CB. Severity of respiratory syncytial virus infection is related to virus strain. J Infect Dis. 1997;175(4):814–20.
19. Douglas RG. Pathogenesis of rhinovirus common colds in human volunteers. Ann Otolaryngol. 1970;79:563–71.
20. Bardin PG, Johnston SL, Pattemore PK. Viruses as precipitants of asthma symptoms II. Physiology and mechanisms. Clin Exp Allergy. 1992;22(9):809–22.
21. Corne JM, Holgate ST. Mechanisms of virus induced exacerbations of asthma. Thorax. 1997;52:380–9.
22. Papadopoulos NG, Sanderson G, Hunter J, Johnston SL. Rhinoviruses replicate effectively at lower airway temperatures. J Med Virol. 1999;58(1):100–4.
23. Chidlow GR, Laing IA, Harnett GB, Greenhill AR, Phuanukoonnon S, Siba PM, et al. Respiratory viral pathogens associated with lower respiratory tract disease among young children in the highlands of Papua New Guinea. J Clin Virol. 2012;54(3):235–9.
24. Price WH. The isolation of a new virus associated with respiratory clinical disease in humans. Proc Natl Acad Sci U S A. 1956;42:892–6.
25. Lamson D, Renwick N, Kapoor V, Liu Z, Palacios G, Ju J, et al. 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. 2006;194: 1398–402.
26. Arden KE, McErlean P, Nissen MD, Sloots TP, Mackay IM. Frequent detection of human rhinoviruses, paramyxoviruses, coronaviruses, and bocavirus during acute respiratory tract infections. J Med Virol. 2006;78(9):1232–40.
27. Lau SKP, Yip CCY, Lin AWC, Lee RA, So LY, Lau YL, et al. Cinical 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. 2009;200(1):1096–103.
28. Renwick N, Schweiger B, Kapoor V, Liu Z, Villari J, Bullmann R, et al. A recently identified rhinovirus genotype is associated with severe respiratory-tract infection in children in Germany. J Infect Dis. 2007;196:1745–60.
29. Miller EK, Edwards KM, Weinberg GA, Iwane MK, Griffin MR, Hall CB, et al. A novel group of rhinoviruses is associated with asthma hospitalizations. J Allergy Clin Immunol. 2009;123:98–104.

30. Miller EK, Khuri-Bulos N, Williams JV, Shehabi AA, Faouri S, Al Jundi I, et al. Human rhinovirus C associated with wheezing in hospitalised children in the Middle East. J Clin Microbiol. 2009;46(1):85–9.
31. Linsuwanon P, Payungporn S, Samransamruajkit R, Posuwan N, Makkoch J, Theanboonlers A, et al. High prevalence of human rhinovirus C infection in Thai children with acute lower respiratory tract disease. J Infect. 2009;59(2):115–21.
32. Calvo C, García-García ML, Sanchez-Dehesa R, Román C, Tabares A, Pozo F, et al. Eight year prospective study of adenoviruses infections in hospitalized children. Comparison with other respiratory viruses. PLoS One. 2015;10(7):e0132162.
33. Kunz AN, Ottolini M. The role of adenovirus in respiratory tract infections. Curr Infect Dis Rep. 2010;12(2):81–7.
34. Iskander M, Robert B, Lambert S. The burden of influenza in children. Curr Opin Infect Dis. 2007;20(3):259–63.
35. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292(11):1333–40.
36. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011;378(9807):1917–30.
37. Lafond KE, Nair H, Rasooly MH, Valente F, Booy R, Rahman M, et al. Global role and burden of influenza in pediatric respiratory hospitalizations, 1982–2012: a systematic analysis. PLoS Med. 2016;13(3):e1001977.
38. Counihan M, Shay DK, Holman RC, Lowther SA, Anderson LJ. Human parainfluenza virus-associated hospitalizations among children less than five years of age in the United States. Pediatr Infect Dis J. 2001;20(7):646–53.
39. Reed G, Jewett PH, Thompson J, Tollefson S, Wright PF. Epidemiology and clinical impact of parainfluenza virus infections in otherwise healthy infants and young children <5 years old. J Infect Dis. 1997;175(4):807–13.
40. Iwane MK, Edwards KM, Szilagyi PG, Walker FJ, Griffin MR, Weinberg GA, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics. 2004;113(6): 1758–64.
41. Henrickson KJ. Parainfluenza viruses. Clin Microbiol Rev. 2003;16(2):242–64.
42. Gardner SD. The isolation of parainfluenza 4 subtypes A and B in England and serological studies of their prevalence. J Hyg. 1969;67(3):545–50.
43. van den Hoogen BG, de Jong JC, Kuiken T, Groot R, Fouchier RAM, Osterhaus ADME. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med. 2001;7:719–24.
44. de Graaf M, Osterhaus ADME, Fouchier RAM, Holmes EC. Evolutionary dynamics of human and avian metapneumoviruses. J Gen Virol. 2008;89(12):2933–42.
45. Beneri C, Ginocchio CC, Manji R, Sood S. Comparison of clinical features of pediatric respiratory syncytial virus and human metapneumovirus infections. Infect Control Hosp Epidemiol. 2015;30(12):1240–1.
46. Edwards KM, Zhu Y, Griffin MR, Weinberg GA, Hall CB, Szilagyi PG, et al. Burden of human metapneumovirus infection in young children. N Engl J Med. 2013;368(7): 633–43.
47. Madhi SA, Ludewick H, Kuwanda L, van Niekerk N, Cutland C, Klugman KP. Seasonality, incidence, and repeat human metapneumovirus lower respiratory tract infections in an area with a high orevalence of human immunodeficiency virus type-1 infection. Pediatr Infect Dis J. 2007;26(8):693–9.
48. Boivin G, De Serres G, Côté S, Gilca R, Abed Y, Rochette L, et al. Human metapneumovirus infections in hospitalized children. Emerg Infect Dis. 2003;9(6):634–40.
49. Dollner H, Risnes K, Radtke A, Nordbo SA. Outbreak of human metapneumovirus infection in Norwegian children. Pediatr Infect Dis J. 2004;25(5):436–40.

50. Esper F, Martinello RA, Boucher D, Weibel C, Ferguson D, Landry ML, et al. A 1-year experience with human metapneumovirus in children aged <5 years. J Infect Dis. 2004;189(8):1388–96.
51. Greenberg SB. Update on human rhinovirus and coronavirus infections. Semin Respir Crit Care Med. 2016;37(04):555–71.
52. Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci U S A. 2005;102(36):12891–6.
53. Arthur JL, Higgins GD, Davidson GP, Givney RC, Ratcliff RM. A novel bocavirus associated with acute gastroenteritis in Australian children. PLoS Pathog. 2009;5(4):e1000391.
54. Kapoor A, Slikas E, Simmonds P, Chieochansin T, Naeem A, Shaukat S, et al. A new bocavirus species in human stool. J Infect Dis. 2009;199(2):196–200.
55. Kapoor A, Simmonds P, Slikas E, Li L, Bodhidatta L, Sethabutr O, et al. Human bocaviruses are highly diverse, dispersed, recombination prone, and prevalent in enteric infections. J Infect Dis. 2010;201(11):1633–43.
56. Allander T. Human bocavirus. J Clin Virol. 2008;41(1):29–33.
57. Berry M, Gamieldien J, Fielding B. Identification of new respiratory viruses in the new millennium. Viruses. 2015;7(3):996.
58. Gharabaghi F, Hawan A, Drews SJ, Richardson SE. Evaluation of multiple commercial molecular and conventional diagnostic assays for the detection of respiratory viruses in children. Clin Microbiol Infect. 2011;17(12):1900–6.
59. Calvo C, García-García ML, Blanco C, Vázquez MC, Frías ME, Pérez-Breña P, et al. Multiple simultaneous viral infections in infants with acute respiratory tract infections in Spain. J Clin Virol. 2008;42(3):268–72.
60. Franz A, Adams O, Willems R, Bonzel L, Neuhausen N, Schweizer-Krantz S, 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(4):239–45.
61. Nascimento MS, de Souza Ferreira AV, Rodrigues JC, Abramovici S, de LVF SF. High rate of viral identification and coinfections in infants with acute bronchiolitis. Clinics. 2010;65:1133–7.
62. Richard N, Komurian-Pradel F, Javouhey E, Perret M, Rajoharison A, Bagnaud A, et al. The impact of dual viral infection in infants admitted to pediatric intensive care unit associated with severe bronchiolitis. Pediatr Infect Dis J. 2007;27(3):213–7.
63. Cilla G, Onate E, Perez-Yarza E, Montes M, Vicente D, Perez-Trallero E. Viruses in community-acquired pneumonia in children aged less than 3 years old: high rate of viral coinfection. J Med Virol. 2008;80:1843–9.
64. Arruda E, Jones M, Escremim de Paula F, Chong D, Bugarin G, Notario G, et al. The burden of single virus and viral coinfections on severe lower respiratory tract infections among preterm infants: a prospective birth cohort study in Brazil. Pediatr Infect Dis J. 2014;33(10):998–1003.
65. Rhedin S, Lindstrand A, Rotzén-Östlund M, Tolfvenstam T, Öhrmalm L, Rinder MR, et al. Clinical utility of PCR for common viruses in acute respiratory illness. Pediatrics. 2014;133(3):e538–e45.
66. Scotta MC, Chakr VCBG, de Moura A, Becker RG, de Souza APD, Jones MH, et al. Respiratory viral coinfection and disease severity in children: A systematic review and meta-analysis. J Clin Virol. 2016;80:45–56.
67. Lim FJ, de Klerk N, Blyth CC, Fathima P, Moore HC. Systematic review and meta-analysis of respiratory viral coinfections in children. Respirology. 2016;21(4):648–55.
68. Goka EA, Vallely PJ, Mutton KJ, Klapper PE. Single and multiple respiratory virus infections and severity of respiratory disease: a systematic review. Paediatr Respir Rev. 2014;15(4):363–70.
69. Asner SA, Science ME, Tran D, Smieja M, Merglen A, Mertz D. Clinical disease severity of respiratory viral co-infection versus single viral infection: a systematic review and meta-analysis. PLoS One. 2014;9(6):e99392.

70. Shinjoh M, Omoe K, Saito N, Matsuo N, Nerome K. In vitro growth profiles of respiratory syncytial virus in the presence of influenza virus. Acta Virol. 2000;44(2):91–7.
71. Pinky L, Dobrovolny HM. Coinfections of the respiratory tract: viral competition for resources. PLoS One. 2016;11(5):e0155589.
72. Canducci F, Debiaggi M, Sampaolo M, Marinozzi MC, Berrè S, Terulla C, et al. Two-year prospective study of single infections and co-infections by respiratory syncytial virus and viruses identified recently in infants with acute respiratory disease. J Med Virol. 2008;80(4):716–23.
73. Marguet C, Lubrano M, Gueudin M, Le Roux P, Deschildre A, Forget C, et al. In very young infants severity of acute bronchiolitis depends on carried viruses. PLoS One. 2009;4(2):e4596.
74. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449(7164):804–10.
75. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, et al. Disordered microbial communities in asthmatic airways. PLoS One. 2010;5(1):e8578.
76. Lederberg J, McCray A. 'Ome sweet' omics-a genealogical treasury of words. Scientist. 2001;15:8–10.
77. Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? Nat Rev Microbiol. 2009;7(12):887–94.
78. Garcia-Rodriguez J, Fresnadillo Martinez M. Dynamics of nasopharyngeal colonization by potential respiratory pathogens. J Antimicrob Chemother. 2002;50(Suppl S2):59–73.
79. Murphy T, Bakaletz L, Smeesters P. Microbial interactions in the respiratory tract. Pediatr Infect Dis J. 2009;28(10):121–6.
80. Ryan KJ, Ray CG, editors. Sherris medical microbiology. New York: McGraw Hill; 2004.
81. Bridy-Pappas AE, Margolis MB, Center KJ, Isaacman DJ. Streptococcus pneumoniae: description of the pathogen, disease epidemiology, treatment, and prevention. Pharmacotherapy. 2005;25(9):1193–212.
82. Torres A, Blasi F, Peetermans WE, Viegi G, Welte T. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. Eur J Clin Microbiol Infect Dis. 2014;33(7):1065–79.
83. Kalin M. Pneumococcal serotypes and their clinical relevance. Thorax. 1998;53(3):159–62.
84. Kuhnert P, Christensen H, editors. Pasteurellaceae: biology, genomics and molecular aspects. Poole: Caister Academic Press; 2008.
85. Taubenberger JK, Hultin JV, Morens DM. Discovery and characterization of the 1918 pandemic influenza virus in historical context. Antiviral Ther. 2007;12(4 Pt B):581–91.
86. Gilsdorf JR. What the pediatrician should know about non-typeable Haemophilus influenzae. J Infect. 2015;71(Suppl 1):S10–S4.
87. Murphy TF. Branhamella catarrhalis: epidemiology, surface antigenic structure, and immune response. Microbiol Rev. 1996;60(2):267–79.
88. Goldstein EJC, Murphy TF, Parameswaran GI. Moraxella catarrhalis, a human respiratory tract pathogen. Clin Infect Dis. 2009;49(1):124–31.
89. Aniansson G, Aim B, Andersson B, Larsson P, Nylen O, Peterson H, et al. Nasopharyngeal colonization during the first year of life. J Infect Dis. 1992;165(Suppl 1):S38–42.
90. Faden H, Harabuchi Y, Hong JJ. Epidemiology of Moraxella catarrhalis in children during the first 2 years of life: relationship to otitis media. J Infect Dis. 1994;169(6):1312–7.
91. Leach AJ, Boswell JB, Asche V, Nienhuys TG, Mathews JD. Bacterial colonization of the nasopharynx predicts very early onset and persistence of otitis media in Australian aboriginal infants. Pediatr Infect Dis J. 1994;13(11):983–9.
92. Wertheim HFL, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005;5(12):751–62.
93. Tong SYC, Davis JS, Eichenberger E, Holland TL, Fowler VG. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603–61.

94. Margolis E, Yates A, Levin BR. The ecology of nasal colonization of Streptococcus pneumoniae, Haemophilus influenzae and Staphylococcus aureus: the role of competition and interactions with host's immune response. BMC Microbiol. 2010;10(1):59.
95. Lysenko ES, Ratner AJ, Nelson AL, Weiser JN. The role of innate immune responses in the outcome of interspecies competition for colonization of mucosal surfaces. PLoS Pathog. 2005;1:e1.
96. Lysenko ES, Lijek RS, Brown SP, Weiser JN. Within-host competition drives selection for the capsule virulence determinant of Streptococcus pneumoniae. Curr Biol. 2010;20(13): 1222–6.
97. Madhi SA, Adrian P, Kuwanda L, Cutland C, Albrich WC, Klugman KP. Long-term effect of pneumococcal conjugate vaccine on nasopharyngeal colonization by Streptococcus pneumoniae-and associated interactions with Staphylococcus aureus and Haemophilus influenzae colonization-in HIV-Infected and HIV-uninfected children. J Infect Dis. 2007;196: 1662–6.
98. Jacoby P, Watson K, Bowman J, Taylor A, Riley TV, Smith DW, et al. Modelling the co-occurrence of Streptococcus pneumoniae with other bacterial and viral pathogens in the upper respiratory tract. Vaccine. 2007;25(13):2458–64.
99. Pettigrew MM, Gent JF, Revai K, Patel JA, Chonmaitree T. Microbial interactions during upper respiratory tract infections. Emerg Infect Dis. 2008;14(10):1584–91.
100. Brealey JC, Sly PD, Young PR, Chappell KJ. Viral bacterial co-infection of the respiratory tract during early childhood. FEMS Microbiol Lett. 2015;362(10). pii: fnv062.
101. O'Brien KL, Walters MI, Sellman J, Quinlisk P, Regnery H, Schwartz B, et al. Severe Pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis. 2000;30(5):784–9.
102. Palacios G, Hornig M, Cisterna D, Savji N, Bussetti A, Kapoor V, et al. Streptococcus pneumoniae coinfection is correlated with the severity of H1N1 pandemic influenza. PLoS One. 2009;4(12):e8540.
103. Martén-Loeches I, Sanchez-Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C, et al. Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A(H1N1) virus. Chest. 2011;139(3):555–62.
104. Duttweiler L, Nadal D, Frey B. Pulmonary and systemic bacterial co-infections in severe RSV bronchiolitis. Arch Dis Child. 2004;89(12):1155–7.
105. Kneyber MCJ, van Oud-Alblas HB, van Vliet M, Uiterwaal CSPM, Kimpen JLL, van Vught AJ. Concurrent bacterial infection and prolonged mechanical ventilation in infants with respiratory syncytial virus lower respiratory tract disease. Intensive Care Med. 2005;31(5): 680–5.
106. Randolph AG, Reder L, Englund JA. Risk of bacterial infection in previously healthy respiratory syncytial virus-infected young children admitted to the intensive care unit. Pediatr Infect Dis J. 2004;23(11):990–4.
107. Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HKF. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax. 2006;61(7):611–5.
108. Resch B, Gusenleitner W, Mueller WD. Risk of concurrent bacterial infection in preterm infants hospitalized due to respiratory syncytial virus infection. Acta Paediatr. 2007;96(4): 495–8.
109. Heiskanen-Kosma T, Korppi M, Jokinen C, Kurki S, Heiskanen L, Juvonen H, et al. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. Pediatr Infect Dis J. 1998;17(11):986–91.
110. Kim PE, Musher DM, Glezen WP, Barradas MCR, Nahm WK, Wright CE. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis. 1996;22(1):100–6.
111. Weinberger DM, Givon-Lavi N, Shemer-Avni Y, Bar-Ziv J, Alonso WJ, Greenberg D, et al. Influence of pneumococcal vaccines and respiratory syncytial virus on alveolar pneumonia. Israel Emerg Infect Dis. 2013;19(7):1084–91.

112. Bénet T, Sylla M, Messaoudi M, Sánchez Picot V, Telles J-N, Diakite A-A, et al. Etiology and factors associated with pneumonia in children under 5 years of age in Mali: a prospective case-control study. PLoS One. 2015;10(12):e0145447.
113. Purcell K, Fergie J. Concurrent serious bacterial infections in 2396 infants and children hospitalized with respiratory syncytial virus lower respiratory tract infections. JAMA Pediatr. 2002;156(4):322–4.
114. Titus MO, Wright SW. Prevalence of serious bacterial infections in febrile infants with respiratory syncytial virus infection. Pediatrics. 2003;112(2):282–4.
115. Bloomfield P, Dalton D, Karleka A, Kesson A, Duncan G, Isaacs D. Bacteraemia and antibiotic use in respiratory syncytial virus infections. Arch Dis Child. 2004;89(4):363–7.
116. Hall CB, Powell KR, Schnabel KC, Gala CL, Pincus PH. Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. J Pediatr. 1988;113(2):266–71.
117. Techasaensiri B, Techasaensiri C, Mejias A, McCracken GH, Ramilo O. Viral coinfections in children with invasive pneumococcal disease. Pediatr Infect Dis J. 2010;29:519–23.
118. Honkinen M, Lahti E, Österback R, Ruuskanen O, Waris M. Viruses and bacteria in sputum samples of children with community-acquired pneumonia. Clin Microbiol Infect. 2012;18(3):300–7.
119. Lauinger IL, Bible JM, Halligan EP, Bangalore H, Tosas O, Aarons EJ, et al. Patient characteristics and severity of human rhinovirus infections in children. J Clin Virol. 2013;58(1):216–20.
120. Madhi SA, Ludewick H, Kuwanda L, Niekerk NV, Cutland C, Little T, et al. Pneumococcal coinfection with human metapneumovirus. J Infect Dis. 2006;193(9):1236–43.
121. Proud D, Leigh R. Epithelial cells and airway diseases. Immunol Rev. 2011;242(1):186–204.
122. Vareille M, Kieninger E, Edwards MR, Regamey N. The airway epithelium: soldier in the fight against respiratory viruses. Clin Microbiol Rev. 2011;24(1):210–29.
123. Melvin JA, Bomberger JM. Compromised defenses: exploitation of epithelial responses during viral-bacterial co-infection of the respiratory Tract. PLoS Pathog. 2016;12(9):e1005797.
124. Smith CM, Sandrini S, Datta S, Freestone P, Shafeeq S, Radhakrishnan P, et al. Respiratory syncytial virus increases the virulence of Streptococcus pneumoniae by binding to penicillin binding protein 1a. A new paradigm in respiratory infection. Am J Respir Crit Care. 2014;190:196–207.
125. Pittet LA, Hall-Stoodley L, Rutkowski MR, Harmsen AG. Influenza virus infection decreases tracheal mucociliary velocity and clearance of Streptococcus pneumoniae. Am J Respir Cell Mol Biol. 2010;42(4):450–60.
126. Suzuki K, Bakaletz LO. Synergistic effect of adenovirus type 1 and nontypeable Haemophilus influenzae in a chinchilla model of experimental otitis media. Infect Immunol. 1994;62(5):1710–8.
127. Sajjan U, Wang Q, Zhao Y, Gruenert DC, Hershenson MB. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. Am J Respir Crit Care. 2008;178(12):1271–81.
128. Ghoneim HE, Thomas PG, McCullers JA. Depletion of alveolar macrophages during influenza infection facilitates bacterial superinfections. J Immunol. 2013;191(3):1250–9.
129. Nakamura S, Davis KM, Weiser JN. Synergistic stimulation of type I interferons during influenza virus coinfection promotes Streptococcus pneumoniae colonization in mice. J Clin Invest. 2011;121(9):3657–65.
130. Jamieson AM, Yu S, Annicelli CH, Medzhitov R. Influenza virus-induced glucocorticoids compromise innate host defense against a secondary bacterial infection. Cell Host Microbe. 2010;7(2):103–14.
131. Hament JM, Aerts PC, Fleer A, Dijk H, Harmsen T, Kimpen JL, et al. Enhanced adherence of Streptococcus pneumoniae to human epithelial cells infected with respiratory syncytial virus. Pediatr Res. 2004;55:972–8.
132. Hament JM, Aerts PC, Fleer A, van Dijk H, Harmsen T, Kimpen JL, et al. Direct binding of respiratory syncytial virus to pneumococci: a phenomenon that enhances both pneumococcal

adherence to human epithelial cells and pneumococcal invasiveness in a murine model. Pediatr Res. 2005;58:1198–203.
133. Avadhanula V, Rodriguez CA, Devincenzo JP, Wang Y, Webby RJ, Ulett GC, et al. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. J Virol. 2006;80:1629–36.
134. Avadhanula V, Wang Y, Portner A, Adderson E. Nontypeable Haemophilus influenzae and Streptococcus pneumoniae bind respiratory syncytial virus glycoprotein. J Med Microbiol. 2007;56(9):1133–7.
135. Cundell DR, Gerard NP, Gerard C, Idanpaan-Heikkila I, Tuomanen EI. Streptococcus pneumoniae anchor to activated human cells by the receptor for platelet-activating factor. Nature. 1995;377(6548):435–8.
136. Kimaro Mlacha SZ, Peret TCT, Kumar N, Romero-Steiner S, Dunning Hotopp JC, Ishmael N, et al. Transcriptional adaptation of pneumococci and human pharyngeal cells in the presence of a virus infection. BMC Genomics. 2013;14(1):378.
137. McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and Streptococcus pneumoniae. J Infect Dis. 2003;187(6):1000–9.
138. Huber VC, Peltola V, Iverson AR, McCullers JA. Contribution of vaccine-induced immunity toward either the HA or the NA component of influenza viruses limits secondary bacterial complications. J Virol. 2010;84(8):4105–8.
139. Plotkowski MC, Puchelle E, Beck G, Jacquot J, Hannoun C. Adherence of type I Streptococcus pneumoniae to tracheal epithelium of mice infected with influenza A/PR8 virus. Am Rev Respir Dis. 1986;134:1040–9.
140. Wang JH, Kwon HJ, Jang YJ. Rhinovirus enhances various bacterial adhesions to nasal epithelial cells simultaneously. Laryngoscope. 2009;119:1406–11.
141. Ishizuka S, Yamaya M, Suzuki T, Takahashi H, Ida S, Sasaki T, et al. Effects of rhinovirus infection on the adherence of Streptococcus pneumoniae to cultured human airway epithelial cells. J Infect Dis. 2003;188(12):1928–39.
142. Regev-Yochay G, Raz M, Dagan R, Porat N, Shainberg B, Pinco E, et al. Nasopharyngeal carriage of Streptococcus pneumoniae by adults and children in community and family settings. Clin Infect Dis. 2004;38(5):632–9.
143. Adegbola RA, DeAntonio R, Hill PC, Roca A, Usuf E, Hoet B, et al. Carriage of Streptococcus pneumoniae and other respiratory bacterial pathogens in low and lower-middle income countries: a systematic review and meta-analysis. PLoS One. 2014;9(8):e103293.
144. Madhi SA, Klugman KP. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat Med. 2004;10:811–3.
145. Verkaik NJ, Nguyen DT, de Vogel CP, Moll HA, Verbrugh HA, Jaddoe VWV, et al. Streptococcus pneumoniae exposure is associated with human metapneumovirus seroconversion and increased susceptibility to in vitro HMPV infection. Clin Microbiol Infect. 2011;17(12):1840–4.
146. Smith AM, Adler FR, Ribeiro RM, Gutenkunst RN, McAuley JL, McCullers JA, et al. Kinetics of coinfection with influenza A virus and *Streptococcus pneumoniae*. PLoS Pathog. 2013;9(3):e1003238.
147. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis. 2002;186(3):341–50.
148. Nguyen DT, de Witte L, Ludlow M, Yüksel S, Wiesmüller K-H, Geijtenbeek TBH, et al. The synthetic bacterial lipopeptide Pam3CSK4 modulates respiratory syncytial virus infection independent of TLR activation. PLoS Pathog. 2010;6(8):e1001049.
149. Sajjan US, Jia Y, Newcomb DC, Bentley JK, Lukacs NW, LiPuma JJ, et al. H. influenzae potentiates airway epithelial cell responses to rhinovirus by increasing ICAM-1 and TLR3 expression. FASEB J. 2006;20:2121–3.
150. Kane M, Case LK, Kopaskie K, Kozlova A, MacDearmid C, Chervonsky AV, et al. Successful transmission of a retrovirus depends on the commensal microbiota. Science. 2011;334(6053):245–9.