Outlook

BERKLEY / BELARMINA PERDOMO Y OTROS C. UT TOLIHUILA Y OTROS / 410013333003-2020-00154-00 / PERITAJE Y SUSTITUCIÓN DE PODER

Desde Arturo Sanabria Gomez <asanabria@sanabriagomez.com>
Fecha Lun 18/11/2024 3:11 PM
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2 archivos adjuntos (9 MB)
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Señores
JUZGADO TERCERO ADMINISTRATIVO ORAL DE NEIVA
Vía correo electrónico

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DEMANDANTE: **BELARMIRA PERDOMO LAGUNA Y OTROS**
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LLAMADOS EN GARANTÍA: **UT TOLIHUILA Y OTROS**
RADICADO: **410013333003-2020-00154-00**

ASUNTO: **PERITAJE Y SUSTITUCIÓN DE PODER**

ARTURO SANABRIA GÓMEZ, apoderado de **BERKLEY INTERNATIONAL SEGUROS COLOMBIA S.A.**, adjunto peritaje y sustitución de poder.

Los numerales 1, 7 y 8 de la bibliografía pueden ser descargados en estos links con los números en la cita del peritaje.

1. https://www.aafp.org/pubs/afp/issues/2024/0300/chronic-low-back-pain.html
7. https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0043-1770341
8. https://onlinelibrary.wiley.com/doi/10.1002/ajh.27422

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JUZGADO TERCERO ADMINISTRATIVO ORAL DE NEIVA

E. S. D.

DEMANDANTE:	**BELARMINA PERDOMO LAGUNA Y OTROS**
DEMANDADO:	**EMPRESA COOPERATIVA DE SERVICIOS DE SALUD EMCOSALUD Y OTROS**
RADICADO:	**41001333300320200015400**
ASUNTO:	**SUSTITUCIÓN DE PODER**

ARTURO SANABRIA GÓMEZ, identificado con la cédula de ciudadanía número 79.451.316 expedida en Bogotá, portador de la tarjeta profesional de abogado número 64454 expedida por el Consejo Superior de la Judicatura, apoderado de **BERKLEY INTERNATIONAL SEGUROS COLOMBIA S.A.**, SUSTITUYO el poder conferido a **MARÍA CAMILA MANRIQUE DELGADO**, identificada con la cédula de ciudadanía número 1.144.198.672, portadora de la tarjeta profesional de abogado número 336123 del Consejo Superior de la Judicatura, para que asuma la representación de la aseguradora dentro del proceso de la referencia.

Atentamente,

Arturo Sanabria Gómez

ARTURO SANABRIA GÓMEZ

C.C. 79.451.316 Btá.

T.P. 64454 C.S. de la J.

Acepto:

MARÍA CAMILA MANRIQUE DELGADO

C.C. 1.144.198.672 Cali.

T.P. 336123 C.S. de la J.

INFORME PERICIAL MÉDICO-LEGAL

Perito: Doctora Catalina Vargas Gotuzzo
Identificación Profesional: Médica y Cirujana, Pontificia Universidad Javeriana de Bogotá
Registro Médico: 1019129908

Fecha de Emisión del Informe:
Número de Expediente:
Solicitante:

Artículo 226 del Código General del Proceso.

1. **Nombre:** Catalina Vargas Gotuzzo
   Documento de Identificación: Cédula de ciudadanía 1019129908 de Bogotá D.C
   Identificación Profesional: Médica y Cirujana, Pontificia Universidad Javeriana de Bogotá
   Registro Médico: 1019129908

2. **Domicilio:** Carrera 10 A # 119-30, Apartamento 101. Bogotá, D.C.
   Teléfono: +57 3228397776

3. **Actividad ejercida:** Médico Hospitalario del servicio de Urgencias
4. No tengo
5. No he sido designada como perito en otros casos
6. No he sido designada en procesos anteriores
7. No
8. No
9. No
10. Bibliografía adjuntada

1. Identificación del Paciente o Peritado

- **Nombre:** Flor Inés Laguna de Perdomo
- **Documento de Identificación:** C.C 26591772
- **Edad:** 66 años, 6 meses y 15 días
- **Sexo:** Femenino

2. Motivo de la Evaluación

El presente informe pericial ha sido solicitado con el fin de determinar la existencia de una posible responsabilidad médica en el caso de la paciente Flor Inés Laguna de Perdomo, quien ingresó a la IPS Clínica Emcosalud por cuadro clínico de larga data de evolución consistente en dolor dorso-lumbar y gonalgia bilateral con exacerbación de un día de evolución, que dificulta la bipedestación y la deambulación, sin otra sintomatología asociada.

Se requiere una evaluación exhaustiva de los antecedentes clínicos, el proceso diagnóstico seguido y los procedimientos terapéuticos aplicados, a fin de identificar posibles inconsistencias, omisiones o desviaciones de los estándares aceptados en la práctica médica que pudieran constituir un acto de negligencia, imprudencia o impericia. Asimismo, el informe busca aclarar si el diagnóstico y tratamiento brindado se ajustaron a las guías y protocolos clínicos establecidos y si fueron los adecuados para la condición clínica de la paciente.

En este contexto, se solicita un análisis que permita determinar:

1. Si las actuaciones del personal médico cumplieron con los estándares de la práctica médica aceptada en Colombia.
2. Si hubo alguna demora o fallo en el diagnóstico que pudiera haber agravado la condición de la paciente.
3. Si el tratamiento instaurado fue adecuado y oportuno de acuerdo con las características clínicas presentadas.

Este informe será utilizado en el contexto de un proceso judicial en el cual la paciente y sus representantes buscan establecer la existencia de responsabilidad médica y, de ser el caso, los daños sufridos como resultado de dicha responsabilidad.

3. Antecedentes del Caso

- **Antecedentes personales:** Discopatía, no se aportan adicionales
- **Antecedentes farmacológicos:** ASA (no aportan dosis), Nimodipino (no aportan dosis)
- **Antecedentes quirúrgicos:** Osteosíntesis de antebrazo, osteosíntesis en cara, cistopexia
- **Antecedentes familiares relevantes:** No se aportan en historia clínica
- **Antecedentes alérgicos:** No se aportan en historia clínica

4. Análisis del Caso

Fecha: 20/07/2018 - Hora: 13:13

Paciente femenina de 66 años con antecedente de discopatía (nivel no especificado), quién ingresa a la IPS Clínica Emcosalud por cuadro clínico de larga data de evolución consistente en dolor dorso-lumbar y gonalgia bilateral con exacerbación de un día de evolución, que dificulta la bipedestación y la deambulación, sin otra sintomatología asociada.

Al ingreso la paciente aporta:

- Radiografía de rodillas comparativas (29/05/2018)
- Radiografía de caderas comparativas (02/04/2018)
- Radiografía de columna dorsolumbar (06/03/2018): cambios de discopatía degenerativa L4-L5 y L5-S1
- Doppler venoso de miembros inferiores (10/05/2018): negativo para trombosis venosa profunda, múltiples telangiectasias en ambos miembros inferiores

- Resonancia magnética nuclear (no aportan segmento anatómico 10/02/2014): espondilolistesis GI de L4 sobre L5 - Discopatía lumbar

Es valorada inicialmente por medicina general, quienes encuentran:

Paciente en adecuadas condiciones generales, hemodinámicamente estable, sin signos de dificultad respiratoria, con presencia de dolor de alta intensidad que genera limitación para la bipedestación y la deambulación.

Examen físico:

- Tórax: simétrico, con adecuado patrón de expansibilidad
- Cardio-pulmonar: ruidos cardíacos rítmicos, sin soplos. Murmullo vesicular conservado en ambos campos pulmonares, sin sobreagregados
- Neurológico: alerta, orientado en tiempo, lugar y persona, sin déficit motor ni sensitivo, Glasgow 15/15, simetría facial conservada, RMT ++/+++, fuerza y tono muscular conservados, pares craneales sin déficit, realiza actividades motoras y coordinadas sin inconvenientes, sin signos de focalización
- Examen mental: respuesta adecuada al interrogatoria, sin alteraciones

Solicitan paraclínicos (hemograma, PCR, BUN, creatinina, tiempos de coagulación, electrolitos) y valoración por servicio de ortopedia.

Manejo:

- Tramadol 50 mg subcutáneo ahora
- Dipirona 2 gramos IV (lenta y bien diluida)
- Pregabalina 75 mg VO ahora

En el caso de la paciente femenina de 66 años, con antecedentes de discopatía y un cuadro de dolor dorso-lumbar y gonalgia bilateral de larga evolución, se concluye que el abordaje inicial y el manejo instaurado por el médico fueron adecuados y se ajustaron a los estándares de atención en este tipo de casos.

Desde el ingreso, se realizó una evaluación integral de la paciente, teniendo en cuenta sus antecedentes patológicos y la exacerbación del dolor que comprometía su capacidad para mantenerse de pie y deambular. Se llevó a cabo un examen físico exhaustivo con un enfoque sistémico que abarcó su estado general, así como los sistemas respiratorio, cardiovascular y neurológico, sin hallazgos que sugirieran banderas rojas ni complicaciones que requirieran intervenciones inmediatas adicionales. De acuerdo con las recomendaciones de la revista *American Family Physician*, no se recomienda realizar estudios de imagen de forma rutinaria en casos sin banderas rojas o sin déficit neuromuscular [1], como es el caso inicial de esta paciente.

El tratamiento farmacológico instaurado, conforme a revisiones sistemáticas de la literatura, como las de ***Kamper SJ y colaboradores*** [2] y ***Oliveira CB y colaboradores*** [3], recomiendan los antiinflamatorios no esteroideos (AINEs) como primera línea de manejo. En este caso, el médico tratante prescribió dipirona, un fármaco de este grupo. Dada la

severidad del dolor, se decidió complementar la intervención con un opioide de baja potencia, en concordancia con las indicaciones de la medicina basada en la evidencia.

22/07/2018

La paciente fue valorada por el servicio de medicina interna, quienes registraron en la historia clínica que la paciente reportó mejoría en la sintomatología dolorosa, con signos vitales estables. Durante el examen físico no se evidenciaron alteraciones en los sistemas cardiopulmonar ni neurológico, lo cual respalda la estabilidad clínica en estos sistemas.

En los estudios paraclínicos se observó un recuento de leucocitos de 6700, con un diferencial de linfocitos al 40.7% y neutrófilos al 41.2%, sin signos de infecciones o procesos inflamatorios agudos. La hemoglobina de 7.6 g/dL y el hematocrito de 25.7% indican anemia leve, en un rango que no requería transfusión. Según las guías de práctica clínica de la AABB, se recomienda un umbral restrictivo de transfusión de hemoglobina de 7 g/dL para pacientes adultos hospitalizados que están hemodinámicamente estables, incluidos aquellos en cuidados críticos [4].

El conteo plaquetario de 95,000, aunque reducido, no implicaba un riesgo inmediato de sangrado, aunque ameritaba seguimiento. El riesgo inmediato de sangrado en pacientes trombocitopénicos generalmente se considera significativo cuando el recuento de plaquetas es ≤5 × 10^9/L, que corresponde a menos de 5,000 plaquetas/µL [5].

Los parámetros de función renal, con una creatinina de 1.16 mg/dL y BUN de 23.5 mg/dL, se encontraban dentro de rangos normales, sin evidencia de deterioro renal. Los tiempos de coagulación, con valores de PT, INR y PTT dentro de los límites normales, sugerían una función hemostática adecuada y descartaban coagulopatías hasta el momento.

La conducta médica de continuar con el manejo analgésico previo y realizar un control de hemograma para el seguimiento de la bicitopenia, dada la condición de la paciente con diagnósticos de lumbago en estudio y anemia leve en rango no transfusional fue la adecuada.

23/07/2018 - Medicina general

La paciente fue valorada por medicina general con diagnósticos iniciales de lumbago y bicitopenia en estudio. En esta valoración, se constató que los signos vitales se encontraban dentro de los rangos normales. El examen físico mostró que los sistemas cardiopulmonar y neurológico no presentaban alteraciones. A nivel de la columna, se observó dolor a la palpación de la musculatura paravertebral en la región dorsal, mientras que la prueba de Lasegue fue negativa y no se reportó dolor a la flexión de cadera.

Como parte del enfoque diagnóstico, se solicitó una serie de estudios complementarios: una radiografía de columna dorso-lumbar para evaluar posibles cambios estructurales, un extendido de sangre periférica y pruebas específicas como el Coombs indirecto para descartar causas de bicitopenia. También se incluyeron pruebas serológicas como VIH y VDRL, así como TSH, PCR y VSG, para evaluar posibles causas subyacentes de inflamación, infección o disfunción endocrina. Hasta el momento se encontraba pendiente la valoración por ortopedia ya solicitada.

Se decidió continuar con el mismo plan de manejo, en espera de resultados adicionales que permitieran un diagnóstico más preciso y orientaran las próximas intervenciones.

La conducta del médico en esta valoración es apropiada y bien fundamentada. La solicitud de estudios de imagen y pruebas de laboratorio reflejan un enfoque integral para los diagnósticos de lumbago y bicitopenia en estudio. Este abordaje permite descartar causas subyacentes importantes y orientar el tratamiento adecuado. En general, el plan de manejo demuestra una atención cuidadosa y coordinada, por lo que respaldo plenamente la decisión del médico.

Medicina Interna - 23/07/2024

En valoraciones posteriores por el servicio de medicina interna se realizaron exámenes físicos completos y se revisaron los resultados de los paraclínicos. Por lo que consideraron que la paciente presentaba un cuadro de lumbago de características mecánicas. Llamaba la atención el compromiso de las líneas celulares, evidenciado por una bicitopenia con anemia normocítica y trombocitopenia, junto con un conteo de leucocitos dentro de rangos normales pero con inversión en la fórmula leucocitaria.

Además, se identificó hipercalcemia con un valor de 1.914 mmol/L (referencia: 1.20-1.32), que junto con signos de disminución de la función renal sugieren la necesidad de descartar una neoplasia de células plasmáticas, como el mieloma múltiple, que podría estar contribuyendo al proceso degenerativo en los cuerpos vertebrales. Aunque las imágenes de la cadera y la resonancia magnética de columna no mostraban lesiones líticas, el cuadro clínico justifica una evaluación más profunda para confirmar o descartar esta posibilidad, por lo que se solicita una radiografía de huesos largos y cráneo para descartar lesiones líticas.

En cuanto al manejo, dado la persistencia del dolor, se modificó el tratamiento farmacológico suspendiendo el tramadol y añadiendo fentanilo (2 mg en 100 cc, administrado cada 7 horas), junto con dexametasona, dipirona y acetaminofén para el control del dolor y la inflamación.

El uso de fentanilo en el tratamiento del dolor lumbar crónico está indicado principalmente en situaciones donde otros analgésicos, como los antiinflamatorios no esteroideos (AINEs), no han sido efectivos. Según la literatura médica, el fentanilo ha mostrado eficacia en la reducción del dolor lumbar crónico. [6] Sin embargo, su uso debe ser cuidadosamente considerado debido a los efectos adversos potenciales, como el estreñimiento, náuseas y prurito [6].

23/07/2024

Durante la noche, el hijo de la paciente reportó cambios en su comportamiento y desorientación espacial. Además, mencionó que tuvo dos episodios eméticos postprandiales, lo que llevó a adicionar la administración de un tratamiento antiemético y omeprazol en conjunto con los opioides, de acuerdo con el criterio de medicina general.

Aunque los cambios en el comportamiento de la paciente podrían haber llevado a un ajuste en la infusión de opioides, se observó que su estabilidad hemodinámica y estado de alerta

en ese momento no fueron significativos y no sugieren que estos ajustes hayan tenido un impacto significativo en su fallecimiento.

24/07/2018

Durante el seguimiento por el servicio en medicina interna, la paciente presentó una evolución estacionaria, lo que llevó a sustituir el acetaminofén por acetaminofén con codeína. Además, fue evaluada por el servicio de ortopedia y traumatología, quienes informaron una mejoría parcial del dolor y una evolución favorable. Por ello, decidieron no realizar ajustes en el tratamiento farmacológico previamente establecido e indicaron la continuación de terapia física, dando de alta a la paciente de su servicio.

A las 19 horas, la paciente fue valorada por el servicio de neurocirugía. Durante la evaluación, se constató que la paciente continuaba con dolor, pero sin signos de radiculopatía. La resonancia magnética de la columna dorsolumbar mostró evidencia de una fractura antigua en T12, sin compromiso medular. Sin embargo, el cuadro clínico de la paciente no se explicaba completamente con el reporte de la imagen.

Ante esta situación, se decidió solicitar una gammagrafía ósea para obtener información adicional que ayude a esclarecer la causa del dolor persistente. Se suspendio infusión de fentanilo debido a la mejoría del dolor y se mantuvo el mismo plan de manejo, mientras se esperaban los resultados de los estudios adicionales.

25/07/2018

La paciente continuaba con una evolución estacionaria del dolor, asociado a náuseas y emesis. Por lo tanto, el servicio de medicina general indica una dosis de tramadol y un medicamento antiemético. Horas después, debido a la persistencia del dolor, tanto medicina general como medicina interna reinician la infusión de fentanilo.

26/07/2018

En las valoración diurnas, se encontró una evolución estacionaria de la paciente, por lo que se continuó manejo médico instaurado.

A las 19 horas, la paciente fue valorada por el servicio de medicina interna debido a llamado de enfermería que reportó una crisis hipertensiva, con lecturas de 180/102 mmHg reportadas por el personal de enfermería y 150/90 mmHg al momento de la evaluación médica, lo que sugería un diagnóstico de hipertensión arterial de novo. Durante la valoración, el familiar de la paciente informó que la veía muy somnolienta y que no había tenido deposiciones en la última semana.

A pesar de presentar un puntaje de Glasgow de 15/15 y un examen cardiopulmonar normal, la paciente continuaba experimentando dolor. En respuesta a estos hallazgos, se decidió adicionar un manejo antihipertensivo, analgésico, laxante y se indicó la administración de un enema jabonoso para abordar el problema de la constipación. Con esta intervención se buscó aliviar la incomodidad de la paciente y mejorar su estado general.

Es importante destacar que el episodio hipertensivo no está relacionado con la dosis de fentanilo. Según la FDA, uno de los efectos secundarios del fentanilo es la hipotensión severa y ortostática [7], lo cual es un evento completamente diferente al que presenta el paciente.

27/07/2018

En la valoración realizada por el servicio de medicina interna, la paciente refirió que se sentía bien y presentó un examen físico con hallazgos cardiopulmonares dentro de la normalidad. Sin embargo, los resultados del extendido de sangre periférica revelaron hipocromía moderada, anisocitosis leve, microcitosis leve y poiquilocitosis moderada, además de la presencia de estomatocitos. Se observó que los leucocitos eran positivos y se encontraban en número y forma normales, mientras que las plaquetas mostraron un 15% de macroplaquetas.

Se encontró que la función hepática estaba sin alteraciones, pero se registró un aumento en los niveles de creatinina, lo que apoya la sospecha de un diagnóstico de neoplasia. En función de los hallazgos y el estado de sedación de la paciente, se decidió reducir la dosis de fentanilo a 5 cc/hora para asegurar un manejo adecuado del dolor sin comprometer su estado de alerta.

Resultado RNM: anterolistesis ístmica grado I del cuerpo vertebral de L4, estenosis de los forámenes neurales bilateralmente y signos de compresión radicular derecha de L4. Antigua fractura por compresión axial de aproximadamente un 20% del platillo superior del cuerpo vertebral de T12, estable, osteofito posterior T11-T12 condicionando estenosis del canal medular sin signos de compresión del cono medular.

28/07/2024

Durante la valoración por el servicio de medicina interna, se registró un puntaje de Glasgow de 13/15, y la paciente se encontraba hemodinámicamente estable. Sin embargo, se detectaron agregados respiratorios, con roncus bilaterales y hipoventilación bibasal, lo que sugiere un riesgo de descompensación aguda.

Los resultados de la electroforesis de proteínas mostraron un nivel elevado de 107.0 y una relación albúmina/globulinas de 0.42, lo que indica un nivel bajo de albúmina (29.5%). Para optimizar el manejo médico, se implementaron medidas como la administración de oxígeno suplementario, la realización de una radiografía de tórax, y terapia respiratoria mediante micronebulizaciones con bromuro de ipratropio. Además, se inició el tratamiento con enoxaparina.

Dos horas después, se realizó una revaluación debido a una desaturación de oxígeno que alcanzó el 85%. En respuesta, se disminuyó la infusión de fentanilo a 3 cc/hora y se ajustó la administración de oxígeno mediante una máscara Venturi al 35%. También se solicitaron gases arteriales y electrolitos.

Los resultados de los gases arteriales indicaron un trastorno ácido-base, con un pH de 7.29 que sugiere acidosis. La presión parcial de dióxido de carbono ($PaCO_2$) de 43.4 mmHg se

encontraba dentro del rango normal, lo que indica que no había una contribución respiratoria significativa a la acidosis. El bicarbonato (HCO3-) estaba disminuido a 20 mmol/L, indicando acidosis metabólica. Además, la presión parcial de oxígeno (PaO2) de 54.8 mmHg y la saturación del 83.7% revelan hipoxemia. Un lactato elevado de 4 mmol/L sugiere la presencia de acidosis láctica, probablemente relacionada con hipoperfusión tisular o hipoxia.[7]

En resumen, estos hallazgos son consistentes con una acidosis metabólica acompañada de hipoxemia y acidosis láctica. Es fundamental investigar y tratar la causa subyacente, que podría incluir sepsis, insuficiencia respiratoria o shock. Ante estos resultados, se concluyó que había una falla ventilatoria y choque, por lo que se ajustó la máscara Venturi al 50% y se recomendó la admisión a la unidad de cuidados intensivos (UCI) para un manejo más agresivo.

En la evaluación realizada en la UCI, la paciente fue intubada y se inició soporte vasopresor, además de la colocación de un catéter venoso central (CVC). Durante el examen físico, se encontraron estertores bibasales y secreciones de color salmón en el tubo de intubación, lo que sugiere un posible edema pulmonar de etiología a esclarecer.

Se identificaron criterios de CRAB, que son indicativos de mieloma múltiple:

- **C**: Calcio elevado.
- **R**: Lesión renal.
- **A**: Anemia.
- **B**: Lesiones líticas.

Para profundizar en la evaluación, se solicitaron estudios adicionales, incluyendo una radiografía de tórax portátil de urgencia, un ecocardiograma transtorácico, un electrocardiograma, y análisis de troponina, calcio colorimétrico, albúmina y beta-2 microglobulina. También se pidió la inmunofijación de proteínas en sangre y orina para ayudar a esclarecer el diagnóstico.

Finalmente, se programó una valoración por el servicio de hematología para un manejo más específico de la condición.

La paciente cumplía con los cuatro criterios. Se considera que el enfoque y la impresión diagnóstica realizados por los especialistas fueron correctos, dado que, ante la imposibilidad de realizar un aspirado de médula ósea, los criterios mencionados respaldan el diagnóstico de una patología oncológica subyacente en la paciente [8]. Esta situación requiere tratamiento inmediato tras el diagnóstico [9], motivo por el cual se solicitó en ese momento el concepto del servicio de hematología.

Además, es importante destacar que las patologías oncológicas, especialmente el mieloma múltiple, que fue la principal sospecha diagnóstica de los médicos tratantes, están fuertemente asociadas con un estado pro coagulante en los pacientes. Esto puede crear un entorno favorable para el desarrollo de coágulos [10] que lleguen a la circulación pulmonar, resultando en un tromboembolismo pulmonar (TEP) masivo y, eventualmente, en un cor pulmonale, lo que puede llevar a fallo ventilatorio y de la bomba cardiaca, como se

evidenció en esta paciente. Sin un diagnóstico previo de la patología oncológica subyacente, la prevención de este evento habría sido poco probable.

28/07/2018

Durante la valoración en la UCI, el electrocardiograma reveló una inversión del segmento ST en la cara lateral, lo que sugiere un posible infarto agudo de miocardio (IAM); sin descartar también la posibilidad de un tromboembolismo pulmonar (TEP). Por lo cual en este contexto, se solicitó una curva de troponina para evaluar la función cardíaca.

Como ya se mencionó anteriormente, dada la presencia de una patología procoagulante en estudio, se ordenó un doppler de miembros inferiores, y se decidió no iniciar terapia antiplaquetaria hasta descartar un accidente cerebrovascular (ACV), para lo cual se solicitó una tomografía axial computarizada (TAC) del cerebro. Se esperaban los resultados para solicitar un angiotac de tórax y evaluar la posibilidad de TEP.

Los parámetros de laboratorio mostraron una prolongación del tiempo de protrombina (TP 24.9), tiempo de tromboplastina parcial (TPT 45.9) e INR de 2.13, lo que indica alteraciones en la coagulación. Los análisis también revelaron leucocitos en 7,300, hemoglobina de 9 g/dL, plaquetas en 151,000, BUN de 40 y creatinina de 2.26. La troponina I se encontraba elevada en 618, lo que refuerza la sospecha de daño miocárdico; sin embargo, también se consideraba la posibilidad de un TEP como causa de esta elevación.

A pesar de no aparentar choque séptico, se solicitaron hemocultivos para un diagnóstico más completo. La paciente se encontraba en muy malas condiciones generales, multisoportada, con dosis máximas de noradrenalina y vasopresina. La hemoglobina estaba en un rango no transfusional, y los niveles de urea y creatinina estaban elevados.

En la revaloración, la paciente presentó una evolución tórpida y continuó multisoportada. No se contaba con radiografía de tórax debido a la falta de personal técnico, y se observó falla de bomba y desacople ventilatorio, lo que generó un grave trastorno de la ventilación. Se llegó a una situación de asistolia, limitando las maniobras de reanimación debido a la patología de base. Se declara deceso.

Opinión pericial:

En primer lugar, se procederá a evaluar la conducta médica durante la atención en el servicio de urgencias y en la hospitalización, con énfasis en el manejo del dolor en relación con la consulta inicial y el cuadro clínico. El abordaje del lumbago crónico en el servicio de urgencias, conforme a las guías establecidas, se consideró apropiado, ya que se realizó un

examen físico exhaustivo que descartó banderas rojas. La estrategia farmacológica para el alivio del dolor se fundamentó en la evidencia, comenzando con AINES y opioides débiles. Dada la persistencia y severidad del dolor, se realizó un escalamiento adecuado de la analgesia intravenosa, utilizando un opioide potente con la titulación correspondiente, además de solicitar imágenes diagnósticas como el siguiente paso en el manejo del lumbago crónico, según las guías citadas.

La dosis inicial recomendada de fentanilo es de 100 mcg, la cual debe ser ajustada individualmente hasta alcanzar una dosis que brinde un alivio adecuado del dolor con efectos secundarios tolerables (7). En el caso de la paciente, se estableció una dosis inicial de 135 mcg/hora (2 mg en 100 cc administrados a 7 cc/hora), alineándose con las pautas.

Desde la primera consulta, se solicitaron pruebas complementarias que incluían un hemograma, evaluación de la función renal y tiempos de coagulación, además de una valoración por el servicio de ortopedia. Es importante destacar que el enfoque inicial del médico permitió identificar la bicitopenia, alteraciones en las líneas celulares e hipercalcemia, elementos fundamentales para el posterior diagnóstico de la patología oncológica subyacente en la paciente.

Durante toda su estancia hospitalaria, la paciente recibió un seguimiento riguroso tanto por parte de los servicios de medicina interna como de medicina general, siendo valorada en múltiples ocasiones, lo que permitió atender sus necesidades y las inquietudes de sus familiares. La ausencia de leucocitosis desde el inicio de la sintomatología y la falta de elevación en los reactantes de fase aguda indicaron que el cuadro clínico no sugería una posible infección. Se realizaron todos los estudios pertinentes para esclarecer la patología oncológica de base y, al mismo tiempo, manejar su dolor.

Durante la hospitalización, se manejo la emesis, el estreñimiento y la hipertensión. Además, la alteración del estado de conciencia pudo haber estado relacionada con un desequilibrio hidroelectrolítico.

Cuando la paciente mostró signos de descompensación aguda, la respuesta médica fue adecuada y evidenció una adherencia a las pautas de práctica clínica. Ante la posible falla ventilatoria, se ordenaron de inmediato gases arteriales, una radiografía de tórax y se inició la monitorización de signos vitales, así como el manejo con oxígeno suplementario, constituyendo este último una intervención de primera línea.

Los hallazgos de acidosis metabólica e hipoxemia en los gases arteriales respaldaron la decisión de optimizar el manejo médico con oxígeno suplementario, terapia respiratoria y traslado a Unidad de Cuidado Intensivo. La administración de enoxaparina también se alinea con las prácticas estándar para prevenir complicaciones tromboembólicas, considerando la presentación clínica de la paciente, por lo que esta fue una conducta apropiada en el momento.

En la UCI, el manejo intensivo que incluyó intubación orotraqueal y soporte vasopresor fue adecuado dada la gravedad evidente de su estado clínico. La presencia de estertores bibasales a la auscultación pulmonar y secreciones en el tubo de intubación, junto con los criterios CRAB para mieloma múltiple, llevaron a un abordaje diagnóstico exhaustivo que incluyó estudios de imagen y análisis de laboratorio. Se solicitaron exámenes

multifactoriales para esclarecer la etiología de la falla ventilatoria, la alteración del estado de conciencia y el choque.

Inicialmente, se solicitó una radiografía de tórax para evaluar la función pulmonar y un posible edema pulmonar secundario a un TEP, dado el estado procoagulante asociado a la patología oncológica subyacente. Sin embargo, la radiografía no se pudo realizar por falta de disponibilidad de personal técnico. Además, se pidieron varios estudios para evaluar la función cardiovascular, incluyendo un EKG, ecocardiograma y biomarcadores cardíacos. Debido a la alteración en el estado de conciencia, también se solicitó un TAC de cráneo para descartar un evento cerebrovascular o hemorragia cerebral que pudiera explicar el deterioro neurológico de la paciente. No se identificó ningún foco de infección probable, sin embargo, se realizaron hemocultivos y urocultivos para descartar un posible choque séptico.

Se continuó el proceso diagnóstico de la patología oncológica subyacente, solicitando el concepto del servicio de hematología, un aspirado de médula ósea y pruebas complementarias para confirmar el diagnóstico. Es crucial resaltar que la evaluación y el enfoque diagnóstico por parte de los especialistas fueron correctos, dado que, ante la imposibilidad de realizar un aspirado de médula ósea de inmediato, utilizaron criterios establecidos por la medicina basada en evidencia (Criterios CRAB) que respaldaban el diagnóstico de una patología oncológica subyacente.

Asimismo, es importante mencionar que las patologías oncológicas, en especial el mieloma múltiple, que fue la principal sospecha diagnóstica de los médicos tratantes, están fuertemente asociadas a un estado procoagulante en los pacientes. Esto puede generar un entorno favorable para la formación de coágulos que lleguen a la circulación pulmonar, resultando en un tromboembolismo pulmonar (TEP) masivo y, consecuentemente, en un cor pulmonale, que puede llevar a fallo ventilatorio y de la bomba cardiaca, como se observó en esta paciente.

A pesar del deterioro progresivo, el seguimiento del estado de la paciente evidencia el compromiso del equipo médico por ofrecer la mejor atención posible en circunstancias críticas. Las decisiones, desde la reducción de la terapia antiplaquetaria hasta la espera de resultados diagnósticos antes de iniciar tratamientos adicionales, reflejan un juicio clínico crítico, prudente y bien fundamentado.

En conclusión, las acciones del equipo médico fueron adecuadas y justificadas en el contexto de la presentación clínica compleja de la paciente. Se implementaron intervenciones apropiadas y se mantuvo un enfoque diagnóstico activo, lo que evidencia un compromiso con la atención de calidad en un entorno desafiante. Sin un diagnóstico previo de la patología oncológica subyacente, la prevención de este evento era improbable. Aunque los datos clínicos sugieran que el deceso fue secundario a una complicación de la patología oncológica de base, se considera que hubiera sido fundamental realizar una autopsia médico-legal para esclarecer la causa clara del deceso.

Peritaje – Demandantes:

La paciente ingresó al servicio de urgencias con un cuadro de dolor lumbar crónico agudizado, cuya etiología no era evidente al momento de su llegada. Este síntoma fue el motivo principal de su consulta y, debido a la incertidumbre diagnóstica, se consideró necesario realizar estudios paraclínicos que permitieran esclarecer su causa subyacente. Durante su atención inicial, el equipo médico administró fentanilo en dosis adecuadas, siguiendo las recomendaciones clínicas para el manejo del dolor agudo. Esta decisión se tomó considerando la severidad del dolor, la necesidad de un control sintomático oportuno y la ausencia de contraindicaciones conocidas para el uso de opioides en esta paciente.

El dolor lumbar, en la mayoría de los casos, es un motivo de consulta frecuentemente manejado por ortopedia. Por esta razón, desde su ingreso, se solicitó la valoración por este servicio especializado, con el fin de establecer una conducta diagnóstica y terapéutica adecuada. Asimismo, se consideró prudente la interconsulta con el servicio de neurocirugía, quienes también evaluaron a la paciente y aportaron su perspectiva en el manejo de su cuadro clínico.

En cuanto al tratamiento farmacológico, es importante resaltar que no existían restricciones para el uso de medicamentos como AINES u opioides en esta paciente, por lo que no considero que la administración de estos fármacos haya sido inapropiada. Por el contrario, su uso estaba debidamente justificado, dado el cuadro clínico presentado. En mi opinión, la inestabilidad clínica que desarrolló la paciente no fue consecuencia de los medicamentos administrados, sino que puede atribuirse a una patología de base que no había sido identificada previamente y que era desconocida tanto por la paciente como por sus familiares.

En relación al deterioro respiratorio que presentó durante su hospitalización, no hay evidencia suficiente para concluir que este haya sido causado por una infección respiratoria nosocomial. Desde el momento en que se evidenció el compromiso respiratorio, el equipo tratante actuó de manera diligente, buscando descartar posibles diagnósticos diferenciales y estableciendo un manejo acorde a los hallazgos clínicos y paraclínicos disponibles. La atención brindada siguió los protocolos establecidos para este tipo de situaciones.

Finalmente, en lo que respecta a la posibilidad de una valoración por hematología, considero que esta no habría cambiado de manera significativa el desenlace clínico de la paciente. Aunque dicha interconsulta podría haber aportado elementos adicionales al análisis del caso, no considero que la ausencia de esta haya sido determinante en el desenlace fatal. En mi concepto, la muerte de la paciente estuvo directamente relacionada con la evolución de su patología de base, la cual no había sido identificada antes de su ingreso y que probablemente condicionó la gravedad de su estado clínico.

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YMJ

Transdermal Fentanyl for Chronic Low Back Pain

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Purpose: Chronic low back pain is a common clinical problem. As medication, non-steroidal anti-inflammatory drugs are generally used; however, they are sometimes non-effective. Recently, opioids have been used for the treatment of chronic low back pain, and since 2010, transdermal fentanyl has been used to treat chronic non-cancer pain in Japan. The purpose of the current study was to examine the efficacy of transdermal fentanyl in the treatment of chronic low back pain. **Materials and Methods:** This study included patients (n=62) that suffered from chronic low back pain and were non-responsive to non-steroidal anti-inflammatory drugs. Their conditions consisted of non-specific low back pain, multiple back operations, and specific low back pain awaiting surgery. Patients were given transdermal fentanyl for chronic low back pain. Scores of the visual analogue scale and the Oswestry Disability Index, as well as adverse events were evaluated before and after therapy. **Results:** Overall, visual analogue scale scores and Oswestry Disability Index scores improved significantly after treatment. Transdermal fentanyl (12.5 to 50 μg/h) was effective in reducing low back pain in 45 of 62 patients; however, it was not effective in 17 patients. Patients who experienced the most improvement were those with specific low back pain awaiting surgery. Adverse events were seen in 40% of patients (constipation, 29%; nausea, 24%; itching, 24%). **Conclusion:** Transdermal fentanyl significantly improved visual analog scale scores and Oswestry Disability Index scores in 73% of patients, especially those with specific low back pain awaiting surgery; however, it did not decrease pain in 27% of patients, including patients with non-specific low back pain or multiple back operations.

Key Words: Transdermal fentanyl, low back pain, efficacy, adverse events

INTRODUCTION

Low back pain (LBP) is a common clinical problem and is of major socioeconomic importance. Although any of the spinal structures (intervertebral discs, facet joints, vertebral bodies, ligaments, and muscles) may be a source of LBP, the most likely cause is unclear.

Treatment for chronic LBP includes conservative therapy (exercise), intradiscal electrothermal therapy, spinal fusion, and artificial disc replacement. Several ran-

domized trials have compared surgical and nonsurgical treatment of chronic LBP and have arrived at conflicting conclusions.[1,2] Typical pharmacologic therapy of LBP begins with non-steroidal anti-inflammatory drug (NSAIDs) administration. NSAIDs are useful for mild to moderate LBP; however, they are not effective for severe LBP. Furthermore, they have a high risk of serious gastrointestinal bleeding.[3]

Oral morphine has been available for decades and is often used as a reference against which other treatments are compared.[4] Patients with severe chronic LBP may require oral morphine for effective pain management. The use of oral morphine for treating chronic LBP has been increasing in recent years. However, adverse events and risk of addiction from the extended use of opioid therapy are concerns with this approach.[5]

Transdermal fentanyl may offer advantages over oral morphine and may be preferred by patients.[6] Several large studies have demonstrated the efficacy and safety of transdermal fentanyl in patients with non-cancer pain.[6,7] A controlled-released transdermal therapeutic system can provide systemic delivery of fentanyl at a constant rate for up to 72 hr.[8]

Since 2010, transdermal fentanyl was available for use in Japan to treat chronic non-cancer pain; however, its use in the treatment of chronic LBP has not been reported. The purpose of the current study was to examine the efficacy and tolerability of transdermal fentanyl for the treatment of chronic LBP in a Japanese population.

MATERIALS AND METHODS

The ethics committee of our institution approved the protocol for the human procedures used in this study. Furthermore, the protocol and publication of the study were approved by our institutional review board. This trial was a prospective trial. The patients who participated in this study were selected from outpatients who attended our hospital for LBP. These 62 patients were selected from 412 LBP patients matched to the following criteria.

All patients had LBP for more than three months and were resistant to treatment with oral NSAIDs. Informed consent was obtained from each of the participants. Patients had non-specific chronic LBP, chronic LBP after lumbar surgery, multiple back operations, and specific LBP awaiting surgery (e.g., lumbar disc herniation or spinal stenosis).

Demographic characteristics

Table 1 shows patient demographic characteristics. The pain score was severe in all patients. All patients used NSAIDs; however, NSAIDs were not effective for LBP. The diagnosis was non-specific chronic LBP in 20 patients, LBP after single lumbar surgery in 15 patients, and multiple back operations in 15 patients. There were 12 patients who were awaiting lumbar surgery, including lumbar disc herniation and spinal canal stenosis, and had severe specific LBP. The patients were enrolled consecutively and were opioid-naïve.

Medication

A transdermal fentanyl patch (Janssen, Tokyo, Japan) was applied to all patients for the treatment of LBP. The patch was changed every three days. The starting dose was 12.5 μg/h. If this dose was not effective, it was increased to 25, 37.5 and 50 μg/h, thereafter. If one dose was non-effective for six days, the next highest dose patch was applied for six days. The maximum dose was 50 μg/h. If the patient's visual analogue scale (VAS) score did not decrease by 20%, we defined the medication as "non-effective".

Conservative treatment included exercise (walking, walking in a pool, muscle training, and muscle stretching). Walking and walking in a pool were performed by the patients on their own. Muscle training and stretching was performed for the abdomen and lower extremities by physical therapists. Medications, except for transdermal fentanyl, were allowed. Medications included NSAIDs, vitamins, muscle relaxants, and prostaglandin E1. A physician decided the type of medication for each patient.

Table 1. Demographic Characteristics

Number of patients	62
Sex	Male: 30, Female: 32
Age mean range (range), yrs	62±8.0 (24-80)
Symptom duration, mean (range), yrs	5.5 (1-10)
Pain score before treatment	
Low back pain	
Visual analogue scale	8.4±1.5
Oswestry Disability Index	54±10
Use of NSAIDs	62
Diagnosis	
Non specific chronic low back pain	20 (32%)
Low back pain after single lumbar surgery	15 (24%)
Multiple back operations	15 (24%)
Specific LBP awaiting surgery (e.g., lumbar disc herniation or spinal stenosis)	12 (20%)

NSAIDs, non-steroidal anti-inflammatory drug.

Evaluation of pain score

We evaluated LBP before treatment, one month after treatment, and at final follow-up. Pain scores in patients with specific LBP awaiting surgery was evaluated at seven days before their surgery, which was considered as their final follow-up. If a patient stopped the medication (e.g., non-responder), the pain evaluation from seven days before the last dose was administered was recorded. For the evaluation of pain in all patients, scores from the VAS score (0, no pain; 10, worst pain) and the Oswestry Disability Index (ODI) score (0, no pain; 100, worst pain) were recorded and compared.

Subjective outcomes

At four months after treatment, patients were asked to choose one of the following responses regarding their satisfaction with the treatment: 1) the medication met my expectations; 2) I did not improve as much as I had hoped, but I would undergo the same medication for the same outcome; 3) the medication helped, but I would not undergo the same medication for the same outcome; or 4) I am the same as or worse than I was before the medication.

Adverse events

All adverse events were reported together with an assessment of their severity (mild, moderate, severe) and the investigator's opinion of their relationship to treatment with transdermal fentanyl (none, unlikely, possible, or probable). Antiemetics were used in all patients. Laxatives were prescribed for constipation. Addiction was measured according to previous reports.[9]

Statistical analysis

Data were compared with the Mann-Whitney U-test. $p<0.05$ was considered statistically significant.

Table 2. Dosage of Transdermal Fentanyl

Dosage	Number of patients
μg/hrs	
12.5	41 (66%)
25	14 (23%)
37.5	2 (3%)
50	5 (8%)
>50	0
Average dosage	19.64±1.8 μg/hrs

RESULTS

Dosage of transdermal fentanyl

Table 2 shows the dosage of transdermal fentanyl administered. The patients were administered doses from 12.5 to 50 μg/h. Most patients were administered 12.5 μg/h of transdermal fentanyl. The average dosage was 19.6±1.8 μg/h (mean±S.E.M.).

Evaluation of LBP after treatment

Table 3 shows the results of the evaluation of LBP after treatment in all 62 patients. VAS and ODI one month after treatment were 5.0±0.3 (mean±S.E.M.) and 32±6, respectively, and were significantly less than that before treatment ($p<0.01$). Mean VAS score and ODI score at final follow-up were 4.6±0.3 and 28±6, respectively, and were significantly lower than values obtained before treatment ($p<0.01$).

Transdermal fentanyl was very effective, especially in all patients with specific LBP awaiting surgery, so we divided the patients into the following three groups: 1) transdermal fentanyl was effective (responders), n=32; 2) transdermal fentanyl was effective in patients awaiting surgery (responders), n=12; and 3) transdermal fentanyl was not effective (non-responders), n=18 (Table 4). VAS scores and ODI scores were significantly lower after treatment than before treatment in the two responder groups ($p<0.05$). Also, VAS scores and ODI scores after treatment in the two responder groups were significantly lower than those of the non-responder group ($p<0.05$). However, pain scores one month after treatment and at final follow-up were not significantly lower than those of the non-responder group before treatment ($p>0.05$) (Fig. 1). On the other hand, transdermal fentanyl was more effective in the responders awaiting surgery compared with the other responders ($p<0.05$) (Fig. 2).

The average duration of treatment was significantly shorter in the non-responder group compared with the responder groups, because non-responders did want to continue with the transdermal fentanyl therapy ($p<0.05$) (Table 4). The

Table 3. Pain after Treatment

All patients (n=62)	Pain score before treatment	Pain score 1month after treatment	Pain score after treatment (final)	*p* value
Low back pain				
Visual analogue scale	8.4±1.5*	5.0±0.3†	4.6±0.3‡	*,†$p<0.01$, *,‡$p<0.01$
Oswestry Disability Index	54±10*	32±6†	28±6‡	*,†$p<0.01$, *,‡$p<0.01$

Table 4. Pain after Treatment

	Responder (effective)	Responder (effective) (awaiting surgery)	Non-responder (non-effective)	*p* value
Number of patients	32	12	18	
Pain before treatment				
Visual analogue scale	8.4±0.2	8.8±0.4	8.2±0.2	N.S.
Oswestry Disability Index	50±10	58±12	52±8	N.S.
Pain 1month after treatment				
Visual analogue scale	4.0±0.2*	2.6±0.4†	6.5±0.5‡	*,†p<0.05, *,‡p<0.05, †,‡p<0.01
Oswestry Disability Index	28±7*	18±6†	50±10‡	*,†p<0.05, *,‡p<0.05, †,‡p<0.01
Pain after treatment (final)				
Visual analogue scale	3.9±0.2*	2.5±0.3†	6.9±0.4‡	*,†p<0.05, *,‡p<0.05, †,‡p<0.01
Oswestry Disability Index	25±7*	16±4†	46±8‡	*,†p<0.05, *,‡p<0.05, †,‡p<0.01
Period of treatment (months)	7.1±0.9*	3.1±0.3†	2.5±0.7‡	*,†p<0.01, *,‡p<0.01, †,‡p<0.05
Dosage of transdermal fentanyl (μg/hrs)	19.64±1.8*	14.88±1.2*	23.81±3.6†	*,†p<0.05, *,‡p<0.05, †,‡p<0.05

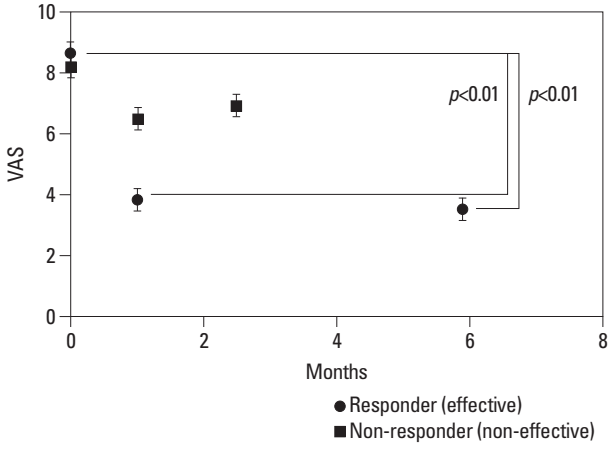

Fig. 1. VAS scores in responders and non-responders. Month 0=before treatment. VAS scores after treatment were significantly lower than those before treatment in the responder group at each time point (p<0.01). However, pain scores one month after treatment and at final follow-up did not differ significantly from those before treatment in the non-responder group (p>0.05). VAS, visual analogue scale.

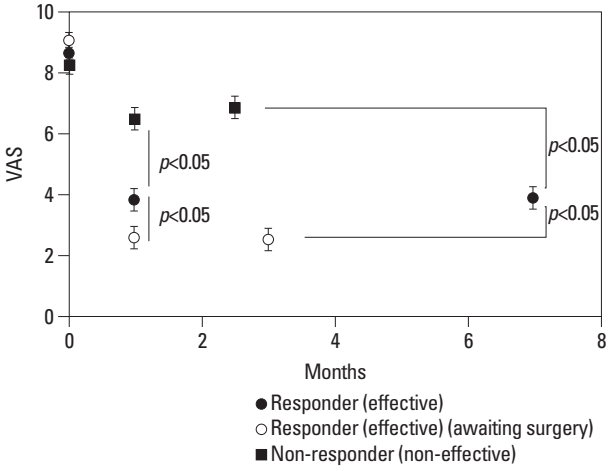

Fig. 2. VAS scores in responders and non-responders. Month 0=before treatment. VAS scores after treatment in the two responder groups were significantly lower than those in the non-responder group at each time point (p<0.05). VAS scores after treatment indicated that transdermal fentanyl was more effective in the responders awaiting surgery compared with the other responders at each time point (p<0.05). VAS, visual analogue scale.

average dosage of transdermal fentanyl in the non-responder group was significantly higher than that in each of the responder groups, because of the insufficiency of the drug (p<0.05) (Table 4).

Subjective outcomes

Details of subjective outcomes after treatment are presented in Table 5. Subjective outcomes were good and fair in 27 and 15 patients, respectively; however, 12 patients and 8 patients reported an unexpected or poor outcome.

Adverse events

Table 6 shows the adverse events reported throughout follow-up. Adverse events were seen in 40% of all 62 patients. The most common adverse events were constipation, nausea, itching, and somnolence. Adverse events were mild in all patients. Itching was seen as a local reaction to the transdermal fentanyl patch. One patient (2%) showed withdrawal symptoms (loss of appetite and motivation) after stopping the transdermal fentanyl patch. However, addiction was not seen in any patient.

DISCUSSION

This is first study to evaluate the efficacy of transdermal fentanyl for the treatment of chronic LBP in a Japanese population. In general, transdermal fentanyl significantly improved

Table 5. Subjective Outcomes (Number of Patients)

	Number of patients (%)
Treatment met my expectations	27 (44)
I did not improve as much as I had hoped, but I would undergo the same treatment for the same outcome	15 (24)
Treatment helped, but I would not undergo the same treatment for the same outcome	12 (19)
I am the same as or worse than I was before the treatment	8 (13)

Table 6. Adverse Events

	Number of patients (%)
Constipation	18 (29)
Nausea	15 (25)
Itching	15 (25)
Somnolence	11 (18)
Withdrawal	1 (2)
Addiction	0 (0)

VAS scores and ODI scores in patients with chronic LBP, especially in patients with specific LBP awaiting surgery; however, it did not decrease pain in 27% of the patients with non-specific LBP or multiple back operations. Adverse events were seen in 40% of patients; however, no addiction was seen.

It has been reported that both weak and strong opioids are effective in the treatment of chronic LBP. Three double-blind RCTs compared opioids to an inactive placebo in the management of chronic LBP.[10-12] In one US trial, 380 outpatients with chronic LBP were enrolled in an open-label phase study and treated with tramadol, followed by enrollment of those who tolerated tramadol into a double-blind, placebo-controlled phase study.[10] Patients treated with tramadol scored significantly better on the VAS, the McGill Pain Questionnaire and the Roland Disability Questionnaire.[10] In another US trial, patients with LBP were randomized to receive either tramadol/acetaminophen or a placebo for 91 days. Tramadol/acetaminophen significantly improved the final scores for VAS, the Roland Disability Questionnaire, and a 36-Item Short-Form Health Survey from baseline levels.[11] In the third trial, 333 patients with chronic LBP were randomized to receive tramadol/acetaminophen or a placebo in Canada. The tramadol/acetaminophen combination showed efficacy in pain reduction, measures of physical functioning and quality of life.[12]

Several authors have reported the effectiveness of transdermal fentanyl for the treatment of chronic LBP.[11,12] Allan, et al.[13] compared the efficacy and safety of transdermal fentanyl and sustained-release morphine in strong-opioid-naïve patients with chronic LBP. Transdermal fentanyl was effective in the treatment of chronic LBP and was associated with less constipation compared with sustained-release morphine. Kosinski, et al.[14] reported the efficacy of transdermal fentanyl in patients with chronic LBP and compared pain relief and patient's health-related quality of life score improvement. Health-related quality of life score improvement was greatest among patients experiencing the greatest pain relief from transdermal fentanyl. In the current study, transdermal fentanyl significantly improved VAS scores and ODI scores in Japanese patients with chronic LBP, and these findings are similar to those of other studies.

In the current study, transdermal fentanyl was more effective in patients who were awaiting surgery and had specific LBP due to apparent disc herniation or spinal stenosis, compared with the other responders or non-responders. Non-responders included patients with non-specific LBP and LBP after surgery, but did not include patients with specific LBP. Transdermal fentanyl was not effective at one month and final follow-up in non-responders. Furthermore, the average dosage of transdermal fentanyl was significantly higher in the non-responder group than in the responder groups because of the insufficiency of the drug. In a previous study, it was reported that there were no differences in age, sex, and type or duration of pain between responders and non-responders after the application of transdermal fentanyl.[15] The difference in response to treatment between responders and non-responders could be detected at three weeks.[15] Lack of response after one month had a stronger negative predictive value than the presence of response after one month. The most influential factors for predicting a response were employment status and use of high doses of opioids.[15] Considering previous reports and the results of the current study, a lack of response after one month and use of a high dosage of opioids may have a negative predictive value for response to opioids.

Kalso, et al.[16] analyzed available randomized, placebo-controlled trials of opioids for efficacy and safety in patients with chronic non-cancer pain. About 80% of patients experienced at least one adverse event, with constipation (41%), nausea (32%) and somnolence (29%) being the most common.[16] As most of the studies analyzed were short-term fol-

low-up studies, they did not allow for conclusions to be made concerning problems with tolerance and addiction.[16] A systematic review revealed that opioids are commonly prescribed for chronic LBP and may be efficacious for short-term pain relief, but their long-term efficacy is unclear.[17] Substance use disorders are common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in 5 to 24% of cases.[15] In the current study, the most common adverse events reported were constipation, nausea, itching, and somnolence; however, addiction was not documented in any patient. The current results may be due to the short-term follow-up period of the study.

In conclusion, we evaluated the efficacy of transdermal fentanyl for severe chronic LBP in a Japanese population. Transdermal fentanyl significantly improved pain scores in 73% of patients with LBP; however, about 27% of patients demonstrated a non-response. Non-responders included patients with non-specific LBP and pain after lumbar surgery. Treatment was most effective in patients with specific LBP awaiting surgery, and pain relief was seen in all patients in that group. Adverse events were reported in 40% of all of the patients. In patients with chronic LBP resistant to NSAIDs, transdermal fentanyl may be a good therapeutic agent to reduce pain.

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Emergency department interventions for adult patients with low back pain: a systematic review of randomised controlled trials

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ABSTRACT

Background Most low back pain trials have limited applicability to the emergency department (ED) because they provide treatment and measure outcomes after discharge from the ED. We investigated the efficacy and safety of pharmacological and non-pharmacological interventions delivered in the ED to patients with non-specific low back pain and/or sciatica on patient-relevant outcomes measured during the emergency visit.

Methods Literature searches were performed in MEDLINE, EMBASE and CINAHL from inception to week 1 February 2020. We included all randomised controlled trials investigating adult patients (≥18 years) with non-specific low back pain and/or sciatica presenting to ED. The primary outcome of interest was pain intensity. Two reviewers independently screened the full texts, extracted the data and assessed risk of bias of each trial using the Physiotherapy Evidence Database (PEDro) scale. The overall quality of evidence, or certainty, provided by a set of trials evaluating the same treatment was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which considers imprecision, inconsistency, indirectness and bias in the evidence.

Results Fifteen trials (1802 participants) were included with 12 of 15 at low risk of bias (ie, PEDro score >6). Based on results from individual trials and moderate quality evidence, ketoprofen gel was more effective than placebo for non-specific low back pain at 30 min (mean difference (MD) −15.0, 95% confidence interval (CI) −21.0 to −9.0). For those with sciatica (moderate quality evidence), intravenous paracetamol (acetaminophen) (MD −15.7, 95% CI −19.8 to −11.6) and intravenous morphine (MD −11.4, 95% CI −21.6 to −1.2) were both superior to placebo at 30 min. Based on moderate quality of evidence, corticosteroids showed no benefits against placebo at emergency discharge for non-specific low back pain (MD 9.0, 95% CI −0.71 to 18.7) or sciatica (MD −6.8, 95% CI −24.2 to 10.6). There were conflicting results from trials comparing different pharmacological options (moderate quality evidence) or investigating non-pharmacological treatments (low quality evidence).

Conclusion Ketoprofen gel for non-specific low back pain and intravenous paracetamol or morphine for sciatica were superior to placebo, whereas corticosteroids were ineffective for both conditions. There was conflicting evidence for comparisons of different pharmacological options and those involving non-pharmacological treatments. Additional trials measuring important patient-related outcomes to EDs are needed.

Key messages

What is already known on this subject

- Hundreds of trials have investigated interventions in people with low back pain or sciatica, although most have limited applicability to emergency care.
- There are few trials that enrol participants, provide treatment and measure outcomes in the emergency department.

What this study adds

- Ketoprofen gel for low back pain and intravenous paracetamol or morphine for sciatica were superior to placebo, whereas corticosteroids were ineffective for both conditions. There was conflicting evidence between different treatment options.
- The results derived from single trials, thus, additional trials measuring patient-reported outcomes and those relevant to the emergency department are needed.

BACKGROUND

Low back pain is the major contributor to years lived with disability worldwide,[1] generating huge burden to healthcare systems.[2] People with low back pain often present to emergency departments (EDs), ranking among the top 10 reasons for presentation in the USA, Canada and Australia.[3] Up to one-third of these patients are admitted to the hospital in Australia,[4] which imposes a high economic burden to the healthcare system. Overuse of opioid medicines is also common in patients with low back pain attending EDs in high-income countries,[5 6] despite potential serious consequences.[7]

There is conflicting evidence on how to manage low back pain in the ED. Although a number of trials have investigated the effectiveness of interventions in this setting,[8–13] most have limited applicability to emergency care. This is because many of these trials provide treatment and measure outcomes after ED discharge. For example, a previous trial in the ED showed that adding an opioid or a muscle relaxant to a nonsteroidal anti-inflammatory drug (NSAID) provided no additional benefits to NSAIDs alone for patients with acute low back pain.[10] However, in this trial, patients were recruited at the time of emergency discharge, provided with a 10-day

supply of the medicine with outcomes measured at emergency discharge, 1-week and 3-month follow-up.

There is evidence that emergency patients are different to those seen in primary care. Serious spinal pathologies, such as spinal abscess and vertebral fracture, are more frequently seen in EDs.[6] Emergency patients tend to report higher levels of anxiety and psychological distress which may influence their experience of pain.[14] Challenges related to the clinical environment, such as time constraints and overcrowding, may impede delivery of some care options in EDs.[15] The ED also has limited opportunity to establish relationships or follow-up when compared with primary care. Thus, a systematic review with a focus on EDs will have direct clinical implications and help guide emergency clinicians on the management of low back pain.

The aim of this systematic review, therefore, is to summarise the evidence from randomised controlled trials that enrolled patients with non-specific low back pain and/or sciatica presenting to EDs where the study intervention is administered, and patient-reported outcomes measured during an ED visit.

METHODS

This systematic review was prospectively registered in PROSPERO (CRD42019123821) and followed the reporting recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[16]

Searches

Literature searches were performed in MEDLINE, EMBASE and CINAHL from inception to week 1 February 2020. The searches used a combination of keywords related to the inclusion criteria of this review such as low back pain and sciatica, ED, and randomised controlled trial (online supplementary appendix 1). In addition, citation tracking was performed from included full-text articles and previous relevant systematic reviews. The searches were not restricted by language or date of publication. Study selection was performed by two independent reviewers (HA and CO) based on screening of titles and abstracts and then relevant full texts were assessed for eligibility. Any disagreements were resolved through consensus between the two reviewers.

Eligibility criteria

Study design

Only randomised controlled trials published in peer-reviewed journals were eligible.

Participants

We included trials investigating patients presenting to EDs with low back pain and/or sciatica. We did not restrict to any specific symptom severity or duration. Trials recruiting patients with spinal canal stenosis or those with serious pathologies (such as infection, vertebral fracture, malignancy, cauda equina syndrome or axial spondylarthritis) were excluded. Trials with mixed populations including other diseases such as rheumatoid arthritis or hip/knee osteoarthrosis were excluded unless they reported separated data or more than 75% of the population was diagnosed with non-specific low back pain and/or sciatica.

Intervention and comparison groups

Randomised controlled trials investigating any type of healthcare intervention delivered for adult patients ≥18 years with non-specific low back pain and/or sciatica during the ED presentation were considered eligible. Similarly, any type of comparison intervention was included in this review such as no treatment, placebo/sham procedures or another pharmacological or non-pharmacological intervention.

Outcomes

We included studies reporting at least two outcome measures from the time of arrival to the time of discharge from the ED. Thus, trials only reporting outcomes at endpoints collected after ED discharge were excluded. The primary outcome of this systematic review was pain intensity measured using a Visual Analogue Scale or Numerical Rating Scale. Secondary outcomes included: time to discharge (length of ED stay), functional measures (eg, ability to walk), adverse events (patients experiencing adverse events), and representation to the ED (proportion of patients representing to the ED within 48 hours).

Data extraction

Two authors (HA and CO) extracted the following information using a standardised data extraction form: sample characteristics (sample size, sex, age, symptoms duration) intervention and comparison groups and outcome data. Any disagreement was resolved through consensus. For pain intensity, point estimates (eg, means, medians) and measures of variability (eg, SD, 95% CIs) were extracted from each study arm for all relevant time points. When change from baseline and final measures were available, we extracted the change or effect estimates based on changes from baseline.[17] If needed, median and IQR were converted to mean and SD.[18] Pain scores were converted to a common 0–100 scale. For adverse events, we extracted the proportion of patients (numerator and denominator) reporting any or specific adverse events from each study arm before ED discharge. In case of missing data, we contacted authors to provide further information on participant's data. If data were not available, we estimated missing data following the recommendations provided in the Cochrane Handbook.[19]

Risk of bias and quality of evidence

Risk of bias was assessed using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale is a valid and reliable tool[20 21] containing 10 scored yes-or-no items for assessment of the internal validity of clinical trials investigating pharmacological and non-pharmacological interventions.[22] Two independent reviewers (HA and CO) assessed the risk of bias of all included studies and resolved any disagreement through consensus. Trials with scores greater than 6 were classified as having low risk of bias.

We assessed the overall quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[23 24] The overall quality of evidence was downgraded one level considering risk of bias (ie, trials classified as having high risk of bias, that is PEDro score <7) and imprecision (ie, trials reporting data for <400 participants). We did not assess inconsistency because the results of the comparisons were based on single trials.[23] Similarly, indirectness was also not assessed, because the inclusion criteria of this review considered population, intervention and outcome measures during an ED visit. The quality of evidence was rated from high to low.

Data analysis

Descriptive statistics were used to summarise demographic data and study characteristics. Mean differences (MD) and 95% CIs were obtained for all included studies. While we originally intended to pool trial results using meta-analysis, this was not appropriate due to substantial clinical heterogeneity related to

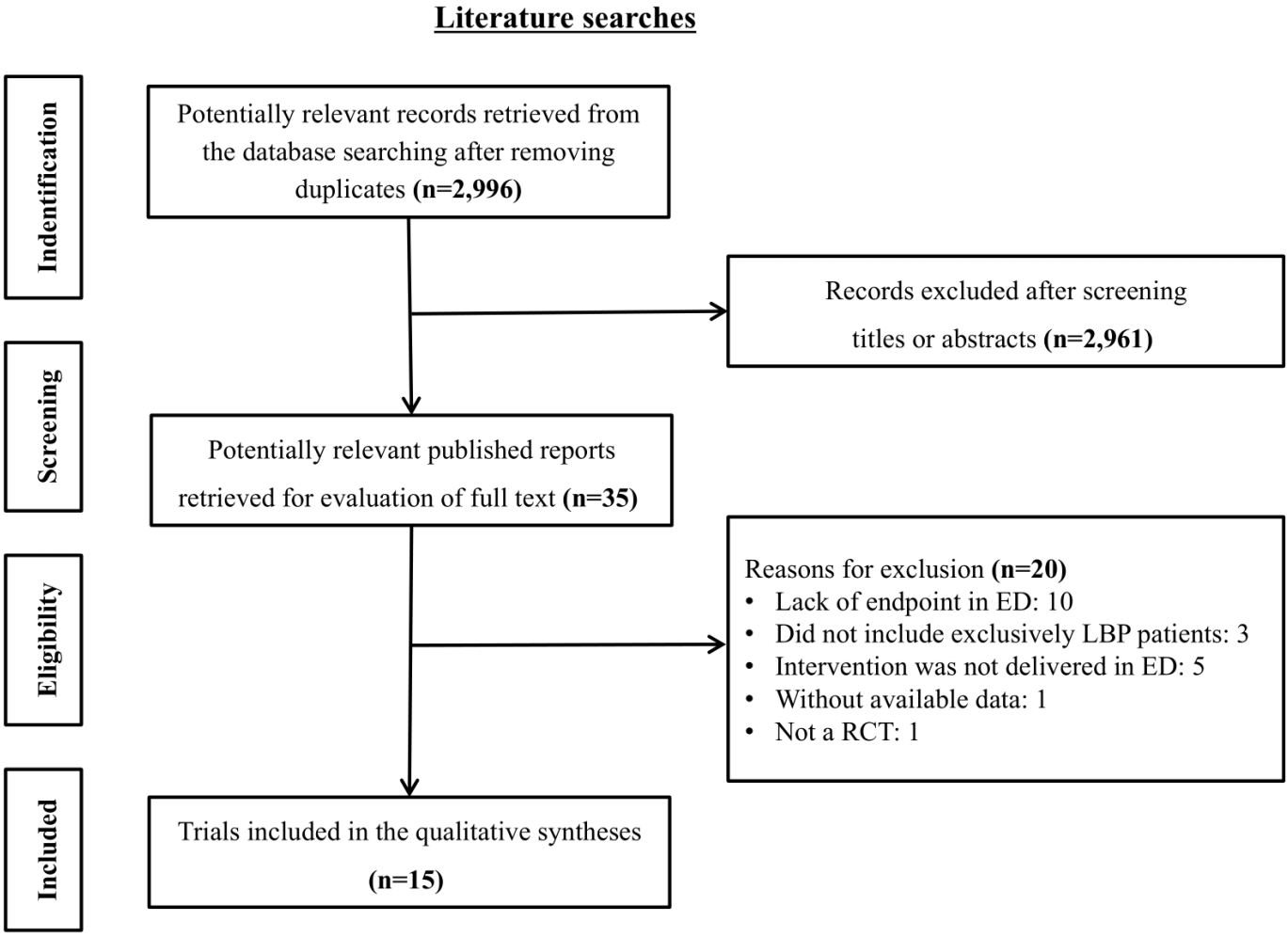

Figure 1 Study flow chart. ED, emergency department; LBP, low back pain; RCT, randomised controlled trial.

the experimental and control interventions. The closest we came to clinically homogeneous trials were three trials with a common control intervention (intravenous placebo), but the experimental interventions were very different (intravenous paracetamol, intravenous dexamethasone and intravenous morphine). We took the view that pooling across such different drugs would have limited clinical applicability for emergency physicians. As pooling would not be appropriate, the results were narratively described. The latest follow-up time reported by each trial was defined as the primary time point as this would be the closest to ED discharge and thus more relevant for emergency physicians. Since this time point varied between included trials, we also report effect sizes for all available time points in the tables and figures. Forest plots were created using Comprehensive Meta-analysis V.3.

RESULTS

Literature searches yielded 2975 records. Of these, 36 records were selected after title and abstracts screening as potentially eligible to be included in this review. Finally, 15 trials were considered eligible and were included.[8 13 25–37] Figure 1 describes the study selection process of this review. Fifteen trials[8 13 25–37] provided data for 1802 participants. Twelve trials[8 26–33 35–37] included patients with non-specific low back pain and three trials[13 25 34] included patients with sciatica. The sample size of the included trials ranged from 30 to 518 participants and the mean age ranged from 31.5 to 45.1 years.

Two trials tested paracetamol,[13 32] seven trials investigated NSAIDs,[28–32 34 37] two trials evaluated corticosteroids,[8 25] one trial investigated two formulations of a muscle relaxant,[35] five trials used opioid medicines,[13 26 28 31 32] one trial used a pharmacotherapy protocol[27] and one trial investigated a combination of thiocolchicoside, lidocaine and tenoxicam.[37] Four trials investigated non-pharmacological interventions including acupuncture,[27 33] a physiotherapy protocol[36] and trigger point injections of an anaesthetic.[29]

The included trials used as comparison interventions a placebo treatment,[28–31 34] NSAIDs,[37] usual ED care (ie, usual therapy provided at the discretion of the treating physician)[33] or walking training/aids.[36] Table 1 describes in detail the characteristics of the included trials, including drug dosages and regimens.

Risk of bias

Table 2 reports risk of bias of the 15 trials using the PEDro scale. Most included trials had low risk of bias; only three trials[27 29 33] had high risk of bias with a PEDro score <7. The most common methodological flaws identified were lack of concealment allocation,[26–29 34 35] and blinding of therapists.[26 27 29 33 36 37] A small proportion of trials did not blind participants or outcome assessors,[27–29 33 37] did not provide data for >85% of participants,[8 25 33] did not perform intention-to-treat analysis,[26 31 34] or did not report similar baseline characteristics.[27] All included trials reported appropriate random allocation, between group differences and variability measures.

Table 1 Characteristics of the included studies

Study name	Country	Source	Sample characteristics	Interventions	Outcomes and endpoint(s)
Akbas *et al*[37]	Turkey	ED of a tertiary care hospital	120 patients with acute LBP (duration of symptoms was not specified) **Group 1:** n=60 (45% female). Median age (IQR): 38.9 (28.3—44.8) **Group 2:** n=60 (48% female). Median age (IQR): 36.9 (27.5—45.0)	**Group 1:** mesotherapy (a minimum of 50 injections) of 2 mg intradermal thiocolchicoside, 16.2 mg lidocaine, and 5 mg tenoxicam **Group 2:** systemic therapy of 50 mg intravenous dexketoprofen for 5 min	Pain (0–10) Adverse events Endpoint: after 15, 30 and 60 min of the intervention
Balakrishnamoorthy *et al*[25]	Australia	EDs of two public hospitals	58 patients with sciatica **Group 1:** n=29 (58% female). Mean age (SD): 38.9 (9.1) **Group 2:** n=29 (44% female). Mean age (SD): 36.9 (9.9)	Both groups received a standardised regimen of regular analgesia (ie, paracetamol/codeine, ibuprofen and oral oxycodone as required), physiotherapy referral and education **Group 1:** single dose of 8 mg intravenous dexamethasone (corticosteroid) in 2 mL **Group 2:** 2 mL of a single dose of 0.9% intravenous sodium chloride	Pain (0–10) Length of stay (minutes) Adverse events Endpoint: at discharge
Behrbalk *et al*[26]	Israel	ED of the Tel-Aviv Sourasky Medical Center	59 patients with acute LBP (less than 3 weeks) **Group 1**: n=30 (53% female). Mean age (SD): 45.0 (11.0) **Group 2**: n=29 (65% female). Mean age (SD): 42.0 (12.0)	**Group 1:** single dose of 0.1 mg/kg (up to 10 mg) intravenous morphine administered in a 150 mL normal saline infusion for 30 min **Group 2:** single dose of 0.1 mg/kg (up to 10 mg) intravenous morphine with 25 mg promethazine administered similarly	Pain (0–100) Length of stay (minutes) Functional outcome (ability to walk) Adverse events Endpoint: after intervention
Cohen *et al*[27]	Australia	Four large EDs in Melbourne — two public and two private	518 patients with acute LBP (duration of symptoms was not specified) **Group 1**: n=174 (48% female). Mean age (SD): 42.1 (15.8) **Group 2**: n=178 (47% female). Mean age (SD): 40.5 (14.5) **Group 3**: n=166 (47% female). Mean age (SD): 40.3 (15.0)	**Group 1:** acupuncture with treatment protocols determined by a panel of specialist acupuncturists, provided predetermined points for each condition **Group 2:** pharmacotherapy according to a standardised protocol based on the relevant national guidelines of the National Institute of Clinical Studies and the National Health and Medical Research Council **Group 3:** combination of the acupuncture and pharmacotherapy treatments	Pain (0–10) Length of stay (hours) Adverse events Endpoint: after an hour
Eken *et al*[32]	Turkey	ED of a tertiary care university hospital	137 patients with acute LBP (starting over the last week), 39% female and mean age (SD) of 31.5 (9.5) **Group 1**: n=46 **Group 2**: n=45 **Group 3**: n=46	**Group 1**: single dose of 1 g intravenous paracetamol in 100 mL normal saline solution **Group 2**: single dose of 0.1 mg/kg intravenous morphine in 100 mL normal saline **Group 3**: single dose of 50 mg intravenous dexketoprofen in 100 mL normal saline solution	Pain (0–100) Adverse events Endpoint: after 15 and 30 min of the intervention
Ergun *et al*[35]	Turkey	ED of tertiary care university hospital	72 patients with LBP (duration of symptoms was not specified) **Group 1**: n=39 (33% female). Mean age (SD): 36.0 (10.0) **Group 2**: n=40 (27% female). Mean age (SD): 38.0 (11.0)	**Group 1**: 2 tablets of 400 mg oral phenyramidol plus 3 mL of intramuscular saline solution **Group 2**: single dose of 800 mg intramuscular phenyramidol plus placebo tablets	Pain (0–100) Adverse events
Eskin *et al*[8]	United States	A suburban ED with an annual patient census of 80 000 patients	79 patients with LBP (last 48 hours or acute exacerbation of chronic low back pain) **Group 1**: n=39 (33% female). Mean age (SD): 39.0 (8.0) **Group 2**: n=40 (27% female). Mean age (SD): 41.0 (9.0)	**Group 1**: single dose of 50 mg oral prednisone **Group 2**: The placebo group received the same regimen as the study group, using an inactive oral tablet	Pain (0–10) Endpoint: at discharge
Fox *et al*[33]	United States	ED of an urban academic medical centre	30 patients with acute and acute-on-chronic LBP **Group 1**: n=15 (53% female). Mean age: 43.0 **Group 2**: n=15 (60% female). Mean age: 38.0	**Group 1**: battlefield acupuncture (placement of indwelling semipermanent needles in up to five prespecified points on the ear, corresponding with established auricular acupuncture points) plus standard therapy **Group 2**: standard therapy provided at the discretion of the treating physician	Pain (0–10) Adverse events Endpoint: 30 min
Innes *et al*[28]	Canada	EDs of six university and community hospitals	113 patients with acute LBP (less than 72 hours) **Group 1**: n=55 (19% female). Mean age (SD): 33.1 (9.8) **Group 2**: n=58 (23% female). Mean age (SD): 36.0 (10.1)	**Group 1**: 10 mg oral ketorolac tromethamine. Then, 10 mg every 4 to 6 hours as needed, up to four doses in 24 hours **Group 2**: 600 mg paracetamol plus 60 mg codeine orally, in the same regimen	Pain (0–10) Adverse events Endpoint: after 30 min, 1, 2, 3, 4, 5, 6 hours of the intervention
Kocak *et al*[29]	Turkey	ED of a tertiary care university hospital	54 patients with acute LBP (less than 48 hours) **Group 1**: n=32 (47% female). Mean age (SD): 40.9 (13.2) **Group 2**: n=22 (36% female). Mean age (SD): 45.1 (13.0)	**Group 1**: single dose of 50 mg intravenous dexketoprofen in 100 cc isotonic solution over 5 min **Group 2**: trigger point injection of anaesthetic (2% lidocaine, 2.5-cc from 100 mg 5-cc of ampoule with 2.5-cc saline mixture). Then, the identified point was needled several times	Pain (0–10) Adverse events Endpoint: after 5, 15, 30 min, and an hour of the intervention
Lau *et al*[36]	Hong Kong	ED of a local acute hospital	110 patients with acute LBP (less than 24 hours) **Group 1**: n=55 (62% female). Mean age (SD): 52.0 (18.0) **Group 2**: n=55 (60% female). Mean age (SD): 49.0 (15.0)	**Group 1**: education session with a Back Care Booklet, mobility training in daily tasks (eg, sitting to standing), walking training and walking aids, and interferential therapy **Group 2:** control group including walking training and prescription of walking aids as indicated	Pain (0–10) Functional outcomes (RMDQ and Back Performance Scale) Endpoint: post-intervention but before discharge.

Continued

Table 1 Continued

Study name	Country	Source	Sample characteristics	Interventions	Outcomes and endpoint(s)
Serinken *et al*[13]	Turkey	ED of four tertiary care hospitals	300 patients with sciatica **Group 1**: n=100 (52% female). Mean age (SD): 44.6 (10.2) **Group 2**: n=100 (57% female). Mean age (SD): 43.7 (9.8) **Group 3**: n=100 (43% female). Mean age (SD): 40.3 (9.5)	**Group 1**: single dose of 0.1 mg/kg intravenous morphine in 100 mL of normal saline **Group 2**: single dose of 1 g intravenous paracetamol in 100 mL of normal saline (Perfalgan, Bristol Myers) **Group 3**: single dose of 100 mL intravenous normal saline	Pain (0–100) Adverse events Endpoint: after 15 and 30 min of the intervention
Serinken *et al*[30]	Turkey	EDs of three tertiary care hospitals	140 patients with acute LBP (less than 24 hours), 44% female and mean age (SD) of 35.0 (12.0) **Group 1**: n=70 **Group 2**: n=70	All the study patients received 50 mg intravenous dexketoprofen (Fastjel, ARVELES) **Group 1**: 2 g of 2.5% ketoprofen gel was administered over the area with pain and tenderness **Group 2**: placebo gel	Pain (0–100) Adverse events Endpoint: after 15 and 30 min of the intervention
Tanen *et al*[34]	United States	ED of a tertiary care medical centre that serves beneficiaries of active duty and retired military personnel	41 patients with acute sciatica **Group 1**: n=20 (36% female). Mean age (SD): 39.0 (12.0) **Group 2**: n=21 (50% female). Mean age (SD): 36.0 (10.0)	**Group 1**: single dose of 100 mg intravenous lidocaine over 2 min followed by a 10-cc normal saline flush **Group 2**: single dose of 30 mg intravenous ketorolac over 2 min also followed by a 10-cc normal saline flush	Pain (0–100) Endpoint: after an hour of the intervention
Veenema *et al*[31]	United States	ED of an urban university hospital	153 patients with LBP (duration of symptoms was not specified) **Group 1**: n=79 (40% female). Mean age (SD): 36.0 (12.1) **Group 2**: n=74 (37% female). Mean age (SD): 35.5 (12.8)	**Group 1**: single dose of 1 mg/kg intramuscular meperidine (pethidine) **Group 2**: single dose of 60 mg intramuscular ketorolac	Pain (0–100) Adverse events Endpoint: after an hour of the intervention

ED, emergency department; ID, intradermal; IM, intramuscular; LBP, low back pain; NSAIDs, non-steroidal anti-inflammatory drugs; ;RMDQ, Roland Morris Disability Questionnaire.

Quality of the evidence: GRADE ratings

The overall quality of evidence of the included interventions on pain intensity varied from low (downgraded for risk of bias or imprecision) to moderate (downgraded for imprecision). The sample size and risk of bias for secondary outcomes were similar to pain intensity, thus the quality of evidence for functional outcomes, length of ED stay and adverse events was also rated as low or moderate. Online supplementary appendix 2 describes the overall quality of evidence using the GRADE approach on pain intensity.

Pain intensity

Figures 2 and 3 detail the effects of the interventions on pain intensity in patients with non-specific low back pain and sciatica, respectively.

Paracetamol

For sciatica, 1 g intravenous paracetamol[13] was more effective than placebo (100 mL intravenous saline) at 15 and 30 min—for example, at 30 min MD was −15.7, 95% CI −19.8 to −11.6. The quality of evidence was moderate.

Non-steroidal anti-inflammatory drugs

For non-specific low back pain, 2 g of 2.5% ketoprofen gel[30] was more effective than placebo gel at 30 min (MD −15.0, 95% CI −21.0 to −9.0). We found that 60 mg intramuscular ketorolac or 1 mg/kg intramuscular meperidine had similar effects at 60 min.[31] There were no differences between 50 mg intravenous dexketoprofen and 1 g intravenous paracetamol at 15 and 30 min.[32] A combination of 2 mg intradermal thiocolchicoside, 16.2 mg lidocaine and 5 mg tenoxicam was more effective than 50 mg intravenous dexketoprofen at 15, 30 and 60 min.[37] These findings are summarised in figure 2.

For sciatica, 30 mg intravenous ketorolac[34] showed no advantage over 100 mg intravenous lidocaine at 60 min (figure 3). The quality of evidence for these comparisons was moderate.

Muscle relaxants

For non-specific low back pain, 800 mg intramuscular phenyramidol was not more effective than two tablets of 400 mg oral phenyramidol at 30, 60, 90 and 120 min (figure 2; moderate quality evidence).[35]

Corticosteroids

For non-specific low back pain, 50 mg oral prednisone[8] was not superior to oral placebo at ED discharge (figure 2). Time of discharge was not reported by the authors.

For sciatica, 8 mg intravenous dexamethasone[25] was not superior to placebo (0.9% intravenous sodium chloride) at emergency discharge (figure 3). The median length of stay ranged from 3.5 to 18.8 hours across both groups. The quality of evidence was moderate.

Opioids

For non-specific low back pain, 0.1 mg/kg intravenous morphine[32] was more effective than 1 g intravenous paracetamol at 15 min (MD −11.4, 95% CI −21.6 to −1.2), but not at 30 min. Similarly, 0.1 mg/kg intravenous morphine was superior to 50 mg intravenous dexketoprofen at 15 and 30 min.[32] We found that 600 mg oral paracetamol plus 60 mg codeine provided similar pain relief to 10 mg oral ketorolac trometh-amine at 30 min and at each hour until 6 hours after the intervention.[28] Similarly, there was no difference between 0.1 mg/kg intravenous morphine plus 25 mg promethazine and 0.1 mg/kg intravenous morphine alone shortly after the administration.[26] These findings are summarised in figure 2.

For sciatica, 0.1 mg/kg intravenous morphine[13] was more effective than placebo at 15 and 30 min—for example, at 30 minutes MD was −39.3, 95% CI −43.5 to −35.1. This same trial[13] showed that 0.1 mg/kg intravenous morphine was more effective than 1 g intravenous paracetamol at 15 and 30 min (figure 3). The quality of evidence was moderate.

Non-pharmacological treatments

For non-specific low back pain, auricular acupuncture plus usual ED care was more effective than usual ED care alone.[33] In another trial with three groups, however, acupuncture was not more effective than pharmacotherapy or acupuncture plus pharmacotherapy, nor was pharmacotherapy superior to acupuncture plus pharmacotherapy.[27] Trigger point injections showed

Table 2 Risk of bias of the included studies according to the PEDro scale

Studies	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% dropout rate	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0–10)
Akbas *et al*[37]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Balakrishnamoorthy *et al*[25]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Behrbalk *et al*[26]	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7
Cohen *et al*[27]	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5
Ergun *et al*[35]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Eken *et al*[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Eskin *et al*[8]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Fox *et al*[33]	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	5
Innes *et al*[28]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Kocak *et al*[29]	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Lau *et al*[36]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Serinken *et al*[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Serinken *et al*[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Tanen *et al*[34]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Veenema *et al*[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9

PEDro, Physiotherapy Evidence Database.

superior pain relief than 50 mg intravenous dexketoprofen at 5, 10, 15, 30 and 60 min.[29] A physiotherapy protocol was not more effective than walking training/aids at ED discharge.[36] The quality of evidence was low.

Functional outcomes

Opioids

There was no difference between 0.1 mg/kg intravenous morphine alone and 0.1 mg/kg intravenous morphine plus 25 mg promethazine on the proportion of patients who were able to walk independently at discharge (percentage difference: −6.2%, 95% CI −13% to 25%), or assisted (percentage difference: −6.2%, 95% CI −13 to 25).[26] The quality of the evidence was moderate.

Non-pharmacological treatments

Physiotherapy was not superior to walking training/aids on disability measured using the Roland Morris Disability Questionnaire (MD −0.3 out of 24 points, 95% CI −2.8 to 2.2) or mobility measured by the Back Performance Scale (MD −0.6 out of 15 points, 95% CI −1.7 to 0.6).[36] The quality of the evidence was moderate.

Length of ED stay

Corticosteroids

We found that 8 mg intravenous dexamethasone vs placebo led to shorter ED stay for patients with sciatica (MD −15.3 min, 95% CI −18.4 to −12.2; moderate quality evidence).[25]

Opioids

Receiving 0.1 mg/kg intravenous morphine alone resulted in significantly shorter visits than taking 0.1 mg/kg intravenous morphine plus promethazine 25 mg in patients with non-specific low back pain (MD −78.0 min, 95% CI −140.0 to −16.0; moderate quality evidence).[26]

Non-pharmacological treatments

There was no statistically significant difference (p=0.87, low quality evidence) in the length of ED stay of patients with non-specific low back pain receiving acupuncture (median 3.8 hours, IQR 2.9–4.9), pharmacotherapy (median 3.9 hours, IQR 2.7–5.3) or acupuncture plus pharmacotherapy (median 3.7 hours, IQR 2.8–4.8).[27]

Adverse events

Table 3 shows adverse event data of 12 trials[13 25–33 35 37] including 1396 patients with non-specific low back pain and 358 patients with sciatica.

Non-steroidal anti-inflammatory drugs

One patient receiving 2 g of 2.5% of ketoprofen gel reported vertigo and another in the placebo group reported nausea (moderate quality evidence).[30]

Muscle relaxants

There was no difference (moderate quality evidence) in the number of patients reporting adverse events after receiving 800 mg intramuscular phenyramidol or 800 mg oral phenyramidol.[35]

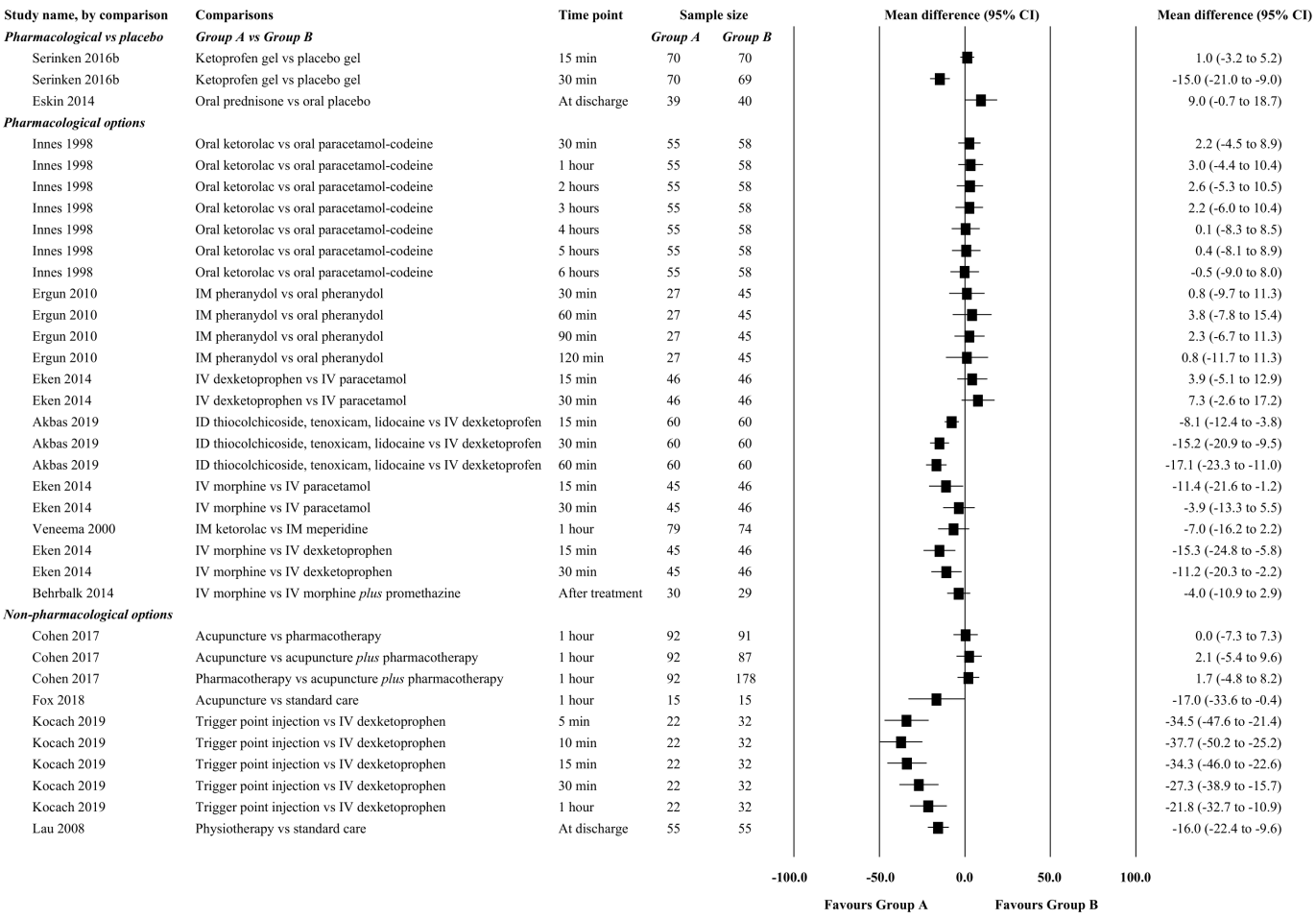

Figure 2 Effects of emergency department interventions on pain scores of patients with non-specific low back pain. ID, intradermal; IM, intramuscular; IV, intravenous.

Corticosteroids

There was no difference (moderate quality evidence) in adverse event rates between patients receiving 8 mg intravenous dexamethasone or placebo.[25]

Opioids

Receiving 0.1 mg/kg intravenous morphine plus 25 mg promethazine resulted in more patients reporting drowsiness and sedation than those receiving 0.1 mg/kg intravenous morphine alone (percentage difference 73%, 95% CI 50% to 85%), but no difference was found for nausea and vomiting (percentage difference 0.1%, 95% CI −13% to 14%).[26] Patients receiving 0.1 mg/kg intravenous morphine or 1 g intravenous paracetamol reported nausea and vertigo.[13] In addition, one patient receiving 0.1 mg/kg intravenous morphine reported hypotension whereas no patients in the placebo group reported adverse events.[13] Patients receiving 1 mg/kg intramuscular meperidine were 10.9 times more likely to experience adverse events (such as dizziness, nausea, sleepiness and dry mouth) compared with those receiving 60 mg intramuscular ketorolac (95% CI 4.6 to 25.7).[31] Similarly, patients receiving 600 mg oral paracetamol plus 60 mg oral codeine were 3.5 times more likely to experience at least one adverse event compared with those receiving 10 mg oral ketorolac tromethamine (95% CI 1.67 to 7.47).[28] There was no

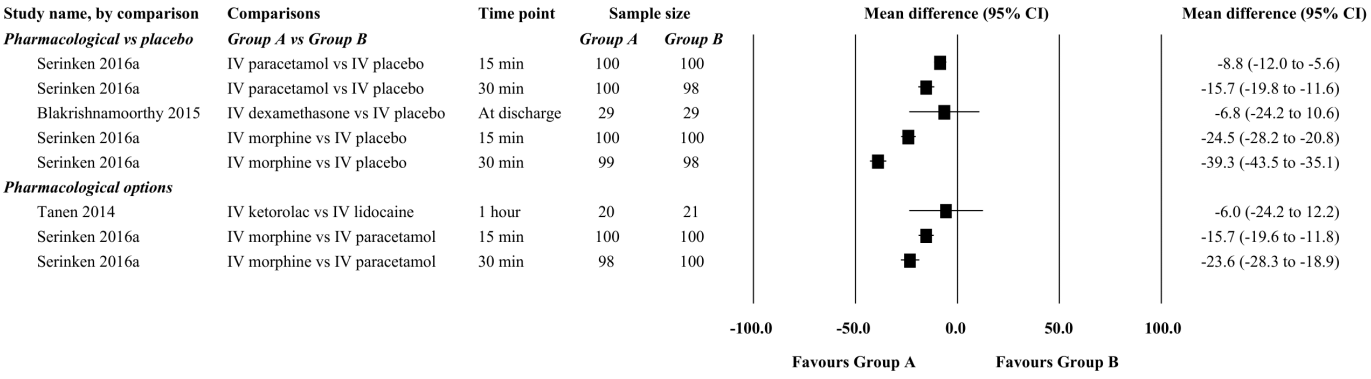

Figure 3 Effects of emergency department interventions on pain scores of patients with sciatica. ID, intradermal; IM, intramuscular; IV, intravenous.

Table 3 Details of the adverse events reported in the included studies

Study name	Group 1 (N of patients or adverse events)	Group 2 (N of patients or adverse events)	Group 3 (N of patients or adverse events)	Description of adverse events data
Balakrishnamoorthy *et al*[25]	8 mg intravenous dexamethasone (NS)	Placebo (NS)	N/A	Incidence of adverse events (ie, nausea, mild headache, light-headedness) but no distinction between the groups (18% vs 15%). One patient receiving intravenous dexamethasone reported peri-anal itching
Behrbalk *et al*[26]	0.1 mg/kg intravenous morphine (n=7)	0.1 mg/kg intravenous morphine plus 25 mg promethazine (n=30)	N/A	No of adverse events: drowsiness and sedation (n=33), nausea and vomiting (n=2), seizures/myoclonus (n=1), headache (n=1)
Cohen *et al*[27]	Acupuncture (n=73)	Pharmacotherapy (n=72)	Acupuncture plus pharmacotherapy (n=71)	No of patients reporting any adverse event
Eken *et al*[32]	1 g intravenous paracetamol (n=4)	0.1 mg/kg intravenous morphine (n=7)	50 mg intravenous dexketoprofen (n=4)	No of patients reporting allergic reactions (n=2), dizziness (n=3), dry mouth (n=2), vertigo (n=1), nausea and vomiting (n=5), mild sedation (n=1), hypotension (n=1)
Ergun *et al*[35]	800 mg intramuscular phenyramidol (n=3)	800 mg oral phenyramidol (n=5)	N/A	No of patients reporting headache, emesis, dry mouth or dizziness (n=8)
Fox *et al*[33]	Battlefield acupuncture (n=2)	Standard therapy (n=0)	N/A	No of patients reporting discomfort at needle insertion site (n=2)
Innes *et al*[28]	10 mg oral ketorolac tromethamine (n=21)	600 mg paracetamol plus 60 mg codeine (n=38)	N/A	No of patients reporting any adverse events per group: ketorolac (n=21) vs paracetamol-codeine (n=38) No of adverse events per group: ketorolac (n=31) vs paracetamol-codeine (n=76)
Serinken *et al*[13]	0.1 mg/kg intravenous morphine (n=4)	1 g intravenous parecetamol (n=3)	Placebo (n=0)	No of patients reporting nausea (n=4), vertigo (n=2), hypotension (n=1)
Serinken *et al*[30]	2 g of 2.5% ketoprofen gel (n=1)	Placebo gel (n=1)	N/A	No of patients reporting nausea (n=1), vertigo (n=1)
Veenema *et al*[31]	1 mg/kg intramuscular meperidine (n=41)	60 mg intramuscular ketorolac (n=8)	N/A	No of adverse events: dizziness (n=19), nausea (n=8), parathesias (n=4), sleepiness (n=11), dry mouth (n=4), hot (n=1), dyspnoea (n=1), pain at site (n=1)

N/A, not applicable; NS, not stated.

difference in the risk of adverse events between 0.1 mg/kg intravenous morphine versus 1 g intravenous paracetamol (RR 1.79, 95% CI 0.56 to 5.69), 0.1 mg/kg intravenous morphine versus 50 mg intravenous dexketoprofen (RR 1.79, 95% CI 0.56 to 5.69), or 1 g intravenous paracetamol versus 50 mg intravenous dexketoprofen (RR 1.00, 95% CI 0.27 to 3.76).[32] The quality of the evidence was moderate.

Non-pharmacological treatments

One study comparing trigger point injection with 50 mg intravenous dexketoprofen did not report any adverse event.[29] In addition, the proportion of patients reporting any adverse event was similar (p=0.84) between acupuncture, pharmacotherapy and acupuncture plus pharmacotherapy.[27] Two patients receiving auricular acupuncture reported discomfort at needle insertion site.[33] The quality of the evidence was low.

Representations

None of the included trials reported rates of representation to the ED within 48 hours.

DISCUSSION

Our review identified 15 randomised controlled trials investigating several interventions for non-specific low back pain and/or sciatica during an ED visit. Compared with placebo, ketoprofen gel showed significant effects in reducing pain intensity in patients with low back pain. Intravenous paracetamol and morphine were both more effective than placebo for sciatica. In contrast, corticosteroids were not effective for low back pain or sciatica. Trials comparing different pharmacological or non-pharmacological treatments showed conflicting results. There was limited evidence on functional outcomes, length of stay and representations. Opioids had an increased risk of transient adverse events compared with NSAIDs. The overall quality of evidence was low or moderate, suggesting that future studies are likely to change our estimates.

Our findings for ketoprofen gel[30] and oral prednisone[8] in patients with low back pain align with the available evidence from primary care.[38 39] The absence of significant differences between some pharmacological treatments has also been observed in trials conducted outside the ED.[9–11 40] Two trials conducted in Turkey found large effect sizes that are rarely seen in low back pain trials.[34 37] Similarly, two high risk of bias trials investigating auricular acupuncture[33] and trigger point injections[29] for low back pain showed surprisingly large effects across all time points. The lack of efficacy of corticosteroids for sciatica[25] also aligns with findings in another systematic review that mainly included primary care data.[41] Some comparisons included in our review (eg, intravenous paracetamol vs intravenous morphine vs placebo for sciatica[13]; ketorolac vs lidocaine for low back pain)[34] have not been investigated in other clinical settings.

None of the trials investigating functional outcomes reported statistically significant differences. The lack of reporting on functional outcomes might reflect the difficulties in collecting these measures in the busy ED setting. Some items of the instruments used measure functional outcomes[42] would not be responsive to change in a short ED visit (eg, 'I got dressed more slowly than usual because of my back pain'). Other instruments that have been shown to be responsive to change over a short period of time, such as the Back Performance Scale,[43] might be more appropriate in ED settings. Another finding from our review was the significant shorter stays for patients with sciatica receiving dexamethasone[25]. Although the use of opioids was associated with an increased risk of adverse events,[13 26 31] most of these events were considered to be minor and transient.

The lack of supporting evidence in the ED is clearer when we look at longer-term outpatient studies. For example, there are numerous trials conducted in community settings showing no additional benefits of muscle relaxants to NSAIDs for acute low back pain,[9 10] yet in the ED there is only one trial of muscle relaxants, which compared two forms of the drug.[35] Nevertheless, a search for trials on the WHO International Clinical

Trials Registry identified 10 ongoing trials investigating several interventions, including acupuncture, patient education, chamomile oil, spinal braces, NSAIDs, exercise, cannabidiol, lidocaine patches and implementation of a model of care. Although some of these ongoing trials may contribute to more definitive conclusions, more trials should be conducted to investigate interventions commonly used in EDs to manage low back pain and sciatica and include patient-reported outcomes (eg, physical function) and specific measures to the ED that are often routinely collected (eg, lenght of stay and representations).

This review was prospectively registered,[44] followed PRISMA reporting guidelines[16] and Cochrane recommendations.[17] We performed a comprehensive search to identify potentially eligible trials and focused on studies measuring outcomes during an ED visit. However, we found great variability across trials, which did not allow us to pool the data. While some trials had a common control intervention, the experimental interventions were markedly different—for example, intravenous morphine versus intravenous dexketoprofen[32] and trigger point injection versus intravenous dexketoprofen.[29] Clinical practice guidelines distinguish between different classes of medicines and types of non-pharmacological treatments, so pooling different medicines would not be helpful to ED physicians who provide care informed by clinical guidelines. Our findings are based on single trials, which may restrict generalisability. Also, the medications tested in the trials might not be readily available in some countries. For example, phenyramidol was the only muscle relaxant investigated in the included trials,[35] but baclofen and orphenadrine are more frequently used in Australia. In addition, replicating these trials could lead to different results. For example, the beneficial effects of antibiotics for patients with chronic low back pain and Modic changes[45] have been disputed after a recent replication trial.[46]

Emergency physicians often use strong pain medicines, such as opioids. For example, a recent study in Australia showed that nearly 70% of patients with low back pain receive an opioid medicine while in the ED.[6] There is, however, limited evidence conducted in ED settings to evaluate the benefits and harms of this practice. The evidence base on the benefits and the dose–response relationship of opioids in this population is weak and there is clear evidence of an increased risk for harms.[7] If emergency physicians are to initiate opioids for low back pain, they should, therefore, follow current primary care guidelines and trial NSAIDs and weak opioids first.[47] Since many emergency patients have contraindications to NSAIDs, primary care guidelines can offer helpful evidence for non-pharmacological options. For instance, educating patients on staying active, providing information to self-manage the condition, and using heat therapy for pain relief are common recommendations in primary care guidelines[47] that emergency physicians should feel comfortable advocating.

CONCLUSION

Our systematic review identified that ketoprofen gel was superior to placebo for patients with non-specific low back pain. Intravenous paracetamol and morphine were both superior to placebo in reducing pain related to sciatica. In contrast, corticosteroids were ineffective for non-specific low back pain or sciatica. Trials investigating different medicines or non-pharmacological treatments revealed conflicting findings. There is a research gap on the effects of interventions on functional outcomes, length of stay and representations. Opioids showed an increased risk of transient adverse events. The overall quality of evidence was low or moderate, thus, additional large high quality trials are needed to better guide emergency physicians in the management of non-specific low back pain and sciatica.

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Contributors CBO, HEA, DMC, BR, MR, CGM and GCM were involved in the design of the review. CBO, HEA and DC developed the search strategy, and performed study selection, data extraction and risk of bias from included studies. CBO, CGM and GCM were involved in the data analysis. All authors were involved in interpretation and discussion of results, drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

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PLOS ONE

RESEARCH ARTICLE

Extracellular vesicle-associated procoagulant phospholipid and tissue factor activity in multiple myeloma

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Abstract

Multiple myeloma (MM) patients have increased risk of developing venous thromboembolism, but the underlying mechanisms and the effect on the coagulation system of the disease and the current cancer therapies are not known. It is possible that cancer-associated extracellular vesicles (EV), carrying tissue factor (TF) and procoagulant phospholipids (PPL) may play a role in thrombogenesis. The aim of this study was to perform an in-depth analysis of procoagulant activity of small and large EVs isolated from 20 MM patients at diagnosis and after receiving first-line treatment compared with 20 healthy control subjects. Differential ultracentrifugation at 20,000 × *g* and 100,000 × *g* were used to isolate EVs for quantitative and phenotypical analysis through nanoparticle tracking analysis, Western blotting and transmission electron microscopy. The isolated EVs were analyzed for procoagulant activity using the calibrated automated thrombogram technique, a factor Xa-based activity assay, and the STA Procoag-PPL assay. In general, MM patients contained more EVs, and immunoelectron microscopy confirmed the presence of CD9- and CD38-positive EVs. EVs in the 20,000 × *g* pellets from MM patients exerted procoagulant activity visualized by increased thrombin generation and both TF and PPL activity. This effect diminished during treatment, with the most prominent effect observed in the high-dose chemotherapy eligible patients after induction therapy with bortezomib, cyclophosphamide, and dexamethasone. In conclusion, the EVs in patients with MM carrying TF and PPL are thus capable of exerting procoagulant activity.

Introduction

Cancer patients have a 4–7-fold higher risk of venous thromboembolism (VTE) than does the general population, but the risk in different cancer types varies, and the frequency of VTE in cancer patients is between 1–8% [1–3]. Patients with multiple myeloma (MM) have a considerably increased risk of VTE, partly because the associated treatment may be thrombogenic [4–

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6]. Although several factors, such as age, acquired protein C resistance, coagulation factor VIII, von Willebrand factor, and interleukin-6, have been proposed as contributors to this hypercoagulable state, the mechanisms causing VTE in patients with MM are not clearly understood [7–9]. A possible contributing factor is an increased level of tissue factor (TF), a central coagulation factor in initiating haemostasis that triggers thrombin generation [10]. It has been reported that aberrant TF expression is linked to cancer pathophysiology, e.g., angiogenesis [11]. Anionic procoagulant phospholipids (PPL), such as phosphatidylserine, act as important cofactors necessary for the formation of coagulation complexes but have also been proposed to be involved in cancer pathogenesis [12]. TF and PPL can be present in plasma in circulating extracellular vesicles (EV) with procoagulant properties. In malignancy, EVs from the cancer cells are involved in several pleiotropic processes, such as metastasis, angiogenesis, and immunomodulation [13,14]. Because they may also carry TF and PPL, likely on the large EVs, so-called microvesicles (MV), these EVs may play a significant role in haemostasis and VTE-risk in various diseases, including MM [15–18]. Auwerda et al [16] reported a microparticle-associated TF-activity in MM patients receiving high-dose chemotherapy (HDCT). The aim of this study was to investigate the procoagulant effect of EVs from patients with newly diagnosed MM compared with controls, hypothesizing that EVs in patients with MM are procoagulant.

Materials and methods

Study population

A total of 20 newly diagnosed patients with MM according to the International Myeloma Working Group criteria, were included in the study at the Department of Haematology, Aalborg University Hospital, Denmark. At inclusion, none of the patients received anti-coagulation therapy and had no history of previous VTE or other malignancies. The patients were staged according to the International Staging System (ISS) for multiple myeloma. Patients eligible for HDCT received three or four series of bortezomib, cyclophosphamide, and dexamethasone (VCD) induction therapy, and then after leukapheresis proceeded to high-dose melphalan with stem cell support. This patient group will be referred to as the VCD induction therapy group. The patients ineligible for HDCT received a conventional treatment consisting of melphalan, prednisone, and bortezomib (MPV) and will henceforth be referred to as the conventional treatment group. Treatment response was assessed through the multiple myeloma treatment response criteria described by the International Myeloma Work Group and as a relative reduction in M-protein post treatment. Plasma samples from 20 healthy partly matched subjects were collected as controls. The study was conducted in agreement with the Declaration of Helsinki and approved by the ethical committee of Northern Jutland (N-20130075). Written informed consent was acquired from all participants at inclusion in the study.

Sample collection and EV isolation

Samples were collected from the patients at diagnosis and after their first-line anti-myeloma treatment, i.e. approximately four weeks after VCD induction therapy (prior to stem cell transplantation) or MPV treatment dependent on treatment regimen. Venous blood was collected in 6-mL 0.105 M (3.2%) trisodium citrate tubes (Becton Dickinson, Franklin Lakes, NJ, USA). Within one hour after collection, platelet-free plasma (PFP) was extracted by a double centrifugation at 2,500 × *g* at room temperature for 15 minutes according to international recommendations [19,20]. Plasma collection was stopped one cm from the buffy coat and the pellet in the consecutive spin. The PFP was stored at -80˚C until analysis. The isolation process of

the EVs consisted of a two-step ultracentrifugation in an Avanti J-30i equipped with a JA-30.50 rotor, k-factor 280 (Beckman Coulter, Brea, CA, USA). The first batch of EVs was pelleted from 1 ml PFP by centrifugation at 20,000 × *g* (20K) for 30 minutes at 4˚C. The 20K pellets were washed once in 1 ml phosphate-buffered saline (PBS) at the same *g*-force and duration. Residual EVs were pelleted by centrifugation of the supernatant at 100,000 × *g* (100K) for 60 minutes at 4˚C. Likewise, the 100K pellets were washed once in 1 ml PBS at the same *g*-force and duration. To create an equal baseline in the coagulation analyses for the different patients and controls, all pellets were finally resuspended in standard pool plasma (SPP). The pellets were resuspended in 200 μl SPP (i.e., they were five times more concentrated). SPP was collected from a single donor analogous to the PFP extraction described above. For the quantitative and phenotypical analyses, pelleted EVs were resuspended in 200 μl PBS.

Nanoparticle tracking analysis

Nanoparticle tracking analysis was applied to determine the size and concentration of particles in the pellets and confirm that their size was equivalent to that of EVs. Particles were tracked on a LM10-HS system with a 405 nm laser (Malvern Instruments, Malvern, UK) and visualized with a Luca-DL EMCCD camera (Andor Technology, Belfast, UK). The 0.1 μm standard silica beads were used to calibrate the analysis settings. Settings applied were camera level 10 and detection threshold 2 with blur 9×9. A total of five videos of 30 seconds each was recorded for the individual samples. Prior to analysis, the samples were diluted in PBS to ensure a particles per frame count within the manufacturer's recommendations. Particles were tracked, quantified, and size enumerated using the Nanosight NTA software version 3.0 (Malvern Instruments).

Western blotting

Western blotting was performed to identify EVs positive for the commonly used EV-marker CD9 and the therapeutic target marker CD38 expressed abundantly on myeloma cells. The pellet pools were lysed with 2 × Laemmli Sample Buffer (Bio-Rad Laboratories, Hercules, CA, USA), boiled for 5 minutes at 95˚C, and separated in MiniProtean TGX 4–15% gels (Bio-Rad Laboratories). The proteins were transferred to Amersham Hybond P 0.20 PVDF blotting membranes (clone M-L13, GE Healthcare, Little Chalfont, UK) for 60 minutes at 100 V and subsequently blocked in 5% (w/v) skim milk blocking buffer for 60 minutes. The membranes were incubated with primary monoclonal mouse anti-CD9 antibody (clone M-L13, BD Pharmingen, San Diego, CA, USA) and monoclonal human anti-CD38 antibody (daratumumab; Jannsen-Cilag A/S, Birkeroed, Denmark) diluted 1:1000 with blocking buffer. Secondary antibodies used were horseradish peroxidase-conjugated polyclonal goat anti-mouse antibodies (Dako, Glostrup, Denmark) and polyclonal goat anti-human antibodies (Abcam, Cambridge, UK). Detection of membranes was performed using ECL Prime Western Blotting detection reagent (GE Healthcare) and the PXi 4 system with the GeneSys software version 1.5.4.0 (Syngene, Cambridge, UK). The bands were quantified with ImageJ 1.50e software (NIH, Bethesda, MD, USA).

Transmission electron microscopy and immunogold labelling

To detect vesicles that structurally resembled EVs in the pellets, transmission electron microscopy was performed. The procedure used was in accordance with previous studies [21,22] with minor modifications. Five microliter pooled pellet suspension was mounted on a carbon-coated, glow discharged 400 mesh Ni grid (SPI supplies, Chester, PA, USA) for 30 seconds,

followed by staining with one drop of 1% (w/v) phosphotungstic acid (Ted Pella, Caspilor AB, Lindingö, Sweden) pH 7.0. Then, the grid was blotted dry on filter paper. Detection of EV subpopulations was achieved through transmission electron microscopy with immunogold labelling. Samples were mounted on carbon-coated, glow discharged 400 mesh Ni grids for 30 seconds and washed three times with PBS. Grids were blocked with 0.5% ovalbumin (Sigma-Aldrich, St. Louis, MO, USA) in PBS and then incubated with primary monoclonal mouse anti-CD9 antibody (clone M-L13, BD Biosciences, Albertslund, Denmark) or anti-CD38 antibody (daratumumab; Jannsen-Cilag A/S) 1:50 in 0.5% ovalbumin in PBS for 30 minutes at 37˚C. After three washes in PBS, the grids were incubated with 10 nm gold-conjugated goat anti-mouse secondary antibody (British BioCell, Cardiff, UK) diluted 1:25 in 0.5% ovalbumin in PBS in advance. The grids were then washed with three drops of PBS and incubated on three drops of 1% cold fish gelatin (Sigma-Aldrich) for 10 minutes per drop. Subsequently, the grids were washed with three drops of PBS and stained with one drop of 1% (w/v) phosphotungstic acid at pH 7.0. The grids were then blotted dry. To visualize the samples, a JEM-1010 transmission electron microscope (JEOL, Tokyo, Japan) operated at 60 keV was used. An electron-sensitive CCD camera (KeenView, Olympus, Tokyo, Japan) was used to capture images and a grid-size replica (2,160 lines/mm) and the ImageJ 1.50r software (NIH, Bethesda, MD, USA) was used to assess size of visualized EVs.

Thrombin generation assay (calibrated automated thrombogram)

Thrombin generation was assessed according to the protocol for the calibrated automated thrombogram (CAT) previously described by Hemker et al [23]. The 80 μL EV suspension was mixed with 20 μL PRP reagent (Thrombinoscope B.V., Maastricht, the Netherlands) containing 1 pM TF and no phospholipids. Coagulation was initiated by addition of 20 μL FluCa buffer containing $CaCl_2$ and fluorogenic substrate (FluCa kit, Thrombinoscope B.V.). The reaction was measured in an automated Fluoroscan Ascent (Thermo Scientific, Waltham, MA, USA) and peak height, lag time, time-to-peak, and velocity index were calculated using the Thrombinoscope software version 5.0 (Thrombinoscope B.V.). Endogenous thrombin potential (ETP, area under the curve) was calculated manually and for the whole test duration of 60 minutes. SPP with buffer (blank, i.e., no addition of EVs) was measured several times to establish a reference range for the SPP on each parameter.

Procoagulant phospholipid activity assay

The STA-Procoag-PPL assay (Diagnostica Stago, Asnieres, France) was used to measure the activity of EV-associated PPL. In this assay, all of the coagulation factors were supplied at physiological levels by PPL-depleted plasma, apart from PPL, which was provided by EVs in the pellets. The 25 μL EV suspension was diluted in 25 μL Owren-Koller buffer. The reaction was triggered by Ca^{2+} and factor Xa (FXa). The assay measures a clotting time (seconds), which is inversely proportional to PPL activity, meaning a shorter clotting time indicates an increased PPL activity. The assay was conducted on a STA-Compact (Diagnostica Stago) in accordance with the manufacturer's protocol. SPP with buffer only (blank) was measured several times to establish a reference range for the PPL clotting time.

MV-TF activity assay

MV-TF activity and MV-FXa generation was measured with an adapted method from Wang et al [24]. First, 600 μL plasma was diluted in 1 mL HBSA buffer (137 mM NaCl, 5.38 mM KCl, 5.55 mM glucose, 10 mM HEPES, 0.1% (w/v) bovine serum albumin, pH 7.4) and centrifuged at 20,000 × *g* for 15 minutes at 4˚C in order to pellet microvesicles. The pellets were washed

once in 1 mL HBSA and resuspended in 180 μL HBSA. The samples were then incubated with monoclonal mouse anti-CD142 antibody (clone HTF-1, BD Pharmingen) or control IgG from mouse serum (Sigma-Aldrich) for 15 minutes at room temperature in a 96-well plate. After incubation, 50 μL HBSA containing 10 mM $CaCl_2$, 73 nM FX (Enzyme Research Laboratories, South Bend, IN, USA), and 2.4 nM factor VIIa (Enzyme Research Laboratories) was added to each sample and incubated for two hours at 37˚C. The reaction was stopped by addition of 25 μL HBSA containing 25 mM EDTA. Then, 25 μL of 4 mM chromogenic Pefachrome FXa 8595 (Pentapharm, Basel, Switzerland) was added to the wells and incubated at 37˚C for 15 minutes. The plate was read at absorbance 405 nm on a Fluostar Optima (BMG Labtech, Ortenberg, Germany). Innovin (Siemens Healthcare, Erlangen, Germany) was used to generate a standard curve to calculate the procoagulant activity of microvesicles.

Statistical analysis

The results are expressed by the means ± standard deviation or as boxplots depicting median, the 25 and 75 percentiles and whiskers min to max. Differences between the two groups and pellets were determined with either Student's *t*-test or the Mann-Whitney U test depending on the distribution type. The Pearson correlation coefficient was used to signify associations between variables. Differences before and after treatment of the MM patients were determined using either paired *t*-tests or the Wilcoxon matched-pairs signed rank test. P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using IMB SPSS Statistics version 24 (SPSS, Chicago, IL, USA) and Graph Pad Prism version 6 (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics

A total of 20 patients with a median age of 72 years (range 40–84) and a male/female distribution of 11/9 were included in this study. Two patients (10%) had stage I, seven (35%) had stage II, and 11 had (55%) stage III disease according to the ISS for multiple myeloma. None of the patients received anti-coagulant prophylaxis at inclusion or during the period they were followed until the collection of the second sample. MM patient characteristics at diagnosis are summarized in Table 1, showing expected abnormalities in some of the patients such as low haemoglobin, slightly increased creatinine, acute phase reaction (increased C-reactive protein, fibrinogen and FVIII) and positive D-dimer. The controls had a median age of 64 years (range 56–67) and a male/female distribution of 11/9. They were all healthy with no biochemical abnormalities. From 16 of the 20 patients, a post-treatment sample was obtained, whereas the remaining four patients died (2–4 months after the initial sample). Five of the 16 patients received the VCD induction therapy. For the 11 remaining patients in the conventional treatment group, 10 received MPV and one was treated with lenalidomide and dexamethasone. Four patients died before a follow-up sample was collected–three from sepsis and one of unknown reasons. Demographic characteristics and treatment response before and after first-line treatment for both treatment groups are listed in Table 2 and additional patient characteristics are listed in the supplemental information (S1 Table).

Isolation and characterization of EVs

In general, significantly more particles ($P < 0.01$) were isolated in the MM pellets than in the control pellets, with the majority of particles isolated from MM patients in the 20K pellet (Fig 1A). In both groups, 20K pellets showed the largest mean particle size ($P < 0.01$) compared to

Table 1. Characteristics of the multiple myeloma patients at diagnosis.

	Multiple myeloma	*Reference range (male / female)*
Number of patients	20	
Age, years	70 ± 10	
Male percentage	55%	
ISS stage		
I	2 (10%)	
II	7 (35%)	
III	11 (55%)	
M-protein, g/L	41.5 ± 19.9	
IgG, *n*	14 (70%)	
kappa	*11 (55%)*	
lambda	*3 (15%)*	
IgA, *n*	6 (30%)	
kappa	*4 (20%)*	
lambda	*2 (10%)*	
INR	1.1 ± 0.2	*<1.3*
APTT, s	30 ± 4	*25–40*
Fibrinogen, μmol/L	9.4 ± 3.3	*5.0–12.0*
D-dimer, mg/L	0.80 ± 0.27	*<0.30*
Antithrombin, ×E9 IU/L	0.88 ± 0.17	*0.80–1.20*
Factor VIII, U/mL	1.60 ± 0.73	*0.60–1.60*
Protein C, U/mL	1.10 ± 0.39	*0.70–1.40*
Creatinine, μmol/L	89 ± 23 / 77 ± 23	*60–105 / 45–90*
Carbamide, mmol/L	7.0 ± 2.6 / 6.2 ± 1.2	*3.5–8.1 / 3.1–7.9*
Pt-estimated GFR, mL/min	74 ± 17	*>60*
κ-chain, free, mg/L	1153.1 ± 3723.9	*3.3–19.4*
λ-chain, free, mg/L	299.8 ± 697.1	*5.7–26.3*
Calcium, mmol/L	2.48 ± 0.15	*2.20–2.55*
CRP, mg/L	7.5 ± 22.7	*<8.0*
Albumin, g/L	30 ± 4	*34–45*
Protein, g/L	106 ± 18	*62–78*
ALAT, U/L	23 ± 10	*10–50*
Haemoglobin, mmol/L	6.7 ± 1.5 / 6.0 ± 0.6	*8.3–10.5 / 7.3–9.5*
Erythrocytes, ×E12/L	3.44 ± 0.80 / 3.18 ± 0.38	*4.30–5.70 / 3.90–5.20*
Platelets, ×E9/L	198 ± 57 / 248 ± 52	*145–350 / 165–400*
Leukocytes, ×E9/L	6.3 ± 2.2	*3.5–10.0*

ISS = international staging system; IgG = immunoglobulin G; IgA = immunoglobulin A; INR = international normalized ratio; APTT = activated partial thromboplastin time; GFR = glomerular filtration rate; CRP = C-reactive protein; ALAT = alanine transaminase.

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the 100K pellets, although only a minor difference was observed for the control pellets (Fig 1B). The 20K pellets in the MM group had the highest percentage (86%) of particles larger than 100 nm in size (Fig 1C). Both control and MM pellets contained $CD9^+$ EVs, but more

Table 2. Demographic characteristics of patients the conventional or induction therapy groups including treatment response.

	Conventional therapy	VCD induction therapy
Number of patients	11	5
Age, years*	76 ± 5	64 ± 5
Male gender	55%	40%
ISS stage		
I	1 (9%)	0 (0%)
II	6 (55%)	2 (40%)
III	4 (36%)	3 (60%)
Treatment		
VCD	0 (0%)	5 (100%)
MPV	10 (91%)	0 (0%)
LEN-DEX	1 (9%)	0 (0%)
Treatment response		
Very good partial response	3 (28%)	4 (80%)
Partial response	4 (36%)	1 (20%)
Stable disease	4 (36%)	0 (0%)
M-protein posttreatment reduction, %	58 ± 25	90 ± 9

*Mean ± standard deviation; LEN-DEX = lenalidomide and dexamethasone.

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$CD9^+$ EVs were present in the MM pellets (more than a 3-fold increase), with the most pronounced signal in the 20K pellets (6-fold) in contrast to the pooled control pellets (Fig 1D). $CD38^+$ EVs were present in MM 20K and 100K pellets, with the most distinct band present in the latter. Both 20K and 100K pooled pellets from the controls displayed faint CD38 bands, and 20K and 100K pellets of MM were 3 to 6-fold stronger, respectively. Immunoelectron microscopy showed that some EVs isolated from both control and MM pellets were $CD9^+$ and $CD38^+$ (Fig 1E).

Procoagulant analysis of EVs

The isolated EVs were resuspended in SPP and analysed for procoagulant activity. EVs in the 20K pellets from MM patients resulted in significantly increased peak height (>1.8-fold, $P < 0.0001$), velocity index (2.7-fold, $P < 0.0001$), and ETP (60%, $P < 0.0001$) compared to the baseline values of the SPP (Fig 2A). Lag time and time-to-peak were both shortened significantly ($P < 0.0001$) in the MM 20K pellets. In addition, the procoagulant phospholipid activity for EVs in the MM 20K pellets showed significantly reduced PPL clotting time ($P < 0.0001$), whereas the MM 100K together with the control 20K and 100K pellets revealed no changes in thrombin generation and PPL activity (Fig 2B). MVs in MM patients contained more TF activity ($P < 0.05$) than those of the controls (Fig 2C).

In general, a profound difference was observed between EVs in 20K and 100K pellets, with the former being the most procoagulant. The increased PPL activity of 20K EVs from MM patients correlated with the shortened lag time and time-to-peak from thrombin generation ($P < 0.01$ and $P < 0.05$, respectively). A clear tendency was present in the correlation between ETP and peak height. Furthermore, the elevated PPL activity of EVs from MM patients correlated to the mean size of the larger particles (i.e., the mean EV size, $P < 0.01$), as seen in the correlation matrix in Fig 2D. The individual correlations are displayed in supplemental information (S1 Fig).

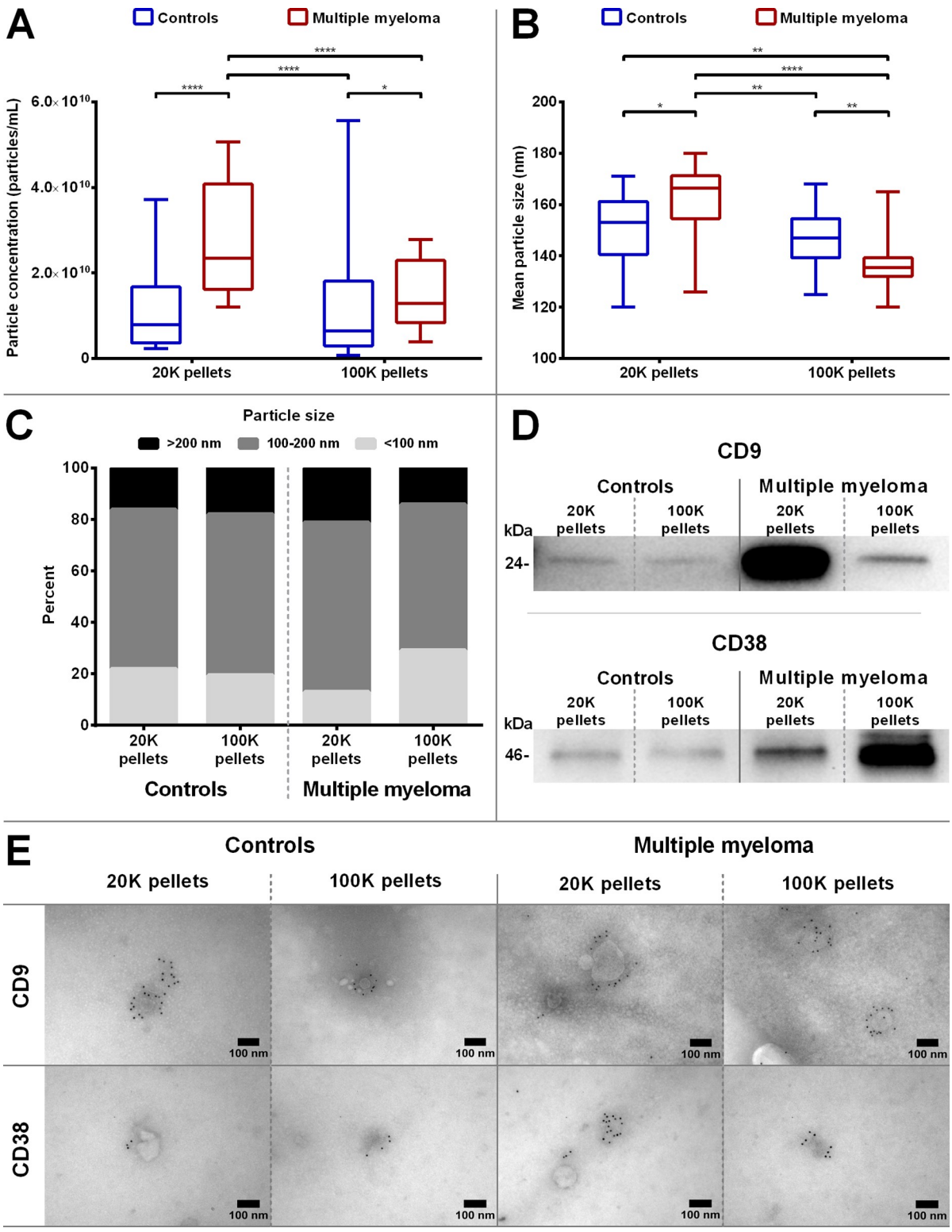

Fig 1. Analysis of EV characteristics. Nanoparticle tracking analysis was performed on each pellet (20K and 100K) for controls and MM patients to determine *A*) particle concentrations and *B*) mean particle size. The boxplots depict the median, the 25 and 75 percentiles and the whiskers min to max. $^{*}P<0.05$; $^{**}P<0.01$; $^{****}P<0.0001$. *C*) The distribution of particle sizes was grouped into three subgroups (<100 nm, 100–200 nm, and >200 nm). *D*) The pellet pools were analysed by Western blotting for EV-marker CD9 and ectoenzyme CD38. Equivalent volumes of each pellet pool (20K and 100K) from both controls and MM were loaded on the gels. As expected, tetraspanin CD9 was present

in all pellet types but enriched in MM pellets, especially in the 20K pellet pool. CD38 was found in all pellet pools, but most abundant in MM pellets (mostly in the 100K pellet pool). *E*) Immunoelectron microscopy images of gold immunolabelled $CD9^+$ and $CD38^+$ EVs in pellet pools of control and MM pellets (20K and 100K pellets). Images include scale bars determined with ImageJ software.

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Treatment of multiple myeloma–possible implications for EVs

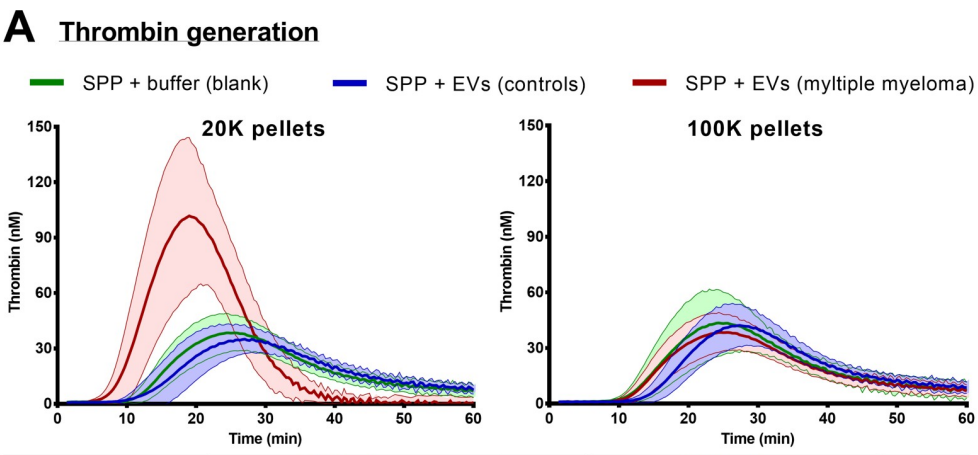
Analysis of procoagulant activity of EVs in 20K pellets on thrombin generation after the patients were treated with or without VCD mostly showed a reduced coagulation activity, but this was most notable in the patients receiving VCD (Fig 3A). The mean ETP was reduced by more than 42% ($P < 0.05$) after treatment in patients receiving VCD induction therapy, whereas the mean ETP for those receiving conventional treatment was reduced by 29% ($P < 0.01$). The mean peak height of the VCD induction group was reduced by more than 50% ($P < 0.05$) compared to a non-significant reduction of 30% in patients in the conventional treatment group. Moreover, in the VCD group, lag time was increased by 25% ($P < 0.05$) and time-to-peak by more than 37% ($P < 0.01$), and these two measures were almost unchanged for the patients treated conventionally. A similar tendency was observed in PPL activity, with a significant median increase in PPL clotting time of 15.9 seconds (65%, $P = 0.063$) in the VCD group after treatment compared to 7.8 seconds (33%, $P = 0.175$) for patients in the conventional treatment group. Fig 3B shows that there was a small decrease in particle quantity and the mean particle size after treatment in both groups but the differences were not significant. The distribution between small and large EVs were not changed much in the conventional treatment group whereas in the VCD group the fraction with the largest particles (>200 nm) diminished by almost 50% (Fig 3B). Graphic illustrations depicting the effect of treatment on each thrombin generation parameter and PPL clotting time for the two treatment regimens, including the individual patients, are listed in the supplemental information (S2 Fig).

Discussion

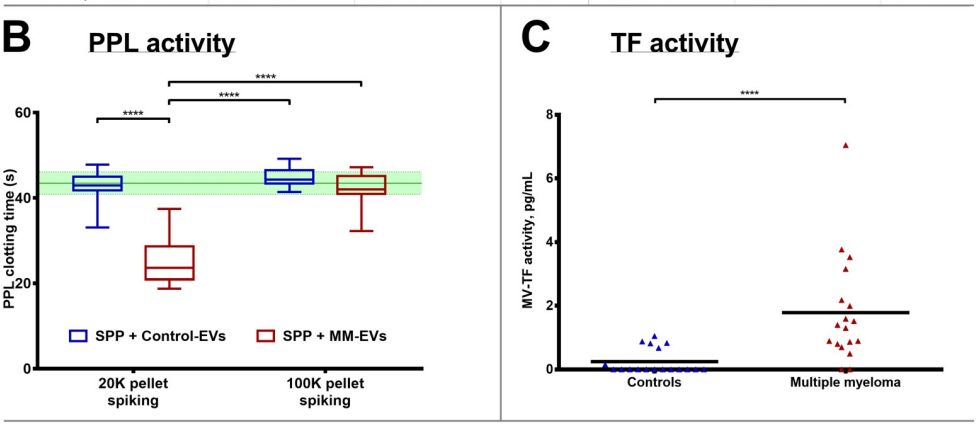
This setup to investigate procoagulant activity demonstrated a substantially higher thrombin generation and both TF and PPL activity in EVs in patients with MM than in healthy control subjects. This increase in procoagulant activity, however, diminished markedly in the patients receiving VCD induction therapy and to a lesser extent in those that received the conventional treatment. These results indicate that the procoagulant activity in MM can be ascribed to the larger EVs, which likely exert their procoagulant activity through PPL and TF. Furthermore, we demonstrated that some of the EVs possibly originate from the cancerous B cells.

EVs secreted by cancer cells have a function promoting their survival, angiogenesis, and immune escape, and therefore, circulating EVs may be present in higher quantities in cases of malignancy [25,26]. In the present study, we isolated EVs through differential ultracentrifugation and detected increased levels of EVs of various sizes in patients with MM (Fig 1A–1C). EVs in both patients and controls were positive for CD9 (Fig 1D and 1E), a marker frequently used for common EVs [27,28]. Most of the $CD9^+$ vesicles were discovered in the 20K pellet, which also contained the largest fraction of EV > 100 nm. Moreover, MM patients contained markedly more $CD38^+$ EVs than did the controls. The elevated expression of CD38 indicates that a substantial fraction of the EVs found in MM are linked to the malignancy, as EVs released by MM cells are known to be enriched in CD38 [29]. Contrary to the CD9 expression, our data suggest that the majority of CD38 are expressed by smaller EVs, since the 100K pellet contained fewer EVs and a larger fraction of EVs were <100 nm compared to the 20K pellet.

We aimed to investigate EVs in MM patients and their potential procoagulant effect on the haemostatic system, which has been demonstrated in other cancers [30,31]. To analyse the



	20K pellets		P	100K pellets		P
	Controls	Multiple myeloma		Controls	Multiple myeloma	
ETP, nM*min	1039 ± 234	1564 ± 375	<0.0001	1048 ± 173	1090 ± 233	0.526
Peak height, nM	42 ± 11	109 ± 40	<0.0001	44 ± 12	46 ± 17	0.474
Velocity index, nM/min	3.3 ± 1.2	11.3 ± 5.6	<0.0001	3.7 ± 1.4	3.9 ± 1.7	0.573
Lag time, min	15.3 ± 2.1	10.1 ± 1.7	<0.0001	15.6 ± 1.5	13.7 ± 2.0	0.0004
Time-to-peak, min	28.3 ± 2.7	20.3 ± 2.7	<0.0001	27.8 ± 1.9	26.3 ± 3.4	0.088



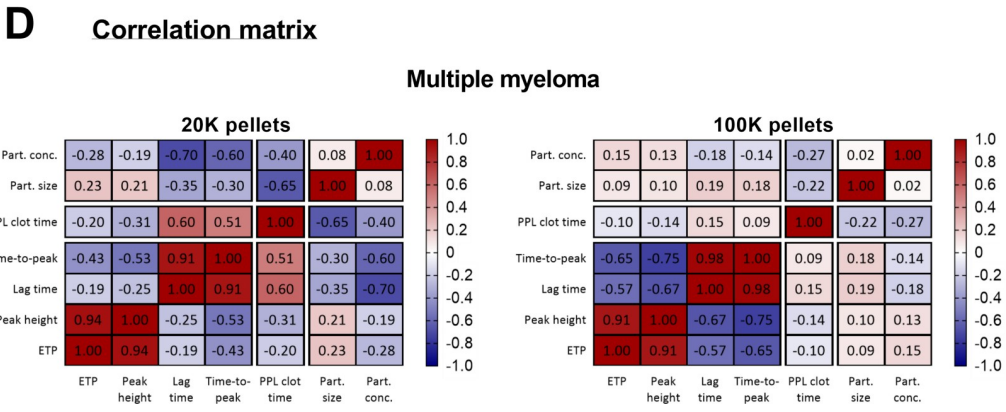


Fig 2. Analysis of procoagulant activity of EVs in SPP. *A*) Thrombograms (mean ± standard deviation) depicting thrombin generation when SPP is 'spiked' with isolated EVs from controls and MM patients. The results on individual thrombin generation parameters (ETP, peak height, velocity index, lag time, and time-to-peak) are listed in the table as the means ± standard deviation including *P*. *B*) PPL activity measured in clotting time differences in SPP 'spiked' with isolated EVs. The boxplots depict the median, the 25 and 75 percentiles and the whiskers min to max and the green line

and area represent the reference range (mean ± standard deviation) of the SPP. *C*) Analysis of MV-associated TF was performed on MV suspensions, and MM patients contained overall more TF than controls. *D*) Correlation matrix depicting the Pearson's r for correlations between coagulation and particle analyses for the MM pellets. $^{****}P<0.0001$.

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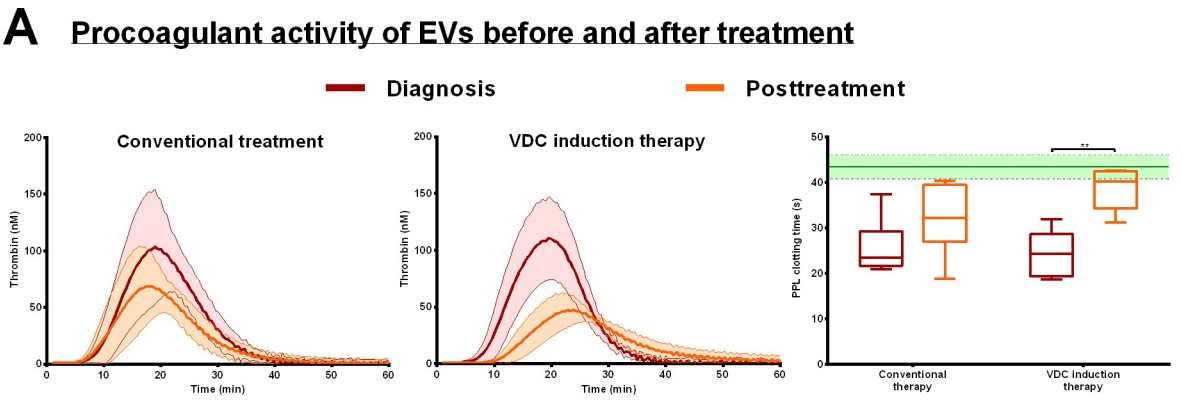
EV-mediated procoagulant activity, we used a model recently described [32], in which differential ultracentrifugation was applied on plasma samples. The CAT method, being a global



	Conventional therapy		*P*	VCD induction therapy		*P*
	Diagnosis	Posttreatment		Diagnosis	Posttreatment	
ETP, nM*min	1578 ± 380	1125 ± 189	0.008	1631 ± 395	939 ± 66	0.027
Peak height, nM	110 ± 45	78 ± 29	0.080	113 ± 35	50 ± 12	0.014
Velocity index, nM/min	11.6 ± 6.4	8.0 ± 3.9	0.206	11.2 ± 3.8	4.3 ± 1.3	0.016
Lag time, min	10.5 ± 1.6	9.8 ± 1.9	0.453	9.4 ± 1.1	12.8 ± 1.8	0.018
Time-to-peak, min	20.7 ± 2.7	20.1 ± 3.0	0.685	19.6 ± 1.2	24.5 ± 2.4	0.007
PPL clotting time, s	31.4 ± 19.9	32.2 ± 7.0	0.017	24.1 ± 5.2	38.8 ± 4.7	0.005

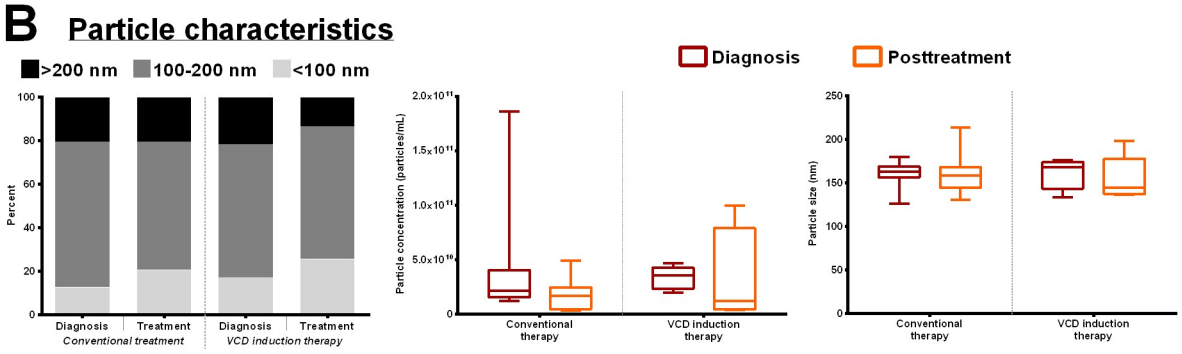


Fig 3. The procoagulant activity of EVs from 20K pellets of MM patients at diagnosis and after the first-line treatment regimen. *A*) (*Left*, *middle*) Thrombograms (mean ± standard deviation) depicting the outcome of EV-mediated thrombin generation before and after conventional therapy (HDCT ineligible patients) or a VCD induction therapy (HDCT eligible patients). The results on individual thrombin generation parameters are listed in the table as the means ± standard deviation including *P*. (*Right*) The effect of treatment on PPL activity of EVs 'spiked' into SPP, $^{**}P<0.01$. The green line and area represent the reference range (mean ± SD) of the SPP. *B*) Size distribution (*left*), particle concentration (*middle*), and mean size (*left*) before and after first-line treatment as measured by the means of nanoparticle tracking analysis. All boxplots depict the median, the 25 and 75 percentiles and the whiskers min to max.

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coagulation test, provides information of the entire system including TF and PPL activity [33–36]. Presence of TF will primarily shorten lag time and time-to-peak, whereas a high PPL activity will increase ETP and peak height [35]. The method has been used to establish thrombin generation as a predictive marker for VTE in MM patients [37,38]. The STA-Procoag-PPL kit specifically measures the PPL activity that may be exerted by EVs. Other studies have demonstrated the effect of PPL-exposing EVs exerting procoagulant activity in different pathological conditions, such as cancer [39–41]. Finally, we performed a FVIIa dependent FXa generation assay on the pellets to detect TF activity. Several modifications of this technique has been used in many other cases to detect TF activity of the larger EVs in relation to VTE occurrence [15,42,43]. This test has also been used to detect elevated TF activity in patients with MM [16,44].

In the present study, we found that patients with MM do contain procoagulant EVs that increase the amount of thrombin generated, as demonstrated by the CAT method. Furthermore, both TF and PPL activity were also increased. The procoagulant EVs are probably the larger EVs since the 20K pellets profoundly reduced both lag time and time-to-peak (Fig 2A), indicating that some EVs in MM patients carry TF embedded in their membrane, which is in accordance with the specific measurements of increased TF activity compared to almost none in the control group (Fig 2C). Furthermore, PPL activity in MM patients is higher in the 20K pellets (Fig 2B), in accordance with increased peak height and velocity index (Fig 2A). Additionally, increased PPL activity in larger EVs correlated with shorter lag time and time-to-peak in the CAT analysis, thus suggesting an association between PPL and TF. Peak height and ETP also showed a similar trend of PPL dependency with higher peak height and ETP with more PPL activity. Both the quantity and size of the large EVs are likely of importance for the procoagulant potency of the EVs, but the overall trend is that the 20K EVs are definitely more procoagulant compared to EVs in the 100K pellets. Since the CD38 positive EVs (which probably are derived from cancer cells) were mainly present in the 100K pellet the procoagulant effect of EVs do not seem to be closely associated to this fraction, but we cannot from this investigation resolve whether the procoagulant EVs are derived from cancer cells or other cells.

The procoagulant activity of EVs from the MM patients diminished after treatment; however, patients treated with induction therapy had the most distinct effect (Fig 3A), eliminating the majority of the procoagulant activity of the EVs. This result may be due to reduction of the amount of particles >200 nm, the supposed MVs, which was reduced considerably after treatment compared to those being treated conventionally (Fig 3B). An important feature to mention is that the patients in the VCD induction therapy group respond better overall to their treatment (Table 2), which may thus impact the reduced procoagulant activity of EVs we observe. The reduction in both lag time and time-to-peak in the VCD induction therapy group indicates reduced TF activity, supported by others reporting decreasing TF activity in MM patients receiving induction chemotherapy [16]. In contrast, Leiba et al [37] reported no difference in thrombin generation in plasma from MM patients after HDCT.

The study is limited by the small sample size, especially after being divided into two treatment groups depending whether or not the patients were eligible for HDCT. Nevertheless, the differences between the MM patents and the controls were quite large and significant. The samples were collected over a period of one and a half year, which may have a minor impact on EV quantity and size distribution, however, the sample collection was uniformly conducted between patients and controls. Furthermore, no VTE events occurred in any group; therefore, we are unable to link procoagulant EVs in MM to an increased VTE risk. There was a minor difference in the mean age between controls and patients, partly because it was difficult to recruit elderly controls. However, the difference is minimal and probably also of minor importance.

In conclusion, we found that patients newly diagnosed with MM contain more and larger EVs in their plasma and that these EVs exert procoagulant activity, resulting in an increased thrombin generation and TF and PPL activity. This EV-mediated procoagulant effect diminishes after the initiation of treatment, especially in patients receiving VCD induction therapy. This finding may explain, at least in part, why MM patients have an increased risk of VTE; however, this warrants confirmation in larger cohorts where the effect of administration of a more thrombogenic anti-myeloma treatment also could be addressed.

Supporting information

S1 Fig. Correlations between coagulation assays and nanoparticle tracking analysis performed on EVs from patients with MM. P-values or non-significant (NS) correlations are depicted in the corresponding colour for 20K or 100K pellets.
(DOCX)

S2 Fig. The effect of treatment on procoagulant EVs in 20K pellets from MM patients eligible for HDCT (n = 11) and those that were not (n = 5). Those eligible received VCD induction therapy, whereas the remainder received conventional therapy. The procoagulant activity was measured by means of thrombin generation represented as ETP, peak height, velocity index, lag time, and time-to-peak. PPL activity was measured before and after treatment as PPL clotting time. The red dots and error bars represent the means ± standard deviation, and the black lines show the development from diagnosis to posttreatment of the individual patients. $^{*}P<0.05$; $^{**}P<0.01$.
(DOCX)

S1 Table. Characteristics of the MM patients at diagnosis and posttreatment in groups with or without HDCT. Of the 16 MM patients, five were eligible for HDCT and received a VCD induction therapy, whereas the remaining 11 received were ineligible for HDCT and thus received conventional therapy. Data are represented as the means ± standard deviation. INR = international normalized ratio; APTT = activated partial thromboplastin time; GFR = glomerular filtration rate; CRP = C-reactive protein; ALAT = alanine transaminase.
(DOCX)

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JAMA | Special Communication

Clinical Practice Guidelines From the AABB
Red Blood Cell Transfusion Thresholds and Storage

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IMPORTANCE More than 100 million units of blood are collected worldwide each year, yet the indication for red blood cell (RBC) transfusion and the optimal length of RBC storage prior to transfusion are uncertain.

OBJECTIVE To provide recommendations for the target hemoglobin level for RBC transfusion among hospitalized adult patients who are hemodynamically stable and the length of time RBCs should be stored prior to transfusion.

EVIDENCE REVIEW Reference librarians conducted a literature search for randomized clinical trials (RCTs) evaluating hemoglobin thresholds for RBC transfusion (1950-May 2016) and RBC storage duration (1948-May 2016) without language restrictions. The results were summarized using the Grading of Recommendations Assessment, Development and Evaluation method. For RBC transfusion thresholds, 31 RCTs included 12 587 participants and compared restrictive thresholds (transfusion not indicated until the hemoglobin level is 7-8 g/dL) with liberal thresholds (transfusion not indicated until the hemoglobin level is 9-10 g/dL). The summary estimates across trials demonstrated that restrictive RBC transfusion thresholds were not associated with higher rates of adverse clinical outcomes, including 30-day mortality, myocardial infarction, cerebrovascular accident, rebleeding, pneumonia, or thromboembolism. For RBC storage duration, 13 RCTs included 5515 participants randomly allocated to receive fresher blood or standard-issue blood. These RCTs demonstrated that fresher blood did not improve clinical outcomes.

FINDINGS It is good practice to consider the hemoglobin level, the overall clinical context, patient preferences, and alternative therapies when making transfusion decisions regarding an individual patient. Recommendation 1: a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 7 g/dL is recommended for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than when the hemoglobin level is 10 g/dL (strong recommendation, moderate quality evidence). A restrictive RBC transfusion threshold of 8 g/dL is recommended for patients undergoing orthopedic surgery, cardiac surgery, and those with preexisting cardiovascular disease (strong recommendation, moderate quality evidence). The restrictive transfusion threshold of 7 g/dL is likely comparable with 8 g/dL, but RCT evidence is not available for all patient categories. These recommendations do not apply to patients with acute coronary syndrome, severe thrombocytopenia (patients treated for hematological or oncological reasons who are at risk of bleeding), and chronic transfusion-dependent anemia (not recommended due to insufficient evidence). Recommendation 2: patients, including neonates, should receive RBC units selected at any point within their licensed dating period (standard issue) rather than limiting patients to transfusion of only fresh (storage length: <10 days) RBC units (strong recommendation, moderate quality evidence).

CONCLUSIONS AND RELEVANCE Research in RBC transfusion medicine has significantly advanced the science in recent years and provides high-quality evidence to inform guidelines. A restrictive transfusion threshold is safe in most clinical settings and the current blood banking practices of using standard-issue blood should be continued.

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More than 100 million units of blood are collected worldwide each year,[1] and approximately 13 million red blood cell (RBC) units are collected in the United States.[2] Despite previously published guidelines,[3-7] there remains substantial variation in the practice of transfusing patients. Physicians often use hemoglobin level to decide when to transfuse,[8] although some guidelines[9,10] maintain that transfusion should be given for symptoms of anemia and not solely based on hemoglobin level.

Transfusion practices for RBCs should be designed to optimize clinical outcomes and to avoid transfusions that are not clinically indicated. Despite the risk of transfusion-transmitted infections and noninfectious adverse events, such as transfusion-related acute lung injury and transfusion-associated circulatory overload, RBC transfusion is relatively safe (**Table 1**). However, transfusing RBCs unnecessarily exposes patients to increased risk and costs without benefit. Consequently, transfusing RBCs at higher hemoglobin thresholds (ie, a liberal transfusion strategy) should be used only if a liberal strategy will improve the outcomes that are important to patients.

In addition to transfusion reactions and infectious risks associated with RBC transfusions, it has been suggested that an RBC storage lesion may result in adverse outcomes. Units of RBCs can be stored up to 42 days. The RBCs stored for longer periods have decreased ability to deliver oxygen due to decreased levels of 2,3-diphsophoglycerate, decreased nitric oxide metabolism, alterations of the RBC membrane leading to increased rigidity, and increased RBC endothelial adherence.[19,20] In addition, the storage medium may contain increased levels of free hemoglobin, iron, potassium, and inflammatory mediators that may lead to deleterious consequences.[19,21] Furthermore, observational studies[22-24] suggested that RBCs stored longer than 2 weeks may be associated with increased morbidity and mortality; however, the data were conflicting.[25-27] These considerations raise the possibility that transfusion medicine services should preferentially provide fresher RBCs for transfusion compared with standard issue RBCs.

In 2012, the AABB (formerly known as the American Association of Blood Banks) published RBC transfusion guidelines based on 19 randomized clinical trials (RCTs) that included 6264 patients.[28] Many of those RCTs were small (median, 120 patients; range, 22 to 2016 patients) and had high risk of bias. During the past 4 years, the number of patients enrolled in RBC transfusion RCTs has more than doubled, and many studies have incorporated methods to minimize the risk of bias and enrolled populations of patients receiving frequent blood transfusions. Therefore, it is timely to reexamine the evidence and provide updated guidance to the medical community.

Thirteen RCTs have evaluated the effect of RBC storage duration of transfused RBCs on patient outcomes (7 since 2012).[29-41] However, there is currently no formal guidance on the optimal length of RBC storage prior to transfusion.

Methods

These guidelines provide recommendations for (1) the clinicians caring for hospitalized adult patients who are hemodynamically stable and candidates for RBC transfusions, and (2) the transfusion medicine services responsible for storing and providing RBCs. The AABB commissioned and funded the development of these guidelines through the AABB clinical transfusion medicine committee. In addition, the board of directors charged the committee to recruit experts with an interest in RBC transfusion from other professional organizations.

Guideline Development Process

A committee of experts was assembled. Most of the experts were current or former members of the AABB clinical transfusion medicine committee (J.L.C., N.M.H., B.J.G., C.S.C., M.K.F., T.G., L.M.K., G.R., J.D.R., and A.A.R.T.). There also were experts appointed by professional organizations as subject matter experts (American Association for the Surgery of Trauma: J.B.H.; Society of Critical Care Medicine: L.J.K.; American College of Cardiology: S.V.R.; American Society of Anesthesiologists: A.S.; and American Society of Hematology: T.G.). The committee also included a patient representative (N.P.). Eight of the physicians were pathologists or hematologists (most with subspecialty expertise in transfusion medicine). The other physicians included an anesthesiologist, cardiologist, internist, critical care medicine physician, trauma or acute care surgeon, and a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist (G.G.).

The committee members had no substantial conflicts of interest (as defined by the AABB conflict of interest policy[42]). Pursuant to the conflict of interest policy, individual members were required to disclose actual and apparent financial, professional, or personal conflicts. Two members were authors on trials included in the systematic review on transfusion thresholds (J.L.C. and S.V.R.), 1 authored a systematic review of transfusion thresholds (J.L.C.), 2 were authors on trials of RBC storage duration (J.L.C. and N.M.H.), and 2 were authors on systematic reviews of RBC storage duration (G.G. and N.M.H.). One member (J.L.C.) was excused when voting on transfusion thresholds for patients with acute myocardial infarction due to his role as principal investigator on a pending grant proposal.

Evidence Review and Grading

Systematic Review

The guidelines were developed based on separately published updated systematic reviews of the literature on transfusion thresholds[43] and RBC storage duration.[44] We performed literature searches of RCTs evaluating transfusion thresholds from 1950 through May 2016 and the storage duration of transfused RBCs from 1948 through May 2016.[43] The systematic review included RCTs in which the transfusion groups were assigned on the basis of a clear transfusion trigger or threshold, which was described as hemoglobin or hematocrit level that had to be reached before a RBC transfusion was administered. Trials of patients treated surgically, medically, or both were included as well as those involving adults or children (but not neonates). For the RBC storage systematic review, the included RCTs enrolled patients admitted to the hospital requiring a RBC transfusion and compared fresher vs standard issue RBC transfusions.[44] The term *standard issue* used in these guidelines is defined as units selected at any point within their licensed dating period, but only a small proportion of RBC units transfused were stored for 36 days to 42 days.

The primary outcome in both systematic reviews was mortality (30-day mortality for transfusion thresholds and a composite of the longest follow-up provided in each trial, including 30 days, 90 days, and in-hospital mortality for RBC storage duration). Secondary outcomes for transfusion thresholds included morbidity (eg, nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, renal failure, infection, rebleeding, or mental confusion); the proportion of patients transfused with allogeneic RBCs, autologous

Table 1. Approximate Risk Per-Unit Transfusion of Red Blood Cells (RBCs)

Adverse Event	Approximate Risk Per-Unit Transfusion of RBCs
Febrile reaction[11]	1:60[a]
Transfusion-associated circulatory overload[12,13]	1:100[b]
Allergic reaction[14]	1:250
Transfusion-related acute lung injury[15]	1:12 000
Hepatitis C virus infection[16]	1:1 149 000
Hepatitis B virus infection[17]	1:1 208 000 to 1:843 000[c]
Human immunodeficiency virus infection[16]	1:1 467 000
Fatal hemolysis[18]	1:1 972 000

[a] Estimated to be 1:91 with prestorage leukoreduction and 1:46 with poststorage leukoreduction.

[b] Indicates the estimated risk per recipient rather than unit.

[c] The estimate is variable depending on the length of the infectious period.

RBCs, or both; hemoglobin levels (the timing of measurement varied among trials); and the number of RBC units transfused. For RBC storage, the secondary outcomes included adverse events and nosocomial infection. The systematic reviews only included RCTs because observational studies evaluating the effect of transfusion are especially prone to confounding by indication and are likely to yield biased results.[45,46]

Each RCT was assessed for the risk of bias for sequence generation, allocation concealment, blinding, and incomplete outcome data using the methods recommended by Cochrane (for transfusion threshold review)[47] and a modified risk of bias assessment tool (for storage duration).[48] Statistical heterogeneity was assessed using both I^2 and χ^2 tests.[47] Existing criteria provided guidance for making inferences regarding subgroup effects.[49] All analyses were performed using Review Manager (RevMan) version 5.2 (Cochrane Collaboration). The relative risks (RRs) and the corresponding 95% CIs were calculated for each trial using random-effects models.[50]

Rating Quality of Evidence

The GRADE method[51,52] was used to develop these guidelines (eAppendix in the Supplement). Evidence profiles were prepared that displayed data in terms of benefits and harms for the most important outcomes. The profiles also were the basis for decisions regarding the rating down of quality for risk of bias, lack of consistency, lack of directness, lack of precision, and possible publication bias. The overall quality of evidence for each outcome was assessed for the systematic review on transfusion thresholds (J.L.C. and Simon Stanworth, MD, DPhil) and for the systematic review on RBC storage (Paul Alexander, PhD, G.G., and N.M.H.). The committee reviewed these ratings and made its final quality ratings and determined the strength of the recommendations during an in-person meeting.

Committee Values and Preferences

With respect to transfusion thresholds, the committee made its recommendations based on the assumption that patients would highly value avoiding the rare but potentially serious adverse effects associated with RBC transfusion. Moreover, the committee placed value on resource conservation related to RBC transfusion. Therefore, when the evidence suggested no harms from withholding transfusion, the committee was prepared to make a strong recommendation for a restrictive threshold. When evidence regarding harms was uncertain, the committee elected not to make a recommendation.

With respect to RBC storage duration, the committee placed a high value on feasibility and resource use considerations for RBC transfusion. Therefore, if evidence suggested no harms in using standard-issue blood, the committee was prepared to make a strong recommendation for continuing with standard practice. The recommendations were voted and then the first (J.L.C.) and last (A.A.R.T.) authors prepared the draft guideline document, which was modified and approved by all committee members and the AABB clinical transfusion medicine committee. Subsequently, the AABB board of directors reviewed and approved the guidelines.

Good Clinical Practice Statement

When deciding to transfuse an individual patient, it is good practice to consider not only the hemoglobin level, but the overall clinical context and alternative therapies to transfusion. Variables to take into consideration include the rate of decline in hemoglobin level, intravascular volume status, shortness of breath, exercise tolerance, lightheadedness, chest pain thought to be cardiac in origin, hypotension or tachycardia unresponsive to fluid challenge, and patient preferences. This practice guideline is not intended as an absolute standard and will not apply to all individual transfusion decisions.

Recommendations

First Recommendation

The AABB recommends a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than a liberal threshold when the hemoglobin level is 10 g/dL (strong recommendation, moderate quality evidence). For patients undergoing orthopedic surgery or cardiac surgery and those with preexisting cardiovascular disease, the AABB recommends a restrictive RBC transfusion threshold (hemoglobin level of 8 g/dL; strong recommendation, moderate quality evidence). The restrictive hemoglobin transfusion threshold of 7 g/dL is likely comparable with 8 g/dL, but RCT evidence is not available for all patient categories. These recommendations apply to all but the following conditions for which the evidence is insufficient for any recommendation: acute coronary syndrome, severe thrombocytopenia (patients treated for hematological or oncological disorders who at risk of bleeding), and chronic transfusion-dependent anemia.

Evidence Summary

A total of 12 587 patients were enrolled in 31 eligible trials.[53-86] Ten trials were conducted in patients undergoing orthopedic surgery, 6 trials included patients treated in critical care units, 5 trials

were conducted in patients undergoing cardiac surgery, 5 trials were conducted in patients with gastrointestinal bleeding, 2 trials included patients with acute coronary syndrome, 2 trials included patients with leukemia or hematological malignancies, and 1 trial was conducted in patients undergoing vascular surgery. The restrictive RBC transfusion protocols commonly used a hemoglobin transfusion threshold of 7 g/dL or 8 g/dL, and liberal protocols used a hemoglobin transfusion threshold of 9 g/dL to 10 g/dL.

The association of restrictive transfusion protocols on 7 outcomes reported in the trials appears in **Table 2**. The primary outcome of 30-day mortality was reported in 23 of 30 RCTs.[53-56,58,60,61,63,64,68-72,74-76,78,79,84-87] In the restrictive transfusion group, the absolute difference in 30-day mortality was 3 fewer deaths per 1000 patients (95% CI, 15 fewer deaths to 18 more deaths per 1000). The quality assessment found no serious risk of bias, inconsistency, indirectness, or publication bias. The overall quality of evidence was moderate for 30-day mortality because the imprecision was judged as serious in that there could be up to 18 more deaths per 1000 in the restrictive transfusion group.

For all other outcomes evaluated, there was no evidence to suggest that patients were harmed by restrictive transfusion protocols, although the quality of the evidence was low for the outcomes of congestive heart failure and rebleeding. In addition, liberal transfusion was not found to be associated with an increased risk of infection as had been previously found in a prior meta-analysis.[88] There was also no difference in the other assessed outcomes (ability to walk, multiple measures of function, fatigue, and length of hospital stay) in the systematic review.[43]

The 30-day mortality for the trials that used a restrictive hemoglobin transfusion threshold of less than 8 g/dL to 9 g/dL (n = 4772) was compared with those using a restrictive hemoglobin transfusion threshold of less than 7 g/dL (n = 5765). The RRs were similar, and there is no evidence that these 2 threshold groups are statistically different (χ^2_1 = 0.34, P = .56, I^2 = 0%; **Figure 1**). However, the clinical settings were different. Most of the trials with the restrictive hemoglobin transfusion threshold of less than 7 g/dL were performed in critical care settings, whereas the clinical settings were more varied with the hemoglobin transfusion threshold of less than 8 g/dL to 9 g/dL.

The subgroup analyses for 30-day mortality by clinical setting[43] did not demonstrate statistically significant evidence to support differences in the subgroups; however, 30-day mortality was significantly lower with the restrictive transfusion threshold than the liberal transfusion threshold in patients with gastrointestinal bleeding (RR, 0.65; 95% CI, 0.43-0.97). Two small trials included 154 patients with acute coronary syndrome. There were 9 deaths with the restrictive transfusion threshold and 2 deaths with the liberal transfusion threshold (RR, 3.88 [95% CI, 0.83-18.13]; P = .08, I^2 = 67.6% for the comparison of these 2 small trials). The results for myocardial infarctions from these 2 trials (n = 154 patients) were then compared with the other 29 trials in all other clinical settings (P = .08, I^2 = 67.6%).

Rationale for Recommendation

The AABB recommendation to use a hemoglobin transfusion threshold of 7 g/dL to 8 g/dL for most hospitalized adult patients who are hemodynamically stable rather than a hemoglobin transfusion threshold of 9 g/dL to 10 g/dL is based on consistent evidence from multiple large RCTs performed in various clinical settings in more than 12 000 patients. With the possible exception of patients with acute myocardial infarction, no data suggest that a restrictive transfusion threshold is harmful compared with a liberal transfusion threshold. A restrictive transfusion threshold approach is associated with reductions in blood use, associated expense, and uncommon but potentially serious adverse events.

The AABB recommends using a restrictive hemoglobin transfusion threshold of 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, but a hemoglobin transfusion threshold of 8 g/dL for patients undergoing orthopedic or cardiac surgery and for those with underlying cardiovascular disease. The reason for the different thresholds is that the RCTs performed in the later groups of patients used a hemoglobin transfusion threshold of 8 g/dL and not a threshold of 7 g/dL. The committee suspects that those patients might tolerate a hemoglobin transfusion threshold of 7 g/dL because the trials using a restrictive threshold of 7 g/dL were performed in critically ill patients compared with other trials with a threshold of 8 g/dL and less critically ill patients. However, this has not been assessed in RCTs and it is possible that functional recovery (in patients undergoing orthopedic surgery) or myocardial infarction rates (in patients undergoing cardiac surgery or with chronic cardiovascular disease) could be adversely affected by a hemoglobin transfusion threshold of 7 g/dL or higher even if mortality is not. An ongoing large trial among patients undergoing cardiac surgery is using a restrictive hemoglobin transfusion threshold of 7.5 g/dL and may provide a definitive answer.[89]

As in the AABB's previous guideline,[28] the committee chose not to recommend for or against a liberal or restrictive transfusion threshold in patients with acute coronary syndrome. There are 2 trials with a total of 154 patients that showed a trend toward a lower risk of death when the liberal transfusion threshold was used.[56,61] This finding is consistent with experimental studies in canines,[90-92] in an observational study of patients undergoing surgery with underlying cardiovascular disease,[93] and in the prespecified a priori hypothesis and direction in the 2 small trials.[56,61] However, small RCTs are known to be unreliable; in fact, the size of the effect observed was larger than anticipated, but the results were not statistically significant.

The AABB also did not make a recommendation for a transfusion threshold in patients treated for hematological or oncological disorders and for those with severe thrombocytopenia who are at risk of bleeding or for those with chronic transfusion–dependent anemia. Red blood cells have been shown to increase platelet responsiveness,[94] especially at lower platelet counts.[95] Data from animal experiments[96] and normal volunteers suggest that anemia increases the bleeding time, even with as little as a 15% decrease in hemoglobin level.[97] For this reason, some clinicians advocate for higher hemoglobin thresholds in patients with severe thrombocytopenia who are at increased risk of bleeding. Except for 2 pilot studies,[86,98] RCTs comparing RBC transfusion thresholds with bleeding as an end point have yet to be performed. Similarly, there have not been RCTs performed in patients with chronic transfusion–dependent anemia. The risks and benefits (ie, improved function, less fatigue) are different for patients receiving chronic transfusions outside the hospital than hospitalized patients in acute care settings.

Second Recommendation

The AABB recommends that patients, including neonates, should receive RBC units selected at any point within their licensed dating

Table 2. Evidence for the Association Between Hemoglobin Transfusion Thresholds and Clinical Outcomes in Hospitalized Adult Patients Who Are Hemodynamically Stable and in Need of a Red Blood Cell Transfusion[a]

	Quality Assessment[b]					No./Total (%) of Patients by Hemoglobin Transfusion Threshold		Effect		
No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Restrictive (7-8 g/dL)	Liberal (9-10 g/dL)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Quality of RCTs
Primary Outcome: 30-d Mortality										
23	Not serious	Not serious	Not serious	Serious[c]	None detected	470/5221 (9.0)	497/5316 (9.3)	0.97 (0.81-1.16)	3 fewer deaths per 1000 (15 fewer deaths to 18 more per 1000)	Moderate
Secondary Outcomes										
Myocardial Infarction (MI)										
16	Not serious	Not serious	Not serious	Not serious	None detected	78/4156 (1.9)	69/4147 (1.7)	1.08 (0.74-1.60)	1 more MI per 1000 (4 fewer MIs to 10 more per 1000)	High
Pulmonary Edema (PE) or Congestive Heart Failure (CHF)										
12	Serious[d]	Not serious	Not serious	Serious[e]	None detected	87/3132 (2.8)	114/3125 (3.6)	0.78 (0.45-1.35)	8 fewer PEs or CHFs per 1000 (13 more PEs or CHFs to 20 fewer per 1000)	Low
Stroke or Cerebrovascular Accident (CA)										
13	Not serious	Not serious	Not serious	Not serious	None detected	49/3675 (1.3)	62/3668 (1.7)	0.78 (0.53-1.14)	4 fewer strokes or CAs per 1000 (2 more strokes or CAs to 8 fewer per 1000)	High
Rebleeding										
6	Not serious	Serious[f]	Not serious	Serious[g]	None detected	215/1489 (14.4)	264/1619 (16.3)	0.75 (0.51-1.10)	41 fewer events per 1000 (16 more events to 80 fewer per 1000)	Low
Pneumonia										
14	Not serious	Not serious	Not serious	Not serious	None detected	239/3140 (7.6)	256/3137 (8.2)	0.94 (0.80-1.11)	5 fewer cases of pneumonia per 1000 (9 more cases to 16 fewer per 1000)	High
Thromboembolism										
10	Not serious	Not serious	Not serious	Not serious	None detected	16/2010 (0.8)	21/2009 (1.0)	0.77 (0.41-1.45)	2 fewer thromboembolisms per 1000 (5 more thromboembolisms to 6 fewer per 1000)	High

Abbreviation: RCT, randomized clinical trial.

[a] This Table addresses the question of whether hospitalized adult patients who are hemodynamically stable should receive a restrictive transfusion approach with a hemoglobin threshold of 7 g/dL to 8 g/dL rather than a liberal transfusion approach with a hemoglobin threshold of 9 g/dL to 10 g/dL.

[b] Evaluates the risk of bias, inconsistency based on the heterogeneity among trials, indirectness based on the generalizability of the results, imprecision based on the width of the 95% CIs, and publication bias based on some trials not being published. The Grading of Recommendations Assessment, Development and Evaluation method (eAppendix in the Supplement) was used.

[c] Could be 1 more death to up to 18 more deaths per 1000 in the restrictive transfusion group.

[d] The blinding of participants and personnel was impossible. The blinding of outcome assessment was inconsistent between trials.

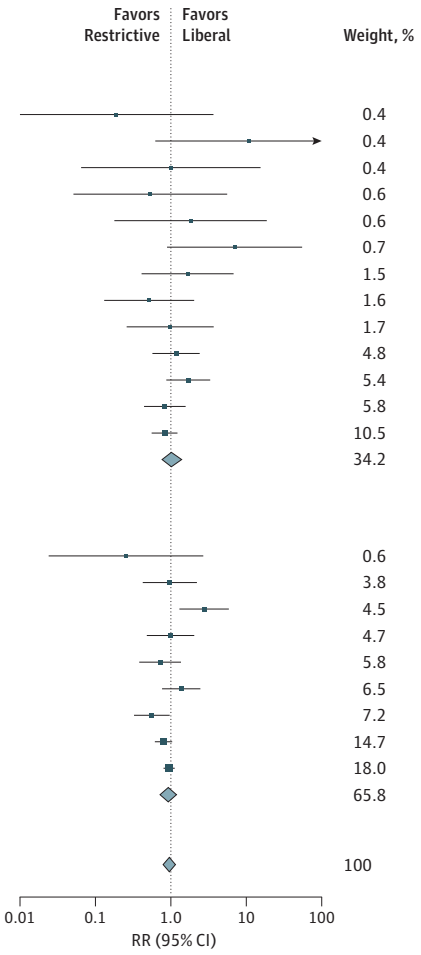
[e] Studies had moderately wide 95% CIs.

[f] I^2 = 58% and P = .04.

[g] Could be 1 more event to up to 16 more events per 1000 in patients in the restrictive transfusion group.

Figure 1. Comparison of 30-Day Mortality Using Restrictive vs Liberal Hemoglobin Transfusion Thresholds in Randomized Clinical Trials

Source	Restrictive Transfusion Threshold: No. of Deaths	Restrictive Transfusion Threshold: Total No.	Liberal Transfusion Threshold: No. of Deaths	Liberal Transfusion Threshold: Total No.	RR (95% CI)	Weight, %
Restrictive threshold, hemoglobin <8 to 9 g/dL						
Lotke et al,[75] 1999	0	62	0	65	Not estimable	
Blair et al,[53] 1986	0	26	2	24	0.19 (0.01-3.67)	0.4
Foss et al,[63] 2009	5	60	0	60	11.00 (0.62-194.63)	0.4
Carson et al,[58] 1998	1	42	1	42	1.00 (0.06-15.47)	0.4
Webert et al,[86] 2008	1	29	2	31	0.53 (0.05-5.58)	0.6
Cooper et al,[61] 2011	2	23	1	21	1.83 (0.18-18.70)	0.6
Carson et al,[56] 2013	7	55	1	55	7.00 (0.89-55.01)	0.7
Parker,[78] 2013	5	100	3	100	1.67 (0.41-6.79)	1.5
Bracey et al,[54] 1999	3	215	6	222	0.52 (0.13-2.04)	1.6
Bush et al,[55] 1997	4	50	4	49	0.98 (0.26-3.70)	1.7
Hajjar et al,[68] 2010	15	249	13	253	1.17 (0.57-2.41)	4.8
Gregersen et al,[64] 2015	21	144	12	140	1.70 (0.87-3.32)	5.4
Jairath et al,[72] 2015	14	257	25	382	0.83 (0.44-1.57)	5.8
Carson et al,[60] 2011	43	1009	52	1007	0.83 (0.56-1.22)	10.5
Subtotal	121	2321	122	2451	1.05 (0.78-1.40)	34.2
Heterogeneity: $\tau^2 = 0.02$; $\chi^2_{12} = 13.14$; $P = .36$; $I^2 = 9\%$						
Tests for overall effect: z score = 0.31; $P = .76$						
Restrictive threshold, hemoglobin <7 g/dL						
DeZern et al,[87] 2016	1	59	2	30	0.25 (0.02-2.69)	0.6
Hébert et al,[70] 1995	8	33	9	36	0.97 (0.42-2.22)	3.8
de Almeida et al,[79] 2015	23	101	8	97	2.76 (1.30-5.87)	4.5
Lacroix et al,[74] 2007	14	320	14	317	0.99 (0.48-2.04)	4.7
Walsh et al,[85] 2013	12	51	16	49	0.72 (0.38-1.36)	5.8
Murphy et al,[76] 2015	26	1000	19	1003	1.37 (0.76-2.46)	6.5
Villanueva et al,[84] 2013	19	416	34	417	0.56 (0.32-0.97)	7.2
Hébert et al,[69] 1999	78	418	98	420	0.80 (0.61-1.04)	14.7
Holst et al,[71] 2014	168	502	175	496	0.95 (0.80-1.13)	18.0
Subtotal	349	2900	375	2865	0.94 (0.74-1.19)	65.8
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_8 = 16.09$; $P = .04$; $I^2 = 50\%$						
Tests for overall effect: z score = 0.53; $P = .59$						
Overall	470	5221	497	5316	0.97 (0.81-1.16)	100
Heterogeneity: $\tau^2 = 0.04$; $\chi^2_{21} = 29.75$; $P = .10$; $I^2 = 29\%$						
Tests for overall effect: z score = 0.29; $P = .77$						
Tests for subgroup differences: $\chi^2_1 = 0.34$; $P = .56$; $I^2 = 0\%$						



The size of the data markers indicates the weight of the trial; RR, relative risk. Trials published after 2012 have been published since the prior AABB transfusion guidelines.

period (standard issue) rather than limiting patients to transfusion of only fresh (storage length: <10 days) RBC units (strong recommendation, moderate quality evidence).

Evidence Summary

There were 13 trials meeting the inclusion criteria.[29-41] The trials included neonates and infants with very low birth weights and children and adults; most patients had an acute critical illness or surgical hemorrhage. The trials that were conducted in North America, South America, Europe, Australia, and Africa compared fresher blood with standard-issue blood; however, the storage duration of the standard-issue blood varied between the trials. In the 2 primary trials involving neonates, the mean storage durations at the time of transfusion were 1.6 days and 5.1 days for fresher RBCs compared with 9.0 days and 14.1 days for standard issue RBCs.[31,35] The storage duration of the transfused RBCs in the trials of adults ranged from a median of 4 days (mean, 12.1 days) for fresher RBCs compared with a median of 19 days (mean, 28 days) for standard issue RBCs.

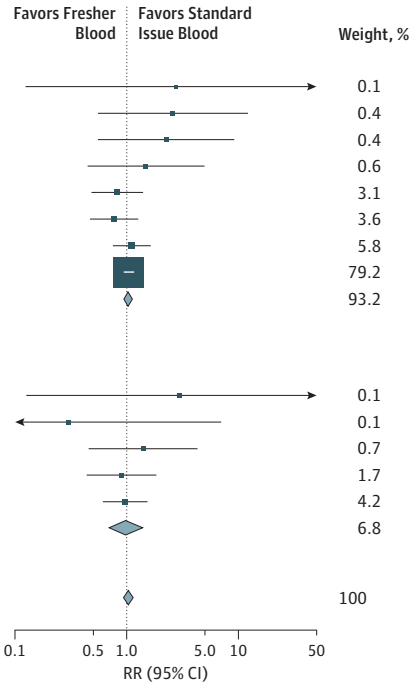
A forest plot shows no evidence that transfusion of fresher RBCs is superior to standard issue RBCs for the outcome of mortality (RR, 1.04; 95% CI, 0.95-1.14) with similar estimates in both adults and infants (**Figure 2**). The association of RBC storage duration on 3 clinical outcomes reported in the trials appears in **Table 3**. The absolute difference in 30-day mortality was 4 more deaths per 1000 with fresher blood (95% CI, 5 fewer deaths to 14 more deaths per 1000).

The RCT quality assessment found no serious risk of bias, inconsistency, indirectness, or publication bias. The overall quality of RCT evidence was moderate for 30-day mortality because the 95% CI included an important decrease in deaths with fresher blood.

There was no evidence to suggest that patients had more adverse events by receiving standard issue RBCs; however, the quality of the evidence was low. For nosocomial infections, there was a higher risk of infection among patients receiving fresher RBCs with an absolute difference of 43 more nosocomial infections per 1000 patients transfused (95% CI, 1 more nosocomial infection to 86 more nosocomial infections per 1000); however, the quality of evidence was low (Table 3).

Figure 2. Association Between Fresher vs Standard-Issue Blood and Mortality in Adults, Neonates, Infants, and Children in Randomized Clinical Trials

Source	Fresher Blood No. of Deaths	Fresher Blood Total No.	Standard Issue Blood No. of Deaths	Standard Issue Blood Total No.	RR (95% CI)	Weight, %
Adults						
Bennett-Guerrero et al,[33] 2009	1	12	0	11	2.77 (0.12-61.65)	0.1
Aubron et al,[34] 2012	5	25	2	26	2.60 (0.55-12.19)	0.4
Schulman et al,[30] 2002	4	8	2	9	2.25 (0.55-9.17)	0.4
Hébert et al,[32] 2005	5	26	4	31	1.49 (0.45-4.98)	0.6
Steiner et al,[41] 2015	23	538	29	560	0.83 (0.48-1.41)	3.1
Kor et al,[37] 2012	17	50	22	50	0.77 (0.47-1.27)	3.6
Heddle et al,[36] 2012	35	309	61	601	1.12 (0.75-1.65)	5.8
Lacroix et al,[40] 2015	448	1211	430	1219	1.05 (0.94-1.17)	79.2
Subtotal	538	2179	550	2507	1.04 (0.95-1.15)	93.2
Heterogeneity: $\tau^2=0$; $\chi^2_7=5.47$; $P=.60$; $I^2=0\%$						
Tests for overall effect: z score = 0.85; $P=.40$						
Neonates, Infants, and Children						
Dhabangi et al,[38] 2013	1	37	0	37	3.00 (0.13-71.34)	0.1
Strauss et al,[29] 1996	0	21	1	19	0.30 (0.01-7.02)	0.1
Dhabangi et al,[39] 2015	7	143	5	143	1.40 (0.45-4.31)	0.7
Fernandes da Cunha et al,[31] 2005	9	26	10	26	0.90 (0.44-1.85)	1.7
Fergusson et al,[35] 2012	30	188	31	189	0.97 (0.61-1.54)	4.2
Subtotal	47	415	47	414	0.99 (0.69-1.42)	6.8
Heterogeneity: $\tau^2=0$; $\chi^2_4=1.46$; $P=.83$; $I^2=0\%$						
Tests for overall effect: z score = 0.06; $P=.96$						
Overall	585	2594	597	2921	1.04 (0.95-1.14)	100
Heterogeneity: $\tau^2=0$; $\chi^2_{12}=7.00$; $P=.86$; $I^2=0\%$						
Tests for overall effect: z score = 0.81; $P=.42$						
Tests for subgroup differences: $\chi^2_1=0.08$; $P=.78$; $I^2=0\%$						



Mortality is based on a composite of the longest follow-up period provided in each trial including 30 days, 90 days, and in-hospital mortality. The size of the data markers indicates the weight of the trial; RR, relative risk.

Rationale for Recommendation

There was consistent evidence in multiple large RCTs performed in a variety of clinical settings among more than 5000 patients. We found no evidence that the transfusion of fresher blood decreased mortality compared with standard-issue blood. However, the RBC storage duration trials did not evaluate patients undergoing a massive or exchange transfusion; neonates and children with underlying renal disease at higher risk of hyperkalemia; patients undergoing intrauterine transfusions; or patients with hemoglobinopathies requiring chronic transfusion support.

Discussion

Transfusion is a common therapeutic intervention for which there is considerable variation in clinical practice.[3-7] If clinicians continue to adopt a restrictive transfusion strategy of 7 g/dL to 8 g/dL, the number of RBC transfusions would continue to decrease.[43] In addition, standard practice should be to initiate a transfusion with 1 unit of blood rather than 2 units. This would have potentially important implications for the use of blood transfusions and minimize the risks of infectious and noninfectious complications.

The average duration of RBC storage in the United States is 17.9 days, although storage duration differs among hospitals and patient populations.[99] Only a small proportion of patients in the RCTs would have been exposed to RBCs near the storage expiration (35-42 days), which could be the products most affected by storage lesions. The standard issue RBC storage duration for neonates is often less than for adult patients; this was true in the 2 primary trials involving neonates.[31,35] However, there was no overall signal that standard issue RBCs were harmful and the overall RR estimate trended toward a lower mortality when standard issue RBCs were used for transfusions.

Limitations

These guidelines are based on the best, but nevertheless incomplete, evidence available today. The hemoglobin transfusion thresholds that have been assessed may not be optimal. The use of hemoglobin transfusion thresholds may be an imperfect surrogate for oxygen delivery. The trials evaluating RBC storage duration have not assessed the effect of long-term storage (near the 42-day expiration for RBC units stored with additive solution); hence, the application of the AABB's recommendation to centers with predominately RBCs stored for longer than 35 days is unknown.

Comparison With Other Guidelines

Red blood cell transfusion guidelines[100-107] from 8 societies during the past 5 years addressed hemoglobin transfusion thresholds. Each of the guidelines recommended a restrictive transfusion strategy with most advising a hemoglobin threshold of 7 g/dL in asymptomatic patients.[101,103,104,106] The updated American Society of Anesthesiology task force guidelines recommended a restrictive hemoglobin transfusion strategy between 6 g/dL and 10 g/dL that was determined by the potential for ongoing bleeding and other clinical variables.[107] In symptomatic patients, these guidelines suggest that

Table 3. Evidence for the Association Between Red Blood Cell (RBC) Storage Duration and Adverse Patient Outcomes[a]

No. of RCTs	Quality Assessment[b]					Storage Duration of RBCs, No./Total (%)		Effect		Quality of RCTs
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Fresher[c]	Standard Issue[d]	Relative Risk (95% CI)	Absolute Risk (95% CI)	
Primary Outcome: 30-d Mortality[e]										
13	Not serious	Not serious	Not serious	Serious	None detected	585/2594 (22.6)	597/2921 (20.4)	1.04 (0.95-1.14)	4 more deaths per 1000 (5 fewer deaths to 14 more per 1000)	Moderate
Secondary Outcomes										
Adverse Events										
3	Not serious	Not serious	Serious	Serious	None detected	288/1781 (16.2)	295/1804 (16.4)	1.02 (0.91-1.14)	1 more adverse event per 1000 (2 fewer events to 4 more per 1000)	Low
Nosocomial Infections										
4	Not serious	Not serious	Serious	Serious	None detected	605/1958 (30.9)	568/1982 (28.7)	1.09 (1.00-1.18)	43 more infections per 1000 (1 more infection to 86 more per 1000)	Low

Abbreviation: RCT, randomized clinical trial.

[a] This Table was modified from the meta-analysis published by Alexander et al[44] with the addition of 1 trial.[39] This Table addresses the question of whether fresher blood compared with standard-issue blood should be used for patients of any age treated for a medical emergency or surgery at hospitals, intensive care units, and emergency departments.

[b] Evaluates the risk of bias, inconsistency based on the heterogeneity among trials, indirectness based on the generalizability of the results, imprecision based on the width of the 95% CIs, and publication bias based on some trials not being published. The Grading of Recommendations Assessment, Development and Evaluation method (eAppendix in the Supplement) was used.

[c] Ten studies defined fresher storage duration as 3 days to 10 days; 2 studies defined it as the freshest blood in inventory; and 1 study defined it as less than 20 days.

[d] Nine studies just used the term *standard issue* and storage duration was not provided, 3 studies defined it as greater than or equal to 20 days, and 1 study defined it as 25 days to 35 days.

[e] Based on a composite of the longest follow-up period provided in each trial including 30 days, 90 days, and in-hospital mortality.

transfusion should be administered to prevent symptoms.[102,103,106] The guidelines from the National Blood Authority of Australia emphasized that the hemoglobin level alone should not dictate transfusion but that it should also be based on clinical status.[103] The guidelines from the National Comprehensive Cancer Network for patients with anemia induced by cancer and chemotherapy did not address whether thrombocytopenia should influence transfusion thresholds but suggested transfusion for symptoms.[106]

In contrast to the AABB recommendations, several guidelines provided specific guidance for patients with acute coronary syndrome that differ from guideline to guideline. The British Committee for Standards in Haematology recommended hemoglobin level be maintained at 8 g/dL to 9 g/dL.[104] The National Comprehensive Cancer Network recommended a hemoglobin transfusion goal of greater than 10 g/dL.[106] The National Blood Authority of Australia recommended that a hemoglobin level greater than 8 g/dL be maintained to possibly reduce mortality but that higher levels are uncertain.[103] The European Society of Cardiology recommended transfusion for patients with a hemoglobin level of less than 7 g/dL unless the patient is not hemodynamically stable.[100] The American College of Physicians recommended a hemoglobin transfusion threshold of 7 g/dL to 8 g/dL in hospitalized patients who have either coronary heart disease or acute coronary syndrome.[105]

The AABB recommendation for RBC storage is more specific than those from other groups, which were promulgated prior to publication of most of the RCTs that provided evidence for the AABB recommendation. For example, the British Committee for Standards in Haematology and the American College of Critical Care Medicine noted a lack of evidence to recommend fresher compared with standard issue RBCs.[10,104] The Australian and New Zealand Society of Blood Transfusion suggested that fresher RBCs (<5 days old) may be indicated in special situations for children and neonates.[108] The guidelines from the Kidney Disease Improving Global Outcomes Work Group suggests use of fresher RBCs for patients with end-stage renal disease may maximize posttransfusion survival.[102]

Research Recommendations

Areas of uncertainty for which RCTs are needed include trials in patient populations outside the intensive care unit that include but are not limited to patients with anemia and thrombocytopenia, patients requiring chronic transfusions and those with coagulopathy, hemorrhagic shock, or both. Furthermore, trials that examine lower hemoglobin transfusion thresholds are needed in patients with acute coronary syndrome and those with cardiovascular disease. A recent meta-analysis of selected trials found a higher risk of acute coronary syndrome but not 30-day morality among patients with cardiovascular disease who received a restrictive transfusion strategy compared with a liberal transfusion strategy.[109] Although ongoing trials[110-112] evaluating RBC storage duration should be completed, additional trials do not appear warranted at this time.

Conclusions

Research in RBC transfusion medicine has significantly advanced the science in recent years and provides high-quality evidence to inform guidelines. A restrictive transfusion threshold is safe in most clinical settings and the current blood banking practices of using standard-issue blood should be continued.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: Carson, Guyatt, Heddle, Grossman, Cohn, Fung, Gersheimer, Kaplan, Katz, Peterson, Ramsey, Roback, Shander, Tobian.
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Administrative, technical, or material support: Carson, Tobian.
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What is usual care for low back pain? A systematic review of healthcare provided to patients with low back pain in family practice and emergency departments.

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Abstract

International clinical practice guidelines for low back pain contain consistent recommendations including universal provision of information and advice to remain active, discouraging routine referral for imaging, and limited prescription of opioids. This systematic review describes usual care provided by first-contact physicians to patients with low back pain. Studies that reported the assessments and care provided to people with low back pain in family practice and emergency departments from January 2000 to May 2019 were identified by searches of PubMed, EMBASE and CINAHL. Study quality was assessed with reference to representativeness of samples, potential misclassification of patients, potential misclassification of outcomes, inconsistent data and precision of the estimate, the findings of high-quality studies were prioritized in the data synthesis. We included 26 studies that reported data from almost 195,000 patients; 18 from family practice, and 8 from emergency departments. Less than 20% of patients with low back pain received evidence-based information and advice from their family practitioner. Around 1 in 4 patients with low back pain received referral for imaging in family practice and 1 in 3 in emergency departments. Up to 30% of patients with low back pain were prescribed opioids in family practice, and up to 60% in emergency departments. Large numbers of patients that saw a physician for low back pain received care that is inconsistent with evidence-based clinical practice guidelines. Usual care included overuse of imaging and opioid prescription, and underuse of advice and

information. Suboptimal care may contribute to the massive burden of the condition worldwide.

Keywords: low back pain; usual care; Family Medicine; emergency department; imaging; Opioids

Introduction

Low back pain (LBP) is an extremely common condition with a mean lifetime prevalence of around 40%[22] and is the leading cause of disability globally.[53] At an individual level, LBP causes limitations to day to day function, impacts mental health, can result in financial hardship and reduces quality of life.[18] The condition also has considerable implications for society as a whole due to the costs of healthcare, reduced work productivity, early retirement and strains on the welfare system.[19, 49]

Recently updated clinical practice guidelines for LBP from Canada, the United States and the United Kingdom (UK) provide some consistent recommendations for how to assess and treat patients with LBP.[2, 30] Reviews of international guidelines show that these recommendations have been largely unchanged since 2000, the only major change being removal of paracetamol as first line care[2, 27] following a large RCT and subsequent systematic review published in 2015.[32, 55] These guidelines are based on high quality evidence and widely endorsed by professional organisations. Recommended assessment involves diagnostic triage[3, 52] based on patient history and physical examination to exclude patients with a problem beyond the lumbar spine (e.g. renal colic) and then categorise patients into one of three groups. A) non-specific LBP, B) lumbar radicular syndromes (sciatica and canal stenosis), or C) a serious pathology affecting the lumbar spine (e.g. infection, fracture, cancer). In family practice and emergency departments, more than 90% of lumbar spine problems fall into categories A or B.[20, 51] There is a perception that people with back pain

who present to ED have on average more severe symptoms, and are more likely present with serious pathology,[12] however, there are few data available to confirm this suspicion. Recommended first line treatment for patients with LBP includes; advice to remain active, and education and reassurance. Adjunctive options include application of heat, manual therapy, non-steroidal anti-inflammatory drugs, and structured exercise and cognitive behavioural therapy for patients with persistent symptoms.[40] Guidelines recommend against imaging unless serious spinal pathology is suspected, and strong analgesics such as opioids should only be prescribed with caution in selected patients.

While these recommendations are well established over several years, and health providers report being aware of them,[42, 54] there are concerns about substantial gaps between guideline recommendations and the care delivered in usual practice.[15] Individual studies report high rates of imaging[11], opioid prescription[9], and inconsistent provision of appropriate advice. However, to date there has been no synthesis of studies that comprehensively report the nature of usual care as delivered by primary contact physicians for this condition. Understanding the nature of usual care in various settings is necessary to identify what aspects of care are most commonly divergent from recommendations, and hence direct efforts to increase provision of evidence-based care. To address this gap we conducted a systematic review of studies that report usual care provided by first contact physicians, the extent to which generalizable data are available will determine how well this review documents usual care for low back pain.

The aim was to synthesize evidence about current management of LBP in family practice and emergency departments (ED). The specific objective was to describe the assessments, treatment advice, imaging, medication and referrals provided in family practice or EDs to patients with LBP.

Methods

Prospectively registered systematic review, PROSPERO 2018 CRD42018070241.

Data sources and Searches

An electronic search was conducted in three databases (EMBASE, PubMed-Medline, and CINAHL) using search terms related to "back pain", "guideline recommendations", and "medical records" from inception to May 2019 (eTable 1, available as supplemental digital content at http://links.lww.com/PAIN/A913). Further potentially relevant studies were identified via consultation with experts and citation tracking on the included studies.

Study Selection

Studies were included if they: (1) reported family practice or ED physicians' assessment and/or treatment of adult patients (aged >18 years) with LBP of any duration and, (2) had a quantitative design assessing actual treatment records. Qualitative studies and studies that measured usual care via recall or hypothetical scenarios/vignettes were not included. Studies that analysed data from prior to 2000 were excluded as we were not interested in historical patterns of practice. Grey literature including non-peer-reviewed literature, theses and letters to the editor were not included. Non-English language studies were included and translated as necessary. A full list of the eligibility criteria appears in eTable 2 (available as supplemental digital content at http://links.lww.com/PAIN/A913). Two reviewers independently screened all titles and abstracts, and then potentially eligible full texts. Disagreements were resolved by discussion, arbitrated by a third reviewer as needed.

Data Extraction

Two reviewers independently extracted study characteristics and outcomes data into an Excel spreadsheet. Study characteristics included; healthcare setting, LBP duration, period of data collection, data source, and sample size. Family practice was defined as primary-contact

outpatient/ambulatory care that was not in ED. For each outcome, data were extracted on collection method, metric used to assess utilisation (e.g. proportion or rate), and the denominator used (e.g. episodes of care, number of patients). Studies most commonly reported the proportion of patients that received a particular aspect of care, which could have been at a single appointment or over a number of visits, we categorised this as 'per patient'. Fewer studies reported the proportion of visits that involved that aspect of care, we categorised this as 'per episode' of care. One study reported the proportion of physicians that delivered that aspect of care; 'per physician'.

Reporting and Methodological Quality

The STROBE (STrength of Reporting in OBservational Studies in Epidemiology) Statement and its extension statement entitled RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) were used to assess the transparency of reporting. We used items from key domains for assessing susceptibility to bias in observational studies as recommended in Sanderson et al.[46] This includes items in 4 domains; representativeness of the sample, potential misclassification of patients, potential misclassification of outcomes, and inconsistent data. Because we used methodological quality to prioritise interpretation of findings, we also considered precision as an indicator of study quality. Included studies were considered high quality if they met criteria for ≥4 of 5 items.

Data Synthesis

Findings from included studies were divided by healthcare setting (family practice or ED) and organised according to outcome category: assessments, treatment advice, imaging, medication, referrals. Within each outcome category (e.g. Imaging) individual types are described separately (e.g. x-ray, CT, MRI, any image). We planned meta-analysis of single proportions, however clinical heterogeneity prevented meta-analysis for any outcome. We

present all available estimates in the tables and focus our interpretation on the range of estimates that came from the high quality studies. A narrow range of high quality estimates from several studies provided greater confidence in the findings, and vice-versa.

RESULTS

Characteristics of included studies

The database and hand searches yielded 989 titles, of which 26 studies were included (Figure 1). The 26 studies reported data from a total of 194,388 patients, 18 studies were in family practice and 8 from emergency departments (Table 1). A further two studies that collected data from mixed settings were not included in the main analyses but findings are reported in eTable 3 (available as supplemental digital content at http://links.lww.com/PAIN/A913). Studies were published between 2003 and 2018. Most studies included patients with LBP of any duration, however, 6 included patients with acute LBP only. Studies most commonly reported data from routinely collected medical records in hospital administrative databases (n= 20), followed by insurance claims or worker compensation databases (n= 3).

Table 1. Included studies

Transparency of Reporting

Most studies met criteria on most items in the STROBE checklist (eTable 4, available as supplemental digital content at http://links.lww.com/PAIN/A913). The main areas of poor reporting related to the extended RECORD checklist items, specifically with respect to data capture from medical records. These included reporting who had access to the database and

created the database of the study, what codes were used select participants and outcome variables from the database, if the codes were validated and if data linkages were required to obtain variables and if so, how the linkage was conducted.

Methodological quality

Nearly all included studies met criteria for consistency of data and representativeness of the sample, 12 used methods to limit bias due to patient misclassification, 15 used methods to limit bias due to misclassification of the outcome, and 15 studies reported on sufficiently large samples to provide precise estimates (eTable 5, available as supplemental digital content at http://links.lww.com/PAIN/A913). We considered sufficient precision to be confidence intervals with a width of 5% or less. According to our criteria, 12 studies provided high quality evidence (Table 1).

Components of usual care

There was often considerable variability in the proportions of patients that received assessments, various types of treatment advice, imaging, medication or referrals. This heterogeneity was in part due to differences in measurement between studies, and precluded meta-analysis. Method of measurement was an important source of heterogeneity, most commonly studies either reported rates (of assessments, images etc) per single patient visit (per patient), or per patient over multiple visits (per episode). To focus on the most reliable estimates of usual care, we only describe results from the high-quality studies in the text of the Results, data from all included studies appears in the Tables.

Assessments

Assessments were categorised into four types; assessment of red flags, history taking, physical examination, and neurological examination. There were no high-quality estimates of

rates for any of the assessments (eTable 6, available as supplemental digital content at http://links.lww.com/PAIN/A913).

Treatment advice

Treatment advice was categorised into five types; education and reassurance, exercise, bed rest, return to work and sickness certificates (Table 2). In family practice settings, two high-quality studies reported that 21% and 23% of patients received education or reassurance, one study reported that 19% of patients received exercise advice, and 3% a sick certificate. There were no high-quality estimates for advice regarding bed rest or return to work. There were no high-quality estimates for any of these types of advice in ED.

Table 2. Rates of treatment advice

Lumbar imaging

Imaging referral was categorised into five types; X-Ray, CT scan, MRI, CT or MRI, any image (Table 3). Four studies reported that between 16 and 20% of patients received referral for X-Ray from family practice, in ED the proportion was 30%. Three studies in family practice reported rates of 2 to 6% for CT scans, and one study in ED reported 6%. Three studies estimated that <1 and 5% of family practice patients were referred for MRI, two ED studies reported 3% and 25%. Ten percent of family practice patients, and 7 to 18% of ED patients received an MRI or CT. Three studies reported that 11 to 26% of family practice patients received referral for an image of any type, and two studies in ED reported 29 and 37%.

Table 3. Rates of imaging

Medication

Medication recommendations were divided into four categories; paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and opioids (including in combination with other analgesics) (Table 4). Where specified in the included studies, the data for EDs relate to medications provided in ED, as opposed to recommended after discharge. In family practice, three studies reported that paracetamol was recommended to 6 to 18% of patients, in ED, the proportion was 4%. NSAIDs were recommended to 36 to 37% of family practice patients, and 50% of ED patients. Muscle relaxants were recommended to 1 to 8% of family practice patients, and 42% of ED patients. Opioids, including in combination with other analgesics were prescribed to 5 to 31% of family practice patients, and two studies in ED reported rates of 17 and 61%.

Table 4. Rates of medication prescription

Treatment referrals

Treatment referrals were divided into four categories; physiotherapy, chiropractic, surgery, medical specialist (Table 5). In family practice, three studies reported that 14 to 27% of patients received physiotherapy referral. Three studies reported that up to 10% of patients were referred from family practice for surgical consult, in ED this figure was 8%. In family practice four studies reported that 1% to 19% of patients received referral to a medical specialist.

Table 5. Rates of referral

DISCUSSION

Statement of main findings

The high-quality estimates for Family Practice suggest around 1 in 4 patients were sent for lumbar imaging, about 20% recommended paracetamol, 35-40% NSAIDs, and up to 30% prescribed opioids. While there were fewer high-quality estimates from ED, the rates of imaging, and medication use were higher (except for paracetamol); around 1 in 3 patients got some type of image, 50% received NSAIDs, and somewhere between 20 and 60% were provided opioids while in ED.

Only around 20% of patients received education, reassurance, and advice regarding exercise from their family practitioner. We found no high-quality data concerning the provision of advice regarding bed rest and return to work, and no high-quality data regarding treatment advice at all for ED settings. Family practitioners referred around 15 to 20% of patients for physiotherapy, 1 to 20% to a medical specialist and up to 6% to a surgeon, approximately 8% of patients in ED were referred for surgical review. We found no high-quality estimates on how many patients received recommended assessments such as red flag assessment, physical, and neurological examination and history taking.

Interpretation in context of other literature

It is important to take a nuanced approach to interpretation of these findings with respect to clinical practice guideline recommendations and epidemiological evidence. For example, guidelines recommend "*Do not routinely offer imaging in a non-specialist setting for people with low back pain without alerting features of serious pathology*"[36] and robust evidence suggests that prevalence of serious spinal pathology, for which imaging is indicated, in primary care is <5%.[20] In this context, rates in excess of 25% appear to indicate overuse of

imaging. However, these data do not tell us about the reasons for imaging referral, and hence what proportion were inappropriate. A recent systematic review of 33 studies considering appropriateness of imaging for low back pain and estimated that referral was inappropriate in 7 to 28% of the patients referred for imaging that presented for care. The same review also found that 60-65% of patients were not referred for imaging despite the presence of red flags or clinical suspicion of serious pathology.[25] Hence, issues of overuse and underuse may both occur. Overuse of imaging may lead to poorer outcome,[14] which means that efforts to reduce the volume of unnecessary imaging are appropriate.[23] However, understanding the reasons for referral is a pre-requisite to designing these efforts, for example some studies suggest that patient or physician beliefs may drive imaging.[24]

Current guidelines recommend that patients are provided NSAIDs as first line pharmacological treatment, and that use of opioids be limited in those with acute low back pain, and not provided at all for chronic low back pain.[36] Our findings show that less than half of patients were prescribed NSAIDs, up to third received opioids in family practice and up to twice that proportion in ED. Clinical practice guidelines do not offer distinct recommendations for care provided in ED and family practice settings. There is a perception that patients who present to ED have on average more severe symptoms, and are more likely to have a serious spinal pathology such as fracture, cauda equina or acute infection.[12] If this is the case higher rates of diagnostic imaging in ED than family practice may be appropriate, although this is not to suggest that the rates observed in our study are reasonable. By the same argument, higher rates of prescription of powerful analgesics may also appear warranted, although this is to ignore important questions about the effectiveness of these medications[1] and well-established concerns regarding potential harms including overdose and death.[10]

While data regarding the provision of advice are sparse, only approximately 1 in 5 patients visiting family practice were provided education, reassurance and advice regarding exercise.

These findings indicate that evidence-based advice was not routinely delivered to patients with LBP in primary care.

High quality estimates come from studies conducted in a small number of countries only. Of the nine high quality family practice studies 3 are from the USA, 3 from Australia and 1 each from Netherlands, Italy and Spain, all of the 4 high quality ED studies come from USA. This raises the question of how well the results from this review represent usual care in other countries. Delivery of the different components of care could be influenced by structural aspects of the healthcare such as access, training of practitioners, and reimbursement processes, legislative constraints operating at the government level, by cultural aspects within a service, region or country, or other factors. We are not able to determine whether variability in the estimates presented in this review are due to any of these factors.

Strengths and limitations

This review was conducted according to contemporary best practice methods including registration of the protocol prior to commencement of data extraction, and double screening and data extraction. Inclusion of studies that made use of routinely-collected data ensured that we gained a true representation of 'usual care', and incorporation of study quality into our data synthesis focused our interpretation on the most reliable estimates.

As is the case for all systematic reviews, clinical and methodological heterogeneity between the included studies leads to variation in the estimates. A further limitation is that many aspects of care are typically not well captured and coded in routine clinical data collection systems. This is most likely to influence our findings related to assessments and treatment advice. The issue is reflected in the fact that we found few high-quality estimates of these components, it also means that we have low confidence that the data reported in lower quality studies provide a reliable reflection for these aspects of usual care. Our study focusses on

usual care provided by physicians, and so may not be generalizable to other healthcare professions such as physical therapists and chiropractors who are first-contact providers in some jurisdictions. We found relatively few studies that provided high quality data and these tended to be concentrated in a small number of western countries, this means that the nature of usual care may deviate substantially from our findings in other countries and jurisdictions. The included studies span approximately 15 years, in this time practice patterns may have changed as new evidence has accumulated, our synthesis does not account for any change over this period.

Implications

The findings point to both overuse and underuse of medical services including imaging, medication prescription and provision of advice in the usual care of people with LBP. Commentators have proposed that responses to these problems may come from the top-down, whereby governments, payers and system administrators enact changes, and from the bottom up, where the public and clinicians alter practice to align with best available evidence.[13] Numerous top-down initiatives may serve this purpose including: removal of capacity within the system to provide inappropriate care, financial restrictions, education and support for clinicians, and revision of diagnostic criteria and thresholds. Additionally, stakeholder (clinicians and patients) engagement, support for shared decision-making, and inclusion of (in)appropriate use recommendations in clinical practice guidelines may improve alignment of clinical services with best available evidence.

From a policy perspective, the findings also highlight the need for health systems to invest in and maintain data collection infrastructure. Robust clinical audits are only possible if there is reliable and complete capture of clinical data, such audits being vital to identify problems and inefficiencies in patient care, and evaluate whether remedial strategies are effective. An important barrier to useful audits of practice involves numerous and disconnected data

collection and storage systems within institutions, for example imaging, medication prescription, admission and clinical notes may all be located in different databases that are not easily linked. It is noted that this presents a barrier to effective care delivery as well as research.

Dependable information about what constitutes usual medical care for low back pain is also critical for interpreting clinical research, as 'usual care' is often used as a comparator (control) in pragmatic trials. If usual care is of poor quality, showing that a new therapy provides better outcome may not provide convincing evidence for the new therapy. At a minimum, it is important to describe the care typically received in the usual care arm[21] so that readers can assess the trial results. These data can also identify system, country and international trends, for example in medication use, or intervention provision. Information such as this can inform research priorities and targets for funding. Our study also highlights the need for much more fine-grained information about the reasons for decisions made in clinical practice. This might involve a field that links medication or imaging referral specifically to an indication. Machine learning applications may also assist in this regard by generating algorithms to convert clinical notes into categorical fields that enable data users to link indications to treatment or referrals. For example, only by understanding the basis for prescription of opioids can we determine whether action needs to be taken, and if so, what the most promising targets for changing prescribing behaviour might be.

Conclusions

Usual care for patients with low back pain did not align well with recommendations in clinical practice guidelines. Around one in four patients that presented to family practice, and one in three that presented to ED with back pain were referred for imaging. Around 35% and 50% of patients received NSAIDs in family practice and ED respectively. Rates of prescribing of opioids were up to 30% in family practice and up to 60% of patients received

an opioid while in ED. Only around 20% of patients received information and advice that aligns with clinical practice guideline recommendations.

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Table 1. Included studies

Author, Country	Data Collection	LBP Duration	Data Source	Sample	Denominator	Quality
Family Practice				**n=166,986**		
Rego [44] Australia	2014	Mixed	Hospital Medical records	146	Per episode	High
Piccoliori [38] Italy	2006	Mixed	Questionnaire	487	Per episode	High
Kale [26] USA	2008-09	Acute	NHAMCS	102,980	Per patient	Low
Mafi [33] USA	1999-2010	Mixed	NHAMCS and NAMCS	23918	Per patient	High
Michaleff [34] Australia	2000-10	Mixed	BEACH	21350	Per patient	High
Breen [6] UK	2007-08	Acute/ Subacute	EMIS, Vision, ISOFT, Synergy databases	648	Per patient	Low
Williams [54] Australia	2005-08	Acute	BEACH	1706	Per patient	High
Crow [8] USA	2002-05	Chronic	NHAMCS	1327	Per patient	Low
Lin [31] Australia	2011	Mixed	Aboriginal Medical Services; "Communicare" electronic clinical records system	44	Per episode	Low
Ramanathan [42] Australia	2009-10	Mixed	Medical record reviews using a web-based tool	6588	Per episode	Low
Chen [7] USA	2013	Mixed	EMR Chart Review	100	Per patient	Low
Bishop b [5] Canada	NR	Acute	Workers compensation board patient reports	428	Per patient	Low
Muntion-Alfaro [35] Spain	2003	Mixed	Clinical histories audit	538	Per episode	Low
Bishop a [4] Canada	NR	Acute	Workers compensation board patient reports	139	Per physician	Low
Fritz [17] USA	2004-08	Acute	SelectHealth, Intermountain EMR	2184	Per episode	High
Suman [50] Netherland	2014	Mixed	Electronic medical records	1242	Per patient	High
Zafar [56] USA	2012-15	Mixed	Computerised physician order system, Dept. Medical Affairs	2513	Per patient	Low
Kovacs [28] Spain	NR	Mixed	Observational study	648	Per patient	High

Emergency Department				**n=27,402**		
Lee [29] USA	2009-11	Acute	Worker's compensation administrative database	2887	Per episode	High
Friedman [16] USA	2002-06	Mixed	NHAMCS	4097	Per patient	High
Potier [39] UK	2013	Mixed	Clinical records/case notes	100	Per patient	Low
Rao [43] USA	2013	Mixed	Electronic medical records	100	Per patient	Low
Nunn [37] Canada	2009-15	Non-urgent	EDIS	325	Per patient	Low
Raja [41] USA	2013-14	Mixed	Electronic health records	3766	Per episode	High
Schlemmer [48] USA	2011-12	Mixed	HEDIS	14838	Per patient	High
Rizzardo [45] Italy	2013	Mixed	Hospital database	1289	Per patient	Low

NHAMCS: National Hospital Ambulatory Medical Care Survey; NAMCS: National Ambulatory Medical Care Survey; BEACH: Bettering the Evaluation and Care of Health survey; EMIS: Egton Medical Information Systems; ISOFT: IT software database; EMR: Electronic Medical Record; EDIS: Emergency Department Information System; HEDIS: Healthcare Effectiveness Data and Information Set; NR: not reported

Table 2. Rates of treatment advice

Advice	Setting	Study	Measure	Proportion (95%CI)	Range of high-quality estimates
Education & Reassurance	Family practice	**Williams[54]**	**Per patient**	**21% (18 to 23%)**	**21 to 23%**
		Michaleff[34]	**Per patient**	**23% (22 to 24%)**	
		Breen[6]	Per patient	0.3% (0 to 1%)	
		Bishop a[4]	Per physician	7% (3 to 11%)	
		Bishop b[5]	Per patient	7% (3 to 11%)	
		Lin[30]	Per patient	20% (11 to 35%)	
		Chen[7]	Per patient	55% (45 to 64%)	
	ED	Potier[39]	Per patient	11% (6 to 19%)	-
Exercise	Family practice	**Michaleff[34]**	**Per patient**	**19% (18 to 20%)**	**19%**
		Breen[6]	Per patient	1% (0.1 to 1%)	
		Bishop a[4]	Per physician	43% (35 to 51%)	
		Bishop b[5]	Per patient	43% (35 to 51%)	
	ED	Nunn[37]	Per patient	3% (1 to 5%)	-
Bed rest	Family practice	Muntion-Alfaro[35]	Per patient	2% (1 to 3%)	-
		Ramanathan[42]	Per episode	3% (1 to 7%)	

		Chen[7]	Per patient	12% (6 to 18%) (advised against)	
		Bishop b[5]	Per patient	17% (11 to 23%)	
		Bishop a[4]	Per physician	21% (14 to 28%)	
Return to work	Family practice	Bishop b[5]	Per patient	17% (11 to 23%)	-
		Bishop a[4]	Per physician	22% (15 to 29%)	
Sickness certificate	Family practice	**Michaleff[34]**	**Per patient**	**3% (3 to 4%)**	**3%**
		Muntion-Alfaro[35]	Per patient	20% (17 to 24%)	
		Breen[6]	Per patient	26% (23 to 30%)	

Estimates from high-quality studies in **bold**

Table 3. Rates of imaging

Image	Setting	Study	Measure	Proportion (95% CI)	Range of high-quality estimates
X-ray	Family practice	**Mafi[33]**	**Per episode**	**16% (15 to 16%)**	**16 to 20%**
		Kovacs[28]	**Per patient**	**16% (13 to 18%)**	
		Michaleff[34]	**Per patient**	**19% (18 to 20%)**	
		Williams[54]	**Per patient**	**20% (18 to 22%)**	
		Breen[6]	Per patient	5% (3.5% to 7)	
		Piccioliori[38]	Per patient	22% (18 to 26%)	
		Kale[26]	Per episode	23% (18 to 28%)	
		Crow[8]	Per episode	62% (59 to 65%)	
	ED	**Friedman[16]**	**Per episode**	**30% (29 to 32%)**	**30%**
		Rizzardo[45]	Per patient	41% (38 to 44%)	
		Potier[39]	Per patient	7% (3 to 14%)	
		Rao[43]	Per patient	8% (4 to 15%)	
		Nunn[37]	Per patient	27% (22 to 32%)	
CT	Family practice	**Kovacs[28]**	**Per patient**	**2% (1 to 3%)**	**2 to 6%**
		Piccoliori[38]	**Per patient**	**4% (3 to 6%)**	
		Williams[54]	**Per patient**	**6% (5 to 7%)**	
	ED	**Friedman[16]**	**Per episode**	**6% (4 to 7%)**	**6%**
		Rizzardo[45]	Per patient	3% (2 to 4%)	
		Rao[43]	Per patient	3% (1 to 8%)	
		Nunn[37]	Per patient	5% (2 to 7%)	
MRI	Family practice	**Williams[54]**	**Per patient**	**<1% (0 to <1%)**	**<1 to 5%**
		Kovacs[28]	**Per patient**	**3% (1 to 4%)**	
		Piccoliori[38]	**Per patient**	**5% (4 to 8%)**	
		Crow[8]	Per episode	3% (2 to 4%)	
		Zafar[56]	Per patient	5% (4 to 6%)	
		Breen[6]	Per patient	9% (7 to 11%)	
	ED	**Friedman[16]**	**Per episode**	**3% (2 to 4%)**	**3 to 25%**
		Raja[41]	**Per patient**	**18% (17 to 19%)**	

		Lee[29]	**Per patient**	**25% (23 to 27%)**	
		Nunn[37]	Per patient	0.6% (0 to 1.4%)	
		Rizzardo[45]	Per patient	1% (1 to 2%)	
		Rao[43]	Per patient	15% (9 to 23%)	
MRI or CT	Family practice	**Mafi[33]**	**Per episode**	**10% (9 to 10%)**	**10%**
	ED	**Friedman[16]**	**Per episode**	**7% (6 to 7%)**	**7 to 18%**
		Schlemmer[48]	**Per patient**	**10% (10 to 11%)**	
		Raja[41]	**Per patient**	**18% (17 to 19%)**	
		Suman[50]	**Per patient**	**11% (9 to 13%)**	
Any image	Family practice	**Michaleff[34]**	**Per patient**	**24% (23 to 25%)**	**11 to 26%**
		Fritz[17]	**Per patient**	**26% (25 to 29%)**	
		Bishop a[4]	Per physician	22% (15 to 29%)	
		Muntion-Alfaro[35]	Per patient	26% (22 to 30%)	
		Rego[44]	Per episode	58% (49 to 65%)	
		Raja[41]	**Per patient**	**29% (27 to 30%)**	
	ED	**Schlemmer[48]**	**Per patient**	**37% (36 to 37%)**	**29 to 37%**
		Nunn[37]	Per patient	30% (25 to 35%)	
		Rizzardo[45]	Per patient	44% (41 to 47%)	
		Rao[43]	Per patient	46% (37 to 56%)	

Estimates from high quality studies in **bold**

Table 4. Rates of medication prescription

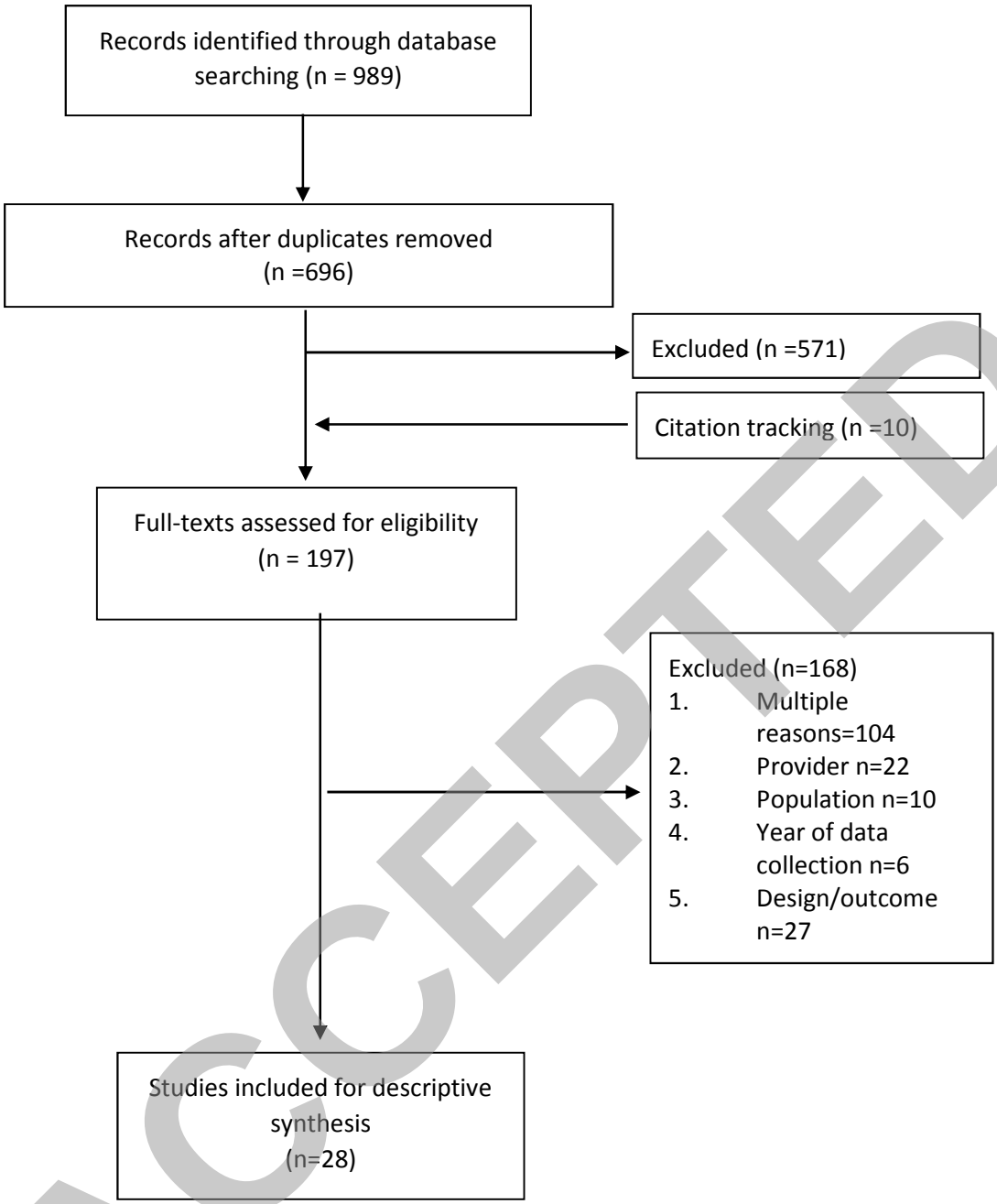
Medication	Setting	Study	Measure	Proportion (95%CI)	Range of high-quality estimates
Paracetamol	Family practice	**Piccioliori[38]**	**Per patient**	**6% (4 to 8%)**	**6 to 18%**
		Michaleff[34]	**Per patient**	**17% (16 to 18)**	
		Williams[54]	**Per patient**	**18% (16 to 20%)**	
		Muntion-Alfaro[35]	Per patient	36% (32 to 41%)	
	ED	**Friedman[16]**	**Per episode**	**4% (4 to 5%)**	**4%**
		Nunn[37]	Per patient	22% (17 to 26%)	
NSAIDs	Family practice	**Michaleff[34]**	**Per patient**	**36% (35 to 37)**	**36 to 37%**
		Williams[54]	**Per patient**	**37% (35 to 40%)**	
		Kovacs[28]	Per patient	57% (53 to 61%)	
		Muntion-Alfaro[35]	Per patient	59% (55 to 63%)	
		Piccioliori[38]	Per patient	82% (79 to 85%)	
	ED	**Friedman[16]**	**Per episode**	**50% (49 to 52%)**	**50%**
		Nunn[37]	Per patient	35% (30 to 41%)	
		Rizzardo[45]	Per patient	62% (59 to 65%)	
Muscle relaxants	Family practice	**Michaleff[34]**	**Per patient**	**<1% (0 to <1)**	**1 to 8%**
		Piccioliori[38]	**Per patient**	**8% (6 to 11%)**	
		Kovacs[28]	Per patient	15% (12 to 18%)	
		Muntion-Alfaro[35]	Per patient	30% (27 to 35%)	
	ED	**Friedman[16]**	**Per episode**	**42% (40 to 43%)**	**42%**
		Nunn[37]	Per patient	7% (5 to 10%)	
Opioids, inc. combination	Family practice	**Williams[54]**	**Per patient**	**5% (4 to 6%)**	**5 to 31%**
		Piccioliori[38]	**Per patient**	**12% (10 to 15%)**	
		Mafi[33]	**Per episode**	**29% (28 to 30%)**	
		Michaleff[34]	**Per patient**	**31% (30 to 32%)**	
		Bishop a[4]	Per physician	40% (32 to 48%)	
	ED	**Lee[29]**	**Per patient**	**17% (15 to 18%)**	**17 to 61%**
		Friedman[16]	**Per episode**	**61% (59 to 62%)**	
		Rizzardo[45]	Per patient	40% (38 to 43%)	
		Nunn[37]	Per patient	50% (47 to 54%)	

Estimates from high quality studies in **bold**

Table 5. Rates of referral

Referrals	Setting	Study	Measure	Proportion (95% CI)	Range of high-quality estimates
Physiotherapy	Family practice	**Michaleff[34]**	**Per patient**	**14% (13 to 15%)**	**14 to 17%**
		Mafi[33]	**Per episode**	**17% (16 to 17%)**	
		Williams[54]	**Per patient**	**17% (15 to 19%)**	
		Breen[6]	Per patient	19% (16 to 22%)	
		Bishop b[5]	Per patient	45% (37 to 53%)	
Chiropractor	Family practice	Breen[6]	Per patient	1% (0.1 to 1.4%)	-
		Bishop b[5]	Per patient	6% (2 to 10%)	
Surgery	Family practice	**Williams[54]**	**Per patient**	**2% (1 to 2%)**	**2 to 6%**
		Fritz[17]	**Per patient**	**3% (3 to 4 %)**	
		Kovacs[28]	**Per patient**	**6% (4 to 8%)**	
		Breen[6]	Per patient	<1% (0.1 to 1%)	
	ED	**Lee[29]**	**Per patient**	**8% (7 to 9%)**	**8%**
		Rao[43]	Per patient	8% (4 to 15%)	
Specialist	Family practice	**Michaleff[34]**	**Per patient**	**1% (1 to 2%)**	**1 to 19%**
		Piccoliori[38]	**Per patient**	**2% (1 to 4%)**	
		Suman[50]	**Per patient**	**8% (7 to 10%)**	
		Fritz[17]	**Per patient**	**19% (18-21%)**	
		Muntion-Alfaro[35]	Per patient	12% (10 to 15%)	
		Crow[8]	Per episode	13% (11 to 15%)	
		Bishop a[4]	Per physician	30% (22 to 38%)	
	ED	Nunn[37]	Per patient	11% (8 to 15%)	-

Estimates from high quality studies in **bold**



ASCO special article abstract

Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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Editor's note: This American Society of Clinical Oncology/Cancer Care Ontario joint Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/hematologic-malignancies-guidelines.

J.M. and T.M. were Expert Panel co-chairs.

Clinical Practice Guidelines Committee approval: November 1, 2018

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PURPOSE To provide evidence-based recommendations on the treatment of multiple myeloma to practicing physicians and others.

METHODS ASCO and Cancer Care Ontario convened an Expert Panel of medical oncology, surgery, radiation oncology, and advocacy experts to conduct a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and some phase II studies published from 2005 through 2018. Outcomes of interest included survival, progression-free survival, response rate, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 124 relevant studies to inform the evidence base for this guideline.

RECOMMENDATIONS Evidence-based recommendations were developed for patients with multiple myeloma who are transplantation eligible and those who are ineligible and for patients with relapsed or refractory disease.

Additional information is available at www.asco.org/hematologic-malignancies-guidelines.

J Clin Oncol 37.

INTRODUCTION

The purpose of this guideline is to provide evidence-based recommendations for the treatment of newly diagnosed and relapsed multiple myeloma. The treatment of multiple myeloma has changed significantly in the last 5 years. Since 2015, four new drugs have been approved, thus providing more options and adding to the complexity of treatment options (Table 1). Numerous large phase III trials have been performed in both the newly diagnosed and relapse/refractory disease settings in an attempt to prioritize various treatments. This guideline will put all the new drugs and randomized trials in context and provide guidance for incorporating the novel drugs.

Epidemiology

In 2018, an estimated 30,770 new cases of multiple myeloma were diagnosed in the United States, representing 1.8% of all new cancer cases. The estimated number of deaths as a result of multiple myeloma in 2018 was 12,770, representing 2.1% of all cancer deaths. Despite significant advances and improvements in overall survival (OS), multiple myeloma remains incurable, and additional treatments are needed. The median survival is just over 5 years, and most patients receive four or more different lines of therapy throughout their disease course. In 2015, there were an estimated 124,733 people living with myeloma, and this number continues to rise as drug therapy improves.[1]

Diagnosis

The majority of patients with myeloma present with symptoms related to organ involvement, including hypercalcemia, renal insufficiency, anemia, and bone lesions (known as calcium, renal failure, anemia, and bone lesions [CRAB] symptoms). A minority of patients are asymptomatic but are found to have abnormal blood and/or urine tests that lead to the diagnosis. The diagnosis requires the presence of clonal plasma cells in the bone marrow or in a biopsy-proven bone or extramedullary plasmacytoma. The specific diagnostic criteria for active multiple myeloma have recently been updated by the International Myeloma Working Group (IMWG) and include the presence of clonal plasma cells plus CRAB features or one of three new biomarkers (Table 2).[2,3]

The new diagnostic criteria are meant to define a population of patients with myeloma who are either symptomatic or will soon become symptomatic and thus require urgent therapy. With these new criteria, many patients who would have previously been defined as smoldering myeloma will now be more appropriately defined as active and in need of therapy. The intent is to facilitate earlier detection and earlier initiation of treatment, with the aim of improving survival.

Staging

The Durie-Salmon system has traditionally been used to define stage in patients with myeloma. According to

THE BOTTOM LINE

Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

Guideline Questions

Transplant-Eligible Population

1. What criteria are used to assess eligibility for autologous stem-cell transplant (ASCT)?
2. What are the options for initial therapy before transplant?
3. What post-transplant therapy should be recommended?
4. What are the response goals for the transplant-eligible patient?

Transplant-Ineligible Population

5. What are the options for initial therapy in transplant-ineligible patients?
6. What are the response goals following initial therapy for transplant-ineligible patients?

Relapsed Disease

7. What factors influence choice of first relapse therapy?
8. How does risk status influence therapy in myeloma (newly diagnosed and relapse)?
9. When and how should response assessment be performed?

Please refer to the data supplement for the complete list of questions and subquestions.

Target Population

Patients with multiple myeloma

Target Audience

Medical oncologists, radiation oncologists, hematologists, surgeons, nurses, advanced practice providers, oncology pharmacists, and patients

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Transplant Eligible

Recommendation 1.1. Patients should be referred to a transplant center to determine transplant eligibility (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 1.2. Chronologic age and renal function should not be the sole criteria used to determine eligibility for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.1. The optimal regimen and number of cycles remain unproven. However, at least three to four cycles of induction therapy including an immunomodulatory drug, proteasome inhibitor (PI), and steroids is advised prior to stem-cell collection (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.2. Up-front transplant should be offered to all transplant-eligible patients. Delayed initial SCT may be considered in select patients (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 2.3. Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drug exposure (more than four cycles), should be avoided in patients who are potential candidates for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.4. Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

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Recommendation 2.5. The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy—patients should be referred for SCT independent of depth of response (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.6. High-dose melphalan is the recommended conditioning regimen for ASCT (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 2.7. Tandem ASCT should not be routinely recommended (Type: evidence based; Evidence quality: intermediate, benefit equals harm; Strength of recommendation: strong).

Recommendation 2.8. Salvage or delayed SCT may be used as consolidation at first relapse for those not choosing to proceed to transplant initially (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.9. Allogeneic transplant for multiple myeloma is not routinely recommended but may be considered in select high-risk patients or in the context of a clinical trial (Type: evidence based; Evidence quality: intermediate, harm outweighs benefit; Strength of recommendation: strong).

Recommendation 3.1. Consolidation therapy is not routinely recommended but may be considered in the context of a clinical trial. For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 3.2. Lenalidomide maintenance therapy should be routinely offered to standard-risk patients starting at approximately day 90 to 110 at 10 to 15 mg daily until progression. A minimum of 2 years of maintenance therapy is associated with improved survival, and efforts to maintain therapy for at least this duration are recommended (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 3.3. For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 3.4. For high-risk patients, maintenance therapy with a PI with or without lenalidomide may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 3.5. There is insufficient evidence to make modifications to maintenance therapy based on depth of response, including minimal residual disease (MRD) status (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 4.1. The quality and depth of response should be assessed by International Myeloma Working Group (IMWG) criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 4.2. The goal of initial therapy for transplant-eligible patients should be achievement of the best depth of remission. MRD-negative status has been associated with improved outcomes, but it should not be used to guide treatment goals outside the context of a clinical trial (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 4.3. It is recommended that depth of response be assessed with each cycle. Frequency of assessment once best response is attained or on maintenance therapy may be assessed less frequently but at minimum every 3 months (Type: evidence based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Recommendation 4.4. Whole-body low-dose computed tomography (CT) scan has been shown to be superior to skeletal survey done with plain x-rays and is the preferred method for baseline and routine bone surveillance. Fluorodeoxyglucose positron emission tomography/CT and/or magnetic resonance imaging may be used as alternatives at baseline. They may also be used in select situations (eg, risk-stratifying smoldering myeloma, for monitoring response of nonsecretory and oligosecretory myeloma, and if CT or skeletal survey is inconclusive) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Transplant Ineligible

Recommendation 5.1. Initial treatment recommendations for patients with multiple myeloma who are transplant ineligible should be individualized based on shared decision making between physicians and patients. Multiple factors should be considered; disease-specific factors such as stage and cytogenetic abnormalities, and patient-specific factors including age, comorbidities, functional status, frailty status, and patient preferences should also be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 5.2. Initial treatment of patients with multiple myeloma who are transplant ineligible should include at minimum a novel agent (immunomodulatory drug or PI) and a steroid if possible (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 5.3. Triplet therapies for patients with multiple myeloma who are transplant ineligible, including bortezomib, lenalidomide, dexamethasone, should be considered. Daratumumab plus bortezomib plus melphalan plus prednisone may also be considered (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 5.4. Physicians/patients should balance the potential improvement in response and disease control with a possible increase in toxicity. Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 5.5. Continuous therapy should be offered over fixed-duration therapy when initiating an immunomodulatory drug or PI-based regimen (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 6.1. The goal of initial therapy for transplant-ineligible patients should be achievement of the best quality and depth of remission (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.2. Depth of response for all patients should be assessed by IMWG criteria (Table 6) regardless of transplant eligibility (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.3. There is insufficient evidence to support change in type and length of therapy based on depth of response as measured by conventional IMWG approaches or MRD (Type: informal consensus; Evidence quality: low, harm outweighs benefit; Strength of recommendation: moderate).

Recommendations 6.4. Upon initiation of therapy, one should define patient-specific goals of therapy. Quality-of-life assessment (including symptom management and tolerability of treatment) should be assessed at each visit to determine if the goals of therapy are being maintained/met, and this should influence the intensity and duration of treatment. Redefining the goals prospectively, based on response, symptoms, and quality of life, is recommended (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.5. It is recommended that patients be monitored closely with consideration of dose modifications based on levels of toxicity, neutropenia, fever/infection, tolerability of adverse effects, performance status, liver and kidney function, and in keeping with the goals of treatment. (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Relapsed Disease

Recommendation 7.1. Treatment of biochemically relapsed myeloma should be individualized. Factors to consider include patient's tolerance of prior treatment, rate of rise of myeloma markers, cytogenetic risk, presence of comorbidities (ie, renal insufficiency), frailty, and patient preference. High-risk patients as defined by high-risk cytogenetics and early relapse post-transplant/initial therapy should be treated immediately. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse (Type: informal consensus/evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

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Recommendation 7.2. All clinically relapsed patients with symptoms due to myeloma should be treated immediately (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 7.3. Triplet therapy should be administered on first relapse, though the patient's tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PIs, immunomodulatory drugs, or monoclonal antibodies) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 7.4. Treatment of relapsed multiple myeloma may be continued until disease progression. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) (Type: evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 7.5. Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 7.6. ASCT, if not received after primary induction therapy, should be offered to transplant-eligible patients with relapsed multiple myeloma. Repeat SCT may be considered in relapsed multiple myeloma if progression-free survival after first transplant is 18 months or greater (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Recommendation 8.1. The risk status of the patients should be assessed using the Revised International Staging System for all patients at the time of diagnosis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.2. Repeat risk assessment at the time of relapse should be performed and should include bone marrow with fluorescence in situ hybridization for myeloma abnormalities seen with progression, including 17p and 1q abnormalities. Fluorescence in situ hybridization for primary abnormalities (translocations and trisomies), if seen in the initial diagnostic marrow, does not need to be repeated (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.3. Assessment of other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty, should also be considered/performed (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.4. In patients with genetic high-risk disease, a triplet combination of PI, immunomodulatory drug, and a steroid should be the initial treatment, followed by one or two ASCTs, followed by a PI-based maintenance until progression (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.5. In patients with renal insufficiency, drugs should be modified based on renal clearance (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.6. In patients with plasma cell leukemia or extramedullary disease, cytotoxic chemotherapy may have a role (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 9.1. The IMWG revised response criteria should be used for response assessment (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 9.2. All measurable parameters need to be followed, including light and heavy chain analysis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 9.3. All responses excluding marrow and imaging should be confirmed as per IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 9.4. Response assessment should be performed after one cycle of therapy, and once a response trend is observed, it may be done every other cycle and less frequently once patient is in a plateau (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

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Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/hematologic-malignancies-guidelines. Patient information is available at https://www.cancer.net/

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

this system, there are three stages (I, II, or III), and each stage is further classified into A or B, depending on whether there is evidence of renal dysfunction upon diagnosis (B). The system attempts to differentiate levels of disease burden and activity based on four factors: baseline hemoglobin, serum calcium, level of M-protein in blood and/or urine, and the presence and number of lytic bone lesions.

More recently, the International Staging System (ISS) and the Revised-ISS (R-ISS) have been more commonly used to define disease stage. The ISS system takes into account levels of serum albumin and serum β2-microglobulin (B2M), whereas the R-ISS also includes serum lactase dehydrogenase (LDH) and results from bone marrow fluorescence in situ hybridization (FISH) testing (Table 3).[4,5]

GUIDELINE QUESTIONS

This clinical practice guideline addresses several overarching clinical questions: In transplant-eligible patients:

1. What criteria are used to assess eligibility for autologous stem-cell transplant (ASCT)?
2. What are the options for initial therapy before transplant?
3. What post-transplant therapy should be recommended?
4. What are the response goals for the transplant-eligible patient? In transplant-ineligible patients:
5. What are the options for initial therapy in transplant-ineligible patients?
6. What are the response goals following initial therapy for transplant-ineligible patients, and in patients with relapsed disease?
7. What factors influence choice of first relapse therapy?
8. How does risk status influence therapy in myeloma (newly diagnosed and relapse)?
9. When and how should response assessment be performed?

Please refer to the Data Supplement for the complete list of questions and subquestions.

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel also included representatives from Cancer Care Ontario, in an effort to avoid duplication of guidelines on topics of mutual interest (Appendix Table A1, online only). The Expert Panel, co-chaired by T.M. and J.M., met via teleconference, a face-to-face meeting, webinars, and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review (2005 to 2018) of phase III randomized clinical trials (RCTs), phase II studies to address specific key questions, and clinical experience. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: patients with active myeloma and relapsed or refractory myeloma
- Interventions that focused on pharmacologic interventions (induction, consolidation, maintenance chemotherapy), ASCT, and supportive care.
- Study designs included were systematic reviews, meta-analyses, RCTs, and larger phase II studies for questions with limited data, including issues addressing the older adult population.

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals, editorials, commentaries, letters, news articles, case reports, narrative reviews, or observational studies, or published in a non-English language.

TABLE 1. Drugs Used in the Treatment of Patients With Multiple Myeloma

Agent	Route	Dose	Schedule
Immunomodulatory drugs			
Thalidomide	Oral	50-200 mg	Daily
Lenalidomide	Oral	5-25 mg	Daily for 21 of 28 days
Pomalidomide	Oral	1-4 mg	Daily for 21 of 28 days
Proteasome inhibitors			
Bortezomib	Subcutaneous/ intravenous	0.7-1.6 mg/m^2	Once or twice weekly
Carfilzomib	Intravenous	20-70 mg/m^2	Once or twice weekly for 3 or 4 weeks
Ixazomib	Oral	2.3-4 mg	Weekly for 3 or 4 weeks
Monoclonal antibodies			
Daratumumab	Intravenous	16 mg/kg	Weekly → every 2 weeks → monthly
Elotuzumab	Intravenous	10 mg/kg	Weekly → every 2 weeks → monthly
Alkylators			
Cyclophosphamide	Oral	50 mg	Daily
		300-500 mg/m^2	Weekly
Melphalan	Oral	9 mg/m^2	Daily × 4 days/cycle
Melphalan	Intravenous	140-200 mg/m^2	Once for transplant
HDAC inhibitors			
Panobinostat	Oral	10-20 mg	Three times weekly for 2 or 3 weeks
Steroids			
Dexamethasone	Oral	20-40 mg	Weekly
Prednisone	Oral	25-50 mg	Every other day
Anthracyclines			
Doxorubicin HCl liposomal	Intravenous	30 mg/m^2	Every 3 weeks

Abbreviation: HDAC, histone deacetylase.

The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[6] In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation. Please refer to the Methodology Supplement for further details.

TABLE 2. Diagnostic Criteria for Active Multiple Myeloma

Diagnostic Criteria
2014 IMWG criteria
Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bone or extramedullary plasmacytoma
Any one or more of the following myeloma-defining events (attributed to the plasma cells)
Hypercalcemia (greater than upper limit of normal)
Renal insufficiency: serum creatinine > 2 g/dL or creatinine clearance < 40 mL/min
Anemia: hemoglobin < 10 g/dL or > 2 g/dL below lower limit of normal
Bone lesions: one or more osteolytic lesions (as demonstrated on imaging studies)
New criteria
Involved/uninvolved serum free light chains ratio ≥ 100, and the involved serum free light chain level > 100 mg/dL or greater
Clonal bone marrow plasma cells ≥ 60%
Two or more focal lesions based on MRI studies of the skeleton

NOTE. Adapted with permission from Rajkumar et al.[3]

Abbreviations: IMWG, International Myeloma Working Group; MRI, magnetic resonance imaging.

TABLE 3. Revised International Staging System

Stage	ISS Criteria
I	ISS stage I (β_2-M $<$ 3.5 mg/L and serum albumin $\geq$ 3.5 g/dL) and normal LDH, no abnormal FISH
II	Neither stage 1 or stage III
III	β_2-M $>$ 5.5 mg/L and elevated serum LDH, or abnormal FISH: presence of t(4;14), t(14;20), or 17p deletion

NOTE. Adapted with permission from Palumbo et al.[5]

Abbreviations: FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase.

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/hematologic-malignancies-guidelines, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (GLIDES and BRIDGE-Wiz), and quality assessment.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The updated search will be guided by the signals[7] approach, which is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. The Methodology Supplement (available at www.asco.org/hematologic-malignancies-guidelines) provides additional information about the signals approach. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 124 studies[8-131] met eligibility criteria and form the evidentiary basis for the guideline recommendations. These included 26 systematic reviews,[8-32,131] two pooled analyses,[33,34] 93 RCTs,[35-126,130] and three phase II studies.[127-129] The identified trials focused on transplant-eligible and -ineligible patients and patients with relapsed diseases. The primary outcomes reported included OS, progression-free survival (PFS), response rate, toxicity, and quality of life. Further details on the characteristics and outcomes of these studies can be found in the Data

Supplement. A systematic review Prisma flow diagram is also shown in Figure 1.

Study Quality Assessment

Study quality was formally assessed for all RCTs and systematic reviews identified. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as randomization, blinding, allocation concealment, intention to treat, funding sources, etc., generally indicating a low to high potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results. Appendix Table A2 (online only) shows the risk of bias assessment for some of the major trials. Please refer to the Data Supplement for the assessment results of other studies identified. The Methodology Supplement also includes more information on definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

TRANSPLANT-ELIGIBLE POPULATION

Clinical Question 1

What criteria are used to assess eligibility for ASCT?

Recommendation 1.1. Patients should be referred to a transplant center to determine transplant eligibility (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Data from transplant registries and SEER data suggest that only a proportion of potentially transplant-eligible patients with multiple myeloma in the United States undergo SCT, influenced in part by several factors, including age, socioeconomic status, and comorbidities.[132] Therefore, the panel strongly recommends that patients with multiple myeloma should be referred to a transplant center early in the course of their care to determine eligibility for SCT. In addition, patients who present with significant disease-related debility can, with therapy, become transplant eligible and should then be referred for transplant evaluation.

Recommendation 1.2. Chronologic age and renal function should not be the sole criteria used to determine eligibility for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Chronologic age alone or a specific age cutoff is not optimal to determine transplant eligibility. In a phase II trial, there were no differences in transplant-related mortality (TRM) in patients 60 to 65 years of age versus 65 to 70 years of age, with low ($< 1\%$) TRM in both cohorts.[123] Retrospective registry data also demonstrate reduced TRM and improved OS with ASCT in older adults in recent years (in adults age 65 to 69 years and those age $\geq$ 70 years), possibly because of improved supportive care.[133]

There are no prospective data to evaluate the impact of organ function on eligibility for SCT. Data from transplant registries do not indicate an adverse impact of renal function on survival following SCT, and renal function alone should not be used to determine SCT eligibility.[134]

While several studies have used dose-reduced melphalan (70 to 140 mg/m^2) in older adults, low TRM has also been reported following full-dose melphalan.[135] A prospective trial comparing SCT with no SCT in the older adult (Intergroupe Francophone du Myelome [IFM] 99-06; ClinicalTrials.gov identifier: NCT00367185) demonstrated superior PFS and OS for nontransplant therapy.[63] It is relevant to note that supportive care strategies have improved since; the study used reduced-dose melphalan (tandem transplant with melphalan 100 mg/m^2), and TRM was highest in the transplant arm (toxic deaths = 5%).

Clinical Question 2

What are the options for initial therapy before transplant?

Recommendation 2.1. The optimal regimen and number of cycles remain unproven. However, at least three to four cycles of induction therapy including an immunomodulatory drug, proteasome inhibitor (PI), and steroids are advised prior to stem-cell collection (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are two randomized trials that have compared the use of PI plus immunomodulatory drug and dexamethasone versus PI plus cyclophosphamide and dexamethasone (bortezomib, thalidomide, dexamethasone *v* bortezomib, cyclophosphamide, dexamethasone and carfilzomib, lenalidomide, dexamethasone *v* carfilzomib, cyclophosphamide, dexamethasone) as induction therapy in transplant-eligible patients.[66,93] Both studies demonstrated statistically increased rates of achieving at least very good partial response (VGPR) in the PI plus immunomodulatory drug plus dexamethasone arm after four cycles of therapy. One study also showed improved minimal residual disease (MRD) negativity rates in the KRd arm.[66] Thus, the use of a PI with an immunomodulatory drug and dexamethasone is the preferred induction therapy in transplant-eligible patients. If an immunomodulatory drug is not immediately available, cyclophosphamide is an acceptable substitute until it becomes available. There are no randomized trials that have attempted to identify the optimal number of induction cycles prior to stem-cell collection. Historically, based upon the initial schema of vincristine, doxorubicin and dexamethasone chemotherapy, most clinical trials have arbitrarily included four cycles of induction therapy.[136] However, current data from trials incorporating triplet therapy show that the depth of response has improved

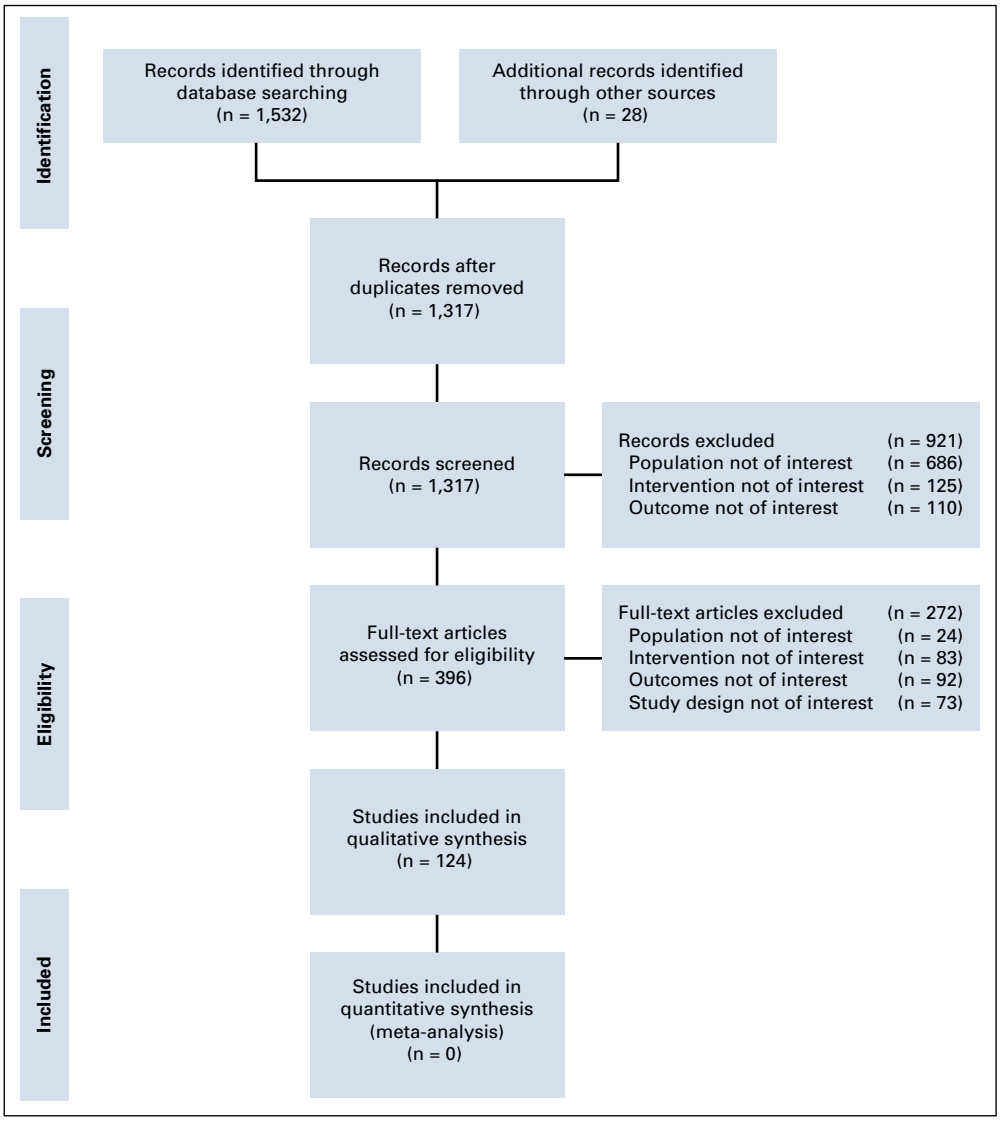

FIG 1. Prisma flow diagram.

significantly and the majority of patients achieve at least a very good partial remission within four cycles of therapy. In fact, the largest incremental decrease in paraprotein levels is observed following the first cycle of therapy and then, in general, a less steep decline is observed, with very small incremental decreases in paraprotein seen beyond three to four cycles of therapy. Therefore, it is recommended that three to four cycles of induction therapy be administered in those planned to proceed to autologous transplant.

Recommendation 2.2. Up-front transplant should be offered to all transplant-eligible patients. Delayed initial SCT may be considered in select patients (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Several contemporary RCTs have compared consolidative autologous transplant to conventional chemotherapy followed by delayed transplant as initial therapy for patients with newly diagnosed multiple myeloma.[35,68,106,137] All of these trials uniformly demonstrated improved PFS in patients who received up-front transplant therapy. One caveat is that these studies incorporated induction regimens containing either PIs or immunomodulatory drugs but not both together, suggesting a less potent induction and an unfair comparator to transplant. More recently, the IFM in France, in conjunction with the Dana-Farber Cancer Institute (DFCI) in the United States, IFM/DFCI 2009 (ClinicalTrials.gov identifier: NCT 01191060), performed a large randomized trial comparing induction therapy with lenalidomide, bortezomib, and dexamethasone (RVD) followed by autologous transplant and subsequent consolidation and maintenance versus RVD induction and stem-cell collection followed by consolidation and maintenance (with transplant reserved for first relapse).[35] The results showed a superior PFS in the early transplant group (50 months *v* 36 months; hazard ratio [HR], 0.65; $P < .001$) and improved rates of achieving MRD remission. The OS at 4 years

did not differ between the treatment arms; however, follow-up is still too short to reliably evaluate this endpoint. The majority of patients were able to undergo autologous transplant at disease relapse. Overall, the panel recommends up-front transplant as the standard of care, whereas delayed SCT may be considered in select patients (based on depth of response, risk status, and patient preference).

Recommendation 2.3. Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drugs exposure (more than four cycles), should be avoided in patients who are potential candidates for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. The use of ASCT requires procurement and storage of adequate hematopoietic stem cells. Prior to the incorporation of PIs/immunomodulatory drugs into front-line therapy, oral melphalan-based therapy was considered the standard of care for patients with newly diagnosed multiple myeloma. Emerging data at that time suggested that extended exposure to oral melphalan resulted in deleterious effects on stem-cell yield,[138,139] thus the transition to induction therapy with vincristine, doxorubicin and dexamethasone in SCT-eligible patients. More recently, with increasing use of immunomodulatory drugs, lenalidomide in particular, studies have shown that extensive exposure to lenalidomide (beyond four to six cycles) may also compromise stem-cell yield.[140,141] Although some of the deleterious effects from alkylator and lenalidomide exposure can be overcome by either combination of growth factor and chemotherapy or growth factor and CXCR4 antagonist (plerixafor), prolonged exposure (> cycles) to these agents should be avoided prior to stem-cell mobilization.

Recommendation 2.4. Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. A single ASCT is considered the standard of care based upon the randomized Blood and Marrow Transplant Clinical Trial Network (BMT CTN 0702; ClinicalTrials.gov identifier: NCT01109004) trial comparing single transplant versus single transplant with consolidation versus tandem transplant (all arms with lenalidomide maintenance) in which the PFS was not significantly different between the three arms.[61] Treatment with autologous transplantation followed by maintenance therapy is associated with a median PFS for standard-risk, low-ISS disease of approximately 5 years. During maintenance, most patients have extensive exposure to lenalidomide and upon relapse receive salvage therapy that may compromise future attempts at stem-cell collection. In addition, peripheral blood stem cells may be stored indefinitely without compromising their efficacy. Thus, in consideration for a future salvage transplant, collection of sufficient peripheral blood stem cells should be considered up front in appropriate transplant-eligible patients.

Recommendation 2.5. The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy; patients should be referred for SCT independent of depth of response (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are no randomized trials aimed at assessing the optimal number of induction cycles or identifying the ideal depth of response required prior to proceeding to SCT. It remains unclear if one should treat to maximal response or change induction regimen to achieve maximum response. Achievement of VGPR or better following induction was associated with superior PFS in the IFM-2005-01 trial (ClinicalTrials.gov identifier: NCT00200681); however, in the current paradigm of using an immunomodulatory drug plus PI-based triplet-induction regimen, such data are lacking.[92] Cohort-based studies suggest that post-transplant depth of response is more important than pre-SCT responses when using current triplet-based regimens.[142] Further, there are retrospective cohort-based data that do not support second-line induction therapy compared with immediate transplant.[143,144] Therefore, because autologous transplant is the single most efficacious treatment of multiple myeloma, patients should be referred to SCT independent of the depth of response, including stable disease, with the exception of those patients who demonstrate progressive disease.

Recommendation 2.6. High-dose melphalan is the recommended conditioning regimen for ASCT (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. High-dose melphalan is the standard conditioning regimen for ASCT in multiple myeloma. There have been randomized trials or cohort-based studies comparing high-dose melphalan to melphalan plus total body irradiation or melphalan with other chemotherapy (eg, busulfan, cyclophosphamide, bortezomib) without demonstrable superiority.[77,145] Melphalan doses may be attenuated at the discretion of the transplant physician for age, frailty, obesity, or renal function.[146,147]

Recommendation 2.7. Tandem ASCT should not be routinely recommended (Type: evidence based; Evidence quality: intermediate, benefit equals harm; Strength of recommendation: strong).

Literature review and clinical interpretation. A single ASCT is considered the standard of care based upon the randomized BMT CTN 0702 trial that compared single transplant versus single transplant with consolidation versus tandem transplant (all arms with lenalidomide maintenance), in which the PFS was not significantly different between the three arms.[61] In contrast to the BMT-CTN trial, data from the European Myeloma Network (EMN)-02 trial (ClinicalTrials.gov identifier: NCT01208766)—where patients did not receive immunomodulatory drug–PI induction as commonly used in the United States—demonstrated improved 3-year PFS and OS with tandem SCT in patients with high-risk cytogenetics.[89] In addition, an IFM trial[148] showed benefit for second SCT in patients who achieved less than VGPR following first SCT. Given these discordant findings, up-front tandem SCT may be considered in selected high-risk patients or those with a suboptimal response to first transplant.

Recommendation 2.8. Salvage or delayed SCT may be used as consolidation at first relapse for those not choosing to proceed to transplant initially (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Several retrospective studies and consensus guidelines suggest that salvage SCT can be a safe and potentially beneficial option, particularly in patients with remission duration of 18 months or more following first ASCT.[149] In general, PFS from second SCT is generally 12 to 18 months and shorter than that achieved following first SCT. A prospective trial comparing second salvage SCT to conventional chemotherapy with cyclophosphamide showed improved PFS but not OS.[47] Prospective data evaluating the efficacy or role of delayed SCT in the setting of immunomodulatory drug–PI (triplet) based induction therapy is limited, and mature data from ongoing studies are not yet available.[35,150]

Recommendation 2.9. Allogeneic transplant for multiple myeloma is not routinely recommended but may be considered in select high-risk patients or in the context of a clinical trial (Type: evidence based; Evidence quality: intermediate, harm outweighs benefit; Strength of recommendation: strong).

Literature review and clinical interpretation. Allogeneic transplant is based upon the immunologic potential of generating donor alloreactivity to produce a graft-versus-myeloma effect. In the relapse setting this alloreactivity appears modest, and outcomes of ASCT have been universally poor. More recently, in the up-front setting, efficacy has been demonstrated and the transplant-related morbidity and mortality have decreased substantially with better patient selection and use of reduced-intensity conditioning regimens. However, the long-term efficacy remains debatable: a large US trial, BMT CTN 0102 (ClincialTrials.gov identifier: NCT00075829), showed no PFS or OS benefit comparing tandem autologous transplant to autologous-allogeneic transplant.[74] There are several smaller European studies that suggest benefit for reduced-intensity ASCT.[67,151] However, given the inconsistent and contradictory results, the unclear potential of graft-versus-myeloma immune effects, and the advent of newer options, including monoclonal antibodies and other immune therapeutics, allogeneic transplant should be performed in the context of a clinical trial and in select patients, such as those with R-ISS high-risk disease.

Clinical Question 3

What post-transplant therapy should be recommended?

Recommendation 3.1. Consolidation therapy is not routinely recommended but may be considered in the context of a clinical trial. For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Consolidation therapy is defined as fixed-duration combination therapy post ASCT aimed at improving the depth of response. Although consolidation therapy may increase the depth of response and can improve PFS,[36,43,88] there are limited data to suggest that consolidation can improve OS. In fact, the BMT CTN 0702 trial, which compared single transplant plus lenalidomide maintenance versus single transplant plus RVD consolidation and lenalidomide maintenance, showed no difference in PFS or OS. Thus, there is little evidence to support the use of consolidation therapy following transplant in those receiving maintenance therapy. Although a randomized trial[118] demonstrated that 1 year of thalidomide consolidation given with indefinite prednisone maintenance improved PFS and OS compared with prednisone maintenance alone, the high incidence of thalidomide toxicity limits its current use.

Overall, lenalidomide maintenance has been shown to improve OS and is now a standard of care. There are no data to support using any consolidation approach when lenalidomide maintenance therapy is given.

Recommendation 3.2. Lenalidomide maintenance therapy should be routinely offered to standard-risk patients starting at approximately day 90 to 110 at 10 to 15 mg daily until progression. A minimum of 2 years of maintenance therapy is associated with improved survival, and efforts to maintain therapy for at least this duration are recommended (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Data from RCTs show a consistent PFS and OS benefit with a 25% reduction in the risk of death derived from lenalidomide

maintenance therapy. Treatment with lenalidomide as part of initial pretransplant therapy does not factor into the decision of whether to administer lenalidomide maintenance, and it appears that those who have been treated with lenalidomide as part of induction may derive additional benefit from lenalidomide maintenance. Data support the use of lenalidomide without dexamethasone as a preferred therapy in the maintenance setting.[18,68]

Recommendation 3.3. For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Bortezomib maintenance can be considered, but clinical trials have not been designed in a way to isolate the contribution of its effect as maintenance.[114,130] Evidence is emerging for the use of other agents as maintenance therapy, such as ixazomib[152], and future randomized trials will further define the use of novel agents for maintenance.

Recommendation 3.4. For high-risk patients, maintenance therapy with a PI with or without lenalidomide may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Although a PFS benefit appears to be gained, survival benefit has not been clearly shown for lenalidomide maintenance in patients with ISS stage III disease, those with adverse risk cytogenetics such as t(4;14) or deletion 17p, those with elevated lactate dehydrogenase, or those with low creatinine clearance. Due to the known short PFS on no maintenance therapy, consideration for bortezomib maintenance therapy should be made as part of the treatment plan in patients with adverse cytogenetic features, especially if bortezomib was part of the initial induction therapy, as this may be associated with improved survival.[130] OS benefit has been associated with bortezomib-based therapy in patients with deletion 17p13, and this strategy may be preferred in high-risk patients rather than lenalidomide maintenance alone, given the lack of OS data for high-risk patients on lenalidomide maintenance. Evidence is emerging for the use of ixazomib as maintenance therapy and may also be considered.[152]

Recommendation 3.5. There is insufficient evidence to make modifications to maintenance therapy based on depth of response, including MRD status (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. In a randomized trial assessing the use of fixed duration of lenalidomide maintenance versus maintenance until complete response (CR), patients receiving the fixed duration of 2 years of therapy had significantly improved PFS versus those stopping lenalidomide once CR was achieved.[36] The goal-directed group (until CR) received less lenalidomide and was associated with early relapse. Thus, current data suggest to continue maintenance for at least 2 years irrespective of response, and the optimal duration or depth of response has not been defined. Future clinical trials will address whether the MRD status of patients can be used to guide maintenance therapy.

Clinical Question 4

What are the response goals for the transplant-eligible patient?

Recommendation 4.1. The quality and depth of response should be assessed by IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Response evaluation in multiple myeloma was originally based on the assessment of bone marrow plasma cells as well as serum and urine monoclonal protein concentrations. The definition of a CR only required bone marrow with less than 5% plasma cells, regardless of whether they were clonally restricted. Revised criteria were introduced during the International Myeloma Workshop in 2011. The criteria were modified to include stringent CR, which requires normalization of the serum free light chains assay and absence of clonal plasma cells in the bone marrow by immunohistochemical testing. The revised IMWG criteria have been adopted as the international standard, allowing improved comparison of treatment combinations. Response assessments should be performed serially in individual patients to guide therapy and to assess sensitivity or resistance to therapy.

Recommendation 4.2. The goal of initial therapy for transplant-eligible patients should be achievement of the best depth of remission. MRD-negative status has been associated with improved outcomes, but it should not be used to guide treatment goals outside the context of a clinical trial (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. New technology allows the identification of residual tumor cells in the bone marrow of patients who meet criteria for stringent CR. MRD can be detected using several techniques. Next-generation flow cytometry relies on two eight-color antibody panels targeting cell surface antigens to identify phenotypically aberrant clonal plasma cells and includes detection of cytoplasmic κ and λ light-chain expression to confirm clonality. It has a sensitivity of 1 in 10^5 cells or higher. Next-generation sequencing uses sets of multiple

polymerase chain reaction primers for the amplification and sequencing of immunoglobulin gene segments. DNA sequencing of bone marrow aspirates using the LymphoSIGHT (Sequenta, South San Francisco, CA) platform (or validated equivalent method) has a minimum sensitivity of 1 in 10^5 nucleated cells or higher. MRD testing by sequencing requires a baseline sample, whereas Next Generation Flow does not. Multiple studies have shown improved outcomes in patients who have achieved MRD-negative status by one of these methods. However, there is no universal agreement as to which method is preferred, when the testing should be performed, and at what interval. None of these assays has been validated prospectively. The IMWG has published suggestions on how to incorporate MRD testing into new clinical trials.[153] Overall, MRD-negative status has been associated with improved outcomes;[13,19,28,33,102,110] however, until prospective trials have validated its use, this technology should not be used to guide treatment decisions.

Recommendation 4.3. It is recommended that depth of response be assessed with each cycle. Frequency of assessment once best response is attained or on maintenance therapy may be assessed less frequently but at minimum every 3 months (Type: evidence based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Literature review and clinical interpretation. There are no trials that compare the frequency of response assessment. The recommendation to assess response with each cycle during active treatment is based on the necessity of knowing whether the treatment is effective. This allows the clinician to change courses to a different treatment if the current regimen is proving to be ineffective. Quantification of serum and/or urine M-protein values and serum free light chain levels is considered standard.

Recommendation 4.4. Whole-body low-dose computed tomography (WBCT) scan has been shown to be superior to skeletal survey done with plain x-rays and is the preferred method for baseline and routine bone surveillance. Fluorodeoxyglucose positron emission tomography (FDG-PET)/CT and/or magnetic resonance imaging (MRI) may be used as alternatives at baseline. They may also be used in select situations (eg, risk stratifying smoldering myeloma, for monitoring response of nonsecretory and oligosecretory myeloma, and if CT or skeletal survey is inconclusive) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Skeletal survey using plain x-rays including spine, pelvis, skull, humeri, and femurs has been the standard modality used to screen for bone lesions in multiple myeloma for many years. However, it is well recognized that this modality has limited sensitivity, as there must be 30% trabecular bone loss to identify lytic lesions on x-ray. As well, expert radiologic review of skeletal surveys already reported was able to detect additional abnormalities in 23% of the studied cases.[154] A systematic review of modern and conventional imaging techniques (MRI, WBCT, and FDG-PET/CT), showed that upwards of 80% more lesions were identified using the newer techniques.[131] A few studies compared WBCT to skeletal surveys, and up to 60% more relevant findings are identified on CT, leading to treatment changes in up to 20% of patients.[155] Thus, the IMWG recommends WBCT as the standard diagnostic tool for detecting bone disease in patients with myeloma. However, skull and rib lesions are not well detected by WBCT or MRI, as compared with skeletal surveys;[131] thus, focused x-rays may still be of value if these areas are of concern. Relatively few extra bone lesions were detected by MRI or FDG-PET/CT over WBCT. Studies comparing MRI to FDG-PET/CT have found them to be equivalent in rate of detection of bone lesions in patients with multiple myeloma. MRIs can be useful in screening patients with smoldering multiple myeloma for lesions, as 30% to 50% of such patients will have bone marrow abnormalities. However, MRI may show nonspecific lesions, and one can occasionally overestimate the extent of bony disease. PET/CTs are particularly useful in evaluating extramedullary disease, an equivocal lesion in a patient with smoldering multiple myeloma or solitary plasmacytoma or a patient with nonsecretory or oligosecretory multiple myeloma.

TRANSPLANT-INELIGIBLE POPULATION

Clinical Question 5

What are the options for initial therapy in transplant ineligible patients?

Recommendation 5.1. Initial treatment recommendations for patients with multiple myeloma who are transplant ineligible should be individualized based on shared decision making between physicians and patients. Multiple factors should be considered; disease-specific factors such as stage and cytogenetic abnormalities, and patient-specific factors including age, comorbidities, functional status, frailty status, and patient preferences should also be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Initial therapeutic recommendations for older adults with myeloma will be informed by both disease-specific and patient-specific factors. Disease-specific considerations include stage and cytogenetics. The R-ISS was developed in a cohort that included about one-third older patients, and its prognostic utility is independent of age, confirming its relevance in the older subgroup.[34,156] In addition, the prognostic importance of high-risk cytogenetics is relevant across the age

spectrum. Older adults with deletion 17p, translocation 14; 16, or translocation 4;14 experience shorter PFS and OS.[62,156,157] Patient-specific considerations in older adults center on age-associated vulnerabilities and patient preferences. In a cohort of over 800 older adults, geriatric assessment factors, including functional status (independence in instrumental activities of daily living and activities of daily living) and comorbidities, were associated with OS. Using these factors, a frailty measure stratifying patients as fit, intermediate-fit, or frail was developed and shown to be predictive of nonhematologic toxicity of therapy, treatment discontinuation, and PFS and OS.[34] Other approaches to applying the concept of frailty to risk stratification in older adults with multiple myeloma have included the Revised Myeloma Comorbidity Index and the Geriatric Assessment in Hematology scale,[158-161] though neither has yet been shown to predict toxicity of therapy. See Table 4 for additional information.

Patient preferences are another importance consideration. Older patients often have multiple serious medical conditions and do not necessarily prioritize length of survival over other considerations. Maintaining functional independence, rather than OS, is prioritized by 60% to 75% of older adults with serious medical conditions or cancer.[162-164] Thus, toxicities that result in dependence, such as neuropathy or fatigue, would not be in line with the preferences of many older adults.

In summary, disease factors and patient factors can inform treatment options, which should be triangulated with patient preferences to inform shared decision making between providers and older adults with myeloma.

Recommendation 5.2. Initial treatment of patients with multiple myeloma who are transplant ineligible should include at minimum a novel agent (immunomodulatory drugs or PI) and a steroid if possible (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The introduction of immunomodulatory agents and PIs to the initial treatment of older adults with myeloma who are ineligible for transplant has significantly improved outcomes. The combination of thalidomide, melphalan, and prednisone,[165] as well as the combination of bortezomib, melphalan, and prednisone,[84,87,90,116] is superior to melphalan and prednisone alone. Continuous therapy with lenalidomide and dexamethasone prolongs survival compared with 18 months of thalidomide, melphalan, and prednisone.[40,62] In a randomized trial of melphalan, prednisone, and thalidomide compared with melphalan, prednisone, and lenalidomide, disease-focused outcomes were similar, though quality of life was better with the lenalidomide combination.[120] Table 5 presents a summary of available data on response rates and disease-free and OS as well as toxicities of combinations studies in older adults with myeloma.

Recommendation 5.3. Triplet therapies for patients with multiple myeloma who are transplant ineligible, including bortezomib, lenalidomide, and dexamethasone, should be considered. Daratumumab plus bortezomib plus melphalan plus prednisone may also be considered (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Triplet therapies (which include at least two novel agents) for patients with multiple myeloma who are transplant ineligible, including bortezomib plus lenalidomide plus dexamethasone (VRd) or daratumumab plus bortezomib plus melphalan plus prednisone (D-VMP), may be considered for select patients. VRd has been compared with Rd in a trial involving 472 patients.[60] At a median follow-up of 55 months, median PFS was significantly improved in the VRd group (43 months *v* 30 months in the Rd group; stratified HR, 0.712; 96% CI, 0.56 to 0.906; one-sided *P* value = .0018). The median OS was also significantly improved in the VRd group (75 months *v* 64 months in the Rd group; HR, 0.709; 95% CI, 0.524 to 0.959; two-sided *P* value = .025). Adverse events of grade 3 or higher were reported in 82% of patients in the VRd group and 75% in the Rd group; 23% and 10% of patients discontinued induction treatment because of adverse events, respectively. Subgroup and multivariate analysis revealed that all age groups benefitted in terms of PFS and OS, including those over 75 years, but the differences were statistically significant for PFS only in those younger than 65 years of age and for OS in those over 75 years.

D-VMP[166] has been compared with VMP in a trial involving 700 older patients. At a median follow-up of 16.5 months in a prespecified interim analysis, the 18-month PFS rate was 71.6% (95% CI, 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (HR for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; $P < .001$). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group ($P < .001$), and the rate of CR or better (including stringent CR) was 42.6% versus 24.4% ($P < .001$). In the daratumumab group, 22.3% of the patients were negative for MRD (at a threshold of 1 tumor cell per 10^5 white cells), as compared with 6.2% of those in the control group ($P < .001$). All subgroups, other than minority groups of non–immunoglobulin G type, high-risk cytogenetics, and stage I, benefitted with improved PFS, including patients over 75 years of age. The most common adverse events of grade 3 or 4 were hematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively.

TABLE 4. Comparison of Select Risk-Prediction Models Relevant to Older Adults With Multiple Myeloma

Factors Associated With Increased Risk	International Myeloma Working Group[180]		Revised Myeloma Comorbidity Index[161]		Geriatric Assessment in Hematology Scale[34,160]	
	Parameter	Points	Parameter	Points	Parameter	Points
Age, years	76-80	1	60-69	1		—
	> 80	2	≥ 70	2		—
Performance/functional status	Any ADL dependence	1	KPS 80-90	2	Gait speed ≤ 0.8 m/s	1
	Any IADL dependence	1	KPS < 70%	3	Any ADL dependence	1
Comorbidities	Charlson Comorbidity Index ≥ 2	1	Renal disease: eGFR < 60	1	Diabetes, BMI > 25 kg/m^2 or cancer, lung disease, heart failure, or smoking*	1
			Moderate/severe pulmonary disease	1		
Medications/ polypharmacy		—		—	≥ 5 medications	1
Nutrition		—		—	≤ 8 on MNA-SF	1
Cognition		—		—	≥ 3 errors on SPMSQ	1
Psychosocial		—		—	Felt depressed 3-7 days of past week	1
Other		—	Moderate/severe frailty phenotype	1	Self-reported health fair or poor	1
Cytogenetics		—	Unfavorable	1		—
Total score	Fit	0	Fit	0-3	Range	0-8
	Intermediate fit	1	Intermediate	4-6		
	Frail	2	Frail	7-9		

NOTE. Adapted with permission from Wildes.[203]

Abbreviations: ADL, activities of daily living; BMI, body mass index; eGFR, estimated glomerular filtration rate; IADL, instrumental activities of daily living; KPS, Karnofsky performance status; MMS, Mini Mental Status Exam; MNA-SF, Mini Nutritional Assessment–Short Form; SPMSQ, Short Portable Mental Status Questionnaire.

*See original publication for full details on scoring comorbidities.

Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients. Median OS was not reached in either group at this early follow-up of 15.5 months.

Both VRd and D-VMP provide markedly improved PFS and, importantly, this benefit extends to those over 75 years. VRd provides, in addition, improved OS, again including for those over 75 years of age; D-VMP has not yet shown a survival advantage at the early follow-up period (16.5 months *v* 55 months for VRd). VRd does exhibit increased toxicities compared with Rd, with rates of discontinuation of therapy due to toxicity being 23% versus 10%. D-VMP has been extremely well tolerated up to 16.5 months, with only 0.9% of patients discontinuing therapy for toxicity. Important exclusion criteria in both trials included severe renal dysfunction (< 30 mL/min for D-VMP *v* VMP; < 40 mL/min for VRd *v* Rd).

Triplet therapies, therefore, provide improved response rates, longer PFS, and possibly improved OS. In general, the additional disease control attained with triplet therapies must be balanced with the potential increased toxicity in transplant-ineligible patients. Patients unsuitable for triplet therapy still have excellent options for therapy, including doublets such as lenalidomide-dexamethasone and bortezomib-based regimens such as bortezomib, dexamethasone and bortezomib, cyclophosphamide, dexamethasone.

Recommendation 5.4. Physicians/patients should balance the potential improvement in response and disease control with a possible increase in toxicity. Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Initial dosing of myeloma therapy in the transplant-ineligible population should be individualized. Factors to consider include patient age and comorbidities, renal function, functional status, and patient preferences. In particular, a frailty measure (that incorporates age, comorbidities, and functional status) can predict excessive toxicity and early treatment discontinuation.[34] When patient factors raise the concern for toxicity, as with very old adult patients (> 75 years) or those with multiple comorbidities, initiating treatment with lower doses of antimyeloma agents is reasonable. For example, the starting dose for

TABLE 5. Range of Reported Outcomes From Trials for Patients With Newly Diagnosed Multiple Myeloma Who Are Transplant Ineligible

Regimen	Overall Response Rate (%)	Complete Response Rate (%)	Median PFS (months)	Median OS (months)	Early Deaths/Death Due to Toxicity (%)	Treatment Discontinuation Due to Adverse Events (%)	≥ Grade 3 Fatigue (%)	≥ Grade 3 Neuropathy (%)
Proteasome inhibitor based								
VD	73	3	14.7	49.8	NR	29	11	22
VMP	70-89	4-32	17.3-25	53.1-not reached	2.3-6	9-34	2-8	7-17
CCyD	95	20	NR	87% 2-year OS	NR	14	2	0
Immunomodulatory agent based								
Rd	70-81	3-22	8.9-25.3	30.5-62.3	4.6	7-19	2-11	0-2
MPR	68	3-11	14-24	62% 3-year OS	0.7-2.3	4-18	2-3	0-3
MPR+R maintenance	70.4-84	11.2-16	18.7-31	69%-70% 3-year OS	2	16-41	5	0-2
CyPR	74	0.5	20	68% 4-year OS	3.6	15	2	3
Proteasome inhibitor plus immunomodulatory agent								
RVD lite	86	44	35.1	NR	NR	4	16	2
VMPT-VT	89	38	35.3	61% 5-year OS	4	23	6	16.8
VTD/VTP	80-81	4-28	15.4-34	43-51.5	5	17-38	12	9-27
PI + mAb								
VMP-dara	90.9	42.6	NR	NR	3.20	4.90	NR	1.4

Adapted with permission from Wildes.[203]

Abbreviations: C, carfilzomib; Cy, cyclophosphamide; D, dexamethasone; M, melphalan; NR, not reported; OS, overall survival; P, prednisone; PFS, progression-free survival; R, lenalidomide; T, thalidomide; V, bortezomib.

dexamethasone (when used with lenalidomide) is 20 mg once weekly for patients older than 75; however, further initial dose reduction (8 to 20 mg once weekly) can be considered for frail patients, with subsequent titration based on response and treatment tolerability.[40,70] Renal dysfunction is common in the elderly, and dose reductions for lenalidomide are warranted. These dose reductions do not appear to impact efficacy in the front-line setting, and dosing should be based on creatinine clearance as delineated by the pivotal FIRST trial.[50] Dose adjustment for frontline bortezomib-based regimens is not required for renal impairment.

Recommendation 5.5. Continuous therapy should be offered over fixed-duration therapy when initiating an immunomodulatory drugs or PI-based regimen (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The current era of novel therapies for myeloma has enabled the continuous use of these agents, in contrast to the fixed-duration dosing warranted by conventional chemotherapeutic options of the past. Continuous therapy in transplant-ineligible patients generally refers to treatment administered until progression or intolerance or treatment administered for a prolonged but finite time frame (eg, 2 to 3 years).[167] Lenalidomide and dexamethasone administered until progression was associated with improvement in PFS when compared with the same therapy given for only 18 months or to melphalan plus thalidomide plus prednisone (MPT) given for 18 months (phase III FIRST trial; ClinicalTrials.gov identifier: NCT00689936) in transplant-ineligible patients.[40] Continuous lenalidomide-dexamethasone was also associated with an improvement in OS compared with MPT. In an updated final analysis of the FIRST trial,[62] the majority of patients who required second-line treatment were given a bortezomib-based regimen; second-line outcomes were improved in the continuous lenalidomide-dexamethasone arm compared with MPT, suggesting that initial prolonged therapy did not compromise myeloma sensitivity to subsequent therapy. Palumbo et al[108] analyzed individual patient data from three randomized trials to establish the impact of continuous versus fixed-duration therapy; two of the trials were specific to transplant-ineligible populations. Although interpretation of this study is limited by the heterogeneity of the patient population (transplant eligible and ineligible) and treatment programs (including continuous therapy with lenalidomide- and bortezomib-based regimens), the pooled analysis does suggest an improvement in PFS and OS in patients receiving continuous therapy. As with the FIRST trial, there was again improvement in time from randomization to second progression or death, providing reassurance that ongoing drug exposure does not compromise future disease response. The decision around duration of therapy should be a joint decision between the physician and patient, with careful consideration of patient preferences and values, ongoing and future toxicities, quality of life, and treatment costs (including out-of-pocket expenses). Future studies are warranted to evaluate continuous therapy with less toxic agents, including monoclonal antibodies, and the role of MRD testing for selecting patients who might derive the most benefit from continuous therapy.

Clinical Question 6

What are the response goals following initial therapy for transplant-ineligible patients?

Recommendation 6.1. The goal of initial therapy for transplant-ineligible patients should be achievement of the best quality and depth of remission (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.2. Depth of response for all patients should be assessed by IMWG criteria (Table 6) regardless of transplant eligibility (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.3. There is insufficient evidence to support change in type and length of therapy based on depth of response as measured by conventional IMWG approaches or MRD (Type: informal consensus; Evidence quality: low, harm outweighs benefit; Strength of recommendation: moderate).

Literature review and clinical interpretation. Response evaluation in multiple myeloma was originally based on the assessment of bone marrow plasma cells as well as serum and urine monoclonal protein concentrations. The definition of a CR only required bone marrow with less than 5% plasma cells, regardless of whether they were clonally restricted. Revised criteria were introduced during the International Myeloma Workshop in 2011. The criteria were modified to include stringent CR, which requires normalization of the serum free light chain assay and absence of clonal plasma cells in the bone marrow by immunohistochemical testing. The revised IMWG criteria have been adopted as the international standard, allowing improved comparison of treatment combinations. These criteria can be used whether the patient is transplant eligible or transplant ineligible. Response assessments should be followed serially to determine effectiveness of therapy. Although studies have identified prognostic implications of ongoing MRD positivity or FDG-PET/CT positivity in some populations, such as the transplant-eligible population, such data are still experimental and less explored in the transplant-ineligible group. As well, no studies have adapted therapy based on these results, and, as such, recommendations for changing therapy based on depth of response are not available.

TABLE 6. IMWG Response Criteria

Response	IMWG Criteria*
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow† by immunohistochemistry or immunofluorescence‡
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow†
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 h
	If the serum and urine M-protein are unmeasurable,§ a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
	If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%
	In addition to the above-listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change/stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease§	Increase of ≥ 25% from lowest response value in any one or more of the following:
	Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)‖
	Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)
	Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL
	Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%¶
	Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of:
	Direct indicators of increasing disease and/or end-organ dysfunction (CRAB features).‖ It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice
	Development of new soft tissue plasmacytomas or bone lesions
	Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
	Hypercalcemia (> 11.5 mg/dL [2.65 mmol/L])
	Decrease in hemoglobin of ≥ 2 g/dL (1.25 mmol/L)
	Rise in serum creatinine by 2 mg/dL or more (177 mmol/L or more)
Relapse from CR§ (to be used only if the end point studied is DFS)#	Any one or more of the following:
	Reappearance of serum or urine M-protein by immunofixation or electrophoresis
	Development of ≥ 5% plasma cells in the bone marrow¶
	Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

NOTE. Adapted from the International Myeloma Working Group Web site[205] and Durie et al.[184]

Abbreviations: CR, complete response; CRAB, calcium, renal failure, anemia, and bone loss; DFS, disease-free survival; FLC, free light chain; IMWG, International Myeloma Working Group; MR, minimal response; PR, partial response; sCR, stringent clinical response; VGPR, very good partial response.

*A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a > 90% decrease in the difference between involved and uninvolved FLC levels.

†Confirmation with repeat bone marrow biopsy not needed.

‡Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

§All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse, and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

‖For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

¶Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

#For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Recommendation 6.4. Upon initiation of therapy, one should define patient-specific goals of therapy. Quality-of-life assessment (including symptom management and tolerability of treatment) should be assessed at each visit to determine if the goals of therapy are being maintained/met, and this should influence the intensity and duration of treatment. Redefining the goals prospectively, based on response, symptoms, and quality of life, is recommended (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are several different methods to measure quality of life, with a myeloma-specific quality-of-life scale recently published by Burckhardt and Anderson.[168] It facilitates the assignment of quantitative values to qualitative measurements, with the assessment consisting of 16 questions and resulting in a score of 16 to 112. The score can be used prospectively as patients are being treated. Defining specific goals of treatment is important (ie, is there an individual longevity goal) as these can help guide therapy. This quality-of-life scale can be used to assess quantitative and qualitative measurements in real time and can assist in determining the length and intensity of therapy. For example, if the score decreases by 30 points compared with prior assessment (ie, versus at initiation of treatment), then a re-evaluation of therapy should be initiated.

Recommendation 6.5. It is recommended that patients be monitored closely with consideration of dose modifications based on levels of toxicity, neutropenia, fever/infection, tolerability of adverse effects, performance status, and liver and kidney function, and in keeping with the goals of treatment (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Standard toxicities are determined by the North Central Cancer Treatment Group and should be assessed regularly. The presence and severity of toxicity should be monitored and will strongly influence dose delays, reductions, and potential discontinuations. This should be done in conjunction with the patient's goals and quality of life as discussed in Recommendation 6.4.

RELAPSED DISEASE

Clinical Question 7

What factors influence choice of first relapse therapy?

Recommendation 7.1. Treatment of biochemically relapsed myeloma should be individualized. Factors to consider include patient's tolerance of prior treatment, rate of rise of myeloma markers, cytogenetic risk, presence of comorbidities (ie, neuropathy, renal insufficiency), frailty, and patient preference. High-risk patients as defined by high-risk cytogenetics and early relapse post-transplant/initial therapy should be treated immediately. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse (Type: informal consensus/evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Biochemically relapsed myeloma is defined by IMWG criteria as a rise in serum or urine paraprotein in the absence of clinical signs or symptoms of myeloma.[153] Although the worsening myeloma markers define the clinical relapse, there is no set level of serum or urine paraproteins that consistently corresponds to the development of symptoms. Even in the same patient, paraprotein levels at different time points may produce variating symptoms, and, as such, the timing for initiation of treatment must be individualized.

Whether to start treatment or not requires a re-evaluation of the patient's disease, a discussion with the patient to understand the patient's preference, and a consideration of the patient's prior tolerance to chemotherapy. Repeat imaging should be performed to assess for active bone disease and should include assessment for new lytic lesions and extramedullary disease. For standard-risk patients, a bone-marrow biopsy should be considered to re-evaluate cytogenetic risk. Overall, treatment should be initiated at the time of biochemical relapse in those with high-risk cytogenetics, extramedullary disease, early relapse after transplant or initial therapy, and/or with evidence of rapid rise in myeloma markers. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse. In these patients, close monitoring of symptoms and organ function and frequent assessment of myeloma paraprotein levels are required.

Recommendation 7.2. All clinically relapsed patients with symptoms due to myeloma should be treated immediately (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Patients with relapsed myeloma and evidence for active disease as defined by hypercalcemia, renal dysfunction, anemia, lytic bone lesions (CRAB) or other manifestations attributable to myeloma, such as extramedullary disease or central nervous system myeloma, should be initiated on treatment immediately. Most clinical trials have used the IMWG criteria for progressive disease, which includes criteria for both biochemical and clinical relapse for initiating therapy.[53,55,58,95,107,112]

Recommendation 7.3. Triplet therapy should be administered on first relapse, though the patient's tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PI, immunomodulatory

drug, or monoclonal antibody) in combination with a steroid (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The treatment of relapsed multiple myeloma is complex and does not have a simple algorithm. When available, clinical trials are preferred and should be considered at every phase of treatment.

On first relapse, the choice of therapy should take into account patient-related, disease-related, as well as treatment-related factors. For patients who are fit, triplet is generally recommended over doublet therapy due to improved clinical outcomes. Triplet therapy is defined as containing two novel agents plus steroids. Novel agents include immunomodulatory drugs such as lenalidomide, pomalidomide, or thalidomide; PI such as ixazomib, bortezomib, or carfilzomib; and monoclonal antibodies such as daratumumab and elotuzumab. Doublet therapy is defined as one novel agent with steroids. Multiple randomized studies[53,55,58,95,107,112] as well as meta-analyses[10,17,21,26,31] have shown that triplets are more effective than doublet combinations in improving PFS, overall response rate, and/or OS, even in older adult patients.[58] In fact, the US Food and Drug Administration (FDA) approval of multiple recent drugs such as daratumumab,[55,107] elotuzumab,[53] carfilzomib,[58] ixazomib,[95] and panobinostat[112] have been based on the improved PFS of these drugs used in triplet combinations versus doublets in relapsed and/or refractory myeloma. Data suggest that even the use of alkylating agents as part of triplet therapy yields better outcomes than doublets.[75] Although triplet therapy offers better clinical outcomes, toxicity appears increased in triple versus doublet therapy,[17,21,26,31,58] and this must be considered when selecting therapy. For some patients, prior toxicity may result in the selection of doublet versus triplet therapy. The ENDEAVOR trial (ClinicalTrialos.gov identifier: NCT01568866) demonstrated the superiority of the doublet carfilzomib plus dexamethasone to bortezomib plus dexamethasone in both PFS and OS[52] in relapsed multiple myeloma. In subgroup analyses, carfilzomib, dexamethasone was superior to bortezomib, dexamethasone regardless of cytogenetic risk,[44] number of prior therapy lines,[94] or prior exposure to bortezomib or lenalidomide.[94] Overall, the selection of doublet versus triplet therapy should be individualized.

The best triplet or how to sequence triplet or doublet therapy in the relapse or refractory setting remains unclear. Published RCTs in relapsed myeloma comparing individual triplets or novel agents in triplet combination are lacking. Several network meta-analyses have been performed to ascertain which combination or type of novel agent was more efficacious, with variable results and no obvious conclusion.[9,10,24,31,60] Because the optimal sequence of therapies is unknown and most patients receive between two to more than 10 lines of therapy for relapsed disease, the general strategy has been to use all approved drugs in rational sequential combinations (ie, immunomodulatory drug plus PI plus steroid followed by second-generation immunomodulatory drug plus monoclonal antibody plus steroid followed by second-generation PI plus alkylator plus steroid, and so on).

Although clinical trials are preferred at all treatment time points, as patients become multiply relapsed and resistance develops to immunomodulatory dugs, PI, and antibodies, referral for a novel clinical trial can be considered. In addition, the use of chemotherapeutic agents such as cyclophosphamide, melphalan, or panobinostat[112] may also be considered.

Recommendation 7.4. Treatment of relapsed multiple myeloma may be continued until disease progression. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) (Type: evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. In clinical trials, an extended therapy duration has been associated with better outcomes in patients with newly diagnosed multiple myeloma. However, data on how therapy duration affects the outcomes for patients with relapsed/refractory multiple myeloma are limited, as many randomized trials had a reduction or discontinuation of therapy in the trial design. Subgroup analyses of large prospective trials in which treatment was given until progression have suggested that longer-term therapy is beneficial. In one study of 50 patients, those treated for more than 3 years had a longer median time to progression compared with those treated for 2 to 3 years, regardless of the response rate.[169] In another retrospective study of 67 patients, OS and overall response rates were significantly better for patients treated with lenalidomide and dexamethasone for more than 12 months compared with patients who stopped treatment at less than 12 months for reasons other than progression.[170]

A recent large, retrospective study was conducted in the United States to evaluate the effect of the duration of second-line therapy on OS. From January 2008 to June 2015, a total of 628 patients with newly diagnosed multiple myeloma were noted to have relapsed disease and were observed for response to second-line therapy. With a median duration of second-line therapy of 6.9 months, researchers noted that each additional month of second-line therapy was associated with a reduced adjusted risk of death at 1 year (odds ratio, 0.78; 95% CI, 0.77 to 0.83; $P < .001$). Thus, the authors concluded that there is clinical benefit for maintaining a longer duration of therapy at first relapse.[171]

Current standard practice is for patients who are responding to treatment to continue treatment until disease progression or until unacceptable toxicity. There are no data to guide duration of therapy based on risk assessment or response to treatment, such as achievement of MRD status.

Recommendation 7.5. Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. In the past decade, there has been tremendous progress in the treatment of multiple myeloma, with a number of agents/combinations being approved by the FDA, including monoclonal antibodies (daratumumab, elotuzumab), histone deacetylase inhibitors (panobinostat), PIs (bortezomib, carfilzomib, ixazomib), and immunomodulatory drugs (lenalidomide, thalidomide, pomalidomide) along with historical alkylators and anthracyclines. This wealth of treatment options makes it challenging for the treating clinician to select which drugs to use, as well as when to use them and in what order.

In general, these regimens are tried sequentially based on many factors, including availability, prior therapy, and toxicity profile, as there are no randomized trials available to guide specific treatment sequences.

In the 2017 Journal of Clinical Oncology article by van Beurden-Tan et al,[9] they aimed to synthesize all efficacy evidence, enabling a comparison of all current treatments for relapsed multiple myeloma. They combined evidence from 17 phase III RCTs, including 16 treatments. Of 16 treatment options, the combination of daratumumab, lenalidomide, and dexamethasone was the best option in terms of both ranking and probability of being the best treatment. All three best-treatment options are triple-combination regimens, and all are in combination with lenalidomide and dexamethasone (with daratumumab, carfilzomib, or elotuzumab). This is in line with earlier observations that triplet combinations are better than doublets[9] and are preferred if tolerated as outlined above.

Prior treatments are important in deciding which regimen will be used. Patients who relapse more than 1 year after their treatment will likely respond to a repeat course of the previous therapy. If patients relapse during therapy or within 1 year of completing therapy, they are considered less sensitive to these agents and should be treated accordingly. For example, in patients progressing on lenalidomide maintenance therapy, salvage therapy with bortezomib and a monoclonal antibody can be considered. In bortezomib-refractory cases, lenalidomide with monoclonal antibody can be used. In double-refractory cases, pomalidomide combinations with monoclonal antibodies[172] or cyclophosphamide[173] are reasonable options.

This is particularly important in high-risk patients. Lui et al[209] performed a meta-analysis in relapsed multiple myeloma including patients with del(17p). Thirteen prospective studies were evaluated involving 3,187 patients with multiple myeloma and 685 with del (17p). The authors concluded that combined therapy (triplets and doublets) with second-generation PIs, monoclonal antibodies, and immunomodulatory drugs are associated with improved outcomes in patients with del (17p).

Recommendation 7.6. ASCT, if not received after primary induction therapy, should be offered to transplant-eligible patients with relapsed multiple myeloma. Repeat SCT may be considered in relapsed multiple myeloma if PFS after first transplant is 18 months or greater (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Literature review and clinical interpretation. There are many options for the treatment of relapsed or refractory multiple myeloma and for transplant-eligible patients; this includes the use of salvage hematopoietic cell transplantation. There are two general settings for which to consider salvage ASCT.

1. Relapse with no prior transplant. After initial chemotherapy and collection of stem cells, patients can either proceed to early (up-front) ASCT or can opt for delayed ASCT at the time of relapse.

There have been several randomized trials comparing early versus delayed transplant; only one[35] included patients receiving induction with an immunomodulatory agent and a PI. In this multicenter trial (IFM/DFCI 2009), 700 adults 65 years of age or younger with symptomatic newly diagnosed myeloma were randomly assigned to receive induction triplet regimen followed by either early or delayed transplant at relapse. Early transplant was associated with higher rates of CR (59% *v* 48%; $P = .03$) and achievement of MRD (79% *v* 65%; $P < .001$) and a longer median PFSPFS (50 *v* 36 months; $P < .001$). At the median follow-up of 44 months, OS at 4 years did not differ significantly (81% *v* 82%).[35] In the RVD-alone group, salvage transplantation was administered to 79% of patients with symptomatic relapse, and this likely contributed to the lack of OS difference. These results suggest that early transplant delays disease progression, that the majority of patients who defer transplant will be able to undergo transplant at relapse, and that this delay

does not appear to impact OS. Thus, for those patients who do not undergo SCT as part of their initial treatment, high-dose chemotherapy followed by ASCT at relapse is feasible.

2. Relapse in setting of prior SCT. Treatment options for relapsed multiple myeloma after an ASCT include a second ASCT, novel chemotherapy regimens, or in select cases a nonmyeloablative alloSCT, preferably as part of a clinical trial.

Alvares et al[174] found that patients with a PFS of less than 18 months after first ASCT had a median OS of less than 6 months, whereas those with a PFS of 18 months or more showed a median OS approaching 3 years.

A Mayo Clinic study that reviewed 345 patients who relapsed after ASCT found that the median OS was 10.8 months for patients in the early-relapse group (≤ 12 months from ASCT) as compared with 41.8 months in the late-relapse group (> 12 months from ASCT; $P < .001$). Hence, the authors recommended offering novel nontransplant therapies for patients in the early-relapse group due to poor outcomes with SCT.[175]

In the era of novel agents, the only RCT to evaluate the role of salvage ASCT in patients with myeloma at first relapse/progression after prior ASCT was the United Kingdom Myeloma X study (ClinicalTrials.gov identifier: NCT00747877). In this trial, 174 patients with first progression or relapsed disease at least 18 months after prior ASCT were treated with anthracycline-based chemotherapy and were randomly assigned to further treatment with ASCT or to oral cyclophosphamide. After a median follow-up of 31 months, second ASCT resulted in a longer median time to progression (19 *v* 11 months; HR, 0.36).[47]

In a large single-institution retrospective analysis of 200 patients undergoing second ASCT for relapsed multiple myeloma,[176] a partial or greater response was noted in 80% by day 100. At a median follow-up of 57 months, the median PFS and OS times following second ASCT were 15 and 42 months, respectively. Outcomes were worse among patients who had an initial remission duration less than 18 months and in those who had less than a partial response to re-induction therapy prior to SCT.

The IMWG has recommended consideration of a second SCT in those who tolerated the initial transplant well and had at minimum PFS of 12 to 18 months.[149]

Allogeneic hematopoietic cell transplantation has the potential of producing cure; however, its use is limited by high rate of treatment-related mortality and the risk of significant morbidity, especially from graft-versus-host disease. The treatment-related mortality associated with alloSCT is decreasing with the advent of nonmyeloablative preparative regimens, but this seems to reduce its efficacy in myeloma. The largest case series of nonmyeloablative allogeneic transplant in relapsed refractory disease is from the European Society for Blood and Marrow Transplantation. In a study involving 229 patients undergoing nonmyeloablative transplantation, the 3-year OS and PFS rates were 41% and 21%, respectively. Patients with prior transplant and primary progressive disease did worse, and those with graft-versus-host disease did better. This study demonstrated feasibility of nonmyeloablative transplants in carefully selected patients.[177]

At present, allogenic transplant is reserved for young patients with high-risk myeloma who have short durations of response and are willing to accept the high treatment-related morbidity and mortality risk. Clinical trials should be strongly considered.

Clinical Question 8

How does risk status influence therapy in myeloma (newly diagnosed and relapse)?

Recommendation 8.1. The risk status of the patients should be assessed using the R-ISS for all patients at the time of diagnosis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Every patient who is diagnosed with multiple myeloma should undergo risk stratification using R-ISS.[4,5] The R-ISS incorporates the original ISS (serum B2M and serum albumin), while adding prognostic information obtained from the serum LDH and chromosomal abnormalities (CAs) detected by plasma cell–specific interphase FISH. CAs are divided into high risk (del17p, t[4;14], t[14;16]) or standard risk. R-ISS stage I is ISS stage I with normal LDH and standard-risk CA. R-ISS stage II is neither stage I nor stage III. R-ISS stage III is stage III ISS (β_2M ≥ 5.5 mg/dL) with high LDH and/or high-risk CA.

Patients with R-ISS stage I, II, and III had 5-year OS rates of 82%, 62%, and 40%, respectively.

This risk stratification helps to determine prognosis and may impact treatment choice, with high-risk patients being treated more aggressively. The R-ISS can also be used for risk stratification of patients with relapsed multiple myeloma and should be performed at the time of disease relapse.[178]

Recommendation 8.2. Repeat risk assessment at the time of relapse should be performed and should include bone marrow with FISH for myeloma abnormalities seen with progression, including 17p and 1q abnormalities. FISH for primary abnormalities (translocations and trisomies), if seen in the initial diagnostic marrow, does not need to be repeated (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Nearly all patients with multiple myeloma have abnormalities

on FISH that can be broadly divided into translocations and trisomies.[179,180] These abnormalities are typically referred to as primary abnormalities and do not routinely change during the course of the disease. As myeloma evolves, patients may acquire new high-risk abnormalities such as 17p deletion and 1q amplification. Acquisition of these secondary abnormalities is typically associated with more aggressive disease behavior and shorter survival.[111,181] Therefore, a bone marrow examination with interphase FISH can reveal additional prognostic information in the setting of relapsed multiple myeloma. In patients with known abnormalities, a limited FISH panel to assess for new high-risk abnormalities is adequate.

Recommendation 8.3. Assessment of other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty should also be considered/performed (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Other disease-related factors that affect risk stratification include the development of extramedullary plasmacytomas or evolution into secondary plasma cell leukemia. These findings suggest more aggressive disease, place the patient in a high-risk category, and have an effect on prognosis.[37] Patient-related factors like age, performance status, renal dysfunction, as well as frailty score (IMWG score http://www.myelomafrailtyscorecalculator.net/) also play an important role in risk stratification at relapse.[34] Patients who progress while receiving therapy or within the first year of diagnosis also have a poor prognosis. Similarly, the duration of the interval between the last therapy and biochemical or clinical relapse is also critically important. Relapse soon after discontinuing therapy or within 18 months of ASCT or while receiving maintenance therapy suggests more aggressive disease. These patients should be considered to have high-risk disease regardless of their cytogenetic or FISH abnormalities.

Recommendation 8.4. In patients with genetic high-risk disease, a triplet combination of PI, immunomodulatory drug, and a steroid should be the initial treatment, followed by one or two ASCTs, followed by a PI-based maintenance until progression (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Patients with high-risk myeloma appear to have the best outcome when they achieved a deep response following initial therapy. One of the most effective approaches in inducing deep responses is to initiate therapy using a triplet combination of a PI, immunomodulatory drug, and steroid, and then to use consolidation including an ASCT and post-transplant maintenance therapy.[60] The use of a PI and immunomodulatory drug as initial therapy is associated with improved OS in myeloma. A recent phase III trial (IFM/DFCI 2009) confirms improved response and PFS when transplant is used as part of initial therapy.[35] A recent European phase III trial,EMN02, (ClinicalTrials.gov identifier: NCT01208766) and retrospective data demonstrate improved outcomes for high-risk disease when tandem autologous transplantation is used. However, data from the recent US phase III trial, STAMINA, (ClinicalTrials.gov identifier: NCT01863550) did not demonstrate an improvement for tandem SCT, and the role of tandem ASCT for high-risk disease remains unclear. Prospective, randomized data assessing the optimal maintenance therapy in high-risk disease are unavailable. However, in a meta-analysis of lenalidomide maintenance, the only group of patients with limited benefit was high-risk disease. In contrast, the HOVON-65 clinical trial (EudraCT No. 2004-000944-26) that incorporated bortezomib as maintenance as well as part of induction therapy had better outcomes for the high-risk patients.[97] Given these data, incorporation of a PI, immunomodulatory drug, and steroid as part of the induction therapy followed by ASCT followed by PI based maintenance (with or without immunomodulatory drug) appears to be the best approach for high-risk patients.

Recommendation 8.5. In patients with renal insufficiency, drugs should be modified based on renal clearance (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Renal dysfunction is a common finding in patients with multiple myeloma at the time of diagnosis, with nearly 30% of the patients having some degree of renal dysfunction. As such, the Cockroft-Gault formula or similar creatinine clearance assessment tool should be routinely used to estimate clearance prior to initiating therapy. Many of the medications used to treat myeloma will need dosage modifications based on the degree of renal dysfunction. The treating physician should modify the doses of antimyeloma therapies accordingly, especially the immunomodulatory drugs such as lenalidomide and pomalidomide, and should follow the product insert guidelines. Monoclonal antibodies and most PIs do not need dose modifications in the setting of renal insufficiency, but ixazomib should be dose reduced in context of renal insufficiency as per the product insert.

Recommendation 8.6. In patients with plasma cell leukemia or extramedullary disease, cytotoxic chemotherapy may have a role (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are very few prospective data to guide treatment of patients with extramedullary disease or plasma cell leukemia. Retrospective studies have examined the use of combination chemotherapy, such as dexamethasone, platinum, doxorubicin, cyclophosphamide, and etoposide, that includes cytotoxic agents such as anthracyclines and alkylating agents and have shown good response rates.[182] In general the durability of responses is short. However, given the aggressive nature of plasma cell leukemia or extramedullary disease, it is reasonable to consider using these combinations to debulk the disease as a bridge to more definitive therapy. Clinical trials are encouraged in this patient population.

Clinical Question 9

How and when should response assessment be performed?

Recommendation 9.1. The IMWG revised response criteria should be used for response assessment (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The IMWG response criteria for multiple myeloma have been used for assessment of disease response since they were introduced over a decade ago.[153,183-185] The uniform response criteria incorporated previously used European Bone Marrow Transplantation Registry criteria[183] and provided a consistent platform for disease response assessment in multiple myeloma. The original IMWG criteria have been revised over time to incorporate additional tests that have been introduced for measuring disease burden in multiple myeloma. Multiple studies over the years have validated the impact of various levels of response on survival outcomes in multiple myeloma.[27,99,142] These responses are currently used as measures of success for regulatory end points as well. The most recent revision of the response criteria further clarifies several points regarding the practical implementation of the response criteria.[153] Consistent application of these standard response criteria will allow for comparison of results from multiple clinical trials and also the degree of success with different therapies in a given patient.

Recommendation 9.2. All measurable parameters need to be followed, including light and heavy chain analysis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. There are multiple disease measures that can be followed in patients with multiple myeloma. In general, disease response assessment in myeloma includes evaluation of the level of protein in the blood or urine, the proportion of plasma cells in the bone marrow (or in the peripheral blood in the case of plasma cell leukemia), and, if present, the size of plasmacytoma, assessed on imaging or clinical examination.[153] The level of monoclonal protein in the blood has traditionally been measured using serum protein electrophoresis. In the setting of certain immunoglobulins such as IgA, which can be difficult to quantify, the quantitation of the immunoglobulin by nephelometry can be used in place of serum protein electrophoresis. In patients with predominantly light chain monoclonal protein, the serum free light chain assay can be used for measurement of monoclonal kappa or lambda light chain levels. In patients with very low levels of monoclonal protein, immunofixation with isotype-specific antibodies can detect presence of the monoclonal protein. In the urine, the monoclonal protein can be measured using electrophoresis similar to what is done in the blood; however, formal quantitation requires a 24-hour urine sample with assessment of total protein and M-protein levels. The parameters that need to be followed in any individual patient depend greatly on the ability to measure the parameter in question at the time of initiating therapy. The IMWG guidelines provide the specific minimum thresholds for each of the measurable parameters used to assess response in multiple myeloma. In general, if there is measurable serum monoclonal protein then it should be followed, otherwise a measurable urine monoclonal protein should be followed. Over time, resistance to novel drug therapy can occur and the disease can evolve to becoming oligosecretory, nonsecretory, or even light chain disease only (light chain escape). Thus, serum free light chain levels should also be followed in addition to serum protein electrophoresis.

Recommendation 9.3. All responses excluding marrow and imaging should be confirmed as per IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The requirement of confirmatory testing was introduced into the IMWG criteria to ensure that laboratory variations are accounted for. While a minimum gap was previously prescribed between the initial testing and the confirmatory testing, the recent versions of the criteria have eliminated this requirement.[153,184] At this time, a repeat testing can be done on the same day from a separate blood draw, or the urine can be done a day apart to meet the requirement of confirmation. Given that the bone marrow findings and imaging findings are less likely to have variation in interpretation, and given the burden of repeat testing, these do not need to be confirmed.

Recommendation 9.4. Response assessment should be performed after one cycle of therapy, and once a response trend is observed, it may be done every other cycle and less frequently once patient is in a plateau (Type: evidence based; Evidence quality: high,

benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. There are no prospective trials examining the appropriate timing of response assessment and any potential impact of altering therapy based on response status at any given time during the disease course. The recommendations are primarily based on the reported guidelines and practical implementation of the guidelines. Studies examining the impact of kinetics of response on outcomes in myeloma have demonstrated mixed results.[117,186,187] A rapid response has been associated with poorer outcomes in earlier studies with traditional treatment approaches but does not appear to be the case with newer therapies. Some of the observations may be the result of the high-risk patients, especially those with high-risk cytogenetics and high proliferative rates, being more sensitive to therapeutic interventions, especially with the traditional cytotoxic drugs. On the contrary, a slow and sustained deepening of response over time (time to plateau) has been recently reported to be a predictor of better survival. Given this heterogeneity in the impact of response kinetics, timing of response assessment cannot be based on the need for changing any treatment approaches and needs to be based more on the practical aspects. Assessment of the response using the paraprotein measurements and/or imaging should be evaluated in the context of the clinical picture. Assessment after one to two cycles will allow evaluation to ensure that the disease is not progressing based on the response criteria, in which case a change in therapy will be warranted. If the response after one to two cycles is stable disease, but there is evidence of clinical deterioration or lack of improvement, such as worsening end organ damage, a potential change in therapy should be addressed. Evidence of response at the end of the first cycle will be reassuring to the patient and provider. Once there is evidence of sustained disease response, then checking the response every other cycle will be adequate and can decrease the testing burden on the patient, especially as there is no evidence of improved outcomes by immediate intervention at the time of relapse, as discussed in section 7.0. However, if there is evidence of progression at any time, it should be repeated at the minimum during the next cycle, or sooner if there is evidence of clinical deterioration to confirm the progression. Once the patient is in plateau, the frequency can be altered to less-frequent testing that aligns best with the frequency of visits required for therapy and other logistical factors. Once there are results showing a trend toward increasing paraprotein, more frequent testing should be resumed, preferably every cycle until the patient meets criteria for progression or treatment is changed. Figure 2 provides a visual interpretation of these recommendations in the management algorithm.

PATIENT AND CLINICIAN COMMUNICATION

In the last 15 years, patients with multiple myeloma have enjoyed a plethora of new treatment options with significantly improved PFS and OS, especially for the more than 80% majority classified as standard risk. We have at least 10 new FDA-approved therapeutics for myeloma since 2003, with more coming. This dilemma of riches is a mixed blessing for both patients and clinicians as we must now choose the best therapeutic options at each stage of initial disease and multiple relapses.

There is no one-size-fits-all treatment for patients with myeloma, especially with autologous transplantation and other cellular therapy now part of our armamentarium. Clinical care pathways and patient-oriented care models have created an environment of additional complexity beyond transplantation (or not) and multiple drug and immunotherapy combination approaches. When recognized myeloma experts cannot always agree on best treatments, it is understandable that general oncologists and patients also find treatment decisions difficult.

Trust, ongoing education, and clear communication between physicians, patients, families, and oncology allied health personnel are essential. Patients with myeloma still die of their cancer, but most will live long enough to study and learn about their disease and their treatment options. A few become extremely educated and can help develop and promote myeloma clinical trials. Patients are empowered with factual information by support groups, national foundations, social media, and by each other. They expect greater roles in their own decision making and care, because patients understand that the final decision in their treatment is made by them, not by their physician.

It is vital that clinicians understand, accept, and encourage patient interest and education regarding their informed myeloma treatment decisions. Physicians should take the necessary time to orient their patients regarding their care but also make available recommended sources for information, including both print materials and trusted online sites. Encourage patients, family, and caregivers to keep good records, and especially to note changes in symptoms or health conditions after active treatment begins. Remind them that reporting an adverse effect will only improve their ability to receive optimal treatment and not immediately make them ineligible to continue receiving their current treatment.

Establish an atmosphere in which patients feel empowered to share what they have learned, such as a new potential clinical trial or a new therapeutic for which they might be eligible. Skillful physicians understand that the most satisfying clinician–patient relationships and best therapeutic decisions occur when those decisions are shared, not dictated.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician

Communication: American Society of Clinical Oncology Consensus Guideline.[188]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[189-191]

Based on the SEER database, African Americans are 26% more likely to receive no treatment of newly diagnosed multiple myeloma. Similarly, they are 37% less likely to undergo ASCT for myeloma.[192] Americans enrolled in Medicaid in addition to Medicare are 21% more likely not to be treated for a new diagnosis of myeloma.[132]

Age-related disparities are also prevalent in the treatment of multiple myeloma. While younger patients have greatly benefited from novel therapies, this benefit is less pronounced in patients older than 75 years of age, in part due to undertreatment.[132] Older age has been found to increase the odds of not having any treatment by 7% per every year of age.[132] It is important to consider that patients over the age of 75 with multiple myeloma are functionally heterogeneous and can be divided into fit, intermediate fit, and frail groups based on several easily available comprehensive geriatric assessment tools.[193]

Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Increasing costs of novel antimyeloma treatment, particularly oral agents, have placed further financial barriers to timely and efficient myeloma treatment in the United States. It has been shown that beneficiaries of Medicare with low-income subsidy have higher use of immunomodulatory drugs compared with other Medicare recipients. Appropriate emphasis in policy making on novel oral agent coverage will be important to address this inequality in health care.[194]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

Cytopenias occur not infrequently with current myeloma therapies including alkylating agents and novel agents. Grade 3 to 4 anemia has been reported in 3% to 19% of cases with novel agents, and thus erythropoiesis-stimulating agents and optimal iron supplementation should be considered if myeloma-related anemia does not improve with chemotherapy. Thrombocytopenia is common with PIs such as bortezomib and carfilzomib as well as immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide), and thus dose reduction should be performed accordingly and treatment interrupted in the event of grade 4 thrombocytopenia. Neutropenia is a common adverse event with immunomodulatory drugs and the monoclonal antibody daratumumab, with incidence increasing in the relapsed setting and in combination therapy. Thus, in patients considered to be at high risk for febrile neutropenia, granulocyte colony-stimulating factor is recommended.[195]

It is crucial to select appropriate therapy in the case of renal impairment. Bortezomib and thalidomide may be administered without any dose adjustment, while adjustment of the starting dose of lenalidomide and pomalidomide should be made accordingly. Bortezomib has an additional advantage of rapid clearance of the free light chains, thus accelerating kidney response.[195]

Finally, as bone disease associated with myeloma is an important cause of morbidity and mortality, bisphosphonates are the backbone of supportive care for patients with osteoporosis and lytic lesions. For up-to-date recommendations of the use of bisphosphonate in myeloma,

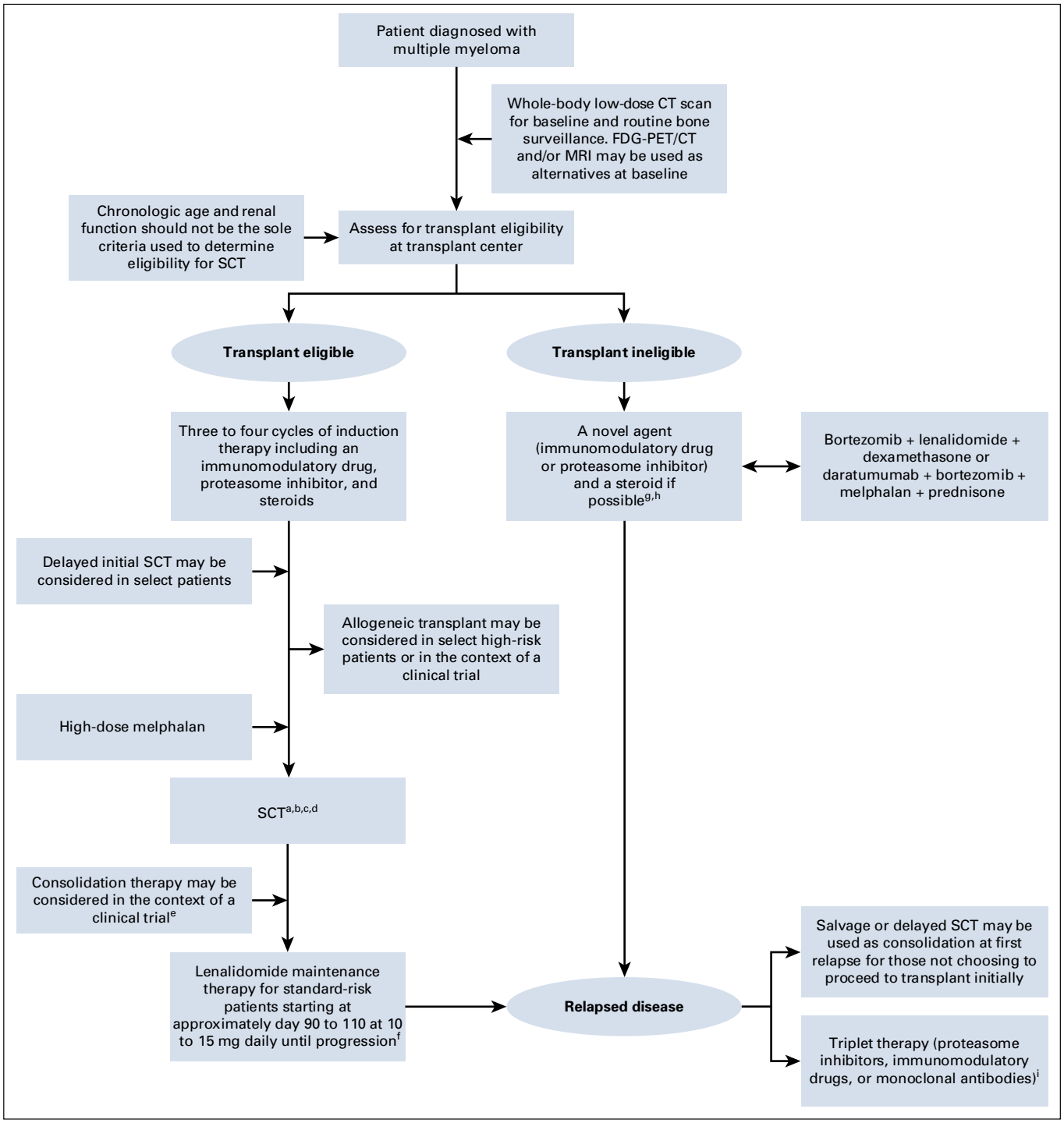

FIG 2. Algorithm on treatment of patients with multiple myeloma. (a) Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drug exposure (more than four cycles), should be avoided in patients who are potential candidates for stem-cell transplant (SCT). (b) Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure. (c) The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy—patients should be referred for SCT independent of depth of response. (d) Tandem autologous SCT should not be routinely recommended. (e) For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered. (f) For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered. For high-risk patients, maintenance therapy with a proteasome inhibitor with or without lenalidomide may be considered. (g) Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability. (h) Depth of response for all patients should be assessed by International Myeloma Working Group criteria. (i) Prior therapies should be taken into consideration when selecting the treatment at first relapse. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging.

TABLE 7. Estimated Cost of Drugs for Multiple Myeloma

Drugs and Regimens	Approximate Drug Cost per Year (in US dollars)*	Comment
Drugs		
Thalidomide	60,000	
Lenalidomide	168,000	
Pomalidomide	192,000	
Bortezomib	50,000	
Ixazomib	111,000	
Carfilzomib	130,000	260,000 (at 56 mg/m^2)
Daratumumab	120,000	
Elotuzumab	120,000	
Panobinostat	96,000	
Cyclophosphamide	5,800	
Melphalan IV	10,000	Per transplant
Dexamethasone	3,400	
Regimens		
VRd	220,000	
KRd	300,000	
VCd	60,000	
DRd	290,000	
D-VRd	340,000	
D-KRd	590,000	

NOTE. Adapted with permission from Rajkumar.[203]

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; D-KRd, daratumumab, carfilzomib, lenalidomide, and dexamethasone; D-VRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

*Source for calculating costs: parenteral drug prices: Centers for Medicare & Medicaid Services[206]; oral drug prices: GoodRx.com.[207]

practitioners are invited to familiarize themselves with recently published ASCO clinical practice guidelines on bone-modifying agents in multiple myeloma.[196]

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[197,198] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[199,200]

Discussion of cost can be an important part of shared decision making.[201] Clinicians should discuss with patients the use of less-expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[201]

Table 7 shows estimated prices for the available treatment options addressed in this guideline. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[201]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data and agents that are not currently available in either the United States or Canada and/or are industry sponsored.

The issue of cost is particularly important in multiple myeloma as many of the agents recently approved may carry a high burden of cost to the patient. These include both oral and parenteral medications. Furthermore, as more of these agents are being used in combination, it may further add to the financial burden of patients. Finally, there is a clear trend for longer treatment periods for patients with myeloma, both in maintenance therapy and at relapse—this may significantly increase costs and must be considered carefully. There is a potential in the future that MRD testing and status may be able to identify patients in whom treatment may be suspended. Incorporating this type of analysis in clinical trials is strongly recommended (and is being done internationally) with the possible effect of reducing duration of therapy, cost burden, and toxicity.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from August 15 through August 27, 2018. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation, with 13 written comments received. A total of 85% of the responses were either agreed or agreed with slight modifications to the recommendations, and 15% of the responses were disagreements. Expert Panel

members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guidelines Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at asco.org/hematologic-malignancies-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[202] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[188] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Role of Bone-Modifying Agents in Multiple Myeloma[196] (http://ascopubs.org/doi/10.1200/JCO.2017.76.6402)

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Data analysis and intrepretation: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

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APPENDIX

TABLE A1. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline Expert Panel Membership

Name (designation)	Affiliation or Institution	Role or Area of Expertise
Joseph Mikhael, MD (co-chair)	City of Hope Cancer Center, Phoenix, AZ and International Myeloma Foundation, North Hollywood, CA	Hematology/oncology
Tom Martin, MD (co-chair)	University of California, San Francisco, CA	Hematology/oncology
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Martha Lacy, MD	Mayo Clinic, Rochester, MN	Hematology/oncology
Madhav V. Dhodapkar, MD	Winship Cancer Institute, Emory University, Atlanta, GA	Hematology/oncology
Sandy Wai Kuan Wong, MD	University of California, San Francisco, CA	Hematology/oncology
Richard F. Little, MD	National Cancer Institute, Bethesda, MD	Hematology/oncology
Alexander Whitley, MD	Central Alabama Radiation Oncology, Montgomery, AL	PGIN representative
Namrata Peswani, MD	Advocate Medical Group, Chicago, IL	PGIN representative
Rahul Seth, MD	Upstate Medical University, Syracuse, NY	PGIN representative
James Omel, MD	Education and Advocacy, Grand Island, NE	Patient representative
Matthew C. Cheung, MD	Sunnybrook Health Sciences Centre, Toronto, ON, Canada	Hematology/oncology (CCO representative)
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Irwin Walker, MD	McMaster University, Hamilton, ON, Canada	Hematology/oncology (CCO representative)
Nofisat Ismaila, MD	American Society of Clinical Oncology, Alexandria, VA	Staff/health research methodologist

Abbreviations: CCO, Cancer Care Ontario; PGIN, Practice Guidelines Implementation Network.

TABLE A2. Study Quality

Trial Name (trial identifier)	Adequate Randomization	Allocation Concealment	Blinding	Blinding					Infrequent Loss to Follow-Up	Selective Outcome Reporting	Other Sources of Bias	Assessment of Bias
				Patients	Health Care Providers	Data Collectors	Outcome Assessors	Data Analysts				
FIRST (NCT00689936)	√	√	√	–	–	√	√	√	√	√	√	Low risk of bias for all key domains
ENDEAVOR (NCT01568866)	√	√	?	–	–	√	√	√	√	√	√	Unclear risk of bias for one or more key domains
CASTOR (NCT02136134)	?	?	?	–	–	–	–	–	√	√	?	Unclear risk of bias for one or more key domains
BSBMT/UKMF Myeloma X Relapse [Intensive] (NCT00747877)	√	√	√	√	√	√	√	√	√	√	√	Low risk of bias for all key domains
PETHEMA/ GEM2010MAS65 (NCT01237249)	?	?	?	?	?	?	?	?	?	√	?	Unclear risk of bias for one or more key domains
GMMG-HD2 (DRKS00008864)	√	√	?	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
IFM2013-04 (NCT01564537)	√	√	X	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
TOURMALINE-MM3 (NCT02181413)	√	?	√	√	√	?	√	?	√	√	√	Unclear risk of bias for one or more key domains
ECOG E1A06 (NCT00602641)	√	?	X	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
ELOQUENT-2 (NCT01239797)	√	√	X	X	X	X	√	√	√	√	√	High risk of bias for one or more key domains
GMMG-MM5 (ISRCTN 05622749)	√	?	X	X	X	X	X	?	√	√	?	High risk of bias for one or more key domains
PANORAMA 1 (NCT01023308)	√	√	√	√	√	√	√	√	√	√	√	Low risk of bias for all key domains
MM-003 (XXXX)	√	√	X	X	X	X	X	X	√	√	X	High risk of bias for one or more key domains

(continued on following page)

TABLE A2. Study Quality (continued)

Trial Name (trial identifier)	Adequate Randomization	Allocation Concealment	Blinding	Blinding					Infrequent Loss to Follow-Up	Selective Outcome Reporting	Other Sources of Bias	Assessment of Bias
				Patients	Health Care Providers	Data Collectors	Outcome Assessors	Data Analysts				
ASPIRE (NCT01080391)	√	√	√	–	–	√	√	√	√	√	√	Unclear risk of bias for one or more key domains
POLLUX (NCT02076009)	√	√	?	X	X	?	?	?	√	√	X	High risk of bias for one or more key domains
MRC Myeloma IX (ISRCTN68454111)	√	√	?	X	X	X	X	√	√	√	X	High risk of bias for one or more key domains
GEM2005 (NCT00443235)	√	√	X	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
MM-015 (NCT00405756)	√	√	√	√	√	√	√	√	√	√	√	Low risk of bias for all key domains
VISTA (NCT00111319)	√	?	?	–	–	–	–	–	√	√	√	Unclear risk of bias for one or more key domains
APEX (NCT00048230)	√	?	?	?	?	?	?	?	√	√	?	Unclear risk of bias for one or more key domains
IFM 99-06 (NCT00367185)	√	√	?	?	?	?	?	?	√	√	√	Unclear risk of bias for one or more key domains
PETHEMA (NCT00461747)	?	?	X	X	X	X	X	X	?	?	?	High risk of bias for one or more key domains

NOTE. √, indicates criteria were met; –, indicates criteria were likely not met; X, indicates criteria were definitely not met; ?, indicates insufficient detail, not reported, and/or uncertain if the criteria were met. Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.

Abbreviations: BSBMT, British Society of Bone Marrow Transplantation; ECOG, Eastern Cooperative Oncology Group; GEM, Groupo Español de Mieloma; GMMG, German Myeloma Multicenter Group; IFM, Intergroupe Francophone du Myeloma; MRC, Medical Research Council; UKMF, UK Myeloma Forum.

TRANSFUSION MEDICINE REVIEWS

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Relationship Between Platelet Count and Bleeding Risk in Thrombocytopenic Patients

Sherrill J. Slichter

Platelets are lost from circulation by 2 mechanisms: senescence and random loss. Approximately 7.1 × 10^3 platelets/μL/d are postulated to be randomly used in maintaining vascular integrity. Thus, in clinically stable patients, major bleeding is unusual unless the platelet count is ≤5 × $10^3/\mu$L. Risk factors for bleeding at higher platelet counts are disseminated intravascular coagulation with contributory clotting factor deficiencies, structural lesions with loss of vascular integrity, and refractoriness to platelet transfusions. Several large studies have documented the safety of lowering the prophylactic platelet transfusion trigger from the previously used 20 × $10^3/\mu$L to 10 × $10^3/\mu$L. A few studies have even suggested that a 5 × $10^3/\mu$L trigger is acceptable. Based on these results, the next step of giving just therapeutic platelet transfusions is being evaluated. In a large retrospective study, the most significant predictor of bleeding was not the patient's platelet count but a history of bleeding in the prior 5 days. These data suggest that attention should be focused on providing aggressive platelet therapy for active bleeding rather than transfusing platelets prophylactically. Therapeutic platelet transfusions have been documented to control bleeding, and mortality rates are not increased when comparing patients receiving therapeutic to that seen in patients receiving prophylactic platelet transfusions.

SEVERAL STUDIES HAVE suggested that platelets provide an endothelial supportive function to prevent bleeding, by plugging gaps in the endothelium of blood vessels. In rabbits with severe thrombocytopenia, electron microscopy studies showed thinning of the endothelial cells with gaps between the cells.[1] Others have proposed that endothelial cells retract and expand intermittently leaving uncovered gaps on the subendothelial basement membrane.[2] Thus, there may be ongoing utilization of platelets to prevent extravasation of red cells through these gaps. Studies performed in thrombocytopenic rabbits showed a loss of red cells into the lymphatic system of thrombocytopenic animals, and there was an inverse relationship between increasing red cell loss and decreasing platelet counts.[3]

Further evidence that platelets support the endothelium comes from studies measuring loss of platelets from the circulation in patients with varying degrees of thrombocytopenia.[4] Radiolabeled platelet recovery and survival measurements were performed in 27 thrombocytopenic patients and 16 normal subjects. These studies showed that platelets are lost from circulation by 2 mechanisms: either senescence with a maximum platelet lifespan of 10.5 days or there is a fixed fraction of platelets amounting to 7.1 × $10^3/\mu$L/d that are removed randomly apparently in the endothelial-supportive functions suggested by the animal studies. At platelet counts above 100 × $10^3/\mu$L, this fixed platelet loss represents too small a fraction of the circulating platelets to effect platelet survival. However, at progressively lower platelet counts, the fixed platelet loss becomes an ever-increasing percentage of the circulating platelets resulting in a

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direct relationship between platelet count and platelet survival at platelet counts of $<100 \times 10^3/\mu L$ (Fig 1).

This study may suggest that, as along as there are approximately 7.1×10^3 platelets/μL/d available to provide an endothelial supportive function, hemostasis may be maintained. If the average blood volume in a 70-kg man is assumed to be 5 L and 7.1×10^9 platelets/L/day are removed randomly, then approximately 5×7.1 x 10^9 or 3.5×10^{10} platelets per day would be needed to maintain hemostasis. However, as only about two thirds of the transfused platelets circulate, the remaining third are pooled in a normal-sized spleen[5]; the actual number of platelets required may be 4.8×10^{10}, which can be met by transfusing one platelet concentrate per day containing at least 5.5×10^{10} platelets (according to US Food and Drug Administration guidelines). However, in addition to these physiologic platelet requirements, many clinically ill thrombocytopenic patients also show platelet consumption related to sepsis, malignancy, and other factors.[6] Thus, somewhat more than one platelet concentrate per day may be required to meet both physiologic and pathologic platelet requirements and to provide for some margin of safety.

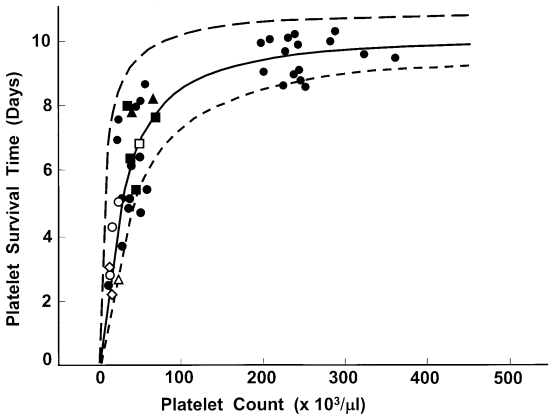

Fig 1. Relationship between platelet count and platelet survival. Relationship between platelet count and the survival of autologous (closed symbols) and donor (open symbols) ^{51}Cr-labeled platelets in normal and thrombocytopenic subjects with no evidence of hypersplenism (circles). Complications included splenectomy (squares), splenomegaly (triangles), and prior transfusions (diamonds). At platelet counts of $<100 \times 10^3/\mu L$, there is a direct relationship between the platelet count and the platelet survival. (Reprinted with permission.[4])

RELATIONSHIP BETWEEN PLATELET COUNT AND BLEEDING RISK IN THROMBOCYTOPENIC PATIENTS NOT RECEIVING PLATELET TRANSFUSIONS

Two studies have directly evaluated hemorrhagic risk in thrombocytopenic patients not being supported by platelet transfusions. In the first study, hospital records of 92 consecutive patients admitted between 1956 and 1959 to the National Cancer Institute were studied; 40 of the patients were adults and 52 were children.[7] There were 34 cases of acute myelocytic leukemia (AML) and 57 cases of acute lymphocytic leukemia. The relationship between platelet count and the frequency of all types of hemorrhage for the 92 patients studied is shown in Figure 2. Even in patients with platelet counts of $<1 \times 10^3/\mu L$, gross bleeding occurred on only 33% of the days. In contrast, at platelet counts between $5 \times 10^3/\mu L$ and $20 \times 10^3/\mu L$, gross bleeding occurred on only 3% of the days, and the authors could not determine a cutoff level in which patients should be transfused prophylactically. However, apparently based on this study, it became common practice to transfuse platelets prophylactically for platelet counts of $\leq 20 \times 10^3/\mu L$. At the time this study was performed, it was not appreciated that aspirin interfered with platelet function. Thus, it is likely that many of these patients became febrile during the period of observation and were probably given aspirin. This suggests that the bleeding risk in nonaspirinated patients may be even lower than suggested by this study.

Fatal intracranial hemorrhage occurred in 16 of these 92 nontransfused thrombocytopenic patients (17%). In 8, the intracranial bleeding was associated with a blastic crisis, and, at autopsy, intracerebral leukostasis and leukemic nodules were found. In this group, platelet levels were relatively high at the time of the hemorrhage, the median platelet count being $10 \times 10^3/\mu L$, and only 1 patient had a platelet count below $5 \times 10^3/\mu L$. This confirms the major role of the leukemia in this type of hemorrhage. In contrast, in the remaining 8 patients, there was no associated blastic crisis, and, in this group, the risk of intracranial hemorrhage was directly related to the platelet level; the highest frequency being 0.76% of the days on which platelet counts were below $1 \times 10^3/\mu L$, and only 1

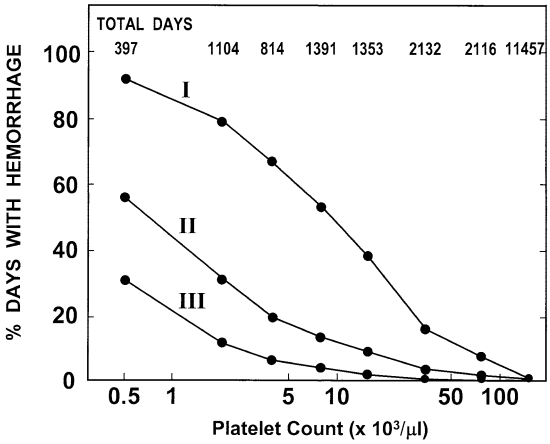

Fig 2. Relationship between hemorrhage and the platelet count in nontransfused thrombocytopenic patients. The percentage of days with hemorrhage for 92 patients is shown for each of 8 platelet count categories (figures across the top are the total number of patient days in each of the categories). Curve I shows data for all hemorrhagic manifestations; curve II shows the data for patients where skin, bleeding, and epistaxis are excluded; and Curve III refers only to grossly visible hemorrhage such as gross hematuria, melena, and hematemesis. (Reprinted with permission.[7])

patient had a platelet count over $5 \times 10^3/\mu L$, and none exceeded $10 \times 10^3/\mu L$.

In an attempt to quantify the relationship between bleeding and platelet count, 20 stable aplastic thrombocytopenic patients on no medications and not receiving platelet transfusions had a small blood sample drawn to permit labeling of their red cells with ^{51}Chromium.[8] After reinfusion of their radiolabeled red cells, a blood sample was drawn daily from the patients, and 24-hour stool collections were obtained. Thus, knowing the radioactivity per milliliter of circulating blood on each study day and the amount of radioactivity present in the daily stool collections, it was possible to determine the volume (mL) of blood lost per day in the stool. Study duration averaged 8.4 ± 3.9 days with a range of 4 to 16 days. It was presumed that these stool blood loss studies would provide an assessment of blood loss through the intact vasculature of the gastrointestinal (GI) track and might also be reflective of the potential for bleeding elsewhere. Figure 3 shows the relationship between platelet count and stool blood loss. At platelet counts of $>10 \times 10^3/\mu L$, stool blood loss was no different from values found in normal subjects (ie, <5 mL/d). At levels between 5 and $10 \times 10^3/\mu$mL, blood loss was only slightly increased above normal (9 mL ± 7/d). However, at platelet counts of $<5 \times 10^3/\mu L$, stool blood loss was markedly elevated in all patients tested (50 mL ± 20/d). Thus, in these 2 studies, that assessed either clinical manifestations of bleeding or stool blood loss, there is remarkable concordance between the onset of serious bleeding and the platelet count. These studies suggest that the required prophylactic platelet transfusion trigger level may well be only $5 \times 10^3/\mu L$ to maintain vascular integrity and, thereby, prevent significant bleeding complications. This platelet count is very similar to the $7.1 \times 10^3/\mu L$/d predicted to be lost in an endothelial supportive function.[4]

TRANSFUSED PLATELETS DO PROVIDE HEMOSTASIS

Complete autopsies were performed on all 57 patients who died of acute leukemia at Roswell Park Memorial Institute during a 2-year period from 1963 to 1965.[9] Thirty patients died before and 27 after the availability of platelet transfusions. This study demonstrated that major hemorrhage was the proximate cause of death in 63% of patients with acute leukemia before versus only 15% after the institution of platelet therapy ($P < .001$).

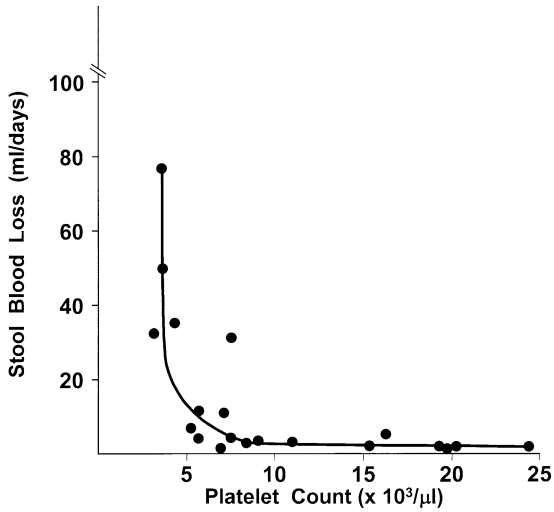

Fig 3. Fecal blood loss in thrombocytopenic patients. When fecal blood loss (expressed as mL of blood/d) was determined in 20 aplastic thrombocytopenic patients, blood loss was less than 5 mL/d at platelet counts greater than $10 \times 10^3/\mu L$. At platelet counts between 5 and $10 \times 10^3/\mu L$, blood loss averaged 9 mL ± 7/d (±1 S.D.). At levels less than $5 \times 10^3/\mu L$, blood loss was markedly elevated at 50 mL ± 20/d. (Reprinted with permission.[8])

Of the 30 patients who did not receive intensive platelet therapy, 15 (50%) had gross intracranial hemorrhage and 27 (90%) had gross pulmonary hemorrhage. In contrast, of the 27 patients who received platelet therapy, only 5 (19%) had gross intracranial hemorrhage, and 14 (52%) had gross pulmonary hemorrhage ($P < .05$ for intracranial hemorrhage and $P < .005$ for pulmonary hemorrhage compared with nontransfused patients). The incidence of GI hemorrhage was slightly lower in the platelet transfusion group, whereas there were no differences in the amount of hemorrhage in the heart or kidneys.

The records of 103 patients who died with acute leukemia during 2 years (1950 and 1955) when platelet transfusions were not available were examined retrospectively for evidence of bleeding on 911 days when their platelet counts were $<50 \times 10^3/\mu L$.[10] Minor bleeding (defined as petechia and ecchymosis, epistaxis, scleral hemorrhage, microscopic hematuria, and guaiac positive stool) occurred in 48% of the patients. Severe bleeding (defined as gross GI bleeding or hematuria) occurred in 12% of the patients. In contrast, in a later prospective study, when prophylactic platelet transfusions became available and were given for platelet counts of $<25 \times 10^3/\mu L$, minor bleeding occurred in only 8% and major bleeding in 2% of the 62 leukemia patients who received a total of 308 transfusions.

A notable change in the mortality of patients with aplastic anemia was observed in Japan in the 1970s after the introduction of platelet therapy.[11] The 5-year fatality rate was reduced from 52.8% (1968-1972) to 39.7% (1973-1977) after platelet transfusions became available ($P < .05$).

In a double-blind study, 21 patients with thrombocytopenia and acute leukemia were randomized to receive either platelets or platelet-poor plasma as prophylaxis against bleeding.[12] Twelve patients were given platelets, and 9 were given platelet-poor plasma in equivalent volumes, every third or fourth day. Seven of the 12 patients receiving platelets prophylactically did not bleed during the study. On the other hand, 8 of 9 patients receiving platelet-poor plasma bled ($P < .05$). Thus, the conclusion was reached that platelet transfusions did improve hemostasis in thrombocytopenic patients.

COMPARISON OF BLEEDING RISKS IN PATIENTS GIVEN PROPHYLACTIC PLATELET TRANSFUSIONS VERSUS ONLY THERAPEUTIC PLATELET TRANSFUSIONS FOR ACTIVE BLEEDING

There have been 2 randomized prospective transfusion trials comparing therapeutic versus prophylactic platelet transfusions to determine whether it is safe to give platelets only at the onset of active bleeding or whether prophylactic platelet therapy is needed. In 1 study,[13] 56 children with acute leukemia were randomly assigned to receive platelets prophylactically at a platelet count of $20 \times 10^3/\mu L$ irrespective of clinical events. The therapeutic group was transfused only when significant bleeding occurred (defined as nasal or oral bleeding requiring packing, gross GI bleeding, gross genitourinary bleeding, any central nervous bleeding, or bleeding requiring a red cell transfusion) and not for thrombocytopenia alone. The time to first bleeding episode was significantly longer (Fig 4) in the prophylactic group. During the entire study period, there were significantly fewer bleeds per 100 patient months in the prophylactic group (1.9 in the prophylactic group compared with 7.9 in the therapeutic group), but the total days of bleeding per 100 patient months was

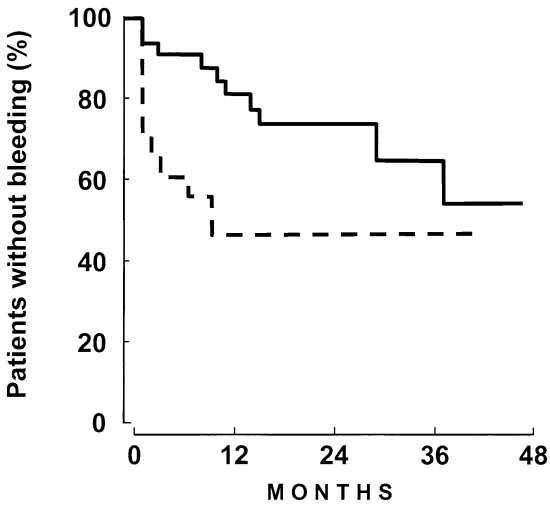

Fig 4. Percentage of patients without bleeding while receiving prophylactic versus therapeutic platelet transfusions. The percentage of patients without bleeding at intervals after randomization is increased in the prophylactic (solid line) as opposed to the therapeutic group (dashed line). There was a significant increase in the initial period, free of bleeding, in the prophylactic compared with the therapeutic group ($P = .014$). (Reprinted with permission.[13])

the same in both groups (9.8 days in the prophylactic group compared with 10.7 days in the therapeutic group). Of the 47 bleeding episodes, 34 were nasal and oral and 10 were GI with approximately the same distribution seen in the 2 groups.

Twenty-five of the 35 patients in the prophylactic group received 284 units of platelets in 76 transfusion episodes. This represents approximately twice the frequency of transfusion as in the therapeutic group and almost 3 times as many platelets were given (Table 1). Of the 11 patients in the therapeutic group who bled, 2 died within 48 hours of the bleed. One of the 10 patients in the prophylactic group who bled died within 48 hours of the bleed. Survival rates were the same for both groups.

In the second study (reported only as an abstract), platelet use was evaluated in 29 adults during intensive induction chemotherapy for acute nonlymphoblastic leukemia.[14] Death caused by hemorrhage, red cell transfusion requirements, and response to therapy were used as criteria for assessing the benefits of prophylactic platelet transfusions. The prophylactic group received platelets for platelet counts below $20 \times 10^3/\mu L$. The therapeutic group received platelets only when they had significant bleeding or had a platelet count below $20 \times 10^3/\mu L$ proceeded in the prior 24 hours by a 50% drop in their platelet count. It is, thus, conceivable that some patients in the therapeutic group were not bleeding, and yet they received platelets. Similar to the other study, platelet use was significantly higher (approximately twice as much) in the prophylactic group compared with the therapeutic group, whereas other study parameters were the same between groups. In addition, there was no increase in the number of red cell transfusions provided in the 2 groups (Table 1).

Table 1. Transfusion Requirements: Prophylactic Versus Therapeutic Platelet Transfusions*

	Prophylactic		Therapeutic	
	Study 1†	Study 2‡	Study 1	Study 2
Number of patients	35	17	21	12
Platelet concentrates or transfusion events	284	32 ± 16	100	16 ± 3
Red cells		7 ± 1		7 ± 1

*Prophylactically transfused patients were given platelets whenever the platelet count was $\leq 20 \times 10^3/\mu L$. Therapeutic patients received platelet transfusions only for evidence of active bleeding.

†In Study 1, data are given as platelet concentrates transfused for 10 months of observation. Data from Murphy et al.[13]

‡In Study 2, data are given as number of transfusions/course (±1 SD).

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In non-randomized studies using only therapeutic platelet transfusions, 70 children with acute lymphocytic leukemia were studied during induction chemotherapy over a 5-year period.[15] Platelets (3-10 U) were given only if there was significant clinical bleeding associated with a platelet count below $20 \times 10^3/\mu L$. There were no deaths caused by hemorrhage, and, among these patients, 84% achieved remission without a single platelet transfusion, despite the fact that 49% had a count below $20 \times 10^3/\mu L$ for a total of 255 days during the induction phase. In another study in 34 adults, 26 with acute leukemia, there were no hemorrhagic deaths using a policy of giving only therapeutic platelet transfusions for bleeding.[16]

In 2 recent nonrandomized prospective studies, as yet reported only as abstracts, therapeutic platelet transfusions were the predominant method of platelet support provided to clinically stable thrombocytopenic patients with AML receiving chemotherapy or for patients undergoing autologous stem-cell transplants.[17,18] For the clinically stable patients (fever $<38°C$, no local infections, no sepsis, no plasma coagulation factor abnormalities, and no intervention except for bone marrow biopsy), no platelet transfusions were given regardless of their morning platelet count.[17,18] Prophylactic platelet transfusions were given to unstable patients with morning platelet counts of $<10 \times 10^3/\mu L$, and therapeutic transfusions were given for World Health Organization (WHO) bleeding grades ≥ 1[18] or ≥ 2.[17] Generally accepted WHO bleeding grades are grade 0, none; grade 1, petechiae, ecchymosis, occult blood in body secretions, and mild vaginal spotting; grade 2, evidence of gross hemorrhage not requiring red cell transfusions over routine transfusion needs (eg, epistaxis, hematuria, hematemesis); grade 3, hemorrhage requiring transfusion of 1 or more units of red cells/d; and grade 4, life-threatening hemorrhage, defined as either massive bleeding causing hemodynamic compromise or bleeding into a vital organ (eg, intracranial, pericardial, or pulmonary hemorrhage).[19]

In 34 patients with AML,[15] the median platelet count before a therapeutic platelet transfusion was

$6 \times 10^3/\mu L$. During the period of severe thrombocytopenia (270 days $<20 \times 10^3/\mu L$ and 157 days $<10 \times 10^3/\mu L$), 50 prophylactic and 35 therapeutic transfusions were given with a mean of 1.5 and 1.0, respectively. There were no WHO grade 4 bleeding episodes, and the 2 grade 3 bleeding episodes were controlled by local measures and platelet transfusions.

Of 44 consecutive patients admitted for autologous peripheral stem cell transplant, there were 54 transplants performed, and, during 348 and 180 days, platelet counts were <20 or $<10 \times 10^3/\mu L$, respectively.[16] Twenty-nine of 54 transplants (54%) had no bleeding, WHO grade 2 bleeding occurred in 14 (26%), and there was no WHO grade 3 or 4 bleeding. Nineteen transplants (35%) were performed without platelet transfusions, and, during the course of 12 transplants (22%), therapeutic platelet transfusions were given at a median count of $9 \times 10^3/\mu L$ (range 2-46 $\times 10^3/\mu L$). The majority of prophylactic platelet transfusions given in these 2 studies were given because of fever.[15,16] Whether this is necessary will be examined in future studies. These studies suggest that the majority of patients who bleed in the absence of prophylactic platelet transfusions can recover after a therapeutic transfusion.

PROPHYLACTIC PLATELET TRANSFUSION TRIGGER TRIALS COMPARING PLATELET TRIGGERS OF $10 \times 10^3/\mu L$ WITH $20 \times 10^3/\mu L$

Seven relatively recent studies[20-26] have evaluated prophylactic platelet transfusion therapy given at platelet counts of $10 \times 10^3/\mu L$ versus the previously accepted standard of $20 \times 10^3/\mu L$. Four of these studies were randomized prospective trials,[20-23] and 3 were nonrandomized.[24-26] Uniformly, these studies showed no increase in bleeding risk or red cell transfusion requirements using the lower transfusion trigger, and 3 of the studies showed substantial decreases in the number of platelet transfusions required and their associated costs (Table 2).

PLATELET TRANSFUSIONS AT A PLATELET TRIGGER OF $5 \times 10^3/\mu L$

Based on some of these prior studies, there has been an increased interest in determining if an even lower platelet transfusion trigger of $5 \times 10^3/\mu L$ would provide effective hemostasis. In 1983, a prospective study of platelet transfusions in pa-

Table 2. Platelet Transfusion Trials Comparing Prophylactic Platelet Transfusion "Triggers" of 10 Versus 20 $\times$ $10^3/\mu L$

10,000/μL Platelet Transfusion Trigger								20,000/μL Platelet Transfusion Trigger								
			Platelet Transfusions							Platelet Transfusions						
Number of Patients	Major Bleeding (%)	Hemorrhagic Deaths	Units		Units Per Thrombocytopenic Day	Transfusions Per Patient	RBC Transfusions	Number of Patients	Major Bleeding (%)	Hemorrhagic Deaths	Units		Units Per Thrombocytopenic Day	Transfusions Per Patient	RBC Transfusions	Cost	Reference
			Concentrates	Apheresis							Concentrates	Apheresis					
78	14	0				10.4 ± 17	6.0	81	17	0				10.2 ± 11	5.9		20
135	22	1				7.1 ± 4.6‖	9.6 ± 5.2	120	20	0				9.0 ± 5.2	9.1 ± 4.1	22%	21
58	18	0	15.4§ (0-152)	3.0‡ (0-16)			7.3 (0-21)	47	17	0	25.4 (0-180)	4.8 (0-33)			8.3 (2-28)	33%	22
37		0				7† (5-11)	11 (8-14)	41		0				11 (6-15)	10 (6-14)		23
103	12	3	54§ (0-647)		0.5§ (0-6.94)			87	14	4	73 (3-943)		0.8 (0.03-30)				24
*	15				0.42			*	18				0.49			$47,235	25
21	42	0				8.4 ± 5.3		27	30	0				8.6 ± 5.5			26

NOTE. Major bleeding was defined as more than petechia, ecchymosis, or epistaxis and usually involved bleeding requiring red cell transfusions. Data for references 20,21,22,25,and 26 are reported as the mean with ranges or ±1 SD. Data for reference 23 are reported as the median (ranges 25 to 75 percentile). Data for reference 24 are reported as the median with ranges. Statistically-significant improvements in the results and cost savings are all in favor of the $10 \times 10^3/\mu L$ compared with the $20 \times 10^3/\mu L$ trigger. If no statistical information is given, the results did not differ.

*Total patients admitted to both arms of the study were 124.

†$P = .07$.

‡$P < .05$.

§$P < .01$.

‖$P < .001$.

tients with newly diagnosed acute leukemia was initiated and ended in 1990.[27] One hundred two consecutive patients being treated for acute leukemia were enrolled. Patients were examined daily for evidence of bleeding whenever their platelet counts were below $50 \times 10^3/\mu L$. The platelet transfusion protocol is given in Table 3. Patient diagnoses were acute nonlymphocytic leukemia (n = 87) or acute lymphocytic leukemia (n = 15). Included were 7 patients with acute progranulocytic leukemia and 4 others who had disseminated intravascular coagulation at admission. Patients were followed during 254 courses of marrow ablative chemotherapy for a total of 6,002 days. Minor bleeding episodes (WHO grade 1) included any mucocutaneous hemorrhages or hematomas not requiring red cell transfusions. Major bleeding episodes included melena, hematemesis, hematuria, and hemoptysis whether or not blood transfusions were required (WHO grade 2). Almost all patients (95%) with platelet counts of $\leq 5 \times 10^3/\mu L$ received a platelet transfusion as per protocol. The results of the study are shown in Figure 5. Thirty-one major bleeding episodes occurred on 1.9% of the study days when platelet counts were $10 \times 10^3/\mu L$ or less and on 0.07% of study days when counts were 10 to $20 \times 10^3/\mu L$. The authors concluded that their study indicated that the threshold for prophylactic transfusions can safely be set at $5 \times 10^3/\mu L$ in patients without fever or bleeding manifestations and at $10 \times 10^3/\mu L$ in patients with such signs. For patients with coagulation disorders or anatomic lesions or for those on heparin, the threshold should be at least $20 \times 10^3/\mu L$. However, because the platelet transfusion protocol (Table 3) established preselected clinical or laboratory findings that mandated transfusions at platelet counts higher than $5 \times 10^3/\mu L$, it cannot be determined whether patients with these findings really needed transfusions at a higher level or whether they would have been effectively protected from bleeding using only the $5 \times 10^3/\mu L$ prophylactic platelet count trigger. Death during induction therapy was related to hemorrhage in 3 patients with intracerebral bleeding. One patient was alloimmune platelet refractory with an unsupportable platelet count of $<1 \times 10^3/\mu L$, another patient had disseminated intravascular coagulation and a platelet count of $55 \times 10^3/\mu L$, and the third patient was on heparin with her lowest documented platelet count being $35 \times 10^3/\mu L$.

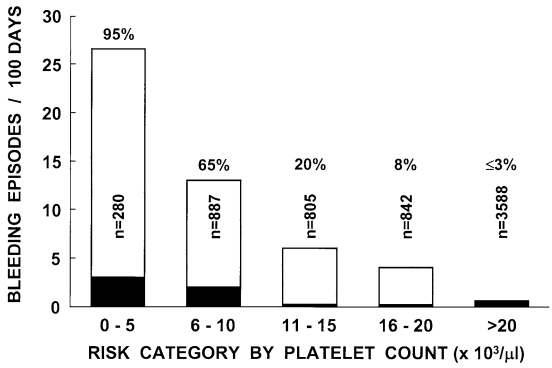

Fig 5. Relationship between bleeding risk and platelet count. Open bars, minor bleeding complications; solid bars, major bleeding complications. Numbers (n) are observed days at risk. Percentages are percent of patients who received platelet transfusions. (Reprinted with permission.[27])

Table 3. Platelet Transfusion Protocol

Morning Platelet Count ($\times 10^3/\mu L$)	Give Prophylactic Platelet Transfusion
0-5	In every case
6-10	In the presence of:
	Fresh minor hemorrhagic manifestations
	Body temperature >38.0°C
11-20	In the presence of:
	Coagulation disorders and/or heparin therapy
	Before bone-marrow biopsy or lumbar puncture
>20	In the presence and until control of:
	Major bleeding complications
	Before minor surgical procedures (other biopsies)
	Before central venous catheter insertion, or arterial punctures

Reprinted with permission.[27]

In another study, 46 patients enrolled in 4 different dose-intensive chemotherapy trials for gynecologic malignancies were transfused prophylactically only for counts of $<5 \times 10^3/\mu L$.[28] Minor bleeding was defined as non–life-threatening hemorrhage and consisted of ecchymosis, mild epistaxis, microscopic hematuria, and intermittent mild melena. Major bleeding was defined as life-threatening hemorrhage and consisted of central nervous system hemorrhage or profuse bleeding not responsive to local measures including gross hematuria and significant melena. There were 11 episodes of thrombocytopenia during the course of these chemotherapy programs when patients developed platelet counts of $<5 \times 10^3/\mu L$. All of these

patients received prophylactic platelet transfusions and none resulted in major hemorrhage.

In addition, there were 100 episodes of severe thrombocytopenia with platelet counts between 5 and 20 $\times$ $10^3/\mu$L for a median duration of 6 days (1-25 days). Of the 38 episodes of thrombocytopenia with platelet counts between 5 to 10 $\times$ $10^3/\mu$L, 24 (63%) received platelet transfusions, and 14 (37%) did not. Only minor bleeding occurred in 17% of those transfused versus 24% of those not transfused ($P = .95$). At platelet counts between 10 to 20 $\times$ $10^3/\mu$L, only 6 of 62 (9%) of patients were transfused, and minor bleeding occurred in 66% of those transfused and in 13% of those not transfused. Overall, only 18 episodes (18%) of severe thrombocytopenia (platelet counts between 5,000/μL to 20,000/μL) resulted in minor bleeding, and, within the 30% who were transfused, 27% had minor bleeding compared with 14% in the 70% of patients not transfused ($P = .2$). There was no evidence of major bleeding in any of these patients. No patients with platelet counts of $>20 \times 10^3/\mu$L received prophylactic transfusions, and none of these patients had any evidence of bleeding. The 18% rate of minor hemorrhage in this study with no episodes of major bleeding is much less than has been suggested in studies in leukemic patients. The most likely explanation is that patients in this study developed only short duration chemotherapy-induced thrombocytopenia that was not associated with sepsis, disseminated intravascular coagulation, or heparin therapy.

A more restrictive platelet transfusion policy was recently instituted for 25 patients with chronic severe aplastic anemia in need of long-term platelet support.[29] Platelet transfusions were given at platelet counts of $<5 \times 10^3/\mu$L in stable patients (body temperature $\leq$38°C, no coagulation disorder, no extensive minor or major bleeding), at platelet counts between 5 and 10 $\times$ $10^3/\mu$L, in case of recent hemorrhage and/or fever $>$38°C, or at platelet counts $>10 \times 10^3/\mu$L in case of major bleeding events ($\geq$WHO grade 2 bleeding). In addition, a policy of progressively-lengthening the transfusion interval up to at least 7 days in outpatients irrespective of the interim course of their platelet counts was also initiated. The study was based on a retrospective analysis of a total of 18,706 patient days with platelet counts of $\leq 10 \times 10^3/\mu$L. Mean pretransfusion platelet counts were $6 \pm 5 \times 10^3/\mu$L. Altogether, 1,135 platelet transfusions were given, 88% at counts $\leq 10 \times 10^3/\mu$L, and 67% at counts ≤ 5 $10^3/\mu$L. Intervals of platelet transfusions of 7 days or longer were achieved in 78% of all outpatient transfusions (mean 11.9 days, median 7 days) in contrast to the 2 to 3 days generally observed. During the period of observation, 3 major nonlethal bleeding complications occurred which were well controlled with platelet transfusions. There were 5 reported deaths from hemorrhage, and these were associated with either alloimmunization in 4 patients or one patient's refusal of further medical treatment including transfusions.

As a followup to the stool blood loss studies in patients with hypoproliferative thrombocytopenia not receiving platelet transfusions,[8] a prospective randomized study evaluated patients prophylactically assigned to receive all their platelet transfusions (6 pooled random donor platelet concentrates stored for 4 to 5 days) for morning platelet counts of either 5, 10, or 20 $\times$ $10^3/\mu$L.[30] Pooled random donor platelets at the end of their dating period were specifically used so the study data would reflect transfusion results with potentially the least effective platelets. Patients had an aliquot of their red cells labeled with ^{51}Chromium, and all stools and a 5-mL daily blood sample were analyzed for radioactivity to determine stool blood loss.

Eighty-one patients were enrolled in the study, and, of these, 45% of the patients had breast cancer, 33% had AML, 11% had non-Hodgkins lymphoma, and the remainder had other types of cancer. Seventy-two percent of the patients received chemotherapy, and 28% received a peripheral blood stem cell transplant. Stool blood loss did not differ among the transfusion trigger groups (Table 4), nor was there a difference in red cell transfusion requirements. However, there were statistically significant differences in the number of platelet transfusion events based on the transfusion trigger (Table 5). Clearly, platelet transfusions effectively prevented stool blood loss at low platelet counts (ie, patients transfused at a platelet trigger of 5 $\times$ $10^3/\mu$L had stool blood loss that averaged 11 ± 2 mL/thrombocytopenic day in this study compared with 50 ± 20 ml/thrombocytopenic day in a prior study of nontransfused patients with platelet counts of $\leq 5 \times 10^3/\mu$L).[8]

Table 4. Stool Blood Loss and RBC Transfusions in Patients Randomly Assigned to Receive Platelet Transfusions for Platelet Triggers of 5, 10, or 20 × $10^3/\mu L$

Transfusion Trigger ($\times 10^3/\mu L$)	Patients	Stool Blood Loss (mL)		RBC-Transfusions	
		Total	Per Thrombocytopenic Day*	Total	Per Thrombocytopenic Day*
5	31	111 ± 29	11 ± 2	4.1 ± 0.6	0.4 ± 0.04
10	26	71 ± 15	6 ± 1	4.8 ± 0.7	0.4 ± 0.04
20	24	136 ± 53	10 ± 3	5.5 ± 1.0	0.4 ± 0.05

NOTE. Data reported as average ±1 SE.

*Total stool blood loss divided by number of days platelet count ≤20 × $10^3/\mu L$.

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POTENTIAL INFLUENCE OF PLATELET TRANSFUSIONS ON DURATION OF THROMBOCYTOPENIA

Another reason to consider the use of a lower platelet transfusion trigger level is the effect of platelet transfusions on thrombopoietin (TPO) levels.[31,32] The identification of TPO[33-35]—the long-sought primary regulator of platelet hemostasis—has allowed TPO levels to be measured in a variety of clinical settings and to also determine the localization of its receptor on different cells. It has been determined that the TPO receptor cMpl is located on both megakaryocytes and platelets.[36] It has been postulated that there is a relatively constant amount of TPO produced,[37] and, as long as the platelet count is normal, only a small amount of the TPO produced is not adsorbed by the circulating platelets and remains available to interact with bone marrow megakaryocytes or earlier progenitor cells to stimulate new platelet production. However, at low platelet counts, more TPO is available to stimulate the production of greater numbers of platelets to re-establish normal platelet counts.

In a rabbit model, animals were made thrombocytopenic by the administration of busulfan.[31] Because the platelet count decreased after the busulfan, there was a reciprocal increase in the TPO level. However, if the thrombocytopenic animals were given a platelet transfusion, there was an associated dramatic decrease in the TPO level showing that the transfused platelets adsorbed TPO.

A relationship between TPO levels and posttransfusion corrected count increment was also observed in 12 thrombocytopenic patients who received 21 platelet transfusions.[32] Pretransfusion TPO levels averaged 404 ± 289 (1 SD) pg/mL compared with 319 ± 211 pg/mL posttransfusion ($P < .01$). Thus, one could hypothesize that the administration of as few platelets as possible, consistent with the maintenance of adequate hemostasis, would be associated with the earliest return of TPO-stimulated marrow platelet production. Some support for this hypothesis is provided by the 5, 10, and 20 × $10^3/\mu L$ platelet trigger trial in which progressively more platelets were transfused at the higher trigger levels.[30] The more platelet transfusions given the longer was the duration of platelet counts of ≤20 × $10^3/\mu L$ (ie, the average duration of thrombocytopenia (±ISE) was 9.6 ± 0.9, 11.9 ± 1.3, and 13.3 ± 1.9 days, respectively, for the 3 arms of the study).

Table 5. Platelet Transfusions in Patients Randomly Assigned to Receive Platelet Transfusions for Platelet Triggers of 5, 10, or 20 × $10^3/\mu L$

Transfusion Trigger ($\times 10^3/\mu L$)	Patients	Thrombocytopenic Days*	PLATELET TRANSFUSIONS				1-Hour CCI†
			Total			Per Day	
5	31	9	2.0	$P = .03$	$P = .001$	0.25	12,700 ± 800
10	26	11	3.5	$P = .04$		0.35	$P = .001$ 11,500 ± 900
20	24	10	5.0			0.58	10,500 ± 800

NOTE. Data for thrombocytopenic days and platelet transfusion reported as the median.

*Days platelet count ≤20 × $10^3/\mu l$ for each study arm.

†CCI = corrected count increment reported as average (+/− 1. S.E.) calculated as: (posttransfusion − pretransfusion platelet count/μL) × body surface area (m^2)/number of platelets transfused × 10^{-11}.

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OTHER LARGE STUDIES EVALUATING THE RELATIONSHIP BETWEEN PLATELET COUNT AND BLEEDING RISK

A retrospective review of all thrombocytopenic adult patients admitted to the Johns Hopkins Oncology Center over 10 years (1988-1997) showed by multivariate analysis no relationship between morning platelet count or lowest platelet count of the day and bleeding in 2,942 patients.[38] Patient days (79,546) included in the study were all inpatient days in which the first morning platelet count was $50 \times 10^3/\mu L$ or less. All patients on the transfusion service were evaluated daily for bleeding through chart review, rounds, review of laboratory values, and review of red cell usage. The WHO bleeding scale of 0 to 4 was used to assess bleeding risk. The majority of patients, 64.4% had hematologic malignancies, 31.4% had solid tumors, 1.3% brain tumors, and 2.9% nonmalignant diagnoses; 46.2% had a bone marrow transplant. The median number of days of thrombocytopenia per patient was 18 with an interquartile range of 6 to 37 days. Severe bleeding occurred on 1.3% of patient days (grade 3 on 1.2% and grade 4 on 0.1%) in 368 patients (13%) lasting for a mean of 2.7 days. Moderate bleeding grade 2 occurred on 11.6% of patient days in 1,689 patients (57%). The mean platelet count on days when the patients were transfused was $20 \times 10^3/\mu L$ versus $33 \times 10^3/\mu L$ on days when the patients were not transfused, and transfusions were given on 53.6% of patient days.

Although there was no relationship between platelet count and bleeding risk, there were several other factors that independently correlated with bleeding including recent hemorrhage in the previous 5 days (odds ratio 6.72), uremia with associated platelet dysfunction (odds ratio 1.64), hypoalbuminemia, a potential surrogate marker for liver dysfunction resulting in coagulation factor deficiencies (odds ratio 1.54), recent bone marrow transplantation with potential contributing factors of severe mucositis, venocclusive disease of the liver, and endothelial damage because of toxicity of the preparative regimen (odds ratio 1.32). The odds ratios of all factors except for previous bleeding were relatively small. These findings suggest that the major goal of transfusion support should be the aggressive therapeutic use of blood products to treat bleeding rather than prophylactic use based on such weak clinical correlates as the platelet count which did not predict bleeding.

In another study[39] in which reliable platelet counting using an automated platelet counter was achieved even with platelet counts as low as $2 \times 10^3/\mu L$, 64 patients were evaluated by hospital nurses for bleeding if their morning platelet count was $<150 \times 10^3/\mu L$ (1,809 patient days). An observed relationship between minor bleeding (comprised of petechiae, cutaneous bleeding, oral bleeding, epistaxis, subconjunctival hemorrhage, microscopic hematuria, bloody pleural or ascitic fluid, and guaiac positive stool or emesis) and platelet counts was observed (Fig 6). However, there was much less of a relationship between major bleeding and platelet count (Fig 7). Major bleeding was classified as central nervous system hemorrhage, gross hematuria, hemoptysis, melena, hematochezia, hematemesis, and vaginal bleeding. Minor bleeding episodes occurred on 1,265 (69.9%) and major bleeding episodes occurred on 317 (17.5%) of the 1,809 patient days of follow-up. On 25% of the patient days in which minor bleeding occurred, major bleeding was also noted; 97.5% of major bleeding episodes were also accompanied by minor bleeding. There was no cen-

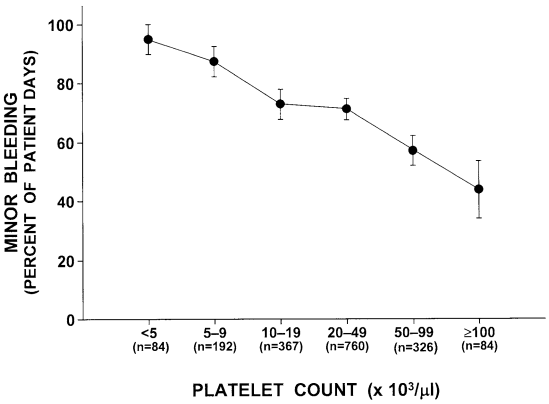

Fig 6. Relationship between minor bleeding and platelet count. Relationship between incidence of minor bleeding (ordinate) and automated platelet counts (abscissa). Bars indicate 95% confidence intervals. n, patient days. One-way analysis of variance revealed that the incidence of minor bleeding was significantly lower on days when the platelet count was $\geq 50 \times 10^3/\mu L$ than when the platelet count was lower ($P < .05$). On days when the platelet count was $\geq 20 \times 10^3/\mu L$, there was significantly less minor bleeding than when the count was $<10 \times 10^3/\mu L$ ($P < .05$). Furthermore, when the platelet count was $\geq 10 \times 10^3/\mu L$, there was significantly less minor bleeding than on days when the count was lower than that value ($P < .05$). (Reprinted with permission.[39])

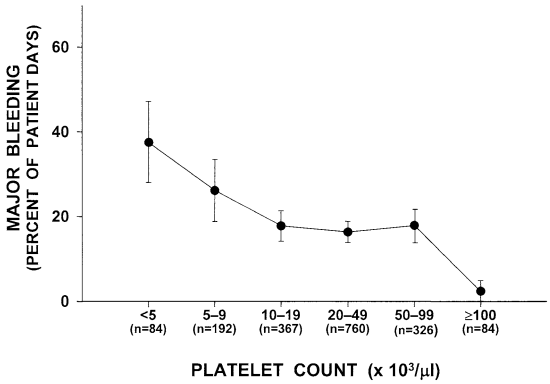

Fig 7. Relationship between major bleeding and platelet count. Relationship between incidence of major bleeding (ordinate) and automated platelet counts (abscissa). Bars indicate 95% confidence intervals. n, patient days. One-way analysis of variance revealed that the incidence of major bleeding was significantly lower on days when the platelet count was ≥100 × $10^3/\mu$L than when the platelet count was lower (P < .05). On days when the platelet count was ≥20 × $10^3/\mu$L, there was significantly less major bleeding than when the count was <10 × $10^3/\mu$L (P < .05). (Reprinted with permission.[39])

tral nervous system or other life-threatening bleeding detected during the study. For both major and minor bleeding, there were no significant differences in the incidence of bleeding between groups of patients with 10 to 20 × $10^3/\mu$L platelets compared with those with platelet counts of 20 to 50 × $10^3/\mu$L. However, this relationship was confounded by the more frequent platelet transfusions received by patients in the former group. Thus, platelet transfusions were administered on 98% of days when patients had platelet counts between 10 and 20 × $10^3/\mu$L compared with 33% of the days when the platelet count was 20 to 50 × $10^3/\mu$L. As in prior studies, substantial increases in the risk of major bleeding only occurred at platelet counts of ≤5 × $10^3/\mu$L.

SPECIAL SITUATION PATIENTS

The majority of the previous discussion about the effects of platelet count on bleeding risk is related to studies performed in patients with acute leukemia undergoing induction chemotherapy. However, there are 2 other major groups of patients who require platelet transfusion therapy, and, therefore, it is relevant to evaluate specifically the relationship between platelet count and bleeding risk in these patients (ie, those undergoing stem-cell transplantation and patients with solid tumors).

Stem-Cell Transplantation

An observational study was conducted at 18 transplant centers in the United States and Canada to evaluate platelet use and hemorrhagic events.[40] The study included 789 patients transplanted in 1995. Moderate bleeding was estimated as blood loss between 250 and 500 mL, possibly needing blood replacement; severe bleeding was estimated as blood loss >500 mL, requiring blood replacement; and life threatening was estimated as blood loss of >1,000 mL or blood loss producing hypotension or intracranial bleeding. Cases of pulmonary hemorrhage, including diffuse alveolar hemorrhage, were graded as life threatening.

Platelets were transfused prophylactically at all 18 transplant centers, and the distribution of platelet transfusion days by morning platelet count is shown in Figure 8, showing that most platelets were transfused at platelet counts between 10 and 19 × $10^3/\mu$L (63% of platelet transfusion days). By contrast, a morning platelet count of <10 × $10^3/\mu$L occurred on only 14% of the platelet transfusion days. One hundred forty-three hemorrhagic events of moderate or greater severity occurred in 89 patients (11%). Most events occurred in patients undergoing allogeneic transplantation (78%) and before platelet recovery (89%). The median (range) time of hemorrhage from the date of stem-cell infusion was 19 days (0-60). The major site of bleeding was genitourinary, often related to che-

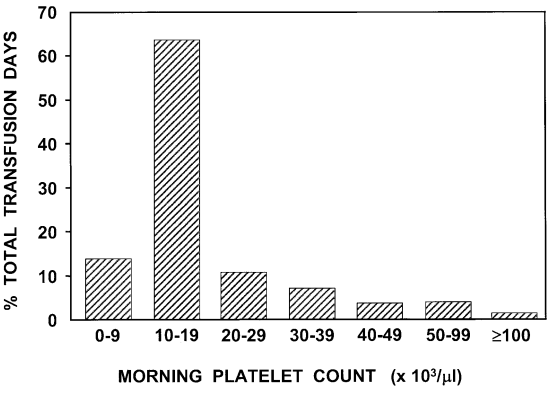

Fig 8. Administration of platelet transfusions to stem-cell transplant patients. The distribution of platelet transfusion days by morning platelet count for all stem-cell transplant patients (n = 789). (Reprinted with permission.[40])

motherapy-induced cystitis. The second most common site of bleeding was GI. Most events (66%) occurred when the morning platelet count was $>20 \times 10^3/\mu L$. Sixteen patients (2%) died from a hemorrhagic event. Because most bleeding occurred when the morning platelet counts were $>20 \times 10^3/\mu L$, this finding suggests that clinical events that occur during the early posttransplant period such as mucositis, graft-versus-host disease, cystitis, and infection may be more important predictors of hemorrhage than platelet count. Using a lower platelet count to "trigger" the prophylactic transfusion of platelets would result in fewer transfusions per patient, decreasing transfusion risk and cost.

Bleeding associated with mortality was investigated in a retrospective analysis of 83 leukemic patients with a terminal course after transplantation.[41] Hemorrhage was classified by established criteria[27] and was found in 38 (46%) of the patients who died after transplantation. Only 2 of these 38 patients had grade 1 bleeding (15%), 16 of 38 (42%) had grade 2 bleeding, 13 of 38 (34%) had grade 3 bleeding; and 7 of 38 (18%) had grade 4 bleeding. Fatal bleeding was identified in 16 (19%) of the 83 patients, and the bleeding was intracranial in 5 patients, gastrointestinal in 5 patients, and generalized in 6 patients. There was no significant differences in the platelet count between the patients with terminal hemorrhage ($25 \times 10^3/\mu L$) versus those without ($31 \times 10^3/\mu L$), indicating that factors other than the platelet count (such as GVHD and white cell counts) were more likely related to hemorrhagic mortality. The overall hemorrhagic incidence was similar in allogeneic and autologous bone marrow transplant populations (18% and 19%, respectively).

Acute bleeding after bone marrow transplantation was also investigated in 1,402 patients receiving transplants at Johns Hopkins Hospital between 1986 and 1995.[42] Bleeding categorization was based on daily scores of intensity used by the blood transfusion service.[38] The overall incidence of bleeding was 34%, with minor bleeding in 10.6%, moderate bleeding in 11.3%, and severe bleeding in 12% of all patients. Fourteen percent of patients had moderate or severe gastrointestinal hemorrhage, 6.4% had moderate or severe hemorrhagic cystitis, 2.8% had pulmonary hemorrhage, and 2% had intracranial hemorrhage. Sixty-one percent had 1 bleeding site, and 34.4% had more than 1 site. Moderate and severe bleeding was more common in allogeneic (31%, $P < .0001$) and unrelated transplants (62.5%, $P < .0001$) compared with autologous transplants (18.5%).

Although the incidence of moderate and severe bleeding varied significantly among diagnoses (higher for patients with AML and chronic myelogenous leukemia [32.0% and 38.2%, respectively] and lower for breast cancer [6.5%] when compared with the rest of the diseases), bleeding incidence was similar in good- and poor-risk prognosis groups within each diagnosis. The higher incidence in allogeneic and unrelated transplant patients compared with autologous transplants may be related to an increased incidence of GVHD and infectious complications in allogeneic compared with autologous transplant patients.

In another study, patients undergoing autologous transplantation experienced, on average, 6.7 days of bleeding compared with 17.8 days of bleeding for allogeneic transplants.[20] By univariate analysis, predictors of major bleeding were Amphotericin B use (odds ratio [OR] 3.8), GVHD (any grade) (OR 3.1), and transplantation type (auto *v* allo) (OR 2.8), and veno-occulsive disease (any grade; OR 4.4; *P* values were .01, .01, .03, and .08, respectively). However, by multivariate regression analysis, only amphotericin B use ($P = .05$; OR = 2.83) was independently associated with major bleeding. Overall, the bleeding risk in bone marrow transplantation may be higher than in patients with acute leukemia or those with solid tumors (see later) and also higher for allogeneic versus autologous transplant recipients.

Solid Tumor Patients

Five retrospective studies of solid tumor patients with thrombocytopenia and associated bleeding have been reported to date.[43-46] No prospective or controlled trials in this population have been reported. Four of these studies confirm the findings in leukemia patients (ie, the rate of bleeding increased as the platelet count decreased, and no clear threshold could be shown) (Table 6).[47]

These studies report a relatively low overall rate (<5% in the 3 largest studies) of major or life-threatening episodes of bleeding except when the platelet count fell below $10 \times 10^3/\mu L$. These observational data also show that hemorrhage at necrotic tumor sites, including fatal hemorrhages, can occur at platelet counts well above $20 \times 10^3/\mu L$. In

Table 6. Thrombocytopenia and Bleeding in Patients with Solid Tumors

	20-50 × $10^3/\mu$L		10-20 × $10^3/\mu$L		<10 × $10^3/\mu$L	
Reference	%	95% CI	%	95% CI	%	95% CI
Belt[43]						
Total cycles of therapy	197		52		21	
All bleeding	9.6	6-15	11.5	4-23	38.1	18-62
Major bleeding	2.5	1-6	7.7	2-19	14.3	3-36
Dutcher[44]						
Days at risk	4,393		576*			
All bleeding	8 episodes/ 1,000 days	6-12	10 episodes/ 1,000 days	4-21		
Goldberg[45]						
Total cycles of therapy	347		142		49	
All bleeding	2.3	1-4	17.6	12-25	40.1	18-45
Major bleeding	<1	<1-2	2.1	<1-6	10.2	3-22
Fanning[46]						
Total cycles of therapy	79		62		38†	
All bleeding	0	0-5	17.7	9-30	18.4	8-34
Major bleeding	0	0-5	0	0-6	0	0-9
Elting[47]						
Total cycles of therapy	700		365		197	
All bleeding	4.7	3-7	10.1	7-14	20.1	15-27
Major bleeding	2.3	1-4	3.6	2-6	7.1	4-12

Abbreviation: CI, confidence interval.

*Data available for 10-20 × $10^3/\mu$L and <10 × $10^3/\mu$L combined.

†Data available for 5-10 × $10^3/\mu$L; data for <5 × $10^3/\mu$L not provided.

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1 study,[44] there was no clear relationship between platelet count and risk of bleeding because the majority of cases of serious bleeding (37 of 44 cases) occurred at platelet counts exceeding 20 × $10^3/\mu$L, often at necrotic tumor sites.

CONCLUSIONS/SUMMARY

Platelet transfusion therapy has clearly decreased the hemorrhagic morbidity and mortality associated with hypoproliferative thrombocytopenia. It is also clear that bleeding risk does not increase substantially until platelet counts are at least <10 × $10^3/\mu$L and probably not until they are <5 × $10^3/\mu$L. Furthermore, in studies in which prophylactic versus therapeutic platelet transfusions were compared, there was no evidence of an increased risk in hemorrhagic mortality with a therapeutic strategy, again suggesting the efficacy of platelet transfusions to maintain hemostasis.

A substantial number of studies have documented that the prophylactic platelet transfusion trigger level can safely be lowered from the previously used 20 × $10^3/\mu$L to 10 × $10^3/\mu$L without substantially increasing bleeding risk. There are currently not enough data to clearly establish that a 5 × $10^3/\mu$L transfusion trigger is safe and effective, but preliminary data from some transfusion trials with severely restricted platelet transfusion criteria as well as stool blood loss studies would suggest that this is a safe transfusion threshold. It has also been shown that, the lower the platelet transfusion trigger, the greater is the reduction in platelets transfused with concurrent decreases in transfusion risks, costs, and possibly also a shorter duration of thrombocytopenia.

It remains to be determined which is the more cost-effective platelet-dosing strategy (eg, high-dose platelet transfusion therapy with the expected decrease in transfusion frequency *v* low-dose platelet transfusion therapy that may result in more frequent platelet transfusions being given). However, there is no reason to presume that, as long as the platelet count is maintained at 5 × $10^3/\mu$L or greater, there would be an increased hemorrhagic risk associated with low dose platelet transfusion therapy. It is gratifying to realize that platelet transfusion therapy has substantially decreased the hemorrhagic morbidity and mortality associated with cancer therapies and, thereby, improved the

quality of life for patients with hypoproliferative thrombocytopenia. With current platelet transfusion therapy, bleeding is a significant problem for the most part only for patients with disseminated intravascular coagulation, patients with specific structural lesions with loss of vascular integrity, and patients who have become refractory to platelet transfusions.

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