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MATERNAL-FETAL CASE STUDIES

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Unusual Dermatologic Findings in an Extremely Low Birthweight Infant: The Genetic Diagnosis

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XIII Consenso SIBEN sobre Traslado Neonatal: Establecer protocolos estructurados para el proceso del traslado neonatal podría mejorar los desenlaces

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RESUMEN

La centralización de los partos de alto riesgo en los hospitales con el más alto nivel de atención es fundamental para ampliar el margen de seguridad materno-neonatal y mejorar los desenlaces. Por lo tanto, es altamente recomendable trasladar oportunamente a las pacientes gestantes portadoras de embarazos de alto riesgo y/o con amenazas de parto pretérmino a centros de atención terciaria, sin embargo, no siempre es posible anticipar los riesgos antenatalmente, lo cual resulta en la necesidad de trasladar a neonatos en estado crítico.
Lamentablemente, la movilización de los recién nacidos compromete aún más su estado de salud, especialmente en los países latinoamericanos.
El presente trabajo resume los resultados del XIII Consenso Clínico de SIBEN de Traslado Neonatal, en el cual colaboraron 65 miembros de SIBEN, neonatólogos y licensiados en enfermería de 14 países de Iberoamérica, que participaron activamente durante el 2022, antes, durante y después de la reunión presencial que se llevó a cabo en Mérida, Yucatán, México el 12 de noviembre del 2022. En esta reunión se consensuaron las recomendaciones aquí vertidas.

AUTHOR DISCLOSURES Drs Lemus-Varela, Golombek, Sola, Davila-Aliaga, Pleitez, Baquero-Latorre, Celiz, Fernandez, Lara-Flores, Lima-Rogel, Mir, Montes Bueno, Neira, Sanchez-Coyago, and Young have disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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SIBEN recomienda mejorar las políticas de regionalización de la salud en Latinoamérica, que exista absoluta equidad e intentar que las unidades de nivel terciario no se concentren únicamente en las grandes ciudades. Es necesario mejorar los procesos del traslado neonatal, protocolizar y sistematizar cada paso a cumplir para mejorar los desenlaces, desde la identificación temprana, siempre que sea posible antenatalmente, mantener en forma continua los canales de comunicación en forma tripartita: hospital de referencia, hospital receptor y equipo del personal que efectúa el traslado y así, trasladar oportuna y correctamente con amplio margen de seguridad a un tercer nivel de atención.

Summary

The centralization of high-risk births in hospitals with the highest level of neonatal care is essential to increase maternal-neonatal safety and improve outcomes. Therefore, it is highly recommended the timely transfer to tertiary care centers of high-risk pregnant women and/or with threats of preterm birth. However, it is not always possible to anticipate the risks prenatally. This results in the need to transfer neonates in critical condition. Unfortunately, the mobilization of these newborns further compromises their health status, especially in Latin American countries.

This narrative reports the results of the XII SIBEN Clinical Consensus on Neonatal Transport. In this Consensus, 65 members of SIBEN (Neonatologists and Nurses from 14 Latin American countries) collaborated during 2022, before, during and after the meeting that took place in Mérida, Yucatan, México on November 12, 2022. In this joint meeting the recommendations conveyed here were agreed upon.

SIBEN recommends improving health regionalization policies in Latin America, ensuring that there is absolute equity and trying to ensure that tertiary level units do not concentrate only in large cities. It is necessary to improve neonatal transport processes and systematically protocolize each step, to improve outcomes. This includes early risk identification, whenever possible prenatally, continuously maintaining communication channels in a three-way manner: referring hospital, receiving hospital and personnel carrying out the transfer. This would lead to a correct and timely transfer with a wide margin of security.

INTRODUCCIÓN

En la década de los setenta, se propuso en Estados Unidos de Norteamérica la regionalización de la atención neonatal como una estrategia para mejorar los resultados, lo cual significó el traslado de neonatos críticos a centros con niveles de atención de alta complejidad. (1) El traslado neonatal ideal es el que ocurre antes de nacer, es decir, el traslado intrauterino o materno-fetal, que permite la centralización de la atención a los embarazos de alto riesgo en un nivel terciario en las mejores condiciones y en el momento adecuado, sin embargo, no todas las patologías neonatales pueden detectarse antenatalmente. Resulta fundamental anticipar oportunamente el nivel de atención correcto, establecer la coordinación previa con los centros asistenciales y con el equipo profesional encargado del traslado. (2)(3)

El concepto del traslado neonatal implica el desplazamiento del recién nacido (RN) desde el centro que deriva (hospital de referencia, remitente o emisor) al centro que recibe (receptor). (2) Los distintos pasos que deben incluirse son: la toma de decisión en el centro de referencia, estabilización del neonato previa al traslado en dicho centro, búsqueda de un hospital receptor adecuado, coordinación y comunicación constante, un medio de transporte correcto y personal con entrenamiento profesional para llevar a cabo el traslado oportuna y correctamente dentro de un amplio margen de seguridad. (2) Es absolutamente necesario estabilizar al neonato antes de su traslado y contar con un equipo de profesionales de la salud expertos en el traslado neonatal, con amplio conocimiento de la reanimación neonatal, de anticipación a los riesgos a enfrentar y de la sistematización del proceso de traslado. Siempre se debe cuidar cada detalle con el objetivo de brindar atención continuada desde la sala de partos, la estabilización y el traslado neonatal, hasta el arribo a la UCIN del hospital receptor. Todo esto impactará positivamente en el desenlace final. (4)

La separación de los padres de su recién nacido enfermo es una experiencia amenazante, estresante, con pérdida del contexto familiar, situación que nos debemos plantear para mejorar la atención integral del RN y sus familias. (4)

En el presente manuscrito se incluyen y resumen indicaciones, tipos, métodos y medios de traslado neonatal, así

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como factores de riesgo, condiciones básicas y fundamentales, material necesario, implementaciones que facilitan y amplían el margen de seguridad antes y durante el traslado neonatal, aspectos éticos y las recomendaciones del XIII Consenso de SIBEN.

TIPOS DE TRASLADO NEONATAL

Existen tres tipos de traslado neonatal:

1. Traslado prenatal o materno-fetal.
2. Traslado neonatal o interhospitalario.
3. Traslado por contrarreferencia o de retorno.

1. TRASLADO PRENATAL O MATERNO-FETAL

Es esencial el traslado de la gestante ante cualquier patología o alteración que precise cuidados intensivos, abordajes diagnósticos o terapéuticos complejos que requieren de un nivel de atención mayor, tanto para el RN, como para la madre. (5)(6)(7)(8)(9)(10)

A mediados de los setenta, se informó acerca de la mejor supervivencia neonatal con el traslado materno-fetal. El traslado materno-fetal resulta más sencillo, seguro y menos costoso en contraste con el neonatal y puede realizarse por vía terrestre o aérea. (11)

La derivación oportuna de la gestante de alto riesgo, con amenaza de parto pretérmino, abombamiento de membranas o ruptura prematura de membranas y con trasladado oportuno a un nivel terciario de atención reportó mejores desenlaces en el binomio. Aún en RN pretérminos de peso extremadamente bajo se ha informado menor incidencia de comorbilidades; consecuentemente mayor sobrevida y mejor pronóstico neurológico. (12,13) La mortalidad es significativamente menor en el traslado materno-fetal, en contraste con el traslado neonatal, y resulta más evidente en embarazos de menos de 28 semanas de edad gestacional. (14)(15)(16)(17)(18)(19)(20) Asimismo, es importante evitar traslados innecesarios, dado el impacto social, familiar y el coste sanitario que esto representa. (21)(22)(23)(24)

En concreto, el traslado materno-fetal intrauterino es el estándar de oro, representa la mejor opción en términos de seguridad, logística, asequibilidad, costos y resultados finales para el binomio, (25) las indicaciones precisas y contraindicaciones del traslado materno-fetal se muestran en el **cuadro 1.**

2. TRASLADO NEONATAL O INTERHOSPITALARIO

Se refiere a trasladar a un neonato hacia otro centro de atención de mayor complejidad. En 2017, la Academia Americana de Pediatría (AAP) y el Colegio Americano de Ginecología y Obstetricia (ACOG), publicaron la 8.ª edición de las Guías para el Cuidado Perinatal, la cual incluye un capítulo titulado: "Transferencia interhospitalaria materna y neonatal", el cual identifica al traslado como un componente esencial de la regionalización en la atención materna y neonatal. (11)

3. TRASLADO DE CONTRARREFERENCIA O DE RETORNO

El traslado de contrarreferencia o de retorno favorece la mejor utilización de camas en un sistema regionalizado, facilita las visitas de los padres a su hijo ya que, en general, el hospital de referencia está más cerca de su domicilio. Además, favorece la relación interpersonal con los profesionales de ambos hospitales y disminuye el coste. Resulta deseable que la madre también sea trasladada al

Cuadro 1. Indicaciones y Contraindicaciones Del Traslado Materno-Fetal

Indicaciones	*Contraindicaciones*
✓ Amenaza de parto prematuro con ≤32 semanas de gestación, con o sin ruptura de membranas	⇒ Desprendimiento de placenta normoinserta con sangrado transvaginal profuso
✓ Embarazo múltiple <34 semanas	⇒ Crisis hipertensiva materna
✓ Restricción de crecimiento intrauterino grave	⇒ Eclampsia
✓ Incompatibilidad sanguínea grave	⇒ Necesidad de cuidados intensivos maternos
✓ Hidropesía fetal	⇒ Parto inminente
✓ Polihidramnios u oligoamnios	⇒ Pérdida de bienestar fetal grave
✓ Preeclampsia grave o síndrome HELLP (hemólisis, aumento de las enzimas hepáticas y plaquetopenia)	⇒ Procidencia de cordón umbilical o extremidades
✓ Malformaciones congénitas que obligan a un tratamiento inmediato	⇒ Distancia extensa al hospital receptor
✓ Diagnóstico prenatal de enfermedad metabólica que necesite control inmediato	⇒ No contar con disponibilidad de camas en el hospital receptor
✓ Patología materna grave o complicaciones serias del embarazo**	⇒ Condiciones precarias climáticas o ambientales que impiden el traslado por cualquier medio

**Las condiciones maternas incluyen: patología cardiológica o hemodinámica, diabetes insulinodependiente o diabetes gestacional descompensada, enfermedad autoinmune o metabólica, hipo/hipertiroidismo, fármaco-dependencia, o toxicomanías, patología psiquiátrica grave y sepsis. Por otro lado, lamentablemente no todas las patologías neonatales se detectan prenatalmente. Se estima que entre 30 y 50% de ellas se diagnostican durante el parto o en el periodo neonatal inmediato(26).

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hospital receptor tan pronto como sea posible, en condiciones de estabilidad. (27)

Se han realizado múltiples avances para reducir la morbimortalidad neonatal, uno de ellos es la regionalización de los niveles de atención neonatal que incluyan la posibilidad de los tres tipos de traslados. Es fundamental identificar oportunamente a los fetos y RN que requieren derivación a centros de alta especialidad. (28)

MEDIOS DE TRASLADO NEONATAL

El traslado neonatal puede realizarse por vía terrestre, vía aérea y marítima o fluvial.

a) Traslado Terrestre

Según los estándares regulados por organizaciones internacionales, el vehículo terrestre debe contar con características específicas con relación a: seguridad, espacio, ventilación, control de temperatura, capacidad de almacenaje del material necesario, sistema de gases medicinales como oxígeno y aire comprimido con mezclador, incubadora específica diseñada para traslado neonatal, preferentemente equipada con ventilador neonatal, sistemas de fijación, generador de corriente y elevación neumática. (2)

MEDIOS DE TRASLADO TERRESTRES: AMBULANCIAS

1. Baja complejidad (traslados electivos o de bajo riesgo).
2. Alta complejidad (traslados de urgencia de RN críticos o de alto riesgo).

b) Traslado Aéreo

Pueden ser aeronaves de ala fija, como los aviones, o de ala giratoria, como los helicópteros. Representan la mejor elección en el caso de traslados a grandes distancias. Se debe tener en cuenta determinados aspectos como:

- ✓ Efecto de la altitud en el paciente.
- ✓ La reducción de la presión barométrica y expansión del aire (especialmente en algunas afecciones, como patologías respiratorias y abdominales).
- ✓ Exceso de ruido a elevados decibeles y/o vibraciones, potencialmente dañinos para el RN.
- ✓ Conocer las condiciones meteorológicas: las bajas temperaturas ambientales representan alto riesgo para el RN, especialmente para el RN pretérmino.
- ✓ Asegurar la disponibilidad de helipuerto o aeropuerto, lo más cercano posible al hospital receptor, donde debe esperar el transporte terrestre (ambulancia equipada). (29)

c) Traslado Marítimo-Fluvial

Botes o yates para transportar RN graves desde islas a tierra firme, en coordinación estrecha con ambulancia terrestre. (39)

Resulta deseable que los traslados que excedan los 250 km o que superen las tres horas por vía terrestre se realicen en avión y, en el caso de distancias intermedias (menores de 250 km o 150 millas, o de difícil acceso) se debería considerar traslado en helicóptero, siempre que se cuente con las facilidades de aterrizaje tanto en el centro emisor como en el receptor. El traslado en helicóptero a menudo equivale a un tercio de tiempo del requerido en traslado terrestre, por lo cual el helicóptero es beneficioso cuando el tiempo es crítico. El helicóptero requiere solo un área pequeña y plana (30 m×30 m) libre de obstáculos para aterrizar, se evita el tráfico terrestre, resulta muy útil en condiciones como inundaciones, tormentas de nieve, tornados u otros desastres naturales. (30) Sin embargo, se debe considerar la interferencia, ruido, vibración y turbulencia. Además, el traslado en helicóptero es significativamente más caro que el viaje por tierra. (31) Se muestran ventajas y desventajas de traslado terrestre y aéreo en el **cuadro 2**. (31)

Ante la necesidad de trasladar al RN por vía aérea, y ante la expansión de los gases por los cambios en las presiones barométricas, se debe prestar atención a los siguientes puntos, en especial cuando se traslade a RNPT extremos.

- ◦ Toda "ventana" artificial (tubo de tórax, paracentesis, tubo orotraqueal, etc.) debe estar permeable.
- ◦ La vía aérea antes de iniciar el transporte y durante el mismo debe estar despejada y en lo posible, libre de secreciones.
- ◦ Evaluar frecuentemente la presencia de aire extrapulmonar (neumotórax) y tener a disposición el equipo para drenarlo en caso de ser necesario.
- ◦ Volar a la menor altitud. (32)

En concreto la elección del vehículo para el traslado neonatal será determinada por tres grupos de variables, (11) tal como se muestra en el **cuadro 3**.

EQUIPO HUMANO PARA EL TRASLADO NEONATAL

El equipo de traslado neonatal debe estar integrado por personal calificado con formación en neonatología y específicamente formación en traslados de RN críticos, con las siguientes características:

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Cuadro 2. Ventajas y Desventajas de Los Medios de Traslado Terrestres y Aéreos

Medio de transporte	Ventajas	Desventajas
Terrestre	✓ Mayor espacio de trabajo ✓ Capacidad de detener el vehículo para realizar ciertos procedimientos ✓ Disponibilidad y menor costo	⇒ Vibraciones, aceleraciones y desaceleraciones repentinas ⇒ Limitaciones por tráfico lento ⇒ Consumo de baterías
Helicóptero	✓ Rapidez entre hospital emisor y hospital receptor (helipuertos) ✓ Áreas inaccesibles	⇒ Elevados decibeles ⇒ Espacio reducido ⇒ Alto costo ⇒ Limitaciones de peso ⇒ Sin presurización
Avión	✓ Cobertura y rapidez de grandes distancias ✓ Menores restricciones climáticas y mayor seguridad ✓ Cabina presurizada ✓ Menor ruido y vibración	⇒ Descompensación hemodinámica asociada a la altitud ⇒ La presión barométrica y la presión inspiratoria de la FiO_2 disminuyen conforme incrementa la altitud con presurización insuficiente ⇒ Si hay descompresión puede ser catastrófica ⇒ Necesidad de ambulancia terrestre en cada extremo ⇒ Costo elevado

- Contar con la experiencia suficiente para proporcionar el cuidado neonatal adecuado, tanto en el hospital de referencia como durante el traslado.
- Amplio conocimiento para reanimación cardiopulmonar, preparación y administración de medicamentos y destreza para la realización de procedimientos.
- Capacidad de anticipar y tratar los posibles problemas o emergencias que se presenten.
- Establecer comunicación efectiva entre el equipo, con el hospital de referencia, el hospital receptor, la familia y, si existe, con el centro coordinador del transporte.
- Conocer y completar en forma constante una hoja de verificación, lista de requisitos o lista de chequeo del equipamiento necesario para traslado, fármacos, consumibles y material en general, debidamente organizado y etiquetado. (33)

FASES DEL TRASLADO NEONATAL

- Administración del traslado. A medida que se desarrolla y protocoliza un programa organizado de traslado neonatal, disminuye la morbimortalidad neonatal y materna. Para el éxito de este programa, su organigrama tiene que incluir un director médico de calidad y un director de programa para llevar a cabo toda la protocolización del equipo humano, el medio de traslado, y el equipamiento y materiales necesarios. Los coordinadores realizan la vinculación entre el hospital de referencia y el receptor. (34)

Cuadro 3. Variables Determinantes Para Elegir el Medio de Traslado Neonatal

GRUPO 1 Variables determinadas por gravedad/ complejidad clínica:	GRUPO 2 Variables determinadas por el sistema de salud:	GRUPO 3 Variables que afectan al vehículo:
Diagnóstico clínico y su gravedad: por ejemplo: prematurez extrema, asfixia perinatal severa, SDR, quirúrgico complejo, quirúrgico estable con necesidad de ayuno prolongado, o recién nacido estable para completar tratamiento en menor nivel de complejidad. Habitáculo sanitario: dimensiones del habitáculo sanitario para asistir al recién nacido en el traslado: limitado, espacioso. Habilidad del personal que remite al paciente para asistir y estabilizar hasta que llegue la ambulancia de traslado.	Disponibilidad de los distintos vehículos existentes para traslado/disponibilidad de personal entrenado. Posibilidad de afrontar distintos costos (bajo, medio, alto).	Velocidad, distancia a recorrer, densidad del tráfico y estimación de la duración del viaje. Ejemplos: <1 h / <50 km / trafico normal <1 h / <80 km / tráfico denso <2 h / 80–240 km / tráfico variable >2 h / >240 km / tráfico variable **Geografía/modificaciones del terreno:** llanura, meseta, montaña, colina, cuenca acuática, edificios a gran altura **Disponibilidad de pistas de aterrizaje**, personal capacitado, vehículos de trasbordo y servicio para despejar el tránsito: aeropuerto, helipuerto **Clima/condición meteorológica:** buen clima, ventisca / sensibilidad a la intemperie

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- Fase de referencia o fase inicial del proceso. (Conocida en algunos países como "la regulación del paciente"). En la llamada inicial se informan las condiciones actuales del RN y los diagnósticos que motivan el traslado. Si la respuesta del hospital receptor es afirmativa, se procede a la siguiente fase.
- Fase pretraslado o fase de planificación, nivel de atención apropiado, medio de traslado correcto e involucración del equipo humano del traslado.
- Fase del viaje hacia el hospital que deriva al RN. Comunicación frecuente entre el equipo y el centro remitente.
- Fase dentro del hospital que deriva al RN. Evaluación lo más detallada posible, sin demoras innecesarias. Comunicación respetuosa con el personal local. Brindar tratamientos requeridos para asegurar en la mayor medida posible un traslado lo menos riesgoso posible.
- Fase del traslado propiamente dicha.
- El proceso completo y todas las fases son fundamentales para llevar a cabo un *triage* apropiado para el RN. El *triage* es un concepto que incluye la clasificación o priorización de la atención oportuna. (34)

ORGANIZACIÓN DEL MODELO DE TRASLADO

El proceso puede organizarse de acuerdo a *"ACCEPT"*, nemotecnia que en inglés significa: *Assessment, Control, Communication, Evaluation, Preparation and Packaging, and Transportation.* (34)

VALORACIÓN (ASSESSMENT)

El equipo de salud del hospital de referencia determina la urgencia del traslado. Quién lleva a cabo el traslado varía según los centros, unidades, hospitales y regiones. En algunos, existe un sistema de traslado neonatal independiente de los hospitales (centros de referencia). En otros es el hospital que recibe al RN el encargado de realizar el traslado y en otros puede ser el hospital que deriva al RN. El líder del equipo de traslado efectúa el *triage.* (34)

CONTROL (CONTROL)

La evaluación inicial detallada generalmente controla la situación.

- ¿Quién será el líder del equipo cuya función es coordinar antes, durante y después del traslado?
- Distribución de funciones y tareas que deben realizarse (atención clínica, equipamiento, medicamentos y recursos en general).
- Determinar el medio de traslado correcto.
- Completar *check list.*
- Confirmar estabilidad del neonato previo al traslado. (34)

COMUNICACIÓN (COMMUNICATION)

Es uno de los elementos clave en el proceso del traslado neonatal. Incluye la comunicación estrecha y eficaz en todo momento entre el personal de salud (equipo de traslado entre sí y con el hospital de referencia y con el equipo que recibirá al RN). La comunicación continua, los canales de comunicación y la coordinación, de acuerdo a la alianza mundial para la seguridad del paciente, es una de las prioridades para realizar un traslado neonatal de alta calidad. Establecer canales de comunicación es un pilar fundamental en el proceso del traslado neonatal. El proceso de comunicación debe ser bidireccional entre los profesionales de la salud involucrados en el proceso, ya que esto favorece la anticipación de acciones necesarias en beneficio del neonato y la madre.

Al llegar al hospital de referencia es muy importante dialogar con el equipo de salud local con sumo respeto profesional y recibir la información actualizada con lujo de detalles. El centro que deriva debe entregar por escrito la historia clínica con información detallada perinatal, antecedentes de importancia, evolución, condiciones actuales, y los resultados laboratoriales y de imágenes que se hayan realizado. (34)

De igual importancia es la comunicación en detalle y sin tecnicismos con los padres o tutores. Esto incluye la solicitud del consentimiento informado. La información de la madre y el padre cuando se realiza el traslado materno-fetal o del RN debe ser precisa, organizada y completa. Este proceso de comunicación también debe ser bidireccional. Los canales de comunicación se dividen en verbales y escritos, la estructura de los mismos se presenta en el **cuadro 4**. (35)

EVALUACIÓN (EVALUATION)

El traslado exitoso necesita una evaluación meticulosa del RN tanto por el médico y el equipo del centro de referencia, el líder del equipo médico y el personal de traslado, y finalmente el médico y enfermería que lo reciben. Por supuesto, esto permite tomar decisiones y acciones oportunas en consecuencia. (34) Es fundamental y absolutamente necesario que todo RN sea apropiadamente estabilizado antes del traslado. El hospital que recibe debe tener preparado equipo humano de salud y módulo completo de recepción. (34)

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Cuadro 4. Estructura de Los Canales de Comunicación

Presentación	Situación Clínica	Documentación	Información
▪ Equipo asistencial. Nombres de las personas que se comunican ▪ Nombre completo del RN y número de registro civil ▪ Edad gestacional ▪ Fecha y hora de nacimiento ▪ Medidas antropométricas ▪ Sexo ▪ Identificación de los padres - nombre completo de su madre y documento de identidad	▪ Antecedentes y alergias ▪ El estado fisiológico del RN, incluido el conjunto completo de signos vitales actuales ▪ Enfermedad actual y exploración física ▪ Pruebas complementarias ▪ Tratamiento ▪ Intervenciones y resultados de las intervenciones realizadas antes de la llegada del equipo de transporte y después de la llegada del equipo de transporte	▪ Documentos de remisión, historia clínica ▪ Informes y pruebas complementarias ▪ Consentimientos informados	▪ Familiares si son los acompañantes: identificación completa y parentesco, número de teléfono, dirección ▪ Sensibilidad del tiempo (ejemplo: emergencia, urgencia, no emergencia, electiva) ▪ Tiempo aproximado de llegada ▪ Disposición inmediata de quirófano ▪ Información adicional, la cual debe intercambiarse durante el contacto

PREPARACIÓN Y EQUIPAMIENTO (PREPARATION AND PACKAGING)

La preparación para el traslado comienza tan pronto como se toma la decisión de transferir al neonato e incluye tres componentes esenciales: la atención clínica, la ubicación y verificación de equipos y la asignación de roles del equipo. La atención clínica se puede optimizar mediante comprobación de las vías respiratorias, circulación, medicamentos, ambiente (incubadora o colchón térmico, necesidad de enfriamiento, por encefalopatía hipóxico-isquémica [EHI]). El equipo humano que realiza el traslado debe estar capacitado en el uso correcto de infraestructura, equipos y fármacos, además de ser competente para realizar cualquier procedimiento necesario en ruta al hospital receptor. (34)

TRASLADO (TRANSPORTATION)

Como se menciona antes, es fundamental que todo RN sea apropiadamente estabilizado antes del traslado. A continuación, describimos los elementos imprescindibles para el traslado de un RN enfermo.

Equipo Necesario Para Realizar el Traslado Neonatal

Todo el equipamiento debe estar inventariado y controlado, asegurando siempre su funcionamiento correcto. Será ligero y portátil, fácil de limpiar y de mantener. Todo el material eléctrico debe estar alimentado por baterías que permitan suficiente autonomía (el doble o el triple del tiempo calculado de transporte) y estar protegido contra interferencias electromagnéticas. (36)

Suministro de gases (oxígeno, aire medicinal y óxido nítrico inhalado portátiles) con conexión rápida.

➢ El tablero debe contar con: regulador de oxígeno, regulador de aire comprimido, aspirador por sistema Venturi y mezclador con flujómetro.

➢ Tubos de oxígeno y de aire comprimido portátiles, de aluminio, de 1 o 1,5 m^3 y 3 m^3 de capacidad, a fin de garantizar el suministro durante el triple del tiempo máximo previsto para el traslado, según la región de cobertura. Deben tener soportes a media altura y al piso. Se debe conocer la cantidad de oxígeno probable a utilizar y el volumen de carga de cada cilindro, el tipo de tubo con su índice, su presión de servicio (psi/bar), las escalas de los manómetros, si estos son de alta o baja presión. (37)

➢ Número mínimo de tanques o cilindros a portar en cada traslado: 2 de oxígeno y 2 de aire comprimido. (37)

Para calcular la cantidad de oxígeno disponible en el tanque o cilindro en minutos, se recomienda utilizar la siguiente fórmula: [Constante del tanque X PSI – PSI residual/flujo en L por minuto = duración en minutos de oxígeno]. Dónde: la constante del tanque que encontramos grabada en la parte superior del tanque, expresada en letras mayúsculas: D, E, M, que tendrán su correspondiente constante, para D: 0,16, E: 0,28, M: 1,56, la multiplicamos por el resultado de la resta de PSI (presión de oxígeno comprimido en el tanque, el cual se lee en el manómetro y lleno corresponde a 2000) – presión del nivel residual de oxígeno mínimo y seguro que corresponde a 200 years se divide entre los litros por minuto indicados para el paciente. Ejemplo: Tenemos un tanque marcado con E, que corresponde a la constante 0,28× (2000-200) dividido entre 1,5 L por minuto que recibe el RN = 336 minutos que corresponden a 5,6 horas.

Otra forma de calcular la cantidad de oxígeno necesaria es tomando en cuenta el volumen minuto del paciente. Si consume por inspiración 300 ml y tiene una frecuencia respiratoria de 20 por minuto, daría un consumo de 6000 ml (6 litros por minuto). Esto se debe calcular en una hora

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multiplicando por 60 years luego por las horas estimadas de traslado y, por último, triplicarlo.

- Mezclador de oxígeno (*blender*) que ofrezca FiO_2 desde 0,21 a 1,0, de 3 years de 10 litros por minuto.
- Sistema de aspiración, regulable.
- Calentador humidificador colocar temperatura entre 36,5°C y 37°C.
- Óxido nítrico portátil (400/800 ppm) (38)

EL COMPARTIMENTO O MÓDULO PARA EL NEONATO DEBERÁ CONTAR CON LA SIGUIENTE DOTACIÓN MÍNIMA EN EQUIPOS

- Incubadora portátil o de traslado.
- Equipo completo de manejo de vías aéreas neonatales, suficientes tubos endotraqueales y cánulas laríngeas.
- Cámara o escafandra (*hood*) neonatal.
- Equipo de venodisección neonatal.
- Manómetro en el aspirador portátil y sondas de aspiración
- Oxímetros de pulso.
- Respirador o ventilador neonatal.
- Colchón de gel con o sin almohadilla de espuma, modificar la bandeja de la incubadora, insertando una sujeción de espuma entre la bandeja y el riel para reducir el movimiento de la bandeja, lo cual resulta en disminución de la vibración y menor riesgo de movilización por aceleración-desaceleración. (39)

MEDICAMENTOS NECESARIOS PARA EL TRASLADO NEONATAL

El objetivo de todo traslado neonatal es mantener al paciente en las mismas condiciones de asepsia, estabilidad térmica, respiratoria, metabólica, hidroelectrolítica, hemodinámica y neurológica que tendría en una unidad neonatal donde fuese atendido por la patología que origina su movilización. (40)

Las medicaciones (incluidos los líquidos) y las dosis necesarias para un proceso de traslado de un RN son similares a las que se utilizan en los servicios de neonatología y varían según el nivel de soporte vital que necesite el RN que será trasladado. (40)

La estandarización de las presentaciones (fórmula farmacéutica y concentración) facilita la transferencia del paciente. Una lista sugerida es:

FLUIDOS INTRAVENOSOS

- Dextrosa 10%
- Dextrosa 5%
- Solución salina al 0,9%

Cuando se participa como sitio receptor, una medida que salva vidas es nunca asumir que el centro que refiere dispone de todo el equipo y fármacos necesarios. Por tanto, debe confirmarse mediante comunicación efectiva, protocolizada y sistematizada, qué medicamentos ha recibido, qué recibe y evaluar qué debe recibir. (41) En el **cuadro 5**, se presentan los fármacos sugeridos para el traslado.

En concreto, es muy importante trasladar al neonato crítico en condiciones de asepsia, estabilidad térmica, respiratoria, metabólica, hidroelectrolítica, hemodinámica y neurológica, igual que si estuviese en la UCIN, con lo cual se reducen significativamente los riesgos. (42)

PUNTOS CLAVE PARA EL TRASLADO NEONATAL POR APARATOS Y SISTEMAS

a) Vía Aérea y Respiratoria

El cuidado de la vía aérea durante el traslado neonatal requiere especial cuidado. La evaluación clínica y radiológica y la experiencia que se tenga en el manejo del soporte respiratorio son vitales para la realización de un traslado exitoso y seguro. (43)

No todos los RN deben intubarse antes del traslado, pese a que la razón principal del traslado fuese respiratoria, como es el caso de los RN pretérmino (RNPt) con síndrome de dificultad respiratoria (SDR). En el pasado, antes de realizar el traslado de RNPt con SDR, en la gran mayoría de los casos se realizaba intubación endotraqueal previo al traslado. (44)(45) Sin embargo, actualmente la meta es favorecer el soporte ventilatorio de protección pulmonar, administración de esteroides prenatales, siempre que sea posible iniciar CPAP desde sala de partos, administración oportuna de surfactante y disponibilidad de modos de ventilación menos invasiva sin tubo endotraqueal

Cuadro 5. Selección de Fármacos o Medicamentos Para el Traslado

Gluconato de calcio	Dobutamina	Adenosina	Dexametasona	Lidocaína
Sulfato de magnesio	Dopamina	Amiodarona	Hidrocortisona	Insulina
Cloruro de sodio	Norepinefrina	Fentanilo	Ampicilina	Vecuronio
Cloruro de potasio	Epinefrina	Morfina	Gentamicina	Prostaglandinas
Bicarbonato de sodio	Milrinona	Fenobarbital	Cefotaxima	Furosemida
Vitamina K	Atropina	Lorazepam	Paracetamol	Bumetanida

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que puedan mantenerse durante el traslado. No obstante, definitivamente es indicación de intubación electiva previamente a iniciar el traslado siempre que exista el riesgo de progreso de la dificultad respiratoria, inminencia de fatiga diafragmática, apneas y gasometría ominosa. (46)

La meta de la SpO_2 para el RN en estado crítico durante el traslado es idéntica a la deseada en la UCIN y se deben seguir las recomendaciones de SpO_2(47). La lectura de la SpO_2 durante el traslado puede ser interferida por el exceso de movimiento o vibraciones. Preferiblemente utilizar saturómetros con tecnología con extracción de señal (SET) que funcionan bien aun con movimiento. (48)

Es menester confirmar que todas las conexiones vinculadas a la administración de gases (aire u oxígeno) estén correctas desde las fuentes de los gases hasta los dispositivos colocados al RN. Se deben revisar todos los sitios de entrada de tubuladuras en la incubadora y fijarlos de modo que sea posible acceder al RN sin inconvenientes. Los parámetros del ventilador de traslado deben ser fijados antes de conectar al RN, y siempre guiándose por la evolución clínica y gasométrica. (44)

El uso de ventilación de alta frecuencia (VAF) permaneció excluido para el traslado neonatal, hasta que los ventiladores de traslado estuvieron disponibles. (49) Algunas incubadoras de traslado neonatal están equipadas con ventiladores capaces de dar soporte en modo convencional y de alta frecuencia. (50) Recientemente se publicó un trabajo de 12 años que muestra el incremento de los traslados llevados a cabo bajo la modalidad de VAF. Los resultados demuestran que el traslado de neonatos con VAF es posible y seguro a pesar de los desafíos que esto significa. (51) Otros estudios realizados concluyen resultados similares, aunque con menor número de RN. (52). La utilización de esta modalidad también parece segura y efectiva en RN con hernia diafragmática congénita. (53)

En RN con hipertensión pulmonar, candidatos a administración de óxido nítrico inhalado (ONi), es importante realizar ecocardiograma para confirmar diagnóstico y descartar cardiopatía congénita, especialmente si un alto porcentaje del flujo sistémico se efectúa a través del ductus por el cortocircuito de derecha a izquierda ya que la disminución de la presión pulmonar por el ONi disminuye el flujo sistémico y disminuiría el gasto cardiaco. Es conveniente colocar sensores de SpO_2 pre y posductales y tomar radiografía de tórax para asegurar adecuados volúmenes pulmonares. Los alvéolos colapsados disminuyen la efectividad del ONi. Mantener los parámetros del respirador que aseguren un buen volumen pulmonar y optimizar la situación hemodinámica. (54)(55)

Durante el traslado se debe asegurar la fijación del tubo de ONi para evitar caídas o desplazamientos, mantener la misma dosis todo el traslado. Si la SPO_2 está por encima de lo correcto, bajar la FiO_2, evitar la discontinuación accidental del flujo de ONi, la hipotermia y la sobreestimulación sensorial y lumínica, conocer y aplicar los protocolos de seguridad durante el traslado e incluso los referidos al recambio ambiental para evitar la acumulación de óxido nítrico residual. Actualmente existen equipos digitalizados que nos permiten controlar la concentración del ONi. (56)

b) Cardiovascular

La estabilidad hemodinámica durante el traslado neonatal es fundamental. Los tres primeros días de edad postnatal representan un período de cambios en la dinámica del sistema cardiovascular que forman parte importante de la adaptación a la vida aeróbica. Al nacer, con el pinzamiento del cordón y el inicio de la respiración se desencadena una cascada de fenómenos complejos para la transición de la vida fetal a la neonatal. La primera respiración y el aumento del contenido arterial de oxígeno se acompañan de aumento en la resistencia vascular sistémica (RVS) y disminución de la resistencia vascular pulmonar (RVP), que conduce al incremento del flujo sanguíneo pulmonar. Algunos neonatos particularmente pretérmino podrían enfrentar incapacidad del miocardio inmaduro para adaptarse al aumento repentino de la RVS. (57)

La presión arterial (PA) ha sido tradicionalmente un determinante de la estabilidad hemodinámica que marca la pauta para considerar compromiso cardiovascular y debe estar incluida en la evaluación clínica de rutina para valorar el estado hemodinámico del RN. (57)

Cuando se considera que el estado cardiovascular es inestable, será recomendable intentar colocar un catéter arterial para el monitoreo de la PA invasiva antes del traslado. No se deben tomar decisiones basadas exclusivamente en el monitoreo de la PA no invasiva en RN gravemente enfermos. Estas mediciones son menos exactas y técnicamente difíciles de obtener durante el traslado. Por otro lado, evaluar necesidad de soporte farmacológico vasoactivo e iniciar antes del traslado, siempre a través de abordaje venoso central. En el **cuadro 6** se presentan los principales factores de riesgo de descompensación hemodinámica y los signos que la apoyan. (57)

En RN con cardiopatía congénita, claramente establecida o sospechada, dependiente del ductus arterioso, debe iniciarse prostaglandinas (PgE_1) en infusión continua antes del traslado. Esto podría favorecer apneas, con lo cual se recomienda evaluar la pertinencia de asegurar la vía

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Cuadro 6. Factores de Riesgo de Descompensación Hemodinámica y Signos de Perfusión Inadecuada

Factores de riesgo de descompensación hemodinámica
• Demora en la transición desde la vida intrauterina a la extrauterina
• Miocardio inmaduro
• Falta de esteroides prenatales
• Conducto arterioso persistente
• Corioamnionitis
• Depresión perinatal/asfixia
• Inmadurez del eje hipotálamo-hipófisis-suprarrenal
• Insuficiencia suprarrenal relativa
• Sepsis
• Enterocolitis necrosante
• Hipovolemia
Signos de perfusión inadecuada
• Taquicardia
• Índice de perfusión <0,7
• Pulsos débiles
• Piel moteada
• Oliguria
• Acidosis metabólica
• Letargia
• Relleno capilar (no es sensible ni específico)

aérea previamente al traslado. Es fundamental en estos RN no usar FiO_2 elevada ya que favorece el cierre del ductus, lo que podría agravar considerablemente la condición clínica. (58)

c) Neurológico

No todos los neonatos requerirán el uso de sedantes durante el traslado. Sin embargo podrían presentar dolor o molestia asociados principalmente a movimientos y a las vibraciones de los medios de transporte y el ruido que exceden los estándares aceptables. Esto es de mayor riesgo en traslados en helicóptero. Es recomendable tomar medidas no farmacológicas como "orejeras", nidos de contención, leche materna, sacarosa al 24% y succión no nutritiva, (61)(62) uso de colchones de gel, arneses, cobertores de incubadoras, y otros. Por tanto, las iniciativas en los cuidados del neurodesarrollo dentro de la UCIN destinadas a reducir los estímulos ambientales nocivos son ampliamente aceptadas y deben llevarse a cabo durante el traslado neonatal. A veces es necesario iniciar sedación antes del traslado ya que los niveles de ruido excesivo tienen efectos adversos en los sistemas endocrino, cardiovascular y auditivo. Los efectos del ruido en los RNPt incluyen cambios en la frecuencia cardíaca, la frecuencia respiratoria, la saturación de oxígeno y la presión arterial, así como efectos negativos a largo plazo en el sistema nervioso central. (59,60)

Frecuentemente los RN con encefalopatía hipóxico-isquémica (EHI) moderada a severa, ≥35 semanas de edad gestacional candidatos a hipotermia terapéutica (HT), deben ser trasladados a centros de nivel III de atención multidisciplinaria con protocolo de enfriamiento terapéutico estandarizado. El periodo de ventana de la HT es durante la fase de reperfusión de la EHI, es decir en las seis primeras horas posnatales, lo cual representa una urgencia terapéutica, ya que la máxima eficacia de la HT se obtiene cuanto más temprano se inicie. (63)(64) Esto ha demostrado incremento de la supervivencia y reducción del daño neurocognitivo.

El traslado neonatal de un RN con EHI debe cumplir el mismo protocolo de traslado que se aplica a cualquier RN crítico, con algunas singularidades que se detallan a continuación. (65)(66)(67)(68)(69)

- Equipo de salud capacitado y entrenado con conocimientos específicos en HT, RCP avanzado y estabilización de RN de alto riesgo, asegurar vía aérea y canalizar vasos umbilicales antes de iniciar HT para evitar dificultades técnicas atribuidas a vasoconstricción.
- Evitar hipertermia.
- Enfriamiento pasivo, que empieza en el mismo lugar de nacimiento.
- La hipotermia pasiva se logra apagando la cuna radiante y las fuentes exógenas de calor para conseguir el rango de 33-35°C y evitar oscilaciones. Si después de un período de tiempo no se lograra, habría otra posibilidad que SIBEN no puede recomendar en función de la evidencia disponible. Incluye ventiladores de aspa o bolsas de gel frío/hielo *("Hot-Cold Gel Pack")*. Estas bolsas nunca deben entrar en contacto con el RN. Deben situarse a unos 10 cm del perímetro del RN para evitar quemaduras por frío y alejarlas cuando la temperatura sea inferior a 35°C.
- Durante el traslado neonatal se debe tomar y registrar la temperatura central (rectal) cada 15 minutos y mantenerla entre 33 years 34°C. Para lograrlo se debe fijar el servocontrol de la incubadora de transporte en 35°C. Si no es suficiente se debe apagar la incubadora y mantener las escotillas abiertas.
- Si la temperatura rectal es <33°C, se debe encender la incubadora.
- La hipotermia profunda (<32°C axilar/central) es el principal riesgo durante el traslado por la tendencia al sobreenfriamiento que acontece en las primeras horas de vida, sobre todo en los RN con EHI severa.
- Lo ideal es trasladar al RN con EHI moderada-severa en HT con sistemas de enfriamiento servocontrolado, con dispositivos de enfriamiento activo de pequeño tamaño, con respaldo de batería, portables y económicos diseñados justamente para el traslado neonatal.

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- En caso de hipotensión arterial, se recomienda iniciar dobutamina o dopamina ya que el evento hipóxico-isquémico perinatal puede ocasionar disfunción miocárdica. De acuerdo a la respuesta evaluar la pertinencia de epinefrina. Evitar hipotensión y todo lo que ocasione disminución del flujo sanguíneo cerebral (FSC), como la hipocapnia y la inadecuada posición de la cabeza y el cuello. Cambiar de posición cada 4 horas, movilizando en bloque y manteniendo la nariz alineada con el resto del cuerpo, no girar solamente la cabeza para evitar oscilaciones del FSC.
- Mantener normoglucemia, un flujo de glucosa entre 4 a 6 mg/kg/minuto que asegure una glucemia >45 mg/dl y <150 mg/dl.
- En caso de presentar convulsiones durante el traslado, se recomienda administrar fenobarbital. Como segunda elección puede ser levetiracetam. Ante un *"status epilepticus"*, iniciar midazolam o lorazepam como tercera alternativa. No usar ácido valproico ya que favorece la hiperamonemia y es hepatotóxico. El tiopental tampoco ya que tiene efectos adversos graves. El uso de fenobarbital profiláctico no se recomienda, pero si hay convulsiones de contexto clínico o si se sospechan, es conveniente iniciar fenobarbital a las dosis neonatales recomendadas y observar durante el traslado y los primeros días en la UCIN. Se debe realizar evaluación electroencefalográfica lo antes posible, preferentemente de amplitud integrada (aEEG) o convencional.
- Previo al traslado colocar sonda vesical para medir la diuresis y realizar balances estrictos. Evitar la hiponatremia secundaria a SIADH (síndrome de secreción inadecuada de hormona antidiurética) o insuficiencia renal con exceso hídrico. Corregir hipocalcemia e hipomagnesemia ya que pueden agravar o potenciar las crisis convulsivas en EHI. Se debe tener especial cuidado con los aportes de potasio, ya que la hipotermia produce cambios en el potasio intracelular. Evitar medicación nefrotóxica.
- Individualizar el tratamiento hidroelectrolítico y hemodinámico a las circunstancias clínicas y hemodinámicas de cada RN con EHI y evitar el exceso de líquido o sobrecargas agudas de volumen.
- La HT desplaza la curva de disociación de la Hb a la izquierda y reduce la entrega de oxígeno a los tejidos y el metabolismo anaerobio no se ve incrementado. Si está elevado el ácido láctico es por gravedad de la asfixia y no por la HT.
- En caso de signos de trastorno de la coagulación tales como sangrado gástrico, hematuria, sangrado en sitios de venopunción, solicitar estudios de laboratorio previamente al traslado. Si las plaquetas son <50.000, transfundir concentrado plaquetario. Tiempo parcial de tromboplastina activada (kPTT o TTPa) >65-80 segundos, en muestras correctas en las primeras horas de edad postnatal, tiempo de protrombina (TP o *Quick*) >15 segundos o <40%, INR (*international normalized ratio*) >3, o fibrinógeno <100 mg/dl: administrar vitamina K (1 mg IV) y 10-15 ml/kg de plasma fresco congelado, es importante evitar sobrecargar la volemia agudamente.
- Evitar el estrés (llanto, molestia), se recomienda fentanilo a 1 mcg/k/dosis administrar en bolo lento, o morfina 0.1 mg/kg/dosis.

d) Metabólico

Los RN en general son susceptibles al estrés por frío. Los RNPt extremos y RN con malformaciones congénitas expuestas son más sensibles a la pérdida de calor en los momentos posteriores al parto, donde esta pérdida de calor suele exceder a la producción del mismo. La hipotermia (temperatura central/axilar menor a 36,5 °C) se asocia con mayor mortalidad neonatal, sepsis de inicio tardío, SDR y hemorragia intraventricular. Así mismo, puede perjudicar la transición a la vida extrauterina, empeorar la acidosis y la utilización de glucosa y afectar la función inmune y la coagulación sanguínea. (70)

Es necesario el adecuado calentamiento de los gases inspirados, así como su humidificación, al igual que el de las incubadoras de traslado y considerar la cambiante temperatura del ambiente. Se debe mantener el ambiente térmico neutro, lo cual puede representar un verdadero desafío durante el traslado. Por otro lado, la hipertermia puede ocasionar cambios físicos que han sido asociados con muerte súbita. (71)

El mantenimiento de un nivel de glucemia por encima de 50 mg/dl en las primeras 48 horas de vida y por encima de 60 mg/dl después asegura un aporte adecuado a nivel de todos los órganos, fundamentalmente del cerebro. Los RN con condiciones inestables generalmente deben mantenerse en ayuno, proveyendo líquidos parenterales con aporte adecuado de glucosa a una tasa inicial de 4 a 6 mg/Kg/min. (72)

Los factores que afectan los niveles de glucemia en el período neonatal son múltiples y cambian a medida que avanza la edad postnatal. El nacimiento prematuro, la asfixia perinatal, los antecedentes maternos de diabetes, infecciones perinatales, SDR, uso de cierto tipo de medicamentos y la temperatura corporal pueden alterar la homeostasis metabólica del

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RN. Se recomienda la medición de glucemia mediante tiras reactivas durante el traslado especialmente en RN de riesgo. (73)

Una vez que se instaura el tratamiento para la hipoglicemia neonatal se debe medir la glucemia cada 30 minutos hasta que sea mayor de 50 mg/dl en dos pruebas consecutivas. Pueden presentarse niveles de glucemia elevados previamente por estrés metabólico, pero posteriormente se agotarán las reservas y podría presentar hipoglucemia. (74)

MODELO CONCEPTUAL DEL TRASLADO NEONATAL

La regionalización del cuidado intensivo neonatal ha disminuido la mortalidad. Sin embargo, en ocasiones no es posible realizar el traslado prenatal o intrauterino y el traslado neonatal se convierte en la mejor opción en la cadena asistencial del RN crítico. Si bien la celeridad del traslado es importante, lo esencial es la calidad de este, que depende de los múltiples factores presentados en el presente Consenso Clínico.

Es fundamental que exista un sistema o modelo conceptual, que inicie con la correcta identificación del RN crítico que necesita traslado apropiado y oportuno, y que se realicen todas las medidas descritas previamente. Es necesario que los neonatólogos del hospital de referencia estén capacitados para la pronta estabilización adecuada y expedita del neonato previo a su traslado, además hay que contar con un equipo de personal altamente capacitado y que pueda brindar reanimación y estabilización neonatal antes y durante el traslado. Lamentablemente, la formación del personal sanitario de transporte, en general, es inadecuada en Latinoamérica. Todos los miembros del equipo humano de traslado deben recibir entrenamiento continuo que permita mantener y actualizar sus capacitaciones. Así mismo, deben ser evaluados periódicamente. Dicho equipo humano debe estar integrado por enfermeras neonatales, terapistas respiratorios, neonatólogos y/o residentes del mayor grado de neonatología. Cada integrante del equipo debe tener muy clara su función. (75)

Con base en la evidencia disponible y la racionalización lógica, se diseñó el siguiente modelo conceptual que permita realizar traslados neonatales en forma protocolizada **(figura)**.

Existen estrategias y programas de estabilización neonatal previos al traslado, estructurados y diseñados para simplificar el proceso de estabilización antes, durante y al arribo del traslado. Una de las más utilizadas: es el programa S.T.A.B.L.E.: *Sugar, Temperature, Artificial breathing, Blood pressure, Laboratory work, Emotional support*, por sus siglas en inglés. Provee una guía integral para el proceso. (76) Otros incluyen:



Figura. Modelo conceptual del traslado neonatal.

ACoRN: *Acute Care of at Risk Newborn*, por sus siglas en inglés, es un programa que fue desarrollado en Canadá para identificar y manejar a los RN de alto riesgo mediante el proceso de evaluación-decisión-acción. (77) TRIPS: *Transport Risk Index of Physiologic Stability*, por sus siglas en inglés, es un puntaje o *score* de gravedad, diseñado para evaluar el riesgo en términos de morbilidad y mortalidad de RN enfermos que serán trasladados a otro hospital y así actuar en consecuencia. (78) Todos los participantes del proceso deben dominar el programa y las guías de reanimación neonatal; NRP: *Neonatal Resuscitation Program*, por sus siglas en inglés, y llevar a cabo las actualizaciones del programa. (79)

RECOMENDACIONES FINALES DEL XIII CONSENSO DE SIBEN SOBRE TRASLADO NEONATAL

El presente manuscrito del XIII Consenso de SIBEN, que representa una extensa edición del trabajo original (80) recomienda las siguientes prácticas basadas en la mejor evidencia científica disponible y que podrían adaptarse a las circunstancias y posibilidades de cada país, región, unidad de cuidados intensivos neonatales y, en general, a los hospitales que trasladan neonatos.

GENERALIDADES

➢ Identificar oportunamente la necesidad del traslado, preferentemente materno-fetal siempre que sea posible.

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- Una vez decidido el traslado, activar inmediatamente canales de comunicación que continuarán hasta finalizar el traslado.
- Redactar la historia clínica del neonato que será trasladado e incluir evolución, condición actual, resultados laboratoriales y de imágenes tomadas en el hospital de referencia.
- Comunicar de inmediato a los padres en cuanto se tome la decisión del traslado explicando detenidamente y en detalle el motivo, las condiciones actuales del RN y los riesgos y beneficios, con palabras sencillas y sin tecnicismos, precisando la ubicación del hospital receptor.
- Solicitar a los padres que firmen la autorización del consentimiento informado de traslado que debe incluir dos testigos.
- Siempre que sea necesario se debe brindar a los padres tiempo a solas para hablar e informar a sus familiares sobre el traslado cuando así lo decidan.
- Permitir a los padres ingresar a la sala en donde se encuentra su hijo(a) previo al traslado e involucrarlos como parte fundamental del proceso de traslado.
- El equipo médico encargado del traslado debe presentarse con los padres antes del traslado y darles confianza y seguridad de que están capacitados, así como responder sus dudas e inquietudes.
- En caso que el padre o madre pueda ir en la ambulancia, se le debe explicar su rol, y lo que puede pasar durante el traslado y en qué forma actuará el equipo si se presenta alguna eventualidad.

ACERCA DEL NEONATO QUE SERÁ TRASLADADO

- Valorar y anticiparse a la intubación endotraqueal, de acuerdo a la evolución o progresión de la patología respiratoria y la vulnerabilidad del RN. Tener en cuenta el tiempo estimado del traslado.
- Asegurar la correcta fijación del tubo endotraqueal para evitar desplazamientos, desconexiones o extubaciones accidentales durante el traslado.
- Realizar radiografía toracoabdominal o USG pulmonar, así como gasometría una vez ajustada la ventilación. Confirmar la permeabilidad del tubo endotraqueal antes de salir.
- Es fundamental estabilizar al neonato crítico antes del traslado.
- Verificar equipo médico de traslado completo y listo y mediante *check list,* confirmar equipamiento, material como tubos endotraqueales, cánulas laríngeas, tubos de toracotomía, etc., así como fármacos para el traslado.
- Siempre implementar medidas no farmacológicas para aliviar el estrés y las molestias, incomodidad o malestar del paciente. No es necesaria la sedación durante el traslado, salvo en casos especiales, como por ejemplo algunos RN con hipertensión pulmonar.
- Analgesia apropiada y oportuna siempre que sea necesaria.
- Monitorización completa y adecuada.
- Si el traslado será largo y el RN amerita, es aconsejable disponer de control de la TA invasiva y la posibilidad de un analizador portátil de gases sanguíneos o monitorización de CO_2 espirado.
- En caso de traslado aéreo, vigilar el efecto de la altitud sobre la expansión del aire y la oxigenación.
- Trasladar al RN en el momento apropiado, con «margen de actuación», es decir, antes de que requiera una asistencia que puede no estar disponible durante el traslado.
- Siempre que sea necesario, asegurar antes del traslado acceso venoso central.
- Preparar de antemano las diluciones de fármacos previsiblemente necesarios durante el traslado, tomar en cuenta que el número de bombas de infusión es limitado.
- Cantidad mínima de fármaco/infusión: el doble de la estimada para la duración del traslado.
- Diluir los fármacos, de forma que la relación ritmo de infusión/dosis sea fácil de deducir o interpretar.
- Rotular apropiadamente los fármacos.
- Posicionar al RN sobre una superficie acolchada y utilizar sujeciones que lo aseguren correctamente para evitar movilizaciones, aceleración-desaceleración.
- Intentar posiciones similares a las fetales (flexionados hacia la línea media), ya que disminuyen el estrés.
- Asegurar un adecuado aislamiento térmico y acústico del RN.
- Elevar la camilla hidráulica dentro del vehículo.
- El conductor del equipo de traslado terrestre debe evitar aceleraciones súbitas y frenados bruscos.
- Cargar y descargar la incubadora desde del vehículo con suavidad.

En RN que se trasladan con hipotermia terapéutica, es muy importante monitorizar la temperatura de forma continua (sensor periférico y central).

ARRIBO AL HOSPITAL RECEPTOR

- Al arribar al hospital receptor, el equipo profesional del traslado debe presentar detalladamente al RN y proveer toda la información solicitada por el equipo receptor y entregar en físico la historia clínica completa, la evolución por escrito, los procedimientos realizados y los resultados de laboratorio y de imágenes en el hospital de origen.

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- Inmediatamente después, informar a los padres de las condiciones del RN a su llegada, aclarar todas sus dudas e inquietudes y asegurarles que su hijo(a) recibirá la atención requerida.
- Posteriormente el personal que recibe al paciente informará a los padres de las condiciones y plan a seguir, preferentemente al pie de la cuna del RN o por llamada telefónica directa.

CONCLUSIONES

En definitiva, el traslado antenatal o materno-fetal es la mejor opción en términos de seguridad, abordaje terapéutico oportuno, calidad de atención y, por supuesto, para obtener los mejores desenlaces materno-neonatales. Sin embargo, no siempre se diagnostican los riesgos o problemas antenatalmente, sino que se detectan al nacer o poco después del nacimiento, con lo cual el traslado neonatal constituye una parte fundamental en la estructura de los servicios asistenciales neonatales. Es necesario contar con protocolos establecidos de traslado neonatal, organizados, sistematizados, con amplio conocimiento, compromiso y actualizaciones periódicas, que permitan garantizar un nivel de atención muy similar al que el RN recibirá en el hospital receptor.

Existen grandes diferencias en el proceso de traslado neonatal en cada país y región de Latinoamérica. Lamentablemente, en la mayoría de los países latinoamericanos no existe un sistema unificado y específico para traslado neonatal, con personal calificado y formado o entrenado para tal fin, ni con el equipamiento requerido. Es necesario centrarse en mejorar la equidad en las prestaciones de servicios de salud y enfocarnos en buscar la excelencia en el proceso del traslado neonatal en aras de mejorar los desenlaces maternos y neonatales. A la vez, hay que hacer todo lo posible para diagnosticar tempranamente embarazos de alto riesgo y derivarlos oportunamente a centros de tercer nivel de atención. En SIBEN nos esforzamos por tratar de reducir la amplia brecha que existe entre lo que se conoce y lo que se lleva a cabo en la práctica cotidiana y es nuestro mejor deseo que la presente narrativa ayude a favorecer el proceso del oportuno y apropiado traslado neonatal.

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American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the issues in the organization of perinatal care (e.g., regionalization, transport, practice guidelines, benchmarking data, quality improvement).
- Know the various types and mechanisms of action of devices to maintain a neutral thermal environment.
- Know the causes, metabolic consequences, and treatment of infants with hypothermia.
- Know the causes, metabolic consequences, and treatment of infants with hyperthermia.
- Know the mechanisms of heat gain and loss.
- Know the definition and physiological implications of a neutral thermal environment.

References

1. Kunz SN, Dukhovny D, Profit J, Mao W, Miedema D, Zupancic JAF. Predicting Successful Neonatal Retro-Transfer to a Lower Level of Care. *J Pediatr*. 2019;205:272–276.e1
2. Moreno Hernando J, Thió Lluch M, Salguero García E, et al. Recomendaciones sobre transporte neonatal. *An Pediatr*. 2013;79(2):117. e1–117.e7
3. Trevisanuto D, Cavallin F, Loddo C, et al. Servizio Trasporto Emergenza Neonatale STEN Group. Trends in neonatal emergency transport in the last two decades. *Eur J Pediatr*. 2021;180(2):635–641
4. Aagaard H, Hall EOC, Ludvigsen MS, Uhrenfeldt L, Fegran L. Parent's experiences of neonatal transfer. A meta-study of qualitative research 2000-2017. *Nurs Inq*. 2018;25(3):e12231 PMID: 29446189.
5. Kaneko M, Yamashita R, Kai K, Yamada N, Sameshima H, Ikenoue T. Perinatal morbidity and mortality for extremely low-birthweight infants: A population-based study of regionalized maternal and neonatal transport. *J Obstet Gynaecol Res*. 2015;41(7):1056–1066

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6. Singh J, Dalal P, Gathwala G, Rohilla R. Transport characteristics and predictors of mortality among neonates referred to a tertiary care centre in North India: a prospective observational study. *BMJ Open*. 2021;11(7):e044625
7. Jordán-Lucas R, Boix H, Sánchez-García L, Cernada M, de las Cuevas I, Couce ML, en representación de las Comisiones de Estándares y Transporte Neonatal, Sociedad Española de Neonatología. Recommendations on the skills profile and standards of the neonatal transport system in Spain. *An Pediatr (Engl Ed)*. 2021;94(6):420el–420eII
8. Blanco D, García-Alix A, Valverde E, Tenorio V, Vento M, Cabañas F. Neuroprotección con hipotermia en el recién nacido con encefalopatía hipóxico-isquémica. Guía de estándares para su aplicación clínica. *An Pediatr*. 2011;75(5):341.e1–341–e20
9. American Academy of Pediatrics. Section on transport medicine. In: Insoft RM, Schwartz HP, (eds). *Guidelines for air and ground transport of neonatal and pediatric patients*. 4rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016;488
10. Karlsen KA, Trautman M, Price-Douglas W, Smith S. National Survey of Neonatal Transport Teams in the United States. *Pediatrics*. 2011;128(4):685–691
11. Perry SE. Fifty years of progress in neonatal and maternal transport for specialty care. *J Obstet Gynecol Neonatal Nurs*. 2021;50(6): 774–788
12. Chien LY, Whyte R, Thiessen P, Matthew D, Aziz K, Lee SK, The Canadian Neonatal Network. Improved outcome of preterm infants when delivered in tertiary care centers. *Obstet Gynecol*. 2001;98(2):247–252
13. Rijken M, Stoelhorst G, Martens S, et al. Mortality and Neurologic, Mental, and Psychomotor Development at 2 Years in Infants Born Less Than 27 Weeks' Gestation: The Leiden Follow-Up Project on Prematurity. *Pediatrics*. 2003;112(2):351–358
14. Niermeyer S, Domek G. Neonatal transport in developing country settings: A systematic review. Montevideo: Pan American Health Organization; 2016. Disponible en: http://iris.paho.org/xmlui/handle/123456789/31317. Accessed on 1 March 2022
15. Helenius K, Longford N, Lehtonen L, Modi N, Gale C. Neonatal Data Analysis Unit and the United Kingdom Neonatal Collaborative. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. *BMJ*. 2019;367:l5678
16. Shah KP, de Regnier RAO, Grobman WA, Bennett AC. Neonatal Mortality After Interhospital Transfer of Pregnant Women for Imminent Very Preterm Birth in Illinois. *JAMA Pediatr*. 2020;174(4):358–365
17. Esqué MT, Salvia MD, Thió M. El traslado intraútero, un dato olvidado en la historia neonatal. *Pediatr catalán*. 2004;64(2):61–67
18. Knox GE, Schnitker KA. In-utero transport. *Clin Obstet Gynecol*. 1984;27(1):11–16
19. Kronick JB, Frewen TC, Kissoon N, et al. Pediatric and neonatal critical care transport: A comparison of therapeutic interventions. *Pediatr Emerg Care*. 1996;12(1):23–26
20. Martínez-Verónica R, López-Gallo L, Rodríguez-Medina D, et al. Transporte neonatal seguro en la población abierta del estado de Jalisco: impacto del programa S.T.A.B.L.E. en la morbilidad y mortalidad. *Bol Med Hosp Infant Mex*. 2011;68(1):34–39
21. Ministerio de Salud Pública. *Guía de Práctica Clínica Para la Atención del Recién Nacido Prematuro*. Organización Panamericana de la Salud/Organización Mundial de la Salud. Primera edición: República Dominicana. 2018. [Internet] Disponible en: www.msp.gob.do
22. Musson RE, Harrison CR. The burden and outcome of in utero transfers. *Acta Paediatr*. 2015;105(5):490–493
23. Bellani P. Estabilización del recién nacido antes del traslado. En Sola A, Golombek S. *Cuidando al recién nacido a la manera de SIBEN*; 1 ed. Argentina; EDISIBEN. 2020; p.913–922
24. Colaco SM, Karande T, Bobhate PR, Jiyani R, Rao SG, Kulkarni S. Neonates with critical congenital heart defects: Impact of fetal diagnosis on immediate and short-term outcomes. *Ann Pediatr Cardiol*. 2017;10(2):126–130
25. Sachs BP, Marks JS, McCarthy BJ, Burton A, Rochat RW, Terry J. Neonatal transport in Georgia: Implications for maternal transport in high-risk pregnancies. *South Med J*. 1983;76(11):1397–1400
26. Celiz M, Montes-Bueno MT, Cardetti M. Sección 3 – Traslado neonatal. En: Montes-Bueno MT, Cardetti M, Sola A. *Técnicas y procedimientos en neonatología a la manera de SIBEN*. 1ra ed. Ed. EdiSIBEN. Quito. 2019. 49–68
27. Munthali K, Harrison C. The continuing impact of capacity on a region's in utero transfer requests. *Acta Paediatr*. 2020;109(6): 1148–1153
28. Del Moral T, Bancalari E. Evolución de la actitud frente al recién nacido prematuro. *Bol Pediatr*. 2010;50:39–42 (supl1):
29. Goswami I, Redpath S, Langlois RG, Green JR, Lee KS, Whyte HEA. Whole-body vibration in neonatal transport: a review of current knowledge and future research challenges. *Early Hum Dev*. 2020;146:105051
30. Cetin I, Schlembach D, Bonnard N, et al. European Standards of Care for Newborn Health: Maternal transfer for specialist care. 2018. Disponible en: https://newborn-health-standards.org/standards/standards-english/birth-transfer/maternal-transfer-for-specialist-care/
31. Bailey V, Szyld E, Cagle K, et al. Modern Neonatal Transport: Sound and Vibration Levels and Their Impact on Physiological Stability. *Am J Perinatol*. 2019;36(4):352–359
32. Kleinman ME. Neonatal Transport, En: Cloherty and Starks. ed. *Manual of Neonatology Care* 8th Edition. India. Wolters Kluwer Health, 2021: 224–235
33. Bose A. Transfer of the Sick Neonate: What Is Needed? *J Trop Pediatr*. 2017;63(3):165–166
34. Woodward GA. Transport Medicine. *en Comprehensive Pediatric Hospital Medicine*. 2007; 68–72. Disponible en:
35. Alejandre C, Gómez J. Transferencia del paciente en el transporte pediátrico y neonatal. *Protoc Diagn Ter Pediatr*. 2021;1:695–703
36. Brennan G, Colontuono J, Carlos C. Neonatal Respiratory Support on Transport. *Neoreviews*. 2019;20(4):e202–e212
37. Comité Nacional de Emergencias y Cuidados Críticos. Consenso sobre el traslado de niños críticamente enfermos. *Arch Argent Pediatr*. 2019;117:S1–S23 Supl 1:
38. Gien J, Nuxoll C, Kinsella JP. Inhaled nitric oxide in emergency medical transport of the newborn. *Neoreviews*. 2020;21(3):e157–e164
39. Millán-García del Real N, Sánchez-García L, Ballestero-Diez Y, et al. Importancia del transporte pediátrico y neonatal especializado. Situación actual en España: Hacia un futuro más equitativo y universal. *An Pediatr*. 2021;95(6):485.e1–485.e10
40. De Sisto CL, Oza-Frank R, Goodman D, Conrey E, Sellhaas C. Maternal transport: an opportunity to improve the system of risk-appropriate care. *J Perinatol*. 2021;41(9):2141–2146

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41. Kronforst KD. Interhospital Transport of the Neonatal Patient. *Clin Pediatr Emerg Med*. 2016;17(2):140–146 Disponible en:
42. Lee SK, Aziz K, Dunn M, et al. Canadian Neonatal Network. Transport Risk Index of Physiologic Stability, Version II (TRIPS-II): A Simple and Practical Neonatal Illness Severity Score. *Am J Perinatol*. 2012;30(5):395–400
43. Whyte HEA, Jefferies AL, Lacaze T, et al. Canadian Paediatric Society, Fetus and Newborn Committee. The interfacility transport of critically ill newborns. *Paediatr Child Health*. 2015;20(5):265–275
44. Gente M, Aufieri R, Agostino R, et al. Neonatal transport study group of the Italian Society of Neonatology (SIN). Nationwide survey of neonatal transportation practices in Italy. *Ital J Pediatr*. 2019;45(1):51
45. Lampe G, Hillman N, Webb E. Management of Neonatal Respiratory Distress in Transport. *Pediatrics*. 2019;144(2_MeetingAbstract): 881–881 Disponible en
46. Cheema B, Welzel T, Rossouw B. Noninvasive ventilation during pediatric and neonatal critical care transport: a systematic review. *Pediatr Crit Care Med*. 2019;20(1):9–18
47. Sola A, Rogido MR, Deulofeut R. Oxygen as a neonatal health hazard: call for détente in clinical practice. *Acta Paediatr*. 2007;96(6):801–812
48. Baquero H, Alviz R, Castillo A, Neira F, Sola A. Avoiding hyperoxemia during neonatal resuscitation: Time to response of different SpO_2 monitors. *Acta Paediatr*. 2011;100(4):515–518
49. Diehl BC. Neonatal Transport: Current Trends and Practices. *Crit Care Nurs Clin North Am*. 2018;30(4):597–606
50. Coe K, Jamie S, Baskerville RM. Managing common neonatal respiratory conditions during transport. *Adv Neonatal Care*. 2014; 14 Suppl 5:S3–10
51. Piloquet J, Genuini M, Kessous K, et al. A twelve-year neonatal and pediatric high-frequency oscillation ventilation transport experience. *Pediatr Pulmonol*. 2021;56(5):1230–1236
52. Jones P, Dauger S, Leger P-L, et al. Mortality in children with respiratory failure transported using high frequency oscillatory ventilation. *Intensive Care Med*. 2015;41(7):1363–1364
53. Zhang Q, Macartney J, Sampaio L, O'Brien K. High Frequency Jet Ventilation during Initial Management, Stabilization, and Transport of Newborn Infants with Congenital Diaphragmatic Hernia: A Case Series. *Crit Care Res Pract*. 2013;2013:937871
54. Martinho S, Adao R, Leite-Moreira AF, Bras-Silva C. Persistent pulmonary hypertension of the newborn. Pathophysiological mechanism and novel therapeutic approaches. *Front Pediatr*. 2020;8:342
55. Lowe C, Trautwein J. Inhaled nitric oxide therapy during the transport of neonates with persistent pulmonary hypertension or severe hypoxic respiratory failure. *Eur J Pediatr*. 2007;166(10): 1025–1031
56. Gianni S, Carroll RW, Kacmarek RM, Berra L. Inhaled nitric oxide delivery systems for mechanically ventilated and nonintubated patients: A Review. *Respir Care*. 2021;66(6):1021–1028
57. Xu XJ, Li LN, Wu WY. Importance of stabilization of the neonatal transport network in critically ill neonates. *J Int Med Res*. 2019;47(8):3737–3744
58. Meckler GD, Lowe C. To Intubate or Not to Intubate? Transporting Infants on Prostaglandin E1. *Pediatrics*. 2009;123(1):e25–e30
59. Gomes ELFD, Santos CMD, Santos ADCS, et al. Autonomic responses of premature newborns to body position and environmental noise in the neonatal intensive care unit. *Rev Bras Ter Intensiva*. 2019;31(3):296–302
60. Harrison C, McKechnie L. How comfortable is neonatal transport?: Neonatal transport. *Acta Paediatr*. 2012;101(2):143–147
61. Kumar P, Denson SE, Mancuso TJ, Committee on Fetus and Newborn, Section on Anesthesiology and Pain Medicine. Premedication for Nonemergency Endotracheal Intubation in the Neonate. *Pediatrics*. 2010;125(3):608–615
62. Lemus-Varela MdL, Sola A, Golombek S, et al. Consenso Clínico de Dolor y Estrés Neonatal, de la Sociedad Iberoamericana de Neonatología (SIBEN). Consenso sobre el abordaje diagnóstico y terapéutico del dolor y el estrés en el recién nacido. *Rev Panam Salud Publica*. 2014;36(5):348–354
63. Weiss MD, Tang A, Young L, et al. Transporting neonates with hypoxic-ischemic encephalopathy utilizing active hypothermia. *J Neonatal Perinatal Med*. 2014;7(3):173–178
64. Arnáez J, Vega C, García-Alix A, et al. Programa multicéntrico para la atención integral del recién nacido con agresión hipóxico-isquémica perinatal (ARAHIP). *An Pediatr*. 2015;82(3): 172–182
65. Leon RL, Krause KE, Sides RS, Koch MB, Trautman MS, Mietzsch U. Therapeutic Hypothermia in Transport Permits Earlier Treatment Regardless of Transfer Distance. *Am J Perinatol*. 2022;39(6):633–639
66. Akula VP, Hedli L, Meurs KV, Gould J, Peiyi K, Lee H. Neonatal transport in California: findings from a qualitative Investigation. *J Perinatol*. 2019;40(3):394–403
67. O'Reilly KM, Tooley J, Winterbottom S. Therapeutic hypothermia during neonatal transport. *Acta Paediatr*. 2011;100(8):1084–1086; discussion e49
68. Golombek SA, Capítulo V. *Sección 3. Encefalopatía hipóxico-isquémica en el recién nacido a término: Cuidando al recién nacido a la manera SIBEN*. 1era Edición - Santa Cruz de la Sierra: SIBEN 2017; Tomo I, págs.: 555–564
69. Segar JL, Chock VY, Harer MW, Selewski DT, Askenazi DJ, Newborn Brain Society Guidelines and Publications Committee. Fluid management, electrolytes imbalance and renal management in neonates with neonatal encephalopathy treated with hypothermia. *Semin Fetal Neonatal Med*. 2021;26(4):101261 PMID: 34140246.
70. Glenn T, Price R, Culbertson L, Yalcinkaya G. Improving thermoregulation in transported preterm infants: a quality improvement initiative. *J Perinatol*. 2021;41(2):339–345
71. Quiroga A, Chattas G, Gil-Castañeda A, et al. *Guía de práctica clínica de termorregulación en el recién nacido*. EDISIBEN.2010. ISBN: 978-598-17.1.
72. Rozance P. Management and outcome of neonatal hypoglycemia. UpToDate. 2022. Disponible en: https://www.uptodate.com/contents/management-and-outcome-of-neonatal-hypoglycemia/print.
73. Alsaleem M, Saadeh L, Kamat D. Neonatal Hypoglycemia: A Review. *Clin Pediatr (Phila)*. 2019;58(13):1381–1386
74. Haninger NC, Farley CL. Screening for hypoglycemia in healthy term neonates: Effects on breastfeeding. *J Midwifery Womens Health*. 2001;46(5):292–301
75. Karagol B, Zencōroglu A, Ipek M, Kundak A, Okumus N. Impact of Land-Based Neonatal Transport on Outcomes in Transient Tachypnea of the Newborn. *Am J Perinatol*. 2011;28(4):331–336
76. Mears M, Chalmers S. Neonatal pre-transport stabilisation caring for infants the STABLE way. *Infant*. 2005;1(1):34–37
77. Aziz K, Ma X, Lockyer J, et al. An evaluation of Acute Care of at-Risk Newborns (ACoRN) a Canadian education program, in Chinese neonatal nurseries. *Pediatr Child Health*. 2020;25(6):351–357

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78. Da Silva GE, de Souza NL, de Oliveira COP, et al. Risk assessment of morbidity and mortality in the neonatal transport. *int arch med*. 2017;10(24)

79. Weiner GM, Zaichkin J. Updates for the Neonatal Resuscitation Program and Resuscitation Guidelines. *Neoreviews*. 2022;23(4): e238–e249

80. Golombek SG, Dávila-Aliaga C, Pleitez Navarrete J. Lemus-Varela L Sola A y Miembros del XIII Consenso: XIII Consenso Clínico SIBEN 2023 Traslado Neonatal (13th SIBEN Clinical Consensus: Neonatal Transport). Ediciones SIBEN 2023. Argentina. ISBN 978-1-7923-9847-6

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Disorders of Coagulation in the Newborn

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EDUCATION GAPS

Coagulopathy is common in neonates and can arise from myriad causes. As both congenital and acquired causes can contribute to a coagulopathic state, it is important for clinicians to be able to distinguish between the 2, begin an initial diagnostic evaluation, and initiate treatment promptly.

OBJECTIVES *After completing this article, readers should be able to:*

1. Initiate an appropriate initial evaluation for a neonate suspected to have a congenital or acquired coagulopathy.
2. Identify when a neonate has a disorder of primary hemostasis, secondary hemostasis, or a disorder of the fibrinolytic system based on symptoms and laboratory testing.
3. Recognize which common coagulation abnormalities correspond to patterns of laboratory tests.

ABSTRACT

The coagulation system in newborns varies from that of children and adults, with many circulating hemostatic factors being lower in the newborn. Infants are also susceptible to diseases and conditions in the pregnant person affecting their coagulation system, which can make it difficult to rapidly identify the cause behind coagulopathy in a neonate. Coagulation disorders can result in high levels of infant morbidity and mortality, which makes early diagnosis and prompt treatment critical. This review outlines the clinical characteristics, diagnosis and management, epidemiology, and etiologies of both common and uncommon congenital and acquired forms of neonatal coagulopathy.

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ABBREVIATIONS

α2-AP	alpha-2 antiplasmin
aPTT	activated partial thromboplastin time
CMV	cytomegalovirus
DIC	disseminated intravascular coagulation
FVIII	factor VIII
FIX	factor IX
FXIII	factor XIII
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HPA	human platelet alloantigen
HSV	herpes simplex virus
ICH	intracranial hemorrhage
ITP	immune thrombocytopenia
KHE	kaposiform hemangioendothelioma
KMP	Kasabach-Merritt phenomenon
NAIT	neonatal alloimmune thrombocytopenia
PT	prothrombin time
SGA	small for gestational age
TA	tufted angioma
TAR	thrombocytopenia absent radii
VKDB	vitamin K deficiency bleeding disorder
vWD	von Willebrand disease
vWF	von Willebrand factor

The many different proteins and cells that take part in the intricate coagulation system all work toward the goal of homeostasis or hemostasis. A visual representation of the coagulation cascade, including the different pathways and associated laboratory tests, is shown in the Figure. Coagulopathies can broadly be thought of as disorders of primary hemostasis, disorders of secondary hemostasis, or disorders of the fibrinolytic system, with different laboratory values

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associated with each disorder (Table 1). Primary hemostasis involves platelet aggregation and the development of the platelet plug in response to vascular injury. (1) Secondary hemostasis is the deposition of insoluble fibrin after activation of hemostatic factors, and the fibrinolytic system is responsible for the dissolution of thrombi. (2)(3) Such disorders can be acquired, in response to medications or other diseases, or can be congenital, arising from genetic mutations and specific deficiencies.

HEMOSTASIS OVERVIEW

Primary hemostasis relies on platelets adhering to areas of vascular injury, attaching to the exposed matrix of collagen and von Willebrand factor (vWF). (1) Platelets then become activated, changing the phospholipids exposed on the cell surface and resulting in platelet aggregation, which subsequently creates the initial platelet plug. (1) Occurring simultaneously is the initiation of the coagulation cascade, or secondary hemostasis, which results in insoluble fibrin generation from a series of protein reactions. (3)(4)(5) This cascade, composed of serine proteases and cofactors, can arise via 2 different pathways, the intrinsic or the extrinsic pathway, which converge on the common pathway.

The extrinsic pathway is triggered when blood makes contact with extravascular cells, which possess tissue factors, resulting in the activation of factor V, which then activates factor X, the first factor of the common pathway. (3)(4) The extrinsic and common pathways are represented in a prothrombin test (PT). (6) In the absence of exposure to tissue factors, the coagulation cascade can also arise from the intrinsic pathway, where the contact system activates after exposure to invasive pathogens and certain materials in the blood. (4)(7) The contact system is composed of factor XII, prekallikrein, and high-molecular-weight kininogen, and reacts to substances including collagen, platelets, and certain bacteria, beginning the cascade. (4)(7)(8) This also ends with activation of factor X, which aids in the generation of thrombin and then fibrin. (4)(5) The intrinsic and common pathways are represented in the activated partial thromboplastin time (aPTT) test. (6) Fibrin is the terminal result of the common pathway, leading to hemostasis and preventing hemorrhage, but this thrombus is then regulated by the fibrinolytic system, which eventually dissolves the thrombus. (2) Plasmin is the primary regulator of fibrinolysis, removing the thrombus when the blood vessel is healed and its integrity is restored. (2)

EPIDEMIOLOGY

Coagulopathy is relatively common in newborns, with adults and children having relatively different coagulation systems than infants. Until an infant has reached 32 weeks' gestational age, their platelet count is reduced compared with older children, and platelet function is decreased. (9) Many coagulation factors are also decreased in neonates, including factors II, VII, IX, X, XI, and XII, antithrombin, and protein C. (9) In contrast, factors V, VIII, and XIII, and fibrinogen have normal levels, whereas vWF is increased. (9)(10) As a result of these alterations, neonates can have up to a 25% chance of bleeding during admission to the NICU, with prematurity increasing risk. (11) One of the most serious bleeding complications includes intraventricular hemorrhage, which can affect 23% of infants born at less than 32 weeks' gestational age, with increasing gestational age being protective. (12) Infants with sepsis, lower birthweight, or the presence of a patent ductus arteriosus have an increased risk. (12)

DISORDERS OF PRIMARY HEMOSTASIS

Impairment of primary hemostasis is frequently responsible for serious bleeding events in infants. Various factors,

Table 1. Diagnosis Based on Coagulation Panel Abnormalities

Type of Disorder	Platelet Count	PT/INR	aPTT
Disorders of Primary Hemostasis			
Quantitative disorders	Decreased	Normal	Normal
Qualitative disorders	Normal or decreased	Normal	Normal
vWD	Normal	Normal	Prolonged
Congenital thrombotic thrombocytopenic purpura	Decreased	Normal	Normal
Collagen and vascular disorders	Normal	Normal	Normal
Disorders of Secondary Hemostasis			
Vitamin K deficiency	Normal	Prolonged	Normal or prolonged
Hemophilia A: Factor VIII deficiency	Normal	Normal	Prolonged
Hemophilia B: Factor IX deficiency	Normal	Normal	Prolonged
Factor XIII deficiency	Normal	Normal	Normal

aPTT=activated partial thromboplastin time, INR=international normalized ratio, PT=prothrombin time, vWD=von Willebrand disease.

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including heredity, maternal acquisition, infections, and drugs, can impair primary hemostasis in the neonate. Gestational age (premature infants typically exhibit slightly lower platelet counts compared with those born at full term), hypoxia, acidosis, higher vWF concentrations and enhanced function, lower plasma level and activity of other coagulation proteins, elevated hematocrit count, large erythrocytes during the first day after birth, and platelet hyperreactivity are other factors to consider. (9)(10) In addition to an accurate medical and family history, physical examination, coagulation testing, and potential hematology consultation can help identify a disorder of primary hemostasis (Table 2 and Table 3).

Quantitative Disorders of Primary Hemostasis

Impaired Platelet Production. Platelets are formed through the fragmentation of megakaryocytes in the bone marrow. This process begins during early fetal life and increases in number to adult concentrations in the peripheral blood around 22 weeks' gestation. (13) Newborns have developmental

Table 2. Quantitative Disorders of Primary Hemostasis

Disorder	Pattern of Inheritance/ Transmission	Clinical Signs and Symptoms	Diagnosis	Management
Neonatal alloimmune thrombocytopenia	Transfer of platelet-specific antibodies	Thrombocytopenia Risk of bleeding ICH is common	Platelet count Plasma levels of anti-HPA-1A in parents	Donor-matched platelet transfusion Intravenous IgG
Immune thrombocytopenia in the birthing parent	Transfer of platelet-specific antibodies	Thrombocytopenia Risk of bleeding ICH is rare	Birthing parent and infant platelet counts	Intravenous IgG Corticosteroids
Thrombocytopenia from preeclampsia	N/A	Maternal hypertension with or without thrombocytopenia Low birth weight infant	Clinical history and platelet counts	Platelet transfusion
Congenital infection	Congenital or perinatal transmission	Variable: • Toxoplasmosis: petechiae, hepatosplenomegaly, jaundice, low birth weight, hydrocephalus, intracranial calcifications, microcephaly • Rubella: microcephaly, developmental delay, hearing impairment, hepatosplenomegaly, retinopathy, congenital glaucoma, cataracts, intrauterine growth restriction, congenital heart defects, and purpura • CMV: sensorineural hearing loss, microcephaly, intracranial calcifications, hepatitis, purpura, retinitis and severe thrombocytopenia • HIV: sepsis, growth faltering • HSV: sepsislike illness, thrombocytopenia, consumptive coagulopathy, and acute liver failure	Clinical manifestations with viral or infectious disease testing	Antiviral or antibacterial treatments
Thrombocytopenia absent radii syndrome	Autosomal recessive	Bleeding and thrombocytopenia that improves over time May have cardiac and renal abnormalities	Clinical manifestations Genetic testing	Platelet transfusion
Wiskott-Aldrich syndrome	X-linked recessive	Thrombocytopenia Eczema Immunodeficiency	Genetic testing	Intravenous IgG Platelet transfusion Corticosteroids
Congenital amegakaryocytic thrombocytopenia	Autosomal recessive	Purpura, petechia, and bleeding (early) Aplastic anemia and leukemia (late)	Bone marrow biopsy Genetic testing	Platelet transfusion Stem cell transplant

CMV=cytomegalovirus, HIV=human immunodeficiency virus; HSV, herpes simplex virus, ICH=intracranial hemorrhage, Ig=immunoglobulin, N/A=not applicable.

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Table 3. Qualitative Disorders of Primary Hemostasis

Disorder	Pattern of Inheritance/ Transmission	Clinical Signs and Symptoms	Diagnosis	Management
Glanzmann thrombasthenia	Autosomal recessive	Mild to severe bleeding	Flow cytometry with the absence of GPIIb/IIIa receptor Platelet aggregation studies	Factor VIIa Aminocaproic acid Platelet transfusion
Bernard-Soulier syndrome	Autosomal recessive	Mild to severe bleeding	Flow cytometry: absence of glycoprotein IB, V, and IX on platelet surfaces and platelet aggregation studies	Platelet transfusion
Gray platelet syndrome	Autosomal dominant, autosomal recessive, or X-linked	Bleeding Splenomegaly	Peripheral smear review and no α-granules on electron microscopy	Platelet transfusion Desmopressin Splenectomy
Hermansky-Pudlak syndrome	Autosomal recessive	Bleeding Oculocutaneous albinism Vision abnormalities Possible immunodeficiency	Clinical findings Lack of platelet δ granules on electron microscopy	Platelet transfusion Desmopressin
von Willebrand disease	Autosomal dominant (type 1 and most type 2) or autosomal recessive (type 3)	Frequent mucocutaneous bleeding, with spontaneous joint or muscle bleeding and/or hematomas in type 3 disease	aPTT and FVIII activity vWF ristocetin-cofactor activity vWF antigen levels	Antifibrinolytics, desmopressin vWF concentrates alone and/or a combination of FVIII:vWF
Congenital thrombotic thrombocytopenic purpura	Autosomal recessive	Hyperbilirubinemia Thrombocytopenia Stroke and other arterial thromboembolic events, ischemia, and renal disease	ADAMTS13 activity	ADAMTS13 replacement
Collagen and vascular disorders	Typically autosomal dominant	Bleeding Skin and joint hypermobility (Ehlers-Danlos syndrome) Arteriovenous malformations Telangiectasis (hereditary hemorrhagic telangiectasia)	Clinical and family history	Antifibrinolytics

aPTT=activated partial thromboplastin time, FVIII=factor VIII, vWD=von Willebrand disease.

immaturities in hematopoiesis and are thus more susceptible to peripheral cytopenia, particularly in high-demand states, if they have defects in thrombopoiesis and myelopoiesis. For instance, prolonged intrauterine hypoxia resulting from placental dysfunction might cause both thrombocytopenia and polycythemia in small-for-gestational-age (SGA) newborns owing to impaired thrombopoiesis. (14) Multiple studies indicate that plasma concentrations of thrombopoietin, which controls thrombopoiesis, are elevated in both full-term and preterm neonates compared with healthy adults. (15) Conversely, neonatal megakaryocyte progenitors may have higher proliferative rate potential and more sensitivity to thrombopoietin than adult progenitors. (16) However, compared with adult megakaryocytes, they produce fewer platelets per cell and are smaller. (17)

In normal circumstances, the adult bone marrow adapts to heightened platelet requirements by enlarging megakaryocytes and increasing their ploidy, thereby boosting megakaryocyte mass. (18) However, neonates with thrombocytopenia can augment the quantity of their megakaryocytes but are unable to affect their size. (18) A small neonatal megakaryocyte may thus have limited ability to respond to increased demand and thrombocytopenia. (18)

When platelets adhere to areas of vascular damage, they release biological mediators and the contents of granules to facilitate plasma coagulation reactions. (1) Following endothelial damage, platelets attach to the underlying basement membrane collagen, initiating the primary stage of hemostasis and engaging with subendothelial vWF. (1) Glycocalicin serves as an indicator of heightened platelet turnover, whereas interleukin 6 levels rise in reaction to thrombocytopenia. (19) Neonates experiencing intrauterine growth restriction and thrombocytopenia exhibited undetectable levels of glycocalicin in their plasma, indicating compromised thrombopoiesis. (19) In addition, alloimmunization

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against platelets can occur during pregnancy or after receiving a transfusion, resulting in the swift destruction of incompatible platelets. (20)

Neonatal Alloimmune Thrombocytopenia. Neonatal alloimmune thrombocytopenia (NAIT) is rare (1 in 1,000 births) and is triggered by the transfer of platelet-specific alloantibodies or human leukocyte antigen antibodies from the pregnant person across the placenta, which then recognize the corresponding antigens in the infant. (21) The human platelet alloantigens (HPAs) from the non–birth parent may differ from those of the birth parent, leading to the production of antibodies in the pregnant person against an unfamiliar antigen. As early as 15 weeks of gestation, these immunoglobin G antibodies can be transplacentally transmitted to the fetal circulation, causing thrombocytopenia, and can persist until they are cleared. (22)(23) The likelihood of NAIT recurring in subsequent pregnancies has been projected to exceed 80%, with subsequent presentations having greater severity and an increased risk of bleeding. (24)

NAIT is diagnosed based on clinical and serologic findings. Clinical findings related to thrombocytopenia include ecchymosis, petechiae, purpura, and bleeding. Intracranial hemorrhage (ICH) stands out as one of the most critical complications and can be detected during pregnancy as early as the 20th week of gestation. (25) However, NAIT frequently remains undetected during prenatal screening because universal screening is not routinely conducted. Screening tools include the detection of plasma levels of anti-HPA-1a, the most common antigen involved in white pregnant persons. (24) Fetal HPA genotyping through amniocentesis is rarely used given the invasive nature of the procedure. (24)

Postnatally, NAIT should be considered in a newborn with thrombocytopenia within 48 hours of delivery after excluding other factors contributing to thrombocytopenia. The birth parent's platelet count should be obtained if a neonate has thrombocytopenia without an identified cause because it can distinguish NAIT from other autoimmune thrombocytopenias such as immune thrombocytopenia (ITP). (24) Final diagnosis can then be made with platelet immunologic testing of both parents. (24) In addition to this testing, anti-HPA antibodies in blood in the birth parent and genotyping in the non–birth parent can identify the risk of recurrence in subsequent pregnancies. (23)(24)

For prenatal management, intravenous immunoglobin with or without steroid administration is the preferred treatment and can be given to pregnant persons as early as 18 weeks' gestation. (24) Fetal platelet counts can be measured through cordocentesis, with findings of severe thrombocytopenia warranting treatment. (24) Postnatally, infants with platelet counts less than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$) should be screened for ICH with head ultrasonography and given a platelet transfusion if platelets fall below $30 \times 10^3/\mu L$ ($30 \times 10^9/L$). (24) The threshold for transfusion decreases if the newborn is actively bleeding or has an intracranial or extracranial hemorrhage, and it is important not to postpone treatment while waiting for confirmation testing. (24) Infants should be given donor-matched platelet transfusions, because antibodies from the birth parent might persist in the infant's bloodstream, and platelets may not stabilize until these antibodies are cleared from the infant's circulation. (24) In addition, intravenous immunoglobin may be necessary while antibodies are cleared. (24)

ITP in the Pregnant Person. ITP in the pregnant person causes neonatal thrombocytopenia because of active transplacental transport of antiplatelet antibodies from the pregnant person, which then act against fetal platelet surface glycoproteins. In ITP, platelet counts in the birth parent are low whereas infant platelet counts are variable. If platelet counts in the infant are initially decreased, platelets should continue to be monitored after birth as platelet counts may continue to fall postnatally. (26) Platelet counts will typically normalize by 4 to 6 weeks after birth. (26) Thrombocytopenia is significant enough in 9% to 15% of infants born to persons with ITP that treatment is required but fortunately, only 0% to 1.5% of infants have ICH. (26) Infants with platelet counts less than $50 \times 10^3/\mu L$ ($50 \times 10^9/L$) may need to be monitored even though the risk for ICH is low. (26)

Congenital Neonatal Infections.

Cytomegalovirus

Cytomegalovirus (CMV) can cause neonatal infection from congenital or perinatal transmission, and can manifest as sensorineural hearing loss, microcephaly, intracranial calcifications, hepatitis, pneumonia, purpura, retinitis, SGA, and severe thrombocytopenia. Diagnosis is achievable by detecting CMV in both urine and saliva of the neonate through polymerase chain reaction, with sensitivities ranging from 93% to 100%. (27) Pregnant persons with mononucleosislike illness and/or with fetal anomalies suggestive of congenital CMV should be tested. (27)(28) Treatment includes 6 months of valganciclovir therapy in newborns showing symptoms with CNS involvement between 32 weeks' gestation and less than 1 month of age. (28) It is important to monitor for myelosuppression during the full course of treatment. (28)

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Toxoplasmosis

Neonatal toxoplasmosis presents with petechiae, hepatosplenomegaly, jaundice, low birthweight, hydrocephalus, intracranial calcifications, microcephaly, seizures, retinitis, and microphthalmia. (29) Diagnosis is achieved through anti-*Toxoplasma gondii* immunoglobulin (Ig)M/IgA and IgG, indirect ophthalmoscopy to identify retinochoroiditis, and the detection of calcification and hydrocephalus via brain magnetic resonance imaging and computed tomography. (30) If pregnant persons are diagnosed during gestation through serologic or amniotic fluid testing, treatment with spiramycin can be offered early in pregnancy, or pyrimethamine and sulphonamide in the third trimester through delivery. (30) In the infant, therapy includes a combination of pyrimethamine and sulfonamide for 12 months. (30) It is important to monitor for bone marrow suppression throughout the treatment course because of folate metabolism inhibition. (30)

Rubella

Congenital rubella syndrome is an uncommon cause of thrombocytopenia in infants. Clinical characteristics include microcephaly, developmental delay, hearing impairment, hepatosplenomegaly, retinopathy, congenital glaucoma, cataracts, intrauterine growth restriction, congenital heart defects, and purpura. (31) Thrombocytopenia can be secondary to bone marrow suppression (particularly in SGA infants) but the exact etiology remains unknown. (32)

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) type 1 infection remains a major contributor to morbidity and mortality among children in low- and middle-income nations, with over a third of HIV-1–positive infants succumbing to the infection during childhood if left untreated. (33) Thrombocytopenia, sepsis, and failure to thrive have been identified as common findings in symptomatic patients. (34) Early diagnosis and immediate treatment via the initiation of antiretroviral therapy are imperative and critical for children younger than 18 months who have been exposed to perinatal HIV-1. Diagnosis is established by using molecular virologic assays, such as HIV-RNA or HIV-DNA tests. (33)

Herpes Simplex Virus

In infants, herpes simplex virus (HSV) infection can present as a widespread or disseminated disease affecting various organs, localized central nervous system involvement with or without skin symptoms, or infection restricted to the skin, eyes, and/or mouth. (35) Symptoms of HSV infection may appear any time from birth to 6 weeks of age, but infants with disseminated disease typically experience an earlier onset and present with symptoms resembling sepsis. (35) The infant may have thrombocytopenia, consumptive coagulopathy, and acute liver failure within the initial 30 days after birth. (35) Diagnosis is completed through HSV polymerase chain reaction assays from any skin vesicles, cerebrospinal fluid, whole blood, and surface swabs of the conjunctiva, nasopharynx, mouth, and anus. (35) When HSV infection is suspected or confirmed, prompt treatment with intravenous acyclovir should be initiated.

Preeclampsia. With an incidence of 2% to 6% in the United States, preeclampsia is the most common pregnancy-related complication in pregnant patients. (36) Its primary pathologic characteristics result from the activation of platelets and a widespread ischemic disorder due to endothelial dysfunction. Mechanisms considered for the etiology of thrombocytopenia include decreased platelet production and decreased circulating megakaryocyte progenitors, as well as increased immune-mediated platelet consumption. (36) Thrombocytopenia is observed in SGA infants, possibly stemming from consumptive coagulopathy, platelet destruction, and vascular pathology. (36) In SGA newborns, elevated erythropoietin levels and impaired thrombopoiesis may be the result of intrauterine hypoxia. (14) In addition, infants born to persons with preeclampsia have significantly lower platelet counts, lower megakaryocyte colony-forming units, and decreased megakaryocyte counts. (36)

Congenital Thrombocytopenia Syndromes. Congenital thrombocytopenia syndromes should be considered in infants who present with bleeding near birth that is out of proportion to their thrombocytopenia, have an associated family history, and have additional nonhematologic clinical findings. Thrombocytopenia absent radii (TAR), amegakaryocytic thrombocytopenia, and Wiskott-Aldrich syndrome are the primary platelet disorders with these manifestations but rare inborn errors of metabolism, such as Gaucher disease and methylmalonic acidemia, can also be considered. (26)

TAR is an autosomal recessive disorder in which infants have bilateral absent radii with thumbs and present with bleeding, petechial rash, and purpura near the time of birth. (37)(38) Bleeding and thrombocytopenia are more severe early in life and will often improve as the infant grows older. (38) Infants with TAR are predisposed to cow milk intolerance, which temporally correlates to worsening thrombocytopenia. (38) Both cardiac and renal abnormalities can be seen as part of TAR. (38) The diagnosis is

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established through clinical observations, which can be validated via genetic testing.

Congenital amegakaryocytic thrombocytopenia is inherited in an autosomal recessive fashion with severe (type 1) and mild to moderate (type 2) types. (39)(40) Purpura, petechiae, and bleeding can occur in the first month of age. (39)(40) Other hematologic manifestations include aplastic anemia and leukemia as a late manifestation. (39)(40) Bone marrow biopsy will show a reduction in megakaryocytes, and genetic testing of the *c-MPL* gene will lead to a definitive diagnosis. (39)(40) At present, hematopoietic stem cell transplantation stands as the only curative treatment option. (41)

Wiskott-Aldrich syndrome has the clinical hallmarks of thrombocytopenia, eczema, and immunodeficiency, with an X-linked recessive inheritance pattern. (42) The small platelets and thrombocytopenia are thought to be due to splenic destruction. (42) Infants can have failure to thrive and are susceptible to infections from encapsulated organisms. (42) Treatments may include intravenous immunoglobulin, platelet transfusions, and corticosteroids. (42)

Medications. Medications can also be a cause of quantitative platelet disorders, particularly in well-appearing infants with no other identified causes of thrombocytopenia. Common causes include antibiotics, heparin, phenytoin, and indomethacin. (26)(37)

Qualitative Disorders of Primary Hemostasis

Qualitative Platelet Disorders. Although rare, inherited qualitative platelet disorders should be considered in infants with early-onset bleeding that is persistent and disproportionate to the platelet count, and with an abnormal peripheral blood smear. There may be a family history of autosomal dominant, autosomal recessive, or X-linked inheritance. On peripheral blood smear, platelets can be large or have abnormal morphology. (37) Definitive diagnosis can be challenging, with platelet function testing, flow cytometry, and genetic testing all being used. Some qualitative platelet disorders, such as Glanzmann thrombasthenia and Bernard-Soulier syndrome, carry an increased risk for isoimmunization or alloimmunization after platelet transfusions leading ultimately to ineffective platelet transfusions. (37)

Glanzmann thrombasthenia is an autosomal recessive quantitative or a qualitative platelet disorder. It is found more frequently in certain ethnic groups and consanguinity. (37) The clinical signs of bleeding vary in severity, from mild to potentially life-threatening. (37) Platelet transfusions are the mainstay of treatment, with factor VIIa and aminocaproic acid for mucosal hemorrhages. (37) Both platelet morphology and numbers are normal during evaluation, and identification of defects in platelet glycoprotein IIB/IIIa leads to a definitive diagnosis. (37)

Bernard-Soulier syndrome causes bleeding due to large platelets that have poor adhesion. (37) It has an incidence of less than 1 per million and can manifest in infancy, though 16 years is the mean age of diagnosis. (37)(43) Affected patients can have severe life-threatening hemorrhage with an estimated 16% mortality rate but can also have only unexplained purpura. (43) Life-threatening hemorrhage may be out of proportion to their thrombocytopenia. (37) Platelet transfusions are the mainstay of treatment, and definitive diagnosis is via flow cytometry, showing an absence of glycoprotein IB, V, and IX on platelet surfaces. (37)(43)

Gray platelet syndrome is named after the appearance of the washed-out gray platelets seen on peripheral smears. It is caused by an absence of platelet α-granules which leads to bleeding, splenomegaly, and myelofibrosis. (44) Genetic inheritance can be autosomal dominant, autosomal recessive, or X-linked. (44) Patients present with bleeding diathesis near the time of birth, easy bruising, and low platelet counts. (44) Diagnosis is made by the appearance of large, gray washed-out platelets on peripheral smear and the lack of α-granules on the electron microscope. (37)(44)

Inherited via an autosomal recessive pattern, patients with Hermansky-Pudlak syndrome present with bleeding diathesis, oculocutaneous albinism, vision abnormalities, and in some variants, immunodeficiency and neutropenia. (45) Additional clinical findings are postprocedural bleeding, easy bruising, and colonic bleeding and may include ocular conditions (ie, nystagmus, strabismus), pulmonary fibrosis, and granulomatous colitis. (45) The diagnosis is clinical, with additional findings of impaired secondary aggregation, and the absence of platelet δ granules (dense bodies) on an electron microscope. (37)(45)

Von Willebrand Disease. Von Willebrand disease (vWD) is the most prevalent hereditary bleeding disorder and results from an anomaly in vWF, a glycoprotein essential for platelet adhesion to the subendothelium following vascular injury. (1) In addition, vWF stabilizes factor VIII (FVIII) in the coagulation cascade, shielding it from degradation. (46) Inheritance is autosomal dominant for type 1 vWD and most forms of type 2, and autosomal recessive for type 3. (46) Type 1, a quantitative defect, is the most common form, but can have a range of clinical severity. (46)(47) If symptomatic, the initial presentation includes frequent mucocutaneous bleeding, with spontaneous joint or muscle bleeding and/or hematomas in type 3 disease. (46)

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Diagnosis is made through measurement of aPTT and FVIII activity, vWF ristocetin-cofactor activity, and vWF antigen levels. Therapies include tranexamic acid, desmopressin, high-purity vWF concentrates alone, and/or a combination of FVIII:vWF, based on the severity of the disease. (46) There is a relative contraindication to the use of desmopressin in children younger than 2 years, but it may be considered if accompanied by careful management with fluid restriction, prevention of hyponatremia, and monitoring of both electrolyte levels and urine output. (46)

Thrombotic Thrombocytopenia Purpura. Congenital thrombotic thrombocytopenia purpura is a rare autosomal recessive inherited condition of ADAMTS13 metalloprotease deficiency. (48) Symptoms include hyperbilirubinemia, thrombocytopenia, stroke and other arterial thromboembolic events, ischemia, and renal disease. (48) Treatment with ADAMTS13 replacement reduces the incidence of end-organ damage. (48)

Collagen and Vascular Disorders. Collagen is a key component of basement membrane function and provides structural support for cellular behavior and signaling. Mutations in collagen IV, VI, VII, XV, XVII, and XVIII are rare but cause diseases affecting multiple systems. (49) Collagen IV mutations, being the most prevalent structural basement membrane element, can lead to a range of multisystemic disorders, encompassing cerebral small vessel disease, intracerebral hemorrhage, kidney disorders, ocular abnormalities, and myopathy. (49)

Distinguishing features of other inherited connective tissue disorders such as Ehlers-Danlos syndrome, consist of susceptibility to easy bruising and bleeding. This arises from mutations in the genes for fibrillar collagen proteins (collagen type I, III, and V) and presents with skin and joint hypermobility, spontaneous hematomas secondary to minimal trauma, delayed wound healing, and fragility of the blood vessels and internal organs. (50)

Hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome, is a genetic disorder inherited in an autosomal dominant pattern, characterized by bleeding resulting from abnormal blood vessels. (51) Patients usually have subclinical arteriovenous malformations in the lungs and liver, and carry a high risk for bleeding and other complications including pulmonary hypertension and hemorrhagic stroke. (51) Other symptoms include epistaxis, anemia from gastrointestinal bleeding, and telangiectasias of the lips, fingertips, and buccal mucosa. (51)

DISORDERS OF SECONDARY HEMOSTASIS

Secondary hemostasis refers to the process of fibrin formation via the coagulation cascade, primarily involving coagulation factors and activated cell surfaces. Diagnosis of inherited bleeding disorders affecting secondary hemostasis relies on a combination of coagulation tests, family history, and clinical history (Table 4).

Hemophilia A: Factor VIII Deficiency

Hemophilia A is a hereditary coagulation disorder linked to the X chromosome, resulting from a deficiency in FVIII, with an incidence of around 1 in 5,000 males. (52) Approximately 30% of mutations arise de novo, therefore absence of a family history does not exclude the possibility of the condition. (53)

Table 4. Disorders of Secondary Hemostasis

Disorder	Pattern of Inheritance/ Transmission	Clinical Signs and Symptoms	Diagnosis	Management
Hemophilia A: factor VIII deficiency	X-linked recessive or de novo mutations	Bleeding episodes, often involving joints and muscles, circumcision site bleeding, ICH is rare.	Prolonged aPTT Low factor VIII level	Desmopressin Factor VIII replacement Non-factor therapies
Hemophilia B: factor IX deficiency	X-linked recessive	Frequent bleeding episodes in the neonatal period, muscle and joint bleeding, occasional spontaneous hemorrhages	Prolonged aPTT Low factor IX level	Factor IX replacement
Factor XIII deficiency	Autosomal recessive	Skin bruising, subcutaneous bleeding, bleeding from the umbilical cord, ICH, and soft tissue hematomas	Low Factor XIII level Normal PT, aPTT, and platelet count	Fresh-frozen plasma or cryoprecipitate Factor XIII replacement
Vitamin K deficiency	Prevented by vitamin K prophylaxis at birth	Bleeding through the umbilical cord/stump, cephalohematoma, ICH, gastrointestinal and mucocutaneous bleeding	Prolonged PT with or without aPTT elevation Normal platelets and fibrinogen	Administration of a parenteral dose of vitamin K

aPTT=activated partial thromboplastin time, ICH=intracranial hemorrhage, PT=prothrombin time.

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A suspected diagnosis due to bleeding episodes, often involving joints and muscles, or a family history, should prompt further testing. A prolonged aPTT alongside a normal PT and platelet count is typical of hemophilia A. (54) Severity is based on factor level compared with normal, with mild being 5% to 40%, moderate 1% to 5%, and severe less than 1%. (54) The earliest and most serious complication in neonates with severe hemophilia is ICH, which occurs in 1% to 4% of cases. (54) Extracranial hemorrhage, including subgaleal bleeding and cephalohematoma formation, can also occur. (53)(54) Circumcision site bleeding is common and severe hemophilia can present with spontaneous muscle hemorrhage in the lower extremities, iliopsoas muscle buttocks, and forearms, as well as intra-articular bleeding. (54)

Treatment goals are to achieve hemostasis during acute bleeds and avoid rebleeding. Desmopressin is the preferred hemostatic treatment of individuals with mild disease along with early rehabilitation and pain management. (54) ICH should be suspected with new hypertension, change in mental status or level of alertness, lethargy, or increased fussiness, and treated accordingly. For moderate to severe disease, and for joint bleeds, consecutive days of factor replacement is required. (54) Other novel therapies have become available and include nonfactor therapies and gene therapy. (54)

Hemophilia B: Factor IX Deficiency

Hemophilia B is a rare genetic bleeding disorder linked to the X chromosome, characterized by a deficiency in coagulation factor IX (FIX), occurring in 5 in 100,000 males. (54) Clinical bleeding often corresponds with the levels of FIX activity in the plasma, but certain patients may exhibit variability in the severity of bleeding symptoms. (54) Disease severity is based on the same thresholds as hemophilia A, with severe being less than 1% of normal. (54) If severe, presentation is similar to severe hemophilia A, with frequent bleeding episodes in the neonatal period. (54) Patients with mild to moderate hemophilia B have a wider bleeding phenotype, ranging from bleeding with minor trauma to more severe muscle and joint bleeding and occasional spontaneous hemorrhages. (54)

At birth, there is a reduction in all vitamin K–dependent factors, including FIX, and this reduction is even more pronounced in preterm neonates, posing challenges in diagnosing hemophilia B at birth. (9)(10) Diagnosis can be made by measuring plasma FIX activity levels; genetic analysis is then recommended to establish a causative mutation. (54)

The goal of treatment involves exogenous FIX concentrates to achieve hemostasis and prevent recurrent bleeding and joint destruction. Prophylactic treatment entails regular administration of FIX concentrate to maintain a minimum trough FIX activity of 1% between doses. (54) Emerging treatment approaches for hemophilia include subcutaneous FIX products and gene therapy based on adeno-associated viral vectors. (54)

Factor XIII (FXIII) Deficiency

Congenital FXIII deficiency is a rare autosomal recessive bleeding disorder, affecting roughly 1 in 2 million individuals. (55) Activated FXIII is critical in the final phase of coagulation by enhancing the stability of the fibrin clot. (2) Symptoms can vary from severe, potentially life-threatening bleeding to milder manifestations such as skin bruising, subcutaneous bleeding, bleeding from the umbilical cord, and soft tissue hematomas. Patients with FXIII deficiency will initially form a clot, but this will be unstable and they will have rebleeding. (55) The severity of bleeding is associated with the level of FXIII activity and the severe phenotype has the highest rate of ICH of any bleeding disorder. (56) Diagnosis is difficult because PT, aPTT, platelet count, and thrombin time are normal; specific FXIII assays are required for the diagnosis. (57) In the event of acute bleeding, fresh-frozen plasma or cryoprecipitate can be given if the diagnosis is suspected. If the diagnosis is made, treatment is factor infusions.

Vitamin K Deficiency

Vitamin K deficiency bleeding disorder (VKDB) was initially identified in the 1800s as a hemorrhagic disease of the newborn. (58) In 1961, the American Academy of Pediatrics, recommended that all infants be given a single parenteral dose of vitamin K at birth, which has dramatically reduced the mortality rate of VKDB and the incidence of ICH. (58)(59)

VKDB should be considered in all infants who present with a bleeding diathesis in the first 6 months of age. Newborns are particularly vulnerable to deranged vitamin K metabolism because of limited vitamin K acquisition during gestation and initial lack of gut flora to produce additional vitamin K. (60) ICH, a bleeding umbilical stump, gastrointestinal and mucocutaneous bleeding, and bleeding circumcisions should prompt the clinician to consider the possibility of VKDB. (58)(60)

The etiology and time frame of VKDB is divided into early, classic, and late presentations. Early VKDB occurs in the first 24 hours after birth and is secondary to the

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transplacental acquisition of drugs from the pregnant person that interfere postnatally with the infant's metabolism of vitamin K. (58)(60) Clinical findings consist of cephalohematoma, umbilical stump bleeding, and ICH with a history of medications administered to the pregnant person that reduce the infant's available vitamin K, such as warfarin, anticonvulsants, and antituberculosis medications. (58)(60)

Classic VKDB occurs between 2 and 7 days after birth and arises from insufficient vitamin K intake in newborns. (58)(60) In addition to the impact of medications taken by the pregnant person, classic VKDB deficiency occurs in infants who exclusively drink breast milk, have limited enteral intake, and have received inadequate vitamin K supplementation (ie, zero vitamin K or a single oral dose) at birth. (58) The birth parents of infants with classic VKDB will often have a diet that is low in vitamin K, which occurs in green, leafy vegetables. (60)

Late VKDB manifests between 2 weeks and 6 months of age with ICH and gastrointestinal and mucocutaneus bleeding. (58)(60) Infants with an exclusive mother's own milk diet continue to be at higher risk of late VKDB as well as infants with poor absorption of vitamin K. (60) This includes infants with prolonged diarrhea, liver disease, pancreatic insufficiency, cystic fibrosis, and biliary atresia. (58)(60) Late VKDB has an increased risk in the summer months and in male infants. (58)(60)

A prolonged PT increases suspicion for VKDB, though if the duration is sufficient, aPTT may be increased as well. (60) If both are prolonged, the PT prolongation will be out of proportion to the aPTT. (37)(60) Factor II, VII, IX, and X concentrations will be decreased while platelets and fibrinogen are normal. (37)(58)(60) Head imaging should be conducted to assess for possible ICH.

Management of the acute complications of VKDB consists of administration of a parenteral dose of vitamin K. With adequate treatment, PT and aPTT corrects in 2 to 6 hours, which helps to confirm the diagnosis. (60) As prophylaxis, term infants should receive a single dose of 0.5 to 1.0 mg of vitamin K whereas preterm infants should receive a dose of 0.3 to 0.5 mg/kg if birthweight is below 1,000 g. (58) Oral prophylaxis is less efficacious than intramuscular prophylaxis because of lower parental compliance and inconsistent drug absorption. (58)

DISORDERS OF FIBRINOLYSIS

Qualitative/Quantitative Fibrinogen Disorders

Fibrinogen is a glycoprotein synthesized by the liver and present in the plasma. Rare mutations can lead to either quantitative (type 1) deficiencies or qualitative (type 2) dysfunctional proteins, from 3 possible genes (*FGA, FGB,* and *FGG*). (61) The rarest form, afibrinogenemia, usually manifests during infancy, with prolonged bleeding seen after circumcision and bleeding from the umbilical cord. (61)

Nearly all instances of afibrinogenemia result from null mutations in the *FGA* gene. (62) Although bleeding is the more common manifestation, thrombosis can also occur because of the impaired antithrombin function of fibrin. (61) Hypofibrinogenemia and dysfibrinogenemia disorders are associated more commonly with mild bleeding tendencies, but most patients are asymptomatic and are incidentally identified on abnormal screening coagulation tests. (61) Most hypofibrinogenemias are missense mutations found equally in all 3 genes whereas dysfibrinogenemias are mainly missense mutations in genes *FGA* and *FGG*. (61)

Fibrinogen concentrate, cryoprecipitate, or fresh-frozen plasma is most used in patients with afibrinogenemia and hypofibrinogenemia, whereas antifibrinolytic drugs (ie, aminocaproic acid and tranexamic acid) are used more frequently in dysfibrinogenemia. (61)

Plasminogen Activator Inhibitor 1 Deficiency

Plasminogen activator inhibitor 1 (PAI-1) functions as a urokinase-type plasminogen activator and inhibits tissue-type plasminogen activator as a protease inhibitor. PAI-1 inhibits fibrinolysis, but when absent or nonfunctional, clots are unstable and prematurely break down. (62) Bleeding typically only happens as a result of surgical procedures or trauma, though it can be serious and life-threatening, and difficult to predict as PT and aPTT are normal. (62) Medications like tranexamic acid and aminocaproic acid, which inhibit fibrinolysis, are successful in both treating and preventing instances of bleeding. (62)

α-2 Antiplasmin Deficiency

α-2 Antiplasmin (α2-AP) is another protease inhibitor of fibrinolysis which acts as a primary inhibitor of plasminogen. (2) Fibrinolysis takes place when activating agents act on plasminogen to transform it into the active serine protease plasmin, predominantly tissue plasminogen activator. α2-AP deficiency is an autosomal recessive condition. (63) Aminocaproic acid and tranexamic acid, alongside other inhibitors of fibrinolysis, can be beneficial in treatment. (63)

ACQUIRED COAGULOPATHIES

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a multifactorial condition involving coagulation and immune and

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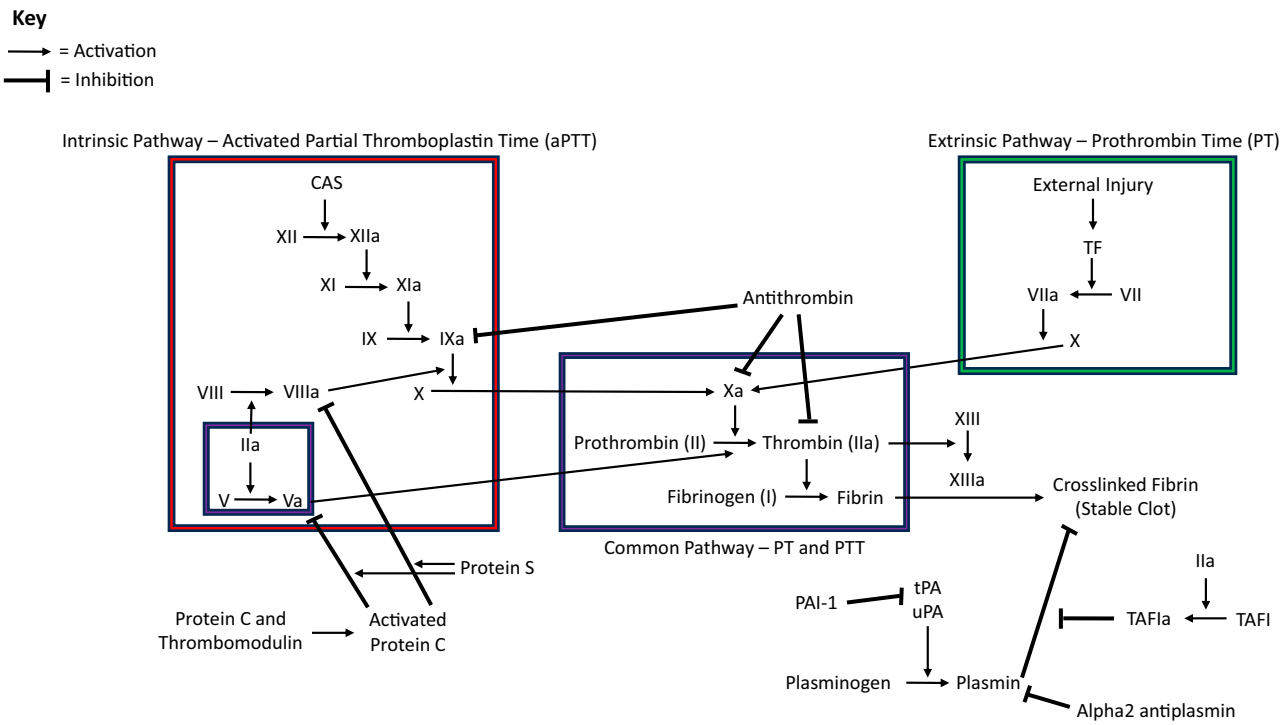


Figure. The classic coagulation cascade. The intrinsic pathway, which is tested by the aPTT, is encompassed in red, the extrinsic pathway, which is tested by the PT, is encompassed in green and the common pathway, which affects both PT and aPTT, is encompassed in purple. aPTT=activated partial thromboplastin time, CAS=contact activation system, composed of prekallikrein, kallikrein, and high-molecular-weight kininogen, PAI-1=plasminogen activator inhibitor 1, PT=prothrombin time, PTT = partial thromboplastin time, TAFI=thrombin activatable fibrinolysis inhibitor, TF=tissue factor, tPA=tissue plasminogen activator, uPA=urokinase plasminogen activator.

inflammatory pathways with excessive thrombin generation. (64) Underlying conditions, including infection, trauma, or malignancy, trigger hemostatic processes and thrombin generation. Thrombin then leads to fibrin formation, involves the fibrinolytic pathway, and depletion of hemostatic factors (proteins C/S, antithrombin) causing small vessel thrombosis and organ dysfunction, significant bleeding, and capillary leak, resulting in third-spacing. (64) As DIC is caused by other underlying disease states, the definitive treatment is based on the underlying disorder. (65) Supportive care can be offered with transfusions, through modulating thrombin generation (heparin or low-molecular-weight heparin), and with antithrombin/anticoagulant factor concentrates.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) may be caused by the mutual atypical activation of both type 1 lymphocytes (ie, natural killer and CD8 cells) and mononuclear phagocytes (ie, dendritic cells and macrophages). (66) It consists of a constellation of symptoms, and one must meet 5 of 8 criteria for diagnosis. (66) These criteria are both clinical, such as splenomegaly and fever and abnormal laboratory values such as cytopenias (≥2 lineages; hemoglobin <10 g/dL [100 g/L] in neonates, platelets $<100 \times 10^3/\mu L$ [100×10^9/L]), decreased natural killer cell function, triglycerides greater than 265 mg/dL (3 mmol/L), ferritin greater than 500 ng/mL (500 μg/L), fibrinogen less than 15,000 mg/dL (150 g/L), hemophagocytosis, and soluble IL-2R levels/CD25 levels greater than 2,400 U/mL. (66) Given that the result of many of these diagnostic tests take time, clinical judgment is critical. Because of the poor specificity and sensitivity, the hallmarks of hemophagocytosis are not required to make the diagnosis. Several genetic conditions predispose individuals to HLH, such as familial HLH, pigmentary disorders, and disorders that increase susceptibility to Epstein-Barr virus infection. (67) Management of HLH involves a combination of immunosuppressive and chemotherapy medications, along with biological agents, to suppress the cytokine storm and target activated T-cells and macrophages. (66)(67)

Liver Disease

Liver disease causes changes in all 3 phases of hemostasis (primary and secondary hemostasis and fibrinolysis). (68) Portal hypertension can cause congestive splenomegaly and sequestration, limiting the number of circulating platelets. (68) Impairment in hepatic synthesis of thrombopoietin, which acts as the main regulator of platelet generation, leads

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to dysregulation of platelet production. (68) The hepatic parenchymal cells produce all the necessary factors except for FVIII, which is produced by endothelial cells, making the reduced production of many factors (II, V, VII, IX, XI, and XIII) a hallmark of liver disease. (68) Conversely, the liver synthesizes all profibrinolytic and antifibrinolytic proteins, except for tissue plasminogen activator and PAI-1, which are produced by endothelial cells. (68) The homeostasis between bleeding and clotting is therefore even more precarious, and predicting whether a patient will bleed or develop thrombosis is challenging.

Vascular Anomalies

Vascular anomalies encompass a wide range of disorders marked by atypical development of lymphatic, arterial, venous, and capillary vessels. In vascular tumors, there is an abnormal increase in endothelial cell proliferation, whereas malformations primarily involve normal endothelial cells but display abnormal vessel arrangements. (69)

Kaposiform hemangioendothelioma (KHE) and tufted angiomas (TA) are benign vascular tumors commonly observed in infancy. KHEs tend to be more locally aggressive and burrow into deeper structures, whereas TAs tend to be more superficial (dermis and subcutis). (69) Kasabach-Merritt phenomenon (KMP) occurs in roughly 70% of patients with KHE and 10% to 20% of those with TA. (69) KMP is characterized by thrombocytopenia, low fibrinogen levels, increased D-dimer, and prolonged PT and aPTT. This is likely caused by platelet entrapment within the abnormal blood vessels of the tumor, leading to the depletion of platelets and coagulation factors. (69)(70) KMP lesions are red/deep purple, warm, tense, and painful. Treatment is complete resection if able or with sirolimus, oral steroids, and vincristine. (70)

Kaposiform lymphangiomatosis is similar to KHE/TA but involves lymphatic vasculature and is mainly found in the soft tissues, bones, spleen, and thoracic cavity. (71) Kaposiform lymphangiomatosis typically is severe, presents early in life, and displays progression. (70)(71) Coagulopathy is akin to KMP and is treated similarly. (71)

Summary

Coagulation disorders in infants can be challenging to diagnose given the physiologic differences in newborns and susceptibility to pregnancy conditions. When concerned about a coagulopathic condition, clinicians should be aware that:

- A comprehensive family and pregnancy history and physical examination can aid in identifying the cause of newborn coagulopathy.
- Initial laboratory screening should include a complete blood cell count with differential, PT, aPTT, and fibrinogen, with additional studies as clinically indicated. Abnormalities in the platelet count, PT, and aPTT will be beneficial in identifying the most common coagulopathic conditions, though there are severe bleeding disorders in which these laboratory findings are normal.
- Hematology consultation can be beneficial in assisting with diagnostic evaluation and management.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and pathophysiology of neonatal thrombocytopenia and thrombocytosis.
- Know the clinical and laboratory manifestations and management of neonatal thrombocytopenia and thrombocytosis.
- Know the inheritance patterns of the common coagulation factor deficiencies.
- Know the causes and pathophysiology of acquired defects in hemostasis.
- Know the clinical and laboratory features and management of acquired defects in hemostasis including intravascular coagulation and hemorrhagic disease of the newborn.
- Know the causes and pathophysiology of congenital defects in hemostasis.
- Know the clinical manifestations, laboratory findings, and management of congenital defects in hemostasis.

References

1. Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. *Blood Rev*. 2011;25(4):155–167
2. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev*. 2015;29(1):17–24
3. Gale AJ. Current understanding of hemostasis. *Toxicol Pathol*. 2011;39(1):273–280

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4. Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. *Crit Rev Biochem Mol Biol*. 2015;50(4):326–336
5. Furie B. Pathogenesis of thrombosis. *Hematology Am Soc Hematol Educ Program*. 2009;2009(1):255–258
6. Winter WE, Flax SD, Harris NS. Coagulation testing in the Core Laboratory. *Laboratory Med*. 2017;48(4):295–313
7. Wu Y. Contact pathway of coagulation and inflammation. *Thromb J*. 2015;13:17
8. Caen J, Wu Q. Hageman factor, platelets and polyphosphates: early history and recent connection. *J Thromb Haemost*. 2010;8(8):1670–1674
9. Campbell SE, Bolton-Maggs PHB. Congenital and acquired bleeding disorders in infancy. *Early Hum Dev*. 2015;91(11):637–642
10. Kenet G, Chan AKC, Soucie JM, Kulkarni R. Bleeding disorders in neonates. *Haemophilia*. 2010;16(suppl 5):168–175
11. Venkatesh V, Curley A, Khan R, et al. A novel approach to standardised recording of bleeding in a high risk neonatal population. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(3):F260–263
12. Poryo M, Boeckh JC, Gortner L, et al. PROGRESS study consortium and NGFN - Nationales Genomforschungsnetz Deutschland. Ante-, peri- and postnatal factors associated with intraventricular hemorrhage in very premature infants. *Early Hum Dev*. 2018;116:1–8
13. Kühne T, Imbach P. Neonatal platelet physiology and pathophysiology. *Eur J Pediatr*. 1998;157(2):87–94
14. Wasiluk A, Mantur M, Kemona H, Szczepański M, Jasińska E, Milewski R. Thrombopoiesis in small for gestational age newborns. *Platelets*. 2009;20(7):520–524
15. Saxonhouse MA, Sola-Visner MC. Thrombocytopenia in the neonatal intensive care unit. *Neoreviews*. 2009;10(9):e435–e445
16. Sola-Visner M. Platelets in the neonatal period: developmental differences in platelet production, function, and hemostasis and the potential impact of therapies. *Hematology Am Soc Hematol Educ Program*. 2012;2012:506–511
17. Murray NA, Roberts IA. Circulating megakaryocytes and their progenitors in early thrombocytopenia in preterm neonates. *Pediatr Res*. 1996;40(1):112–119
18. Ferrer-Marin F, Liu ZJ, Gutti R, Sola-Visner M. Neonatal thrombocytopenia and megakaryocytopoiesis. *Semin Hematol*. 2010;47(3):281–288
19. Sciscione AC, Bessos H, Callan N, Blakemore K, Kickler T. Indicators of platelet turnover in thrombocytopenic infants. *Br J Obstet Gynaecol*. 1997;104(6):743–745
20. Salama A. Alloimmune thrombocytopenias. *J Pediatr Hematol Oncol*. 2003;25 Suppl 1:S39–41
21. Kjeldsen-Kragh J, Killie MK, Tomter G, et al. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. *Blood*. 2007;110(3):833–839
22. Ferro M, Macher HC, Fornés G, et al. Noninvasive prenatal diagnosis by cell-free DNA screening for fetomaternal HPA-1a platelet incompatibility. *Transfusion (Paris.)*. 2018;58(10):2272–2279
23. Donato H. Neonatal thrombocytopenia: A review. I. Definitions, differential diagnosis, causes, immune thrombocytopenia. *Arch Argent Pediatr*. 2021;119(3):e202–e214
24. Norton T, Newberry D, Jnah A. Neonatal alloimmune thrombocytopenia: a concise review. *Adv Neonatal Care*. 2021;21(2):115–121
25. Bertrand G, Kaplan C. How do we treat fetal and neonatal alloimmune thrombocytopenia? *Transfusion (Paris)*. 2014;54(7):1698–1703
26. Gleason CA, Juul SE. *Avery's Diseases of the Newborn*. Tenth Edition; 2017
27. Yamamoto AY, Mussi-Pinhata MM, Marin LJ, Brito RM, Oliveira PFC, Coelho TB. Is saliva as reliable as urine for detection of cytomegalovirus DNA for neonatal screening of congenital CMV infection? *J Clin Virol*. 2006;36(3):228–230
28. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis*. 2017;17(6):e177–e188
29. Hampton MM. Congenital toxoplasmosis: a review. *Neonatal Netw*. 2015;34(5):274–278
30. Carellos EVM, de Andrade JQ, Romanelli RMC, et al. UFMG Congenital Toxoplasmosis Brazilian Group (UFMG-CTBG). High frequency of bone marrow depression during congenital toxoplasmosis therapy in a cohort of children identified by neonatal screening in Minas Gerais, Brazil. *Pediatr Infect Dis J*. 2017;36(12):1169–1176
31. Gudeloglu E, Akillioglu M, Bedir Demirdag T, Unal NA, Tapisiz AA. Congenital rubella syndrome: a short report and literature review. *Trop Doct*. 2023;53(1):171–175
32. Zinkham WH, Medearis DN, Osborn JE. Blood and bone-marrow findings incongenital rubella. *J Pediatr*. 1967;71(4):512–524
33. Golemba MD, Mecikovsky D, Ortíz de Zárate M, et al. Unraveling HIV-1 diagnosis in special pediatric cases. *J Clin Virol*. 2020;131:104343
34. Diaz C, Hanson C, Cooper ER, et al. Disease progression in a cohort of infants with vertically acquired HIV infection observed from birth: the Women and Infants Transmission Study (WITS). *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18(3):221–228
35. Fernandes ND, Arya K, Ward R. Congenital Herpes Simplex. In: *StatPearls*. StatPearls Publishing; 2024. Accessed March 17, 2024. http://www.ncbi.nlm.nih.gov/books/NBK507897/
36. Yang J, Zhang H, Niu J, et al. Impact of preeclampsia on megakaryocytopoesis and platelet homeostasis of preterm infants. *Platelets*. 2016;27(2):123–127
37. Martin RJ, Fanaroff AA, Walsh MC. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 11th ed. Philadelphia, PA: Elsevier; 2019.
38. Cowan J, Parikh T, Waghela R, et al. Thrombocytopenia with absent radii (TAR) syndrome without significant thrombocytopenia. *Cureus*. 2020;12(9):e10557
39. Tirthani E, Said MS, De Jesus O. Amegakaryocytic Thrombocytopenia. In: StatPearls. StatPearls Publishing; 2024. Accessed March 13, 2024. http://www.ncbi.nlm.nih.gov/books/NBK568795/
40. Al-Qahtani FS. Congenital amegakaryocytic thrombocytopenia: a brief review of the literature. *Clin Med Insights Pathol*. 2010;3:25–30
41. Cancio M, Hebert K, Kim S, et al. Outcomes in hematopoietic stem cell transplantation for congenital amegakaryocytic thrombocytopenia. *Transplant Cell Ther*. 2022;28(2):101.e1-101–e6
42. Malik MA, Masab M. Wiskott-Aldrich Syndrome - StatPearls - NCBI Bookshelf. Accessed March 13, 2024. https://www.ncbi.nlm.nih.gov/books/NBK539838/
43. Almomani MH, Mangla A. Bernard-Soulier Syndrome. *In:* StatPearls. StatPearls Publishing; 2024. Accessed March 13, 2024. http://www.ncbi.nlm.nih.gov/books/NBK557671/

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44. Gunay-Aygun M, Zivony-Elboum Y, Gumruk F, et al. Gray platelet syndrome: natural history of a large patient cohort and locus assignment to chromosome 3p. *Blood*. 2010;116(23):4990–5001
45. Introne WJ, Huizing M, Malicdan MCV, O'Brien KJ, Gahl WA, et al. Hermansky-Pudlak Syndrome. In: Adam MP, Feldman J, Mirzaa GM eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed March 13, 2024. http://www.ncbi.nlm.nih.gov/books/NBK1287/
46. Echahdi H, El Hasbaoui B, El Khorassani M, Agadr A, Khattab M. Von Willebrand's disease: case report and review of literature. *Pan Afr Med J*. 2017;27:147
47. Eikenboom JC. Congenital von Willebrand disease type 3: clinical manifestations, pathophysiology and molecular biology. *Best Pract Res Clin Haematol*. 2001;14(2):365–379
48. Scully M. Congenital TTP: next stop, acuity and therapy. *Blood*. 2021;137(25):3469–3471
49. Gatseva A, Sin YY, Brezzo G, Van Agtmael T. Basement membrane collagens and disease mechanisms. *Essays Biochem*. 2019;63(3):297–312
50. Key NS, DE Paepe A, Malfait F, Shovlin CL. Vascular haemostasis. *Haemophilia*. 2010;16 Suppl 5:146–151
51. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet*. 2000;91(1):66–67
52. Soucie JM, Evatt B, Jackson D, The Hemophilia Surveillance System Project Investigators. Occurrence of hemophilia in the United States. *Am J Hematol*. 1998;59(4):288–294
53. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*. 2016;388(10040):187–197
54. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1–158
55. Pelcovits A, Schiffman F, Niroula R. Factor XIII deficiency: A review of clinical presentation and management. *Hematol Oncol Clin North Am*. 2021;35(6):1171–1180
56. Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia*. 2008;14(6): 1190–1200
57. Karimi M, Peyvandi F, Naderi M, Shapiro A. Factor XIII deficiency diagnosis: Challenges and tools. *Int J Laboratory Hematol*. 2018;40(1):3–11
58. Hand I, Noble L, Abrams SA. Vitamin K and the newborn infant. *Pediatrics*. 2022;149(3):e2021056036
59. Committee on Nutrition. Report of Committee on Nutrition: vitamin K compounds and the water-soluble analogues. *Pediatrics*. 1961;28(3):501–507
60. Araki S, Shirahata A. Vitamin K deficiency bleeding in infancy. *Nutrients*. 2020;12(3):780
61. Mohsenian S, Palla R, Menegatti M, et al. Congenital fibrinogen disorders: a retrospective clinical and genetic analysis of the Prospective Rare Bleeding Disorders Database. *Blood Adv*. 2024;8(6):1392–1404
62. Fay WP, Parker AC, Condrey LR, Shapiro AD. Human plasminogen activator inhibitor-1 (PAI-1) deficiency: characterization of a large kindred with a null mutation in the PAI-1 gene. *Blood*. 1997;90(1):204–208
63. Carpenter SL, Mathew P. α2-Antiplasmin and its deficiency: fibrinolysis out of balance. *Haemophilia*. 2008;14(6):1250–1254
64. Toh CH, Alhamdi Y. Current consideration and management of disseminated intravascular coagulation. *Hematology Am Soc Hematol Educ Program*. 2013;2013(1):286–291
65. Wada H, Thachil J, Di Nisio M, et al. The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013 Published online February 4
66. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124–131
67. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332–1343
68. Kujovich JL. Coagulopathy in liver disease: a balancing act. *Hematology Am Soc Hematol Educ Program*. 2015;2015(1):243–249
69. Ricci KW, Brandão LR. Coagulation issues in vascular anomalies. *Semin Pediatr Surg*. 2020;29(5):150966
70. Adams DM, Brandão LR, Peterman CM, et al. Vascular anomaly cases for the pediatric hematologist oncologists—An interdisciplinary review. *Pediatr Blood Cancer*. 2018;65(1):e26716
71. Croteau SE, Kozakewich HPW, Perez-Atayde AR, et al. Kaposiform lymphangiomatosis: a distinct aggressive lymphatic anomaly. *J Pediatr*. 2014;164(2):383–388

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NEO QUIZ

1. Coagulation factors are developmentally regulated and neonates, particularly those born preterm, are at increased risk of bleeding. While multiple coagulation factor levels are decreased in neonates, some are within normal range or increased. Which of the following coagulation factors is increased in neonates compared to adults and children?

   A. Factor II.
   B. Von Willebrand factor.
   C. Factor VIII.
   D. Protein C.
   E. Antithrombin.

2. Coagulation disorders are classified as disorders of primary hemostasis, disorders of secondary hemostasis, or disorders of the fibrinolytic system. Neonatal alloimmune thrombocytopenia (NAIT) is a disorder of primary hemostasis caused by the transplacental transfer of platelet-specific antibodies or human leukocyte antigen antibodies. NAIT occurs in approximately 1 in 1,000 births and presents with thrombocytopenia within 48 hours of birth. NAIT is an important diagnosis that must not be missed because subsequent pregnancies will need to be closely monitored for recurrence. What is the projected risk of NAIT recurrence in a subsequent pregnancy?

   A. 40%.
   B. 50%.
   C. 60%.
   D. 70%.
   E. 80%.

3. A term male neonate has prolonged bleeding after a circumcision. He was born after an uncomplicated pregnancy via cesarean section for breech presentation. He received 1 dose of intramuscular vitamin K at birth. His laboratory evaluation reveals a prolonged activated partial thrombin time (aPTT) with normal prothrombin time (PT) and platelet count. Which of the following diagnoses is most consistent with this clinical presentation?

   A. Factor VIII deficiency.
   B. Von Willebrand disease.
   C. Bernard-Soulier syndrome.
   D. Glanzmann thrombasthenia.
   E. Factor XIII deficiency.

4. A 3-day-old exclusively breastfed neonate born at 41 weeks' gestation develops irritability and altered mental status. He was born at home via uncomplicated vaginal delivery after an uncomplicated pregnancy. Brain imaging reveals the presence of an intracranial hemorrhage and you suspect classic vitamin K deficiency bleeding disorder (VKDB). Which of the following statements regarding VKDB is CORRECT?

   A. Classic VKDB presents between 3 and 21 days after birth.
   B. The presence of prolonged aPTT and normal PT on laboratory evaluations is consistent with the diagnosis of VKDB.
   C. Correction of coagulation test abnormalities within 2 to 6 hours of vitamin K administration helps confirm the diagnosis.
   D. Classic VKDB more commonly occurs in males and during the winter months.
   E. Late VKDB is characterized by spontaneous muscle hemorrhage, particularly of the lower extremities.

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5. Liver disease can be associated with abnormalities in all 3 phases of hemostasis including primary and secondary hemostasis as well as fibrinolysis. All of the following factors are produced by the liver EXCEPT:

   A. Factor XIII.
   B. Factor VII.
   C. Factor II.
   D. Factor VIII.
   E. Factor IX.

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Thrombotic Disorders in the Newborn

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EDUCATION GAP

Thrombus formation is common in neonates and can arise from both congenital and acquired causes, ranging from genetic abnormalities to indwelling catheters. Given this, neonatologists need to be able to identify when a thrombus is provoked, or when additional work is required, and how best to treat it.

OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize which common coagulation abnormalities correspond to patterns of laboratory tests.
2. Recognize the common congenital conditions that place infants at risk for venous thromboembolism.
3. Identify the risk factors for an acquired venous thromboembolism.

ABSTRACT

The coagulation and thrombotic systems of an infant are fundamentally different from those of adults and older children. Hemostatic factors have inherently lower circulation levels in infants and are also affected prenatally by conditions of pregnancy. The unique physiology of neonates can contribute to a procoagulant state, which can result in a high level of morbidity and mortality. This review outlines the epidemiology, clinical characteristics, diagnosis and management, and etiologies of congenital and acquired forms of thrombotic disorders, with a discussion of the evaluation for hypercoagulation.

AUTHOR DISCLOSURES Dr Myers serves on the executive committee for the Council of Pediatric Sub-Specialists and has served as chair of the Organization of Neonatal Training Program Directors. Drs Ostilla, Knopoff, and Morocco have disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

aPL	antiphospholipid
aPTT	activated partial thromboplastin time
AT	antithrombin
CVL	central venous line
DVT	deep vein thrombosis
LMWH	low molecular weight heparin
PT	prothrombin time
UAC	umbilical artery catheter
UFH	unfractionated heparin
UVC	umbilical vein catheter
VTE	venous thromboembolism

The coagulation system involves a careful biological balancing act between coagulation and thrombosis, with a visual representation of the coagulation cascade and the main pathways involved (Fig 1). (1) The figure shows the pathways and associated coagulation tests that clinicians can use to assist in identifying a coagulopathy or a procoagulant state. Primary and secondary hemostasis involve platelet aggregation and insoluble fibrin deposition, respectively, which in turn leads to a mature thrombus at the site of an injury or in response to an insult. (2)(3)(4) A disruption in these pathways can lead to a procoagulant state, in which hemostasis is shifted toward coagulation and thrombus formation, and

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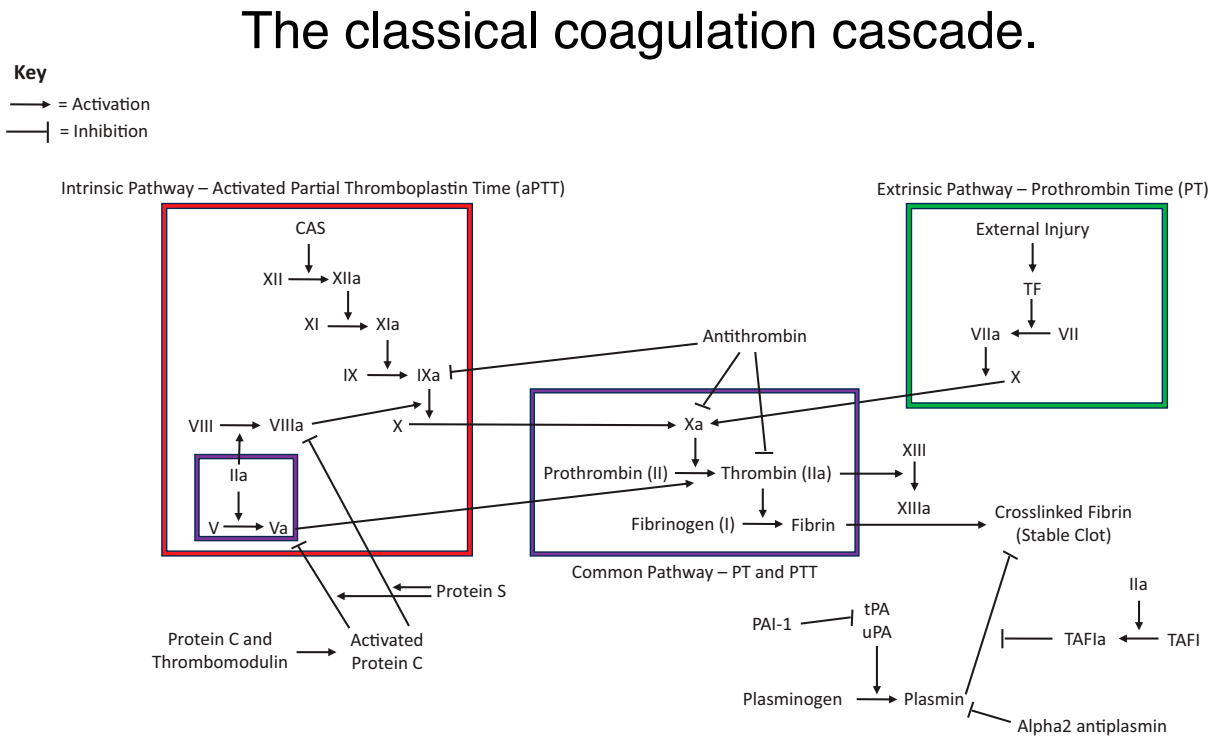


Figure 1. The classic coagulation cascade. The intrinsic pathway, which is tested by the aPTT, is encompassed in red; the extrinsic pathway, which is tested by the PT, is encompassed in green; and the common pathway, which affects both PT and aPTT, is encompassed in purple. aPTT=activated partial thromboplastin time, CAS=contact activation system, composed of prekallikrein, kallikrein, and high-molecular-weight kininogen, PAI-1=plasminogen activator inhibitor 1, PT=prothrombin time, PTT=partial thromboplastin time, TAFI=thrombin activatable fibrinolysis inhibitor, TF=tissue factor, tPA=tissue plasminogen activator, uPA=urokinase plasminogen activator. (Reprinted with permission from Ostilla L, Knopoff K, Myers P, Morocco P. Disorders of coagulation in the newborn. NeoReviews. 2024;25(11):e694.

arise via either a congenital or an acquired cause, such as a line-associated deep vein thrombosis (DVT).

HEMOSTASIS OVERVIEW

The first step in thrombosis involves primary hemostasis, in which platelets bind to the exposed matrix of collagen and von Willebrand factor at sites of vessel injury. (2) These platelets are then activated, causing aggregation and the initial platelet plug, which combines with insoluble fibrin generated by secondary hemostasis, or the coagulation cascade (Fig 2). (2)(4)(5)(6) These steps lead to a stable thrombus, which is resistant to degradation. The 2 main pathways of secondary hemostasis, intrinsic and extrinsic, converge on the common pathway, and are represented by the prothrombin test (PT; encompasses extrinsic and common pathway) and the activated partial thromboplastin time (aPTT; encompasses the intrinsic and common pathway). (7) Once the thrombus is formed, the fibrinolytic system works to eventually dissolve the thrombus after the vessel endothelium has recovered from its injury. (3)

The body contains its own natural anticoagulants in the form of protein C, protein S, and antithrombin (AT), among others. These proteins exist on the other end of the coagulation cascade, working to block thrombus formation. Protein C and protein S are vitamin K–dependent glycoproteins that work to inactivate activated factor V and

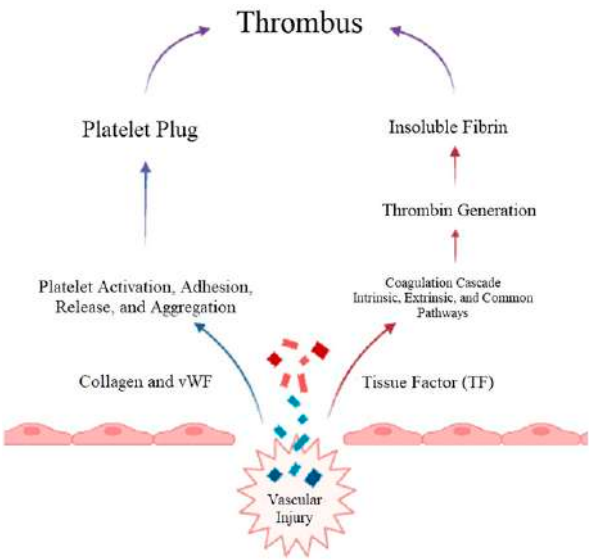


Figure 2. Overview of the infant's response to vascular injury.

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Table. Overview, Management, and Key Points for Thrombotic Disorders in Infants

DISEASE/DISORDER	TAKE HOME POINTS	MANAGEMENT, IF APPLICABLE
AT deficiency	Autosomal dominant Venous and/or arterial thrombosis resistant to heparin treatment Diagnosis made through qualitative functional AT assays	Factor Xa inhibitors AT replacement
Protein C/S deficiency	Autosomal dominant Disseminated intravascular coagulation and neonatal purpura fulminans shortly after birth if homozygous or compound heterozygous Diagnosis by plasma levels or functional assays	Protein C replacement (FFP or Protein C concentrate) Protein S treated with anticoagulation
Factor V Leiden	Autosomal recessive The most common genetic risk factor for thrombosis Diagnosis by activated protein C resistance and direct gene analysis testing	
Prothrombin G20210A mutation	Arterial thrombus and central nervous system thrombosis seen in children <2yo	
Thrombocytosis	Primary–genetic mutation induces megakaryocytic hyperplasia; rare Secondary – infection, inflammation, anemia; related to thrombopoietin produced by the liver in times of stress	Secondary – benign, usually resolves spontaneously
Indwelling catheters	Most common cause of acquired thrombosis in neonates Higher risk with larger lumens, multiple lumens, femoral insertion sites, and temporary lines (peripherally inserted central catheter > port)	Short-term anticoagulation prior to line removal, treatment course varying from 6 wk – 3 mo with repeat imaging
Nephrotic syndrome	Hypercoagulability related to hypovolemia and hemoconcentration Urinary loss of anti-thrombotic proteins and increased platelet activation	Anticoagulation (LMWH) for thrombus and future prophylactic anticoagulation during flares
Antiphospholipid syndrome	Antibody-mediated hypercoagulability Venous and arterial thrombosis Confirmatory testing done 12 wk after suspicion/outside of illness Prolonged PTT without bleeding symptoms and does not correct with mixing study Lupus anticoagulant stronger indicator of thrombotic potential	Anticoagulation for 3 mo or longer with ongoing risk factors

AT=antithrombin, FFP=fresh-frozen plasma, LMWH, low-molecular-weight heparin, PTT=partial thromboplastin time.

factor VIII. (3) AT is another important part of coagulation, a serine protease with the ability to inactivate factor IXa/Xa and thrombin (factor IIa). (4)

EPIDEMIOLOGY

Thrombus formation is relatively common in infants in the NICU with the Pediatric Health Information System reporting that neonates had the second highest rate of venous thromboembolism (VTE) in admitted pediatric patients, at 75 per 10,000 admissions in 2007, only behind adolescents. (8) This number has only increased since 2001, when there were only 44 per 10,000 admissions in infants less than 28 days old, likely because of increased survival among critically ill neonates and their increasing complexity. (8) In infants, an estimated 90% of thrombotic incidents are linked to the use of a venous or arterial access device, with an umbilical vein catheter (UVC) conferring a 12% to 21% risk of thrombosis and an umbilical artery catheter (UAC) a 12% to 35% risk. (9)(10)(11) Risk factors for UVC-associated thrombi include blood transfusions, malposition of the UVC, increased duration of catheter placement, maternal diabetes, sepsis, necrotizing enterocolitis, family history of thrombus, and congenital heart disease. (12)(13) UAC-associated thrombi are more likely to occur in premature infants, with increased duration of catheter placement, sepsis, and perinatal asphyxia. (13) However, thrombi can also develop in the absence of a UVC or UAC; renal vein thrombi are the most common type that accounts for about 10% of thrombotic events in the neonatal period. (9)(14)

EVALUATION FOR HYPERCOAGULATION

When there are concerns for a prothrombotic condition, hematology consultation is recommended to aid in diagnosis and management with an overview provided in the Table. The most important aspects of the initial diagnostic evaluation are family and personal history of thrombosis, thrombus type, and location, and whether the thrombus could be considered

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provoked or unprovoked in the current clinical setting. Risk factors, such as those described later in this review, help guide the decision to a hypercoagulation evaluation for a congenital cause contributing to the thrombus. This initial laboratory testing typically includes evaluation for deficiency in AT, protein C, and protein S, along with factor V Leiden and prothrombin G20210A mutation analysis, and antiphospholipid antibodies, including lupus anticoagulant. (15) Additional testing of factor VIII levels, lipoprotein(a), and homocysteine can also be considered, because all of these may lead to a higher likelihood of thrombosis. (16)

CONGENITAL THROMBOTIC DISORDERS

AT Deficiency

AT deficiency has an autosomal dominant pattern of inheritance. (17) AT is an endogenous anticoagulant, and its shortage leads to the most severe type of thrombophilia, with a 300-fold increase in risk of VTE compared with the normal population. (17) AT functions to inhibit thrombin (factor IIa), activated factor X (Xa), factor IXa, and other serine proteases. (18) Symptoms include unexplained and recurrent venous and/or arterial thromboembolism, which are highly resistant to heparin treatment, DVT, pulmonary embolism, and other hypercoagulable events that can manifest after trauma, shock, sepsis, critical care admission, or surgical procedures. (19)

Diagnosis is difficult in the neonate as the mean AT-III levels in term newborns are 56% of those in the adult, and even lower in premature infants. (20) A thorough examination of family medical records along with quantitative laboratory functional tests can be conducted to help with diagnosis. Laboratory testing is done to assess plasma AT's capability to inhibit the chromogenic activity of exogenous factor IIa or factor Xa. (20)(21) These tests lack sensitivity to detect mild forms of the disease and formal diagnosis is made through qualitative functional AT assays that are best performed after recovery from clinical illness. (21) Treatment of symptomatic infants includes AT-III replacement, factor Xa inhibitors (such as rivaroxaban or apixaban), and AT replacement products in patients with severely low AT levels. (21)

Protein C and S Deficiency

Both protein C and protein S deficiencies are autosomal dominant conditions with varying degrees of penetrance. (22) If homozygous or compound heterozygous, both conditions will show symptoms of disseminated intravascular coagulation and neonatal purpura fulminans shortly after delivery. (22)(23) Other manifestations include retinal thrombosis, renal vein thrombosis, and cerebral vessel thrombosis, which can occur prenatally. (23) If the diagnosis is suspected, protein levels can be measured in the plasma or via functional assays. (23)(24) It is important to take into consideration that in preterm, small-for-gestational-age infants and infants of diabetic mothers, serum protein C levels are lower than those of adults. (25)

Management of affected infants includes protein C replacement therapy with plasma-derived viral inactivated protein C concentrate or fresh-frozen plasma if replacement is unavailable. Protein S deficiency is treated via anticoagulation. (22) In the event of purpura fulminans or large vessel thrombosis, unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) can be used with caution. (22)

Factor V Leiden

Factor V Leiden thrombophilia is an autosomal recessive condition leading to hypercoagulation and elevated thrombosis risk. It is the most common genetic risk factor for VTE and the homozygous mutation occurs in 1 in 5000 individuals of Caucasian origin where it is most common compared with other ethnic groups. (26)(27) The mutation is defined by an inadequate anticoagulant response to activated protein C and symptoms include recurrent and/or unprovoked DVT, pulmonary emboli, and Budd-Chiari syndrome. (26)(28) Budd-Chiari syndrome arises from a thrombosis causing blockage of the hepatic veins, and factor V Leiden testing should be sent on any neonate who presents with, or develops this condition. (29)

Diagnosis of factor V Leiden requires testing for activated protein C resistance as well as direct DNA analysis of the gene F5, which codes for factor V, to identify a mutation. Management depends on clinical manifestations and is treated according to standard guidelines with UFH or LMWH. (26)

Prothrombin G20210A Mutation

The prothrombin G20210A mutation is another well-described cause of thrombosis, and can result in arterial thrombosis and central nervous system thrombosis in children younger than 2 years. (30) With increased levels of prothrombin, about 133% of normal, this mutation contributes to thrombotic risk. (30)(31) Like factor V Leiden, the mutation is seen most commonly in white populations, in whom it is found in 3% to 17% of patients with VTE. (31) Although most patients are heterozygous carriers, in very rare instances a patient can be homozygous

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for the mutation, which seems to increase the likelihood of thrombosis. (30)(32)

The mutation can cause venous or arterial thrombosis, but in patients younger than 2 years, arterial thrombosis is more common, especially in neonates. (30) In any neonate with an unprovoked arterial thrombus, or finding of a central nervous system thrombus, prothrombin gene analysis should be performed to evaluate for the mutation. (30)

THROMBOCYTOSIS

Thrombocytosis, or increased platelet production, can be defined as either a primary or secondary process with secondary (reactive) thrombocytosis being more common among infants. (33) Sick infants face an increased risk of complications due to thrombocytosis because of their inherently low AT, protein C, and protein S levels as well as the smaller diameter of their blood vessels. (30) A family history of thrombotic events should be evaluated in any infant with an unexplained thrombotic event.

Secondary thrombocytosis is a reactive process in which infection, inflammation, or anemia causes an increase in an infant's platelet production. Reactive thrombocytosis is more common among preterm infants, is generally benign, and resolves spontaneously. (34) Thrombopoietin is the growth factor responsible for platelet production and is produced primarily by the liver. During times of stress or infection, hepatic thrombopoietin increases in response to inflammatory interleukins, driving the reactive thrombocytosis commonly observed. (35)

Primary thrombocytosis is uncommon and arises from a genetic mutation that induces hyperplasia of megakaryocytes in the bone marrow. (36) Unlike reactive thrombocytosis, primary thrombocytosis can lead to arterial thrombosis and myocardial infarctions, though affected patients are typically asymptomatic. (35) Patients with chronic myeloproliferative neoplasm essential thrombocythemia present with an increased platelet count; this condition is extremely rare with a global incidence of 0.6 per 100,000 patients per year in pediatric patients. (37) Diagnosis is challenging and is based on the World Health Organization 2016 criteria that requires a combination of thrombocytosis (platelet count $\geq 450 \times 10^3/\mu L$ [$450 \times 10^9/L$]); bone marrow with megakaryocyte proliferation; a *JAK2*, *CALR*, or *MPL* gene mutation; and lack of criteria to diagnose chronic myeloid leukemia, other chronic myeloproliferative neoplasms (such as polycythemia vera), myelodysplastic syndromes, or a myeloid malignancy. (38) This must all occur in the absence of reactive thrombocytosis. (38) Pediatric patients with essential thrombocythemia may experience minor hemorrhage because of poor platelet function despite high circulating platelet counts, and have a low risk of thrombotic complications (4%). (35)(39)

ACQUIRED THROMBOTIC DISORDERS

Indwelling Catheters

Thrombosis associated with central venous lines (CVLs) is "classified into three types: pericatheter sheath, thrombotic occlusion of the catheter lumen, and mural thrombosis, either superficial or deep vein." (40) In neonates, these CVLs are in the form of UVCs/UACs, peripherally inserted central catheter lines, and Hickman catheters (eg, Broviacs).

Thromboses can begin forming within hours of line insertion due to venous injury activating coagulation cascades, fibrin deposition on foreign catheter material, and almost immediate regrowth of surrounding endothelial and smooth muscle cells. (40) Blood flow can be decreased up to 60% around lines, which disrupts laminar flow and then causes additional adhesion of coagulation factors and platelets around the catheter itself. (40) The risk for thromboses is greater in newborns compared with other populations because of their small vessel size and immaturity of their clotting mechanisms especially in the face of hemostatic imbalance caused by fluid status, congenital heart disease, or hypoxia. (41)

Known patient-related risk factors for line-associated clots are malignancy, previous history of thrombosis, and systemic infection. (9)(10)(11)(13)(40)(41) Risk factors associated with the line itself are related to type/lumen size, access location, and time from insertion. Higher risk is conveyed to larger diameter of the catheter, multilumen lines, temporary lines (peripherally inserted central catheters more than ports), and femoral insertion sites. (40) Long-term total parenteral nutrition as well as hyperosmolar solutions convey a higher risk of thrombosis due to catheter-induced occlusion of vessels and increased risk of endothelial vessel damage. (41)

Frequently, in neonates, UFH infusions are started alongside CVL insertion to allow infants to complete their needed treatments (antibiotics, parenteral nutrition, etc). However, these infusions do not decrease the rate of thrombosis but rather reduce occlusion. (41)

Although most thromboses related to catheter events are asymptomatic, clinical manifestations include edema (localized or including surrounding areas/drainage pathways), erythema, and pain/tenderness. The primary treatment approach involves anticoagulation, and the decision to remove the CVL is made on an individual basis. Short-term anticoagulation is recommended before line removal.

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(41) Thromboses in an artery should prompt removal of the line and initiation of LMWH or UFH for at least 10 days. (41) Provoked VTEs are treated for 6 weeks to 3 months with anticoagulation and reimaged before discontinuing therapy to ensure that the thrombosis has completely resolved, or become chronic. (40) Goal anti–factor Xa levels of 0.5 to 1.0 IU/mL when using LMWH and 0.35 to 0.7 IU/mL if using UFH. Of note, neonates require higher doses of enoxaparin, in the range of 1.7 to 2.0 mg/kg every 23 hours, because of the lower levels of AT and large volume of distribution. (41)(42)

Nephrotic Syndrome

Patients diagnosed with nephrotic syndrome are at increased risk for thrombosis (2%–3%), particularly DVTs and renal vein thrombosis. (43) Hypercoagulability stems from thrombocytosis arising from hypovolemia and hemoconcentration; increased platelet activation; urinary losses of AT; deficiency of protein C, protein S, and plasminogen; and increased levels of fibrinogen and factors V and VIII caused by dysregulated compensatory protein synthesis. (43) Congenital nephrotic syndrome is rare and is most commonly found in infants of Finnish descent, with an incidence of 1 in 8,200 live births. (44)

Anticoagulation is usually initiated with LMWH in response to a thrombus, as it has more predictable pharmacokinetics and there is no need for intravenous access. (43) UFH can be used if there is a need for quick reversal or tight titration. (43) Anticoagulation at prophylactic doses should then be used when patients have flares of nephrotic syndrome, to prevent further thrombotic events. (45)

Antiphospholipid Syndrome

Antiphospholipid (aPL) syndrome is an antibody-mediated hypercoagulability with repeated venous and/or arterial thrombotic events, along with other hematologic manifestations, including thrombocytopenia and/or hemolytic anemia. (46) aPL antibodies are a diverse set of immunoglobulins targeting proteins that bind to phospholipids; common screening aPL assays include anticardiolipin antibody, anti-β2 glycoprotein, and lupus anticoagulant. (47) Because in some instances aPL syndrome can be a transient phenomenon in reaction to infection, underlying autoimmune disorders, medications, and/or malignancy, initial testing is done at the time of the event, and repeat confirmatory testing is completed 12 weeks or more later. (46) A prolonged aPTT in the absence of bleeding symptoms or a bleeding history could be from positive aPL antibodies, which can be confirmed if an aPTT mixing study does not appropriately correct. The presence of aPL antibodies alone is insufficient for the diagnosis of aPL syndrome, and patients with aPL antibodies require another insult, such as trauma or a congenital prothrombotic disorder, for thrombus formation to occur. (48) Primary aPL syndrome occurs without any associated disease, whereas secondary aPL syndrome is associated with another condition, such as systemic lupus erythematosus or another autoimmune condition. (48)

aPL antibodies bind and activate endothelial cells, neutrophils, and platelets, resulting in proinflammatory cytokines and complement activation. (48) They also interfere with anticoagulant pathways including fibrinolysis by inhibiting protein C and inhibiting β2GPI, which normally blocks factor Xa formation, thrombin activation, and platelet aggregation. (48) The summation of these effects results in a prothrombotic state, and an increased risk of stroke is seen more often in pediatric cases compared with adult cases, where there is typically an underlying autoimmune condition and more VTE events. (49) Lupus anticoagulant is the stronger indicator of thrombotic potential compared with anticardiolipin antibody, which does not appear to confer thrombotic risk, but triple-positive aPL syndrome has the highest risk. (47)(48) aPL syndrome in pregnant persons can result in the transfer of these antibodies to the fetus via the placenta, but this does not appear to result in perinatal thrombosis. (50)

After a thromboembolic event in the setting of positive aPL, anticoagulation is recommended for at least 3 months or longer if there is an ongoing risk factor. (45) If there are recurrent episodes of thromboembolism, anticoagulation is advised for as long as the risk factor is present. (45)

Summary

Thrombophilia is common in infants, especially neonates hospitalized in the NICU, which confers additional morbidity and mortality. Clinicians caring for such patients should be aware that:

- Hypercoagulability testing may not be indicated based on the clinical scenario surrounding the diagnosis of an acute thrombus.
- CVLs are the most common cause of thrombosis in neonates, but congenital and other acquired prothrombotic states contribute to a small subset of arterial or venous thromboembolism.

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American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and pathophysiology of congenital and acquired thrombotic disorders.
- Know the clinical and laboratory features, management, and potential adverse effects of treatment of congenital and acquired thrombotic disorders.
- Know the causes and pathophysiology of acquired defects in hemostasis.
- Know the clinical and laboratory features and management of acquired defects in hemostasis including intravascular coagulation and hemorrhagic disease of the newborn.
- Know the causes and pathophysiology of congenital defects in hemostasis.
- Know the clinical manifestations, laboratory findings, and management of congenital defects in hemostasis.
- Know the pathogenesis and complications of catheter-related thrombi including umbilical arterial and central venous catheters.

References

1. Ostilla L, Knopoff K, Myers P, Morocco P. Disorders of coagulation in the newborn. *NeoReviews*. 2024;25(11):e694
2. Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. *Blood Rev*. 2011;25(4):155–167
3. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev*. 2015;29(1):17–24
4. Gale AJ. Current Understanding of Hemostasis. *Toxicol Pathol*. 2011;39(1):273–280
5. Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. *Crit Rev Biochem Mol Biol*. 2015;50(4):326–336
6. Furie B. Pathogenesis of thrombosis. *Hematology Am Soc Hematol Educ Program*. 2009;2009(1):255–258
7. Winter WE, Flax SD, Harris NS. Coagulation testing in the core laboratory. *Laboratory Med*. 2017;48(4):295–313
8. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124(4):1001–1008
9. Greenway A, Massicotte MP, Monagle P. Neonatal thrombosis and its treatment. *Blood Rev*. 2004;18(2):75–84
10. Bersani I, Piersigilli F, Iacona G, et al. Incidence of umbilical vein catheter-associated thrombosis of the portal system: A systematic review and meta-analysis. *World J Hepatol*. 2021;13(11):1802–1815
11. Hwang JH, Chung ML, Lim YJ. Incidence and risk factors of subclinical umbilical catheter-related thrombosis in neonates. *Thromb Res*. 2020;194:21–25
12. Park CK, Paes BA, Nagel K, Chan AK, Murthy P. Thrombosis and Hemostasis in Newborns (THiN) Group. Neonatal central venous catheter thrombosis: diagnosis, management and outcome. *Blood Coagul Fibrinolysis Int J Haemost Thromb*. 2014;25(2):97–106
13. Gibson K, Sharp R, Ullman A, Morris S, Kleidon T, Esterman A. Risk factors for umbilical vascular catheter-related adverse events: a scoping review. *Aust Crit Care*. 2022;35(1):89–101
14. Bacciedoni V, Attie M, Donato H, Comité Nacional de Hematología, Oncología y medicina transfusional. Thrombosis in newborn infants. *Arch Argent Pediatr*. 2016;114(2):159–166
15. Middeldorp S, Nieuwlaat R, Baumann Kreuziger L, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. *Blood Adv*. 2023;7(22):7101–7138
16. Raffini L, Thornburg C. Testing children for inherited thrombophilia: more questions than answers. *Br J Haematol*. 2009;147(3):277–288
17. de la Morena-Barrio B, Orlando C, de la Morena-Barrio ME, Vicente V, Jochmans K, Corral J. Incidence and features of thrombosis in children with inherited antithrombin deficiency. *Haematologica*. 2019;104(12):2512–2518
18. Bianchini EP. Antithrombin deficiency: no sugar, no diagnosis!. *Blood*. 2022;140(2):83–85
19. Ehrhardt JD, Boneva D, McKenney M, Elkbuli A. Antithrombin deficiency in trauma and surgical critical care. *J Surg Res*. 2020;256:536–542
20. Seguin J, Weatherstone K, Nankervis C. Inherited antithrombin III deficiency in the neonate. *Arch Pediatr Adolesc Med*. 1994;148(4):389–393
21. Smith N, Warren BB, Smith J, et al. Antithrombin deficiency: a pediatric disorder. *Thromb Res*. 2021;202:45–51
22. Wypasek E, Undas A. Protein C and protein S deficiency: practical diagnostic issues. *Adv Clin Exp Med Off Organ Wroclaw Med Univ*. 2013;22(4):459–467
23. Minford A, Brandão LR, Othman M, et al. Diagnosis and management of severe congenital protein C deficiency (SCPCD): communication from the SSC of the ISTH. *J Thromb Haemost*. 2022;20(7):1735–1743
24. Hepner M, Protein KV. Protein *S*. *Methods Mol Biol*. 2013;992:373–381 doi: 10.1007/978-1-62703-339-8_30 PMID: 23546730
25. Campbell SE, Bolton-Maggs PHB. Congenital and acquired bleeding disorders in infancy. *Early Hum Dev*. 2015;91(11):637–642
26. Kujovich JL. Factor V Leiden thrombophilia. *Genet Med*. 2011;13(1):1–16
27. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. *Implications for venous thromboembolism screening. JAMA*. 1997;277(16):1305–1307
28. Piersigilli F, Auriti C, Seganti G. Budd–Chiari syndrome and factor V Leiden in a neonate. *N Engl J Med*. 2006;355(5):527–528
29. Zhang P, Zhang J, Sun G, et al. Risk of Budd-Chiari syndrome associated with factor V Leiden and G20210A prothrombin mutation: a meta-analysis. *PLoS One*. 2014;9(4):e95719
30. Young G, Manco-Johnson M, Gill JC, et al. Clinical manifestations of the prothrombin G20210A mutation in children: a pediatric coagulation consortium study. *J Thromb Haemost*. 2003;1(5):958–962
31. Jadaon MM. Epidemiology of Prothrombin G20210A mutation in the Mediterranean region. *Mediterr J Hematol Infect Dis*. 2011;3(1):e2011054
32. Bosler D, Mattson J, Crisan D. Phenotypic heterogeneity in patients with homozygous prothrombin 20210AA genotype. *J Mol Diagn*. 2006;8(4):420–425

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33. Gleason CA, Juul SE. *Avery's Diseases of the Newborn*. 10th ed; Philadelphia, PA: Elsevier; 2017
34. Martin RJ, Fanaroff AA, Walsh MC. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 11th ed. Philadelphia, PA: Elsevier; 2019
35. Putti MC, Bertozzi I, Randi ML. Essential thrombocythemia in children and adolescents. *Cancers (Basel)*. 2021;13(23):6147
36. Jeon GW. Pathophysiology, classification, and complications of common asymptomatic thrombocytosis in newborn infants. *Clin Exp Pediatr*. 2021;65(4):182–187
37. Ianotto JC, Curto-Garcia N, Lauermanova M, Radia D, Kiladjian JJ, Harrison CN. Characteristics and outcomes of patients with essential thrombocythemia or polycythemia vera diagnosed before 20 years of age: a systematic review. *Haematologica*. 2019;104(8):1580–1588
38. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405
39. Randi ML, Geranio G, Bertozzi I, et al. Are all cases of paediatric essential thrombocythaemia really myeloproliferative neoplasms? Analysis of a large cohort. *Br J Haematol*. 2015;169(4):584–589
40. Geerts W. Central venous catheter–related thrombosis. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):306–311
41. Revel-Vilk S, Ergaz Z. Diagnosis and management of central-line-associated thrombosis in newborns and infants. *Semin Fetal Neonatal Med*. 2011;16(6):340–344
42. Malowany JI, Knoppert DC, Chan AKC, Pepelassis D, Lee DSC. Enoxaparin use in the neonatal intensive care unit: experience over 8 years. *Pharmacotherapy*. 2007;27(9):1263–1271
43. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. *Pediatr Nephrol*. 2014;29(6):989–997
44. Rheault MN. Nephrotic and nephritic syndrome in the newborn. *Clin Perinatol*. 2014;41(3):605–618
45. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e737S–e801S
46. Lim W. Antiphospholipid syndrome. *Hematology Am Soc Hematol Educ Program*. 2013;2013(1):675–680
47. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood*. 2003;101(5):1827–1832
48. Islabão AG, Trindade VC, da Mota LMH, Andrade DCO, Silva CA. Managing antiphospholipid syndrome in children and adolescents: current and future prospects. *Paediatr Drugs*. 2022;24(1):13–27
49. Avcin T, Cimaz R, Silverman EDED, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics*. 2008;122(5):e1100-1107–e1107
50. Motta M, Boffa MC, Tincani A, Avcin T, De Carolis S, Lachassinne E. Follow-up of babies born to mothers with antiphospholipid syndrome: preliminary data from the European neonatal registry. *Lupus*. 2012;21(7):761–763

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NEO QUIZ

1. An infant of 31 weeks' gestation requires long-term venous access for medication administration and fluid management. After the placement of an umbilical venous catheter, there appears to be prolonged blood oozing at the insertion site. The team suspects a defect in hemostasis. Of the 2 main pathways of secondary hemostasis, testing which of the following would demonstrate a defect in the intrinsic pathway?

   A. Activated partial thromboplastin time (aPTT).
   B. Antithrombin III level.
   C. Bleeding time.
   D. Platelet count.
   E. Prothrombin time.

2. Three weeks after admission to the NICU for management of prematurity, a former 29-weeks gestation infant is found to have a thrombotic incident. Of the following, which is most likely to be linked to this event?

   A. Blood transfusions.
   B. Chorioamnionitis.
   C. Respiratory distress syndrome.
   D. Sepsis.
   E. Venous or arterial access devices.

3. Shortly after delivery, a term infant develops diffuse bruising. On further investigation, the neonate demonstrates signs of disseminated intravascular coagulation and is found to have retinal thrombosis on ophthalmologic examination. Of the following, which condition most likely contributed to these findings?

   A. Antiphospholipid syndrome.
   B. Antithrombin deficiency.
   C. Factor V Leiden.
   D. Protein C and S deficiency.
   E. Prothrombin G20210A mutation.

4. Unlike secondary thrombocytosis, which can be caused by infection, inflammation, or anemia, primary thrombocytosis is a rare condition caused by genetic mutations in the *JAK2*, *CALR,* or *MPL* genes, leading to hyperplasia of megakaryocytes in the bone marrow and thrombocytosis. What platelet count is required to meet the diagnostic criteria of primary thrombocytosis?

   A. $\geq 150 \times 10^9$/L.
   B. $\geq 300 \times 10^9$/L.
   C. $\geq 450 \times 10^9$/L.
   D. $\geq 600 \times 10^9$/L.
   E. $\geq 750 \times 10^9$/L.

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5. Nephrotic syndrome places an infant at increased risk for thrombosis (particularly renal and deep vein thrombosis). This hypercoagulable state stems from thrombocytosis due to hypovolemia and an increase of all of the following except:

   A. Factor V.
   B. Factor VII.
   C. Fibrinogen.
   D. Plasminogen.
   E. Platelet activation.

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Hemoglobinopathies in the Neonate

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EDUCATION GAPS

Neonatologists should know how to recognize and assess for both quantitative and qualitative hemoglobin disorders. Early diagnosis of moderate to severe hemoglobinopathies is crucial as it can prevent morbidity and mortality in patients affected by these conditions.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the pathophysiology, typical presentation, and general complications associated with common quantitative and qualitative hemoglobin disorders.
2. Recognize the difference between α-globin and β-globin mutations and know when each of these related disorders present in the in utero or neonatal period.
3. Interpret newborn screening hemoglobinopathy results to provide early diagnosis and counseling to families.

ABSTRACT

Hemoglobinopathies in neonates constitute a group of disorders influenced by genetic mutations in the human globin genes. They are often broadly categorized into quantitative defects or qualitative defects, though they are not mutually exclusive. In quantitative defects, the mutation causes insufficient production of a normal globin chain, which can range from no production to mild deficiency. These are typically referred to as thalassemias. In qualitative defects, the structure of the hemoglobin is altered. The most common structural hemoglobinopathy is sickle cell disease. During fetal development, distinct globin chains are synthesized, which undergo a progressive switch to adult globin chains perinatally. This affects the timing of the clinical presentation of these disorders and thus, our ability to diagnose them. In this review, we focus on the epidemiology, genetic causes, clinical presentation, and general overview and management of common hemoglobin disorders that may be encountered in the neonatal period.

AUTHOR DISCLOSURES Drs Blankenhorn and Strumph have disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

HPFH	hereditary persistence of fetal hemoglobin
NTDT	nontransfusion dependent
SCD	sickle cell disease
TDT	transfusion-dependent β-thalassemia

Hemoglobinopathies are disorders caused by abnormal production or structure of the hemoglobin protein. Many of these disorders are present in utero or during the neonatal period. In this review, we focus on the structure and

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function of the hemoglobin molecule and then provide a comprehensive discussion of the more common types of hemoglobinopathies.

HEMOGLOBIN PRODUCTION

Hemoglobin is a heterotetrametric protein consisting of 2 polypeptide globin α subunits and 2 polypeptide globin β subunits. The globin subunits are encoded by multigene clusters on chromosome 16 for α-globin and chromosome 11 for β-globin (Fig 1). (1)(2)(3)(4) These globin polypeptides each contain a heme group that can reversibly bind oxygen, allowing it to be delivered to the tissues. Different α-like and β-like globin chains are synthesized during fetal development and neonatal development. The order in which different β-globins are expressed generally follows the order in which they are arranged along chromosome 11: 5′-ε-γ^G-γ^A-δ-β−3′. (2)(4) In the first 8 weeks of gestation, there is a brief period of embryonic globin gene expression. The embryonic chains ζ and ε are the first to be produced during early embryonic life, producing hemoglobin Gower 1, hemoglobin Gower 2, and hemoglobin Portland. After 8 weeks' gestation, the α-globin and γ-globin chains are predominantly expressed, which creates hemoglobin F ($\alpha_2\gamma_2$), termed fetal hemoglobin. Fetal hemoglobin is the most common hemoglobin at birth, accounting for 70% to 90% of hemoglobin in the neonatal period. After birth, the γ-globin chain of fetal hemoglobin is progressively replaced by the β-globin chain of adult hemoglobin termed hemoglobin A, or $\alpha_2\beta_2$, which occurs around 3 to 6 months of age. This is referred to as the hemoglobin switch (see Fig 2). (4)(5)(6) Due to the timing of globin chain switching during development, a premature infant will predominantly express hemoglobin F, which slowly decreases as the infant approaches term gestational age. In adults, hemoglobin F accounts for less than 1% of total hemoglobin, and the most common hemoglobin in adults is hemoglobin A ($\alpha_2\beta_2$) with a minimal amount of the minor hemoglobin A2 ($\alpha_2\delta_2$). (4)

HEMOGLOBINOPATHIES

Hemoglobinopathies are a heterogenous group of disorders caused by genetic mutations in the globin genes. They are often broadly categorized into quantitative defects or qualitative defects, but they are not mutually exclusive. (4) In quantitative defects, the mutation causes insufficient production of a normal globin chain, which can range from no production to mild deficiency. These are typically referred to as the thalassemias. In qualitative defects, the structure of the hemoglobin is altered. The most common structural hemoglobinopathy is sickle cell disease.

EPIDEMIOLOGY OVERVIEW

Historically, hemoglobinopathy variants have been naturally selected because of their protective advantage against severe malaria, resulting in the highest prevalence seen in tropical and subtropical regions affected by malaria. (7)(8)

THALASSEMIAS

Thalassemias are a group of disorders generally characterized by ineffective erythropoiesis and hemolysis. The disorders are often classified based on the type of globin

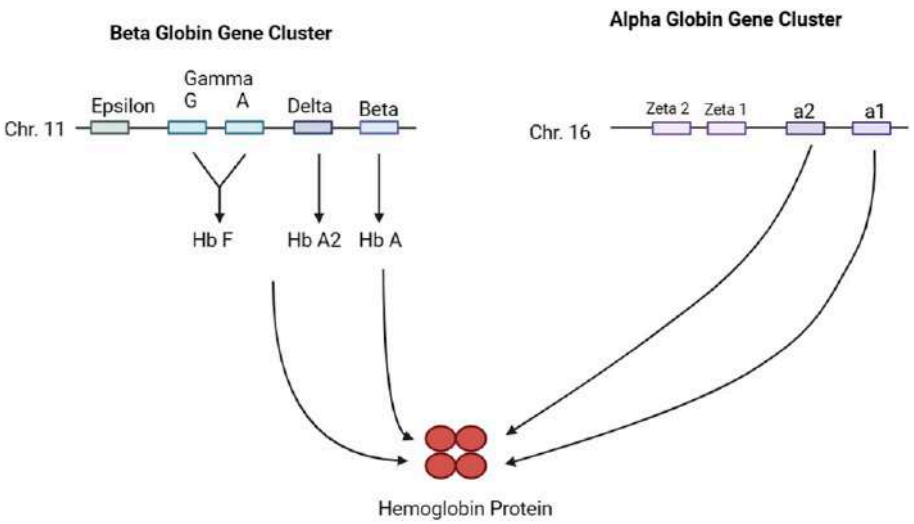


Figure 1. α- and β-globin gene clusters. Diagram of α- and β-globin gene clusters and their expression within the adult hemoglobin protein. The arrangement of genes corresponds with the order of their expression during development. Early fetal life is characterized by the expression of ζ α chains and ε β chains. In adults, hemoglobin chains are predominantly α chains combined with β chains and a smaller amount of γ and δ chains.

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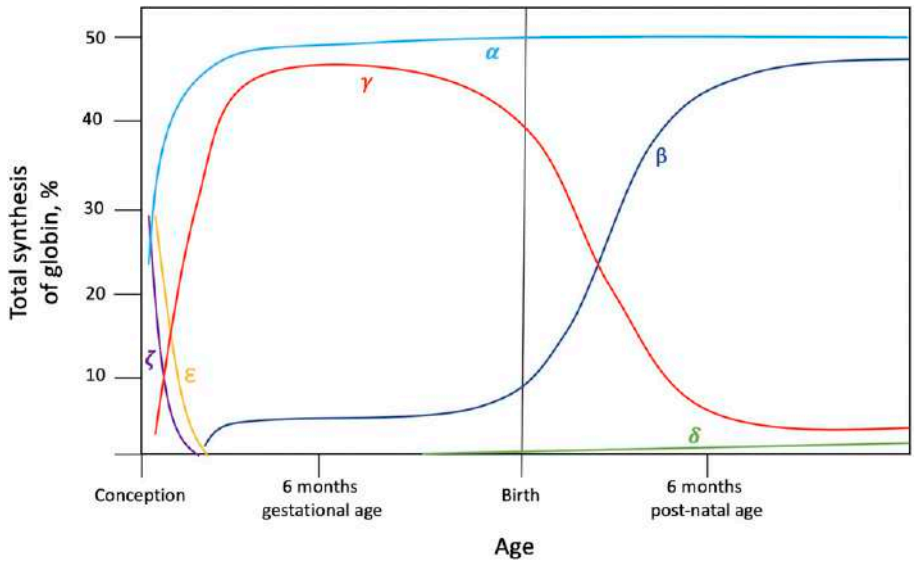


Figure 2. Hemoglobin switch. Schematic diagram depicting the change in hemoglobin chain expression through fetal and early postnatal life. By 6 months of age, γ chains drop precipitously and β chains increase, which corresponds to the time when clinical manifestations of β-thalassemias present.

chain that is affected: α-thalassemias are caused by decreased production of α chains, whereas β-thalassemias are caused by decreased production of β chains. Thalassemias have a wide range of clinical severities based on the number of genes affected, the types of mutations involved, and the subsequent effect on globin production.

Epidemiology of Thalassemias

α-Thalassemia is seen in approximately 5% of the world's population. It is most prevalent in Southeast Asia, specifically Laos and Cambodia; however, it is also present in Africa and regions of the Mediterranean and Middle East. (9) The more severe cis-mutations are seen in Southeast Asia, whereas single gene mutations or trans mutations are more commonly seen in Africa. If both parents have a cis mutation, their offspring will have a 25% chance of having α-thalassemia major leading to hydrops fetalis. Hemoglobin constant spring, the most common type of nondeletional α-thalassemia, is predominantly seen in northeastern Thailand, southern China, and minority populations in Vietnam. (10)

β-thalassemias are less prevalent than α-thalassemias; however, they still affect 1.5% of the global population. Each year approximately 40,000 infants are born with the condition, and half will require regular blood transfusion therapy. Most people with β-thalassemias reside in a geographic region stretching from Africa, through southern Europe and the Middle East, to Southeast Asia. Hemoglobin E- β-thalassemia is most commonly found in Southeast Asia. (11)(12)

α-Thalassemia

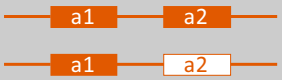
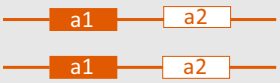
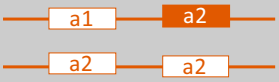
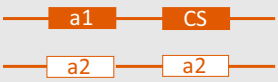
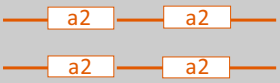
α-Thalassemia is caused by mutations in 1 or more of the 4 α-globin genes. These can range in severity from 1 mutation causing a slightly decreased α-globin production, to a 4-gene mutation leading to no α-globin production. The majority of mutations are deletional, but point mutations have also been reported. When mutations occur on the same chromosome, they are considered to be in cis configuration. When mutations occur on opposite chromosomes, they are considered to be in trans configuration (see Table 1).

α-globin gene expression begins in utero, therefore severe mutations in these genes can be clinically apparent in utero and at birth. α-thalassemia carrier status occurs when 1 α-globin gene is mutated (-α/αα). This is clinically benign as there are 3 other normal-functioning α-globin genes. Mutations of 2 α-globin genes are classified as α-thalassemia trait, which causes low mean corpuscular volume, low mean corpuscular hemoglobin, and normal hemoglobin levels or very mild anemia. Affected individuals have normal growth and development.

Three α-globin deletions with only 1 active α-globin gene (- -/-α) is called deletional hemoglobin H disease. In hemoglobin H disease, the significant decrease in α-globin chains leads to an imbalance with the β-like chains. The excess γ chains (in utero) and β chains (neonatal) form tetramers called hemoglobin Bart (γ4) and hemoglobin H (β4), respectively. (10)(13) These tetramers are highly unstable, leading to precipitation of the hemoglobin in red blood cells, causing direct damage to the red cell membrane and leading

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Table 1. Alpha Thalassemia Mutations

Nomenclature	Gene mutations	Presentation
α-thalassemia carrier		Asymptomatic Borderline low MCV Normal Hemoglobin
α-thalassemia trait Cis mutation		Asymptomatic Mild anemia Low MCV
Trans mutation		
Deletional Hemoglobin H disease		Mild to moderate microcytic anemia Chronic hemolysis Rarely require transfusions
Non-deletional Hemoglobin H – Constant Spring		Moderate to severe microcytic anemia Chronic hemolysis Splenomegaly Often requires transfusions
α-thalassemia major		Hydrops fetalis Not compatible with life unless fetus receives intrauterine transfusions

A list of the common types of α-thalassemia with their corresponding genetic mutations and the resultant phenotypes. α-thalassemia carriers have 1 mutation. α-thalassemia trait refers to persons with 2 mutations, either in a cis or trans configuration. Deletional hemoglobin H disease is due to deletions of 3 of 4 genes. Nondeletional hemoglobin H disease is the result of 2 deletions and a third mutation such as hemoglobin constant spring, which leads to more severe anemia and chronic hemolysis. α-thalassemia major occurs when there are no α genes, which is not compatible with life unless the fetus receives intrauterine transfusions. MCV=mean corpuscular volume.

to chronic hemolysis. Patients often develop hyperbilirubinemia from the hemolysis and splenomegaly due to compensatory extramedullary hematopoiesis. Patients with deletional hemoglobin H often have mild to moderate anemia but do not usually require transfusions. (14)(15) There is a form of nondeletional hemoglobin H disease in which a cis mutation is inherited with a nondeletional mutation of a third α-globin gene. Examples include hemoglobin constant spring, Pakse, and Quong Sze mutations, which, if inherited with 2 α-gene deletions, can result in nondeletional hemoglobin H syndrome. (14) The constant spring mutation causes the production of an abnormally long α-globin protein, which is highly unstable, thus leading to more clinically significant symptoms compared with the deletional form of hemoglobin H disease. People with nondeletional hemoglobin H often require frequent transfusions. (14)(15) Almost all fetuses with hemoglobin Barts hydrops fetalis syndrome, because of a 4 α-globin gene deletion, die in utero or shortly after birth. (14)

For patients with α-thalassemia, management depends on the severity of the phenotype. Most people with hemoglobin H are not transfusion-dependent. However, during acute infections, particularly with parvovirus, that can trigger an aplastic crisis, they may require support with transfusions. Folic acid supplementation can be recommended because of the rapid cell turnover and thus higher folic acid consumption. (16) In patients with severe phenotypes, additional complications, such as iron overload, growth delay, splenomegaly, and cholelithiasis, should be monitored. (15)(16)

Diagnosis of α-thalassemia cannot be determined based on hemoglobin electrophoresis. Genetic testing is required and often done based on family history or clinical suspicion in a patient with microcytic anemia. Preconception counseling is extremely important for those with α-thalassemia. If

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both parents are carriers of a cis mutation, there is a 25% risk in each pregnancy that the fetus will inherit all 4 mutations and therefore lack all α-globin genes. When all α chains are deleted (–/–) the lack of α-globin production is not compatible with life. Affected fetuses may survive the first and second trimesters because of the persistence of embryonic ζ-globin chains, but unless given transfusions, they will go on to develop hydrops fetalis. In addition to hydrops fetalis of the fetus, placentomegaly can occur, as well as potentially life-threatening complications in the pregnant patient (eg, preeclampsia, hemorrhage, and disseminated intravascular coagulation). In utero transfusions have been an effective treatment of these fetuses if detected early enough in pregnancy followed by life-long transfusions in the surviving infants. (16) These couples should receive genetic counseling with prenatal diagnosis in future pregnancies. Prenatal diagnosis can be performed using DNA-based diagnosis via amniocentesis. (15)(16)(17)

β-Thalassemia

β-Thalassemias are most commonly caused by point mutations in 1 of the 2 β-globin genes. These mutations can affect transcription, translation, or post-translation modifications, hence leading to a wide array of clinical severities because of the varying effects on β-globin production. Mutations that lead to mild reductions in β-globin synthesis are denoted as β^{+} whereas mutations leading to the complete absence of β-globin synthesis are denoted as β°. Homozygous β° mutations lead to no detectable β-chain synthesis. As a result of excess α chains, red cell precursors are prematurely destroyed, resulting in chronic hemolysis. (2)(3)

Classification of β-thalassemia was previously based on the symptoms of the patient as well as the degree of anemia. Individuals were classified as having β-thalassemia major, intermedia, or minor. More recently, classification has focused on whether the patient requires transfusions or not, a treatment that is initiated based on the severity of an individual's anemia and/or symptoms. Transfusion-dependent β-thalassemia (TDT) is usually caused by homozygous β° mutations or compound heterozygous β^{+}/β° mutations. Individuals with only 1 β-globin mutation, or homozygous β^{+} mutations, generally do not require transfusions and are classified as non–transfusion-dependent β-thalassemia (NTDT). Phenotypes can be influenced by 3 primary factors:

1. the quantity of *β*-globin chain synthesized by the individual
2. the concurrent inheritance of α-thalassemia, which alters the ratio of α- to *β*-globin chains, thereby alleviating certain hemolytic effects
3. the presence of a mutation that enhances hemoglobin F production, offering partial compensation for the deficiency in *β*-globin chains. (11)(14)

Children with TDT will clinically present around 6 to 12 months of age, coinciding with the time of hemoglobin switch and subsequent drop in hemoglobin F levels with minimal to no hemoglobin A production. Children with NTDT present later in childhood, usually during routine examinations which reveal a microcytic anemia. (2) Diagnosis of β-thalassemia is based on hemoglobin electrophoresis showing elevations in hemoglobin F and hemoglobin A2 with a reduction or absence of hemoglobin A. Genetic sequencing of the β-globin gene can confirm the diagnosis.

Without treatment, children with TDT will develop hepatosplenomegaly and marrow expansion from ineffective erythropoiesis and will suffer from growth and developmental delays, complications of iron overload, and a shortened lifespan. Treatment of TDT consists of red cell transfusions typically made every 3 to 4 weeks. Transfusions are given to target a goal hemoglobin nadir of greater than 9 to 9.5 g/dL (90–95 g/L) to suppress innate erythropoiesis and support oxygen-carrying capacity. Transfusion therapy results in improved growth, decreased skeletal abnormalities, reduced hypersplenism, and decreased gut iron absorption. Generally, children with NTDT do not require transfusions except during special circumstances such as surgeries, acute infections, or to support growth during childhood. (18)

In 2019, the US Food and Drug Administration approved the medication luspatercept for adults older than 18 years with TDT. The medication improves late-stage erythroid maturation, and thus increases hemoglobin levels, leading to a reduction in transfusion requirements. (19) In 2022, gene therapy for thalassemia was approved, the first transformative therapy that allows individuals with TDT to become transfusion-independent. (20)(21)

COMMON STRUCTURAL HEMOGLOBIN VARIANTS

Epidemiology of Structural Variants

Structural hemoglobin variants arise from genetic mutations that cause an abnormal globin chain structure in the hemoglobin. Hemoglobin S, the most prevalent, is seen in high frequencies across sub-Saharan Africa, the Mediterranean, the Middle East, and India, regions with a significant malaria burden. (8)(22) Hemoglobin C is prevalent in West Africa and Southeast Asia and within diverse populations in Africa, South and Central America, and Southern Europe. (23) Hemoglobin E predominantly affects individuals from the

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Indian subcontinent and Southeast Asia, with Thailand, Laos, and Cambodia exhibiting frequencies approaching 60%. (9)

Hemoglobin S Syndromes

Hemoglobin S is caused by a point mutation in codon 6 of the β-globin gene on chromosome 11, resulting in an amino acid substitution in which glutamic acid is replaced by valine. Upon deoxygenation inside the red cell, hemoglobin S will polymerize, leading to a conformational change in the red cell shape into a "sickle." Individuals who inherit 1 hemoglobin S gene have sickle cell trait. These individuals are generally asymptomatic. Sickle cell disease (SCD) is an autosomal recessive group of disorders caused by either the homozygous inheritance of the hemoglobin S gene or a compound heterozygous mutation involving hemoglobin S and another β-globin mutation that can influence sickling. Homozygous inheritance, termed hemoglobin SS, causes the more severe form of the disease. If a patient coinherits a sickle mutation and a hemoglobin C allele, they will have hemoglobin SC disease, which is typically milder than hemoglobin SS. When a sickle mutation is inherited with β-thalassemia, the severity of the resulting sickling disorder depends on the severity of the coinherited β-thalassemia mutation. Coinheritance of a β^0 mutation, which produces no hemoglobin A, results in severe SCD similar to hemoglobin SS. (24)(25)(26)

Children with SCD typically do not present with symptoms until 6 to 12 months of age when fetal hemoglobin levels begin to decrease and hemoglobin S production increases. Sickling of the red cells leads to a combination of intermittent vaso-occlusion in the vasculature as well as chronic hemolysis. This leads to acute complications and chronic organ damage. Common complications include strokes, retinopathy, acute chest syndrome, nephropathy, functional asplenia, and subsequent increased risk for infections, avascular necrosis, and episodes of acute vaso-occlusive pain crises. (22)(24)

Early diagnosis of SCDs is important because early initiation of prophylactic penicillin, usually by the age of 2 months, has been shown to decrease mortality from bacteremia. (27) Disease-modifying therapies such as hydroxyurea and blood transfusions have been shown to decrease complications. Curative therapy includes stem cell transplantation. In 2023, gene therapy for SCD was approved. Through ex-vivo genetic modification, these treatments offer patients a transformative opportunity to drastically ameliorate their disease. Results from ongoing clinical trials have shown drastic improvement in hemoglobin levels and a reduction of vaso-occlusive crises. (28)

Hemoglobin C

Hemoglobin C results from a single amino acid mutation leading to glutamic acid being replaced by lysine in the sixth position of the β-globin chain. Individuals with the hemoglobin C trait (hemoglobin AC) are phenotypically normal whereas individuals who inherit 2 copies of the hemoglobin C allele (hemoglobin CC disease) often have mild chronic hemolytic anemia. Because of chronic hemolysis, individuals have an increased risk of gallstones. Folic acid is often provided to prevent folate deficiency. Typically, transfusions are not needed. (23)

Hemoglobin E

Hemoglobin E is caused by a mutation in the β-globin gene that creates an alternate splice site leading to decreased production of an abnormal β chain. Individuals with hemoglobin E trait can have mild microcytosis and are asymptomatic. Individuals with coinheritance of hemoglobin E and a β-thalassemia mutation can present with an array of phenotypes ranging from mild anemia to severe anemia requiring transfusion support. Modifiers such as the type of β-thalassemia mutation, and whether the individual coinherited α-thalassemia, can affect the phenotype. (2) Individuals who coinherit hemoglobin S and hemoglobin E (hemoglobin SE) exhibit a mild sickle cell phenotype similar to hemoglobin S/β^+ thalassemia.

OTHER VARIANTS

Unstable Hemoglobins

Unstable hemoglobins can result from a mutation in any of the globin chains. Mutations are often inherited in an autosomal dominant pattern. These mutations cause changes in the solubility of the hemoglobin, thus leading to instability and hemoglobin precipitation referred to as Heinz bodies. These precipitates can bind to the red cell membrane causing a change in the membrane leading to breakdown and clearance of the affected cells in the spleen. The red cell lifespan can be severely shortened leading to anemia. (29)

Clinical presentation of unstable hemoglobins is variable, and the severity is linked to the causative variant and its influence on hemoglobin stability. As a result, the spectrum of clinical manifestations can be broad, ranging from no symptoms to severe chronic hemolytic anemia. Of particular importance to the neonatologist, unstable γ-globin mutations can cause transient neonatal hemolytic anemia, which resolves between 6 and 9 months of age because of the transition from fetal to adult hemoglobin. Generally, unstable hemoglobinopathies manifest as mild phenotypes and patients may exhibit mild chronic hemolytic anemia.

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Patients should be educated about prevention, including avoidance of oxidant drugs and prompt evaluation during hemolytic episodes. Infections can often precipitate hemolysis. In patients with severe hemolysis, transfusion support may be required. Others only require transfusions during hemolytic crises, often prompted by infections. Splenectomy can be considered in severe cases, but not as the preferred option because it can cause a hypercoagulable state in some people. (29)

Methemoglobins: Hemoglobin M

Some types of hemoglobin variants, termed hemoglobin M, can result in methemoglobin. Methemoglobin is a condition in which heme iron becomes oxidized. As a result, the oxygen-carrying capacity of blood decreases because oxidized iron cannot reversibly bind oxygen. In most cases, a tyrosine is substituted for a histidine in the proximal and distal sites of the α or β chains, leading to an iron-phenolate complex. (30)

Inheritance of hemoglobin M is autosomal dominant. Affected individuals often have chronic methemoglobinemia. As a result, they typically present with cyanosis. Patients can also have hemolysis and may present with neonatal jaundice. Depending on which chain is mutated, individuals will present at different time points. In the case of α-globin variants, the dusky color of affected infants will be noted at birth. When there is a β-globin variant, the symptoms become apparent only after β chains have replaced the fetal γ chains at 6 to 9 months of age. (31)

Hemoglobin M can be diagnosed with electrophoresis. No effective treatment exists for cyanosis in patients with hemoglobin M, however, individuals are often otherwise asymptomatic.

Hereditary Persistence of Fetal Hemoglobin and *δβ*-Thalassemia

Hereditary persistence of fetal hemoglobin (HPFH) and δβ-thalassemia are benign conditions in which individuals exhibit markedly elevated levels of hemoglobin F into adulthood. δβ-Thalassemia results from a large deletion encompassing both the δ- and β-globin genes. (32) Heterozygotes often are characterized by hemoglobin F levels between 5% and 20% and mild microcytic anemia. HPFH mutations are caused by a large deletion in the region between the γ- and β-globin genes or a point mutation in the γ-globin gene promoter. (32) Deletional HPFH is characterized by hemoglobin F levels of 10% to 20% with no effect on red blood cell indices. (32)

HPFH and δβ-thalassemia are clinically important because elevated hemoglobin F levels can attenuate the disease severity of coinherited β-chain hemoglobinopathies, such as in patients with combined hemoglobin S and HPFH.

NEWBORN SCREENING

Newborn screening programs have the ability to diagnose hemoglobinopathies at birth, thus allowing for early implementation of preventive care. The US newborn screening program began screening for SCD in 1975. Since 2006, all 50 states have adopted universal screening for SCD. However, screening for α- and β-thalassemia is not yet universal in all states. (33)(34)

Advancements in diagnostic technology have led to the adoption of isoelectric focusing or high-performance liquid chromatography for detecting hemoglobinopathy in newborn screening programs. Both technologies have high sensitivity and specificity for the diagnosis of SCD and severe thalassemia. (35)

Interpretation of newborn screening results is based on the order in which the hemoglobin types are reported (Table 2). The diagnostic report lists the primary hemoglobin type detected with the highest concentration, followed by subsequent variants in descending order based on the amount present. For example, a child with a normal hemoglobin phenotype would have the results "FA," signifying the predominant hemoglobin at birth first, hemoglobin F, followed by the smaller amount of hemoglobin A that is detected.

A child with hemoglobin SS would have the results "FS," again signifying the predominant hemoglobin at birth, hemoglobin F, followed by the lesser amount of hemoglobin S that is being produced, and *no* hemoglobin A.

Table 2. Newborn Screen Hemoglobinopathy Interpretation

NEWBORN SCREEN RESULT	PRESUMED DIAGNOSIS
FA	Normal
FAS	Sickle cell trait
FS	Sickle cell anemia: Hemoglobin SS or hemoglobin S/β^0 thalassemia
FSA	Hemoglobin S/β^+ thalassemia
FSC	Hemoglobin SC disease
F	Transfusion-dependent β-thalassemia (β-thalassemia major)
FA Barts	Hemoglobin H disease

Newborn screening results for hemoglobinopathy. The diagnostic newborn screening report lists the primary hemoglobin type detected with the highest concentration, followed by subsequent variants in descending order based on the amount present. F=hemoglobin, A=hemoglobin A, S=hemoglobin S, C=hemoglobin C, Barts=tetramer of γ-globin chains.

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Carriers of hemoglobin S will have the result "FAS," signifying the higher production of normal adult hemoglobin A compared with the amount of hemoglobin S being produced.

Newborn screening results for a child with severe β-thalassemia (ie, Cooley anemia) would show only hemoglobin F and no hemoglobin A, thus signifying the complete lack of normal adult hemoglobin production. Newborns with the β-thalassemia trait often go undetected. Severe α-thalassemia (hemoglobin H disease) can be detected, as the screening methods can detect the fast migrating hemoglobin Barts bands. However, α-thalassemia trait and α-thalassemia carriers often go undetected as the small amount of hemoglobin Barts produced is often below the level of detection. (35)

Universal newborn screening in the United States is an important public health advancement; however, states often have limited capacity to implement systems to ensure access to comprehensive follow-up care. Therefore, it is imperative that neonatologists and general pediatricians are equipped at interpreting the results and appropriately counseling patients on the diagnoses.

CONCLUSIONS

Hemoglobinopathies in neonates encompass a broad range of hemoglobin disorders with a wide array of phenotypes. Children can present perinatally, around 6 to 12 months of age, or later in life, depending on the specific mutations inherited. As a result, neonatologists often have the opportunity to diagnose these disorders. Understanding the physiology of hemoglobin development, having an awareness of the clinical spectrum of hemoglobinopathies, along with the ability to accurately interpret newborn screening results, can lead to early diagnoses and better outcomes in children with more severe phenotypes. As novel treatments such as gene therapy continue to arrive on the scene, prompt diagnosis will be paramount to providing children with early access to these transformative therapies.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the developmental biology of hemoglobin types.
- Know the clinical and laboratory features of neonatal hemoglobinopathies, including the thalassemias.
- Know the indications for and approaches to screening for hemoglobinopathies in the newborn population.

References

1. Higgs DR. The molecular basis of α-thalassemia. *Cold Spring Harb Perspect Med*. 2013;3(1):a011718
2. Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. *N Engl J Med*. 2021;384(8):727–743
3. Thein SL. The molecular basis of β-thalassemia. *Cold Spring Harb Perspect Med*. 2013;3(5):a011700
4. Harteveld CL, Achour A, Arkesteijn SJG, et al. The hemoglobinopathies, molecular disease mechanisms and diagnostics. *Int J Laboratory Hematol*. 2022;44(suppl 1): 28–36
5. Wang X, Thein SL. Switching from fetal to adult hemoglobin. *Nat Genet*. 2018;50(4):478–480
6. Forget BG. Progress in understanding the hemoglobin switch. *N Engl J Med*. 2011;365(9):852–854
7. Taylor SM, Parobek CM, Fairhurst RM. Haemoglobinopathies and the clinical epidemiology of malaria: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(6):457–468
8. Aidoo M, Terlouw DJ, Kolczak MS, et al. Protective effects of the sickle cell gene against malaria morbidity and mortality. *Lancet*. 2002;359(9314):1311–1312
9. Vichinsky EP. Changing patterns of thalassemia worldwide. *Ann N Y Acad Sci*. 2005;1054:18–24
10. Fucharoen S, Viprakasit V. Hb H disease: clinical course and disease modifiers. *Hematology Am Soc Hematol Educ Program*. 2009:26–34
11. Weatherall DJ. The definition and epidemiology of non-transfusion-dependent thalassemia. *Blood Rev*. 2012;26 Suppl 1:S3–6
12. Angastiniotis M, Modell B, Englezos P, Boulyjenkov V. Prevention and control of haemoglobinopathies. *Bull World Health Organ*. 1995;73(3):375–386
13. Chui DH. Alpha-thalassemia: Hb H disease and Hb Barts hydrops fetalis. *Ann N Y Acad Sci*. 2005;1054:25–32
14. Lal A, Vichinsky E. The clinical phenotypes of alpha thalassemia. *Hematol Oncol Clin North Am*. 2023;37(2):327–339
15. Vichinsky EP. Alpha thalassemia major–new mutations, intrauterine management, and outcomes. *Hematology Am Soc Hematol Educ Program*. 2009:35–41
16. Carr S, Rubin L, Dixon D, Star J, Dailey J. Intrauterine therapy for homozygous alpha-thalassemia. *Obstet Gynecol*. 1995;85(5 Pt 2):876–879
17. Pongtanakul B, Sanpakit K, Chongkolwatana V, Viprakasit V. Normal cognitive functioning in a patient with Hb Bart's hydrops successfully cured by hematopoietic SCT. *Bone Marrow Transplant*. 2014;49(1):155–156
18. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. *Blood*. 2011;118(13):3479–3488
19. Cappellini MD, Taher AT. The use of luspatercept for thalassemia in adults. *Blood Adv*. 2021;5(1):326–333
20. Leonard A, Tisdale JF, Bonner M. Gene therapy for hemoglobinopathies: beta-thalassemia, sickle cell disease. *Hematol Oncol Clin North Am*. 2022;36(4):769–795
21. Locatelli F, Lang P, Wall D, et al. CLIMB THAL-111 Study Group. Exagamglogene autotemcel for transfusion-dependent β-thalassemia. *N Engl J Med*. 2024;390(18):1663–1676
22. CDC. Sickle Cell Disease: Data and Statistics. https://www.cdc.gov/sickle-cell/data/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/sicklecell/data.html. Published 2024. Accessed May 4, 2024.

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23. Bibek Karna SKJ, Al Zaabi E. Hemoglobin C disease. In: Island T, ed.: StatPearls; 2024: https://www.ncbi.nlm.nih.gov/books/NBK559043/. Accessed May 1, 2024.
24. Serjeant GR. The natural history of sickle cell disease. *Cold Spring Harb Perspect Med*. 2013;3(10):a011783
25. Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise. *J Clin Invest*. 2007;117(4):850–858
26. Bainbridge R, Higgs DR, Maude GH, Serjeant GR. Clinical presentation of homozygous sickle cell disease. *J Pediatr*. 1985;106(6):881–885
27. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med*. 1986;314(25):1593–1599
28. Sharma A, Boelens JJ, Cancio M, et al. CRISPR-Cas9 Editing of the HBG1 and HBG2 Promoters to Treat Sickle Cell Disease. *N Engl J Med*. 2023;389(9):820–832
29. Gallagher PG. Diagnosis and management of rare congenital nonimmune hemolytic disease. *Hematology Am Soc Hematol Educ Program*. 2015;2015:392–399
30. Mansouri A, Lurie AA. Concise review: methemoglobinemia. *Am J Hematol*. 1993;42(1):7–12
31. Alonso-Ojembarrena A, Lubián-López SP. Hemoglobin M disease as a cause of cyanosis in a newborn. *J Pediatr Hematol Oncol*. 2016;38(3):173–175
32. Bollekens JA, Forget BG. Delta beta thalassemia and hereditary persistence of fetal hemoglobin. *Hematol Oncol Clin North Am*. 1991;5(3):399–422
33. Consensus conference. Newborn screening for sickle cell disease and other hemoglobinopathies. *JAMA*. 1987;258(9):1205–1209
34. US Preventive Services Task Force. Screening for sickle cell disease in newborns: recommendation statement. *Am Fam Physician*. 2008;77(9):1300–1302
35. Hoppe CC. Newborn screening for non-sickling hemoglobinopathies. *Hematology Am Soc Hematol Educ Program*. 2009:19–25

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INDEX OF SUSPICION

Term Neonate With Right-Sided Limb Swelling: A Potpourri of Etiology and Complication

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CASE PRESENTATION

A male neonate weighing 2,800 g (appropriate for gestational age) is born to a nonconsanguineous couple at 39 weeks of gestation via vaginal delivery in an outside hospital. The mother is 28 years old, and antenatal ultrasonography findings are normal. Her blood group is A negative, and she has had no additional antenatal tests. The neonate is vigorous at birth with Apgar scores of 9 and 9 at 5 and 10 minutes, respectively. Anthropometric measurements at birth include length and head circumference of 52 cm and 37 cm, respectively, both between the 50th and 95th percentiles as per a modified Fenton chart. Physical and systemic examination findings at birth are normal and the infant is receiving exclusive breast milk.

On day 3 after birth, diffuse jaundice is noted. An evaluation reveals the infant's blood type is B positive and the mother's blood group O negative, the direct Coombs test is positive, and total serum bilirubin (25 mg/dL [427.6 µmol/L]) is within the exchange transfusion range (cutoff, as per 2022 American Academy of Pediatrics [AAP] hyperbilirubinemia management guideline: 22 mg/dL [376.3 µmol/L]). A double-volume exchange transfusion via umbilical venous catheter is performed in an outside hospital and intensive phototherapy is initiated. The neonate is discharged from the hospital on day 8, exclusively breastfeeding. However, he is later readmitted because of swelling in the right lower extremity, which progressively enlarged over the next 48 hours. In addition, diffuse swelling is observed in the right scapular region and 2 distinct areas of swelling on the scalp. The neonate is referred to our institution for further management on day 12 after birth.

Examination findings at admission to our NICU are summarized in Table 1.

DIFFERENTIAL DIAGNOSIS

- Venous thrombosis: Catheter-induced thrombosis, sepsis, prothrombotic disorder
- Immunodeficiency disorder: Primary immune deficiency disorders, chronic granulomatous disease
- Disseminated bacterial sepsis
- Portal vein thrombosis

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Table 1. Clinical Examination of the Neonate at the Time of Admission to the NICU

EXAMINATION	FINDINGS
Vital signs	
Temperature	97.7°F (36.5°C)
Heart rate	170 beats/min
Respiratory rate	64 breaths/min
Capillary refill time	<3 s
Oxygen saturation	88%
General examination	Marked pallor, jaundice, and edema of the right lower extremity
Head	Two well-defined erythematous, tender cystic fluctuant lesions in the scalp in the right parietal region
Right shoulder	Ill-defined tender erythematous swelling measuring 5×7 cm with normal axillary artery pulsation
Right upper limb	Normal brachial, radial, and ulnar artery pulsation
Right lower limb	Ill-defined tender swelling extending from the upper thigh including the foot, associated with paucity of movements. Femoral and dorsalis pedis pulsation well felt. Limb perfusion: normal
Rest of musculoskeletal examination (contralateral limb and back)	Normal
Central nervous system	Lethargic with poor spontaneous activity, cry, and tone secondary to bilirubin-induced neurologic dysfunction
Abdomen	Hepatosplenomegaly with liver palpable 4 cm below right costal margin, firm and non-tender. Spleen palpable 3 cm below the left costal margin.
Respiratory and cardiovascular system	Normal

FURTHER COURSE

Noninvasive respiratory support was initiated (continuous positive airway pressure of 6 and fraction of inspired oxygen 30%) and milk feeding started via an orogastric tube. The cause of multiple abscesses, limb edema, and anemia was evaluated with laboratory and radiologic investigations (Table 2).

Following initial evaluation, the comorbidities included multiple scalp abscesses, right shoulder abscess, osteomyelitis of the right femur, right lower limb venous thrombosis, portal vein thrombosis, and anemia secondary to sepsis. A multidisciplinary team including neonatology, orthopedic surgery, hematology, radiology, occupational therapy, social work, and lactation counselor were involved in the care of the neonate.

Management of venous thrombosis of limb and portal vein thrombosis included the use of unfractionated heparin with a bolus dose of 28 IU/kg followed by a maintenance dose of 30 IU/kg given for 48 hours (1), with close monitoring of activated partial thromboplastin time as recommended by the pediatric hematologist, and guided by serial limb ultrasonography and Doppler imaging. The neonate was switched to low-molecular-weight heparin after 48 hours at a dose of 1.5 mg/kg administered subcutaneously twice a day, which was continued for 12 weeks. (1) The infant's lower limb was elevated and scrotal support was provided. Monitoring for limb edema, limb girth, and arterial pulsation was conducted every 3 hours because of the risk of compartment syndrome. The neonate had no evidence of ascites or features of decompensated liver disease, with the portal vein and lower limb thrombus resolving by day 21 after birth with the aforementioned measures.

For the management of sepsis, the neonate was initially started on intravenous antibiotics meropenem and amikacin based on a local antibiogram, and ultrasound-guided aspiration of abscess with orthopedic intervention for right femur osteomyelitis was planned.

Scalp abscesses were drained on day 14, following which there was no recurrence. Shoulder abscess required 2 settings of ultrasound-guided drainage on days 20 and 22, after which the abscess subsided. The purulent matter culture from these sites showed methicillin-resistant *Staphylococcus aureus* (MRSA) growth which required broadening the antibiotic spectrum to vancomycin and gentamycin.

On confirmation of the right femur osteomyelitis with fracture noted on radiography and ultrasonography (Fig 3), surgical debridement of right femur granulation tissue with insertion of antibiotic (vancomycin and gentamycin)–impregnated stimulant beads was done during surgery. Granulation tissue culture sent during surgery grew MRSA. On discussion with the microbiologist, intravenous linezolid was added to the regimen, which along with gentamycin, was continued for 6 weeks. Limb movement gradually improved, with normal movements achieved by day 66 after birth (Fig 4).

Early intervention was initiated and the parents were encouraged to participate in the neonate's care throughout the NICU stay. Further evaluation for an underlying prothrombotic state, other immunodeficiencies, brain magnetic resonance imaging, and brainstem-evoked response

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Table 2. Laboratory and Radiological Investigations of the Index Neonate

LABORATORY INVESTIGATION	PATIENT VALUE	NORMAL REFERENCE RANGE
Complete blood cell count		
Hemoglobin, g/dL (g/L)	7.3 (73)	13.4–23.7 (134–237)
Packed cell volume (%)	21.7	45–65
Mean corpuscular volume, μm^3 (fL)	80.9 (80.9)	90–112 (90–112)
Mean corpuscular hemoglobin, pg	25.4	32.5
Mean corpuscular hemoglobin concentration, g/dL	30	32.1
Red cell distribution width, %	16.3	16.18 ± 1.23
Reticulocyte count, %	1.2	0–1
Total leukocyte count, /μL ($\times 10^9$/L)	42,800 (42.8)	5000–20,000 (5–200)
Platelets, $\times 10^3$/μL ($\times 10^9$/L)	6 (6)	1.5–4.7 (1.5–4.7)
Peripheral smear	Microcytic hypochromic anemia. No evidence of hemolysis	
C-reactive protein, mg/dL (mg/L)	11.3 (113)	Up to 1 (10)
Blood culture	Methicillin-resistant *Staphylococcus aureus*	
Blood glucose, mg/dL (mmol/L)	94 (5.2)	60–125 (3.3–6.9)
Blood gas (venous)		
pH	7.36	7.35–7.45
Pco_2, mm Hg (kPa)	44 (5.8)	35–45 (4.7–6)
Po_2 (mm Hg)	46 (6.1)	50–70 (6.6–9.3)
Bicarbonate, mEq/L (mmol/L)	22.8	18–24
Liver enzymes		
Aspartate aminotransferase, U/L (μkat/L)	34 (0.57)	9–80 (0.15–1.34)
Alanine aminotransferase, U/L (μkat/L)	22 (0.37)	13–45 (0.22–0.75)
Total bilirubin, mg/dL (μmol/L)	2.51 (42.9)	
Direct bilirubin, mg/dL (μmol/L)	1.51 (25.9)	
Prothrombin time (s)/activated partial thromboplastin time (s)/international normalized ratio	14.7/27/1.07	
Total protein, g/dL (g/L)	5.8 (58)	6–7.5 (60–75)
Serum albumin, g/dL (g/L)	2.6 (26)	3–5 (30–50)
Serum lactate, mg/dL (mmol/L)	7.21 (0.8)	4.5–19.8 (0.5–2.2)
Thyroid-stimulating hormone, μIU/mL (mIU/L)	5.040	Up to 20
Cranial ultrasonography	Two discrete scalp abscesses. Normal brain parenchyma and cerebral Doppler	
Ultrasonography of the abdomen and kidney-ureter-bladder with a screening of the pancreas (Fig 1)	Normal Doppler-showing hypoechoic thrombus in the main portal vein, left portal vein. No ascites. No liver abscess	
Ultrasonography of the right lower limb (Fig 5)	Complete thrombus within the right common femoral vein, right external iliac vein, and a small part of common iliac vein, with normal flow and compressibility of superficial femoral, popliteal, and tibial veins	
Ultrasonography of the right shoulder (Fig 5)	Abscess in a subcutaneous and intramuscular plane near right shoulder	
Ultrasonography of hip (Fig 2)	Osteomyelitis of the right femur, with a collection of 0.5 mL of purulent material in the femoral area. The hip joint is normal	
Fundus evaluation	Normal	
Immunodeficiency evaluation	Nitroblue tetrazolium test 98% burst cells. (normal)	
	Dihydrorodamine test normal	
	Lymphocyte subset analysis normal	
	B memory and naïve T cell analysis normal	

audiometry for bilirubin-induced neurologic dysfunction was planned on follow-up. At the time of discharge 74 days after birth, the neonate weighed 4,350 g with normal movements at the right shoulder, right upper and lower limb (Fig 6), no purulent matter collection on ultrasonography, and normal neurodevelopment; he continues to receive follow-up care.

The investigations of the neonate from admission to discharge have been summarized in Table 3.

FINAL DIAGNOSIS

MRSA sepsis with multiple abscesses and right femur osteomyelitis and venous thrombosis in a neonate after umbilical venous catheterization.

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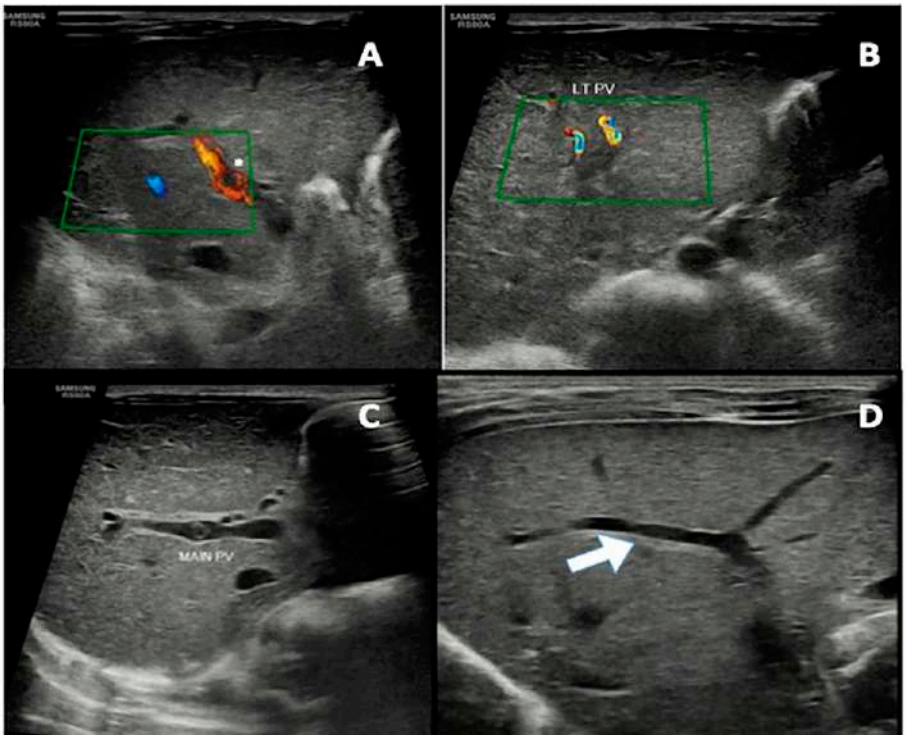


Figure 1. Color Doppler showing hypoechoic thrombus. A. Main portal vein. B. Left portal vein. C. Ultrasonographic scan in B-mode showing thrombus in the main portal vein. D. Resolution of thrombus after treatment.

DISCUSSION

Neonatal thrombosis is a rare complication occurring in 5.1 in 100,000 live births, with more than 95% of cases having an identifiable risk factor. (2) Catheter-related thrombosis and bloodstream infection–associated venous thrombosis (VT) account for 9.2% of cases. (3) The index neonate had an umbilical venous catheter inserted for exchange transfusion and subsequently developed MRSA infection, compounding the risk of VT.

Neonates differ in concentration, production rate of most coagulation factors, and their ability to regulate thrombin and plasmin, placing them at risk for a relative prothrombotic state. Sepsis causes further dysregulation of the innate immune process, predisposing them to immune thrombosis. (4) The clinical manifestations vary from swelling, hyperemia, tenderness, and cyanosis in cases of lower extremity thrombosis to hepatosplenomegaly and ascites with impaired liver function in portal hypertension.

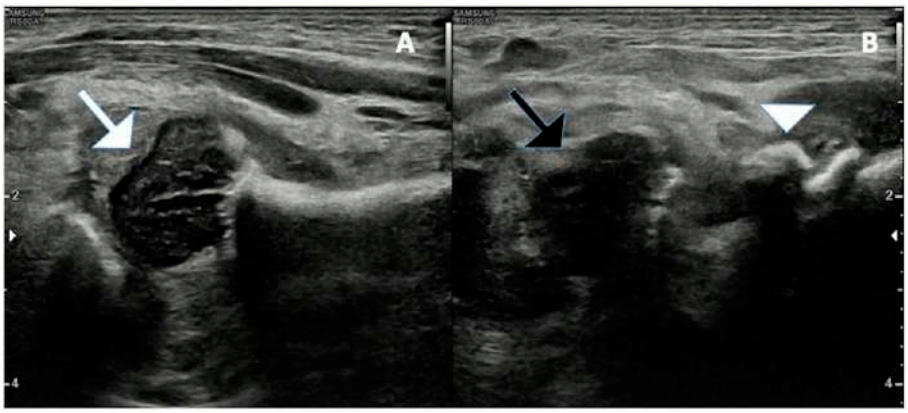


Figure 2. Ultrasonographic scans. A. Normal left femoral head contour (white arrow). B. Distorted irregular right femoral head contour (black arrow) with collection around it, with irregular cortex of the shaft of femur (white arrowhead).

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Figure 3. Radiographs. A. Signs of osteomyelitis of right femur with periosteal reaction and cortical irregularity (white arrow) with soft tissue edema surrounding it. B. Antibiotic beads (STIMULANT) in right hip joint after arthrotomy and purulent matter drainage and joint lavage.

The management of VT in neonates is largely based on consensus guidelines. Factors such as severity of thrombosis, possibility of organ or limb impairment, presence of comorbidities, and risk for bleeding influence the decision to treat or to observe VT. (5) The first-line therapy commonly used for catheter and sepsis-related VT is typically unfractionated or low-molecular-weight heparin administered for 3 months. (6) Thrombolysis therapy with recombinant tissue plasminogen activator is reserved for life-, limb-, and organ-threatening events, including pulmonary embolism with hemodynamic compromise. Drugs such as streptokinase and urokinase are used only on a selective case-to-case basis. (7)

The annual incidence of osteomyelitis in developed countries is around 4 to 5 cases per 100,000 children, with *S aureus* being the most common organism isolated. (8) This is an emergency condition requiring arthrotomy for purulent matter drainage along with the insertion of cemented antibiotic beads. (9) This was similarly done in our case for prolonged local delivery of antibiotics, as the bone sequestrum and its surroundings make it difficult for intravenous antibiotics to penetrate. AAP recommends combination therapy with parenteral vancomycin plus nafcillin or oxacillin plus gentamycin for 14 days for *S aureus* bacteremia and 4 to 6 weeks in case of osteoarticular infection. (10) In the index case, after arthrotomy, the orthopedic team advised conservative management of the pathologic fracture of the femur with passive limb immobilization in the extended position, no application of harness was suggested. Oral paracetamol was given for pain relief.

Etiologic evaluation for VT and multiple abscesses in the neonatal period is quite challenging. Although inherited



Figure 4. A. Central figure of the infant showing right lower limb swelling from thigh to foot caused by osteomyelitis of the femur and cellulitis (methicillin-resistant *Staphylococcus aureus* infection). B. Postarthrotomy purulent matter drainage and intravenous antibiotics led to subsiding of the swelling of the right lower limb.

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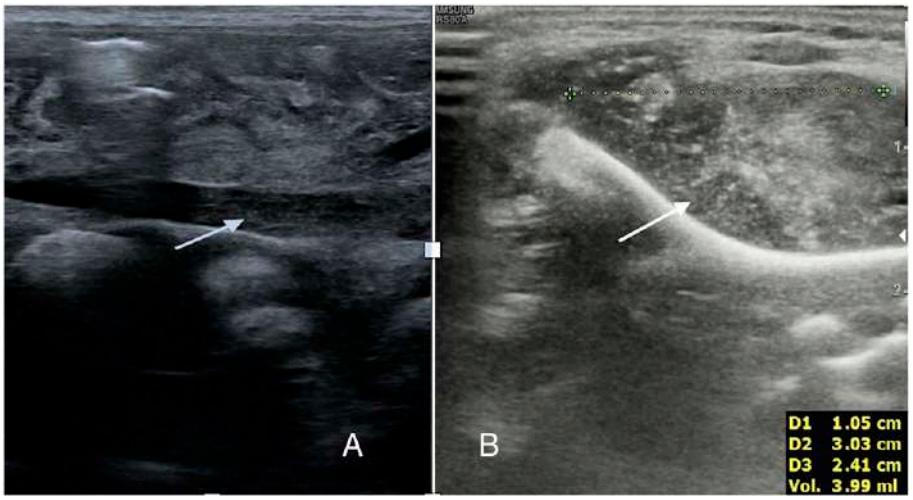


Figure 5. Ultrasonographic scans. A. Thrombosis of the right external iliac vein and common femoral vein (white arrow). B. Scapular abscess (white arrow).

thrombophilia appears to be present in some neonates with both catheter- and sepsis-related VT, the role of thrombophilia testing in neonates with VT is still debatable as it does not appear to acutely influence the type or duration of treatment. Hence, the American Society of Hematology guidelines endorse thrombophilia testing mainly in neonates with non–catheter-related VT. (11) For better management and prognostication of such unusual cases, early screening and diagnosis of primary immune deficiency particularly that of phagocytic cell defect is of paramount importance in neonates with multiple abscesses. (12)



Figure 6. Neonate at the time of discharge.

VT, including portal VT, can be prevented by properly inserting an umbilical venous catheter and preventing displacement of the catheter tip into the portal venous system which might have occurred in our index case. (13) Prevention of MRSA infection with strict infection control practices is of paramount importance as each additional day of exposure in an uncolonized infant increases the acquisition risk of MRSA infection by 6%. (14)

Data on the prognosis of VT in neonates are lacking and follow-up studies in general have shown mortality ranging from 5% to 18%. (15) Long-term complications such as post-thrombotic syndrome and portal hypertension with portal vein thrombosis are to be identified early and managed as per standard recommendations.

LESSONS FOR THE CLINICIAN

- Critically ill neonates and those with sepsis are at major risk of venous thromboembolic events.
- Timely intervention for venous thrombosis can salvage limbs and prevent organ-threatening complications.
- Neonatal osteomyelitis is an emergency that requires prompt medical and surgical intervention.
- Multifocal abscess in a neonate due to MRSA needs to be evaluated for immunodeficiency and needs multidisciplinary care and long-term follow-up

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Table 3. Table Summarizing the Course in the Hospital

DAY AFTER BIRTH	12	14	19	23	28	46	51
Hemoglobin, g/dL (g/L)	7.3 (73)	6.7 (67)	9.4 (94)	7.7 (77)	10 (10)	12.1 (121)	9.3 (93)
Total leukocyte count, /μL ($\times 10^9$/L)	42,800 (42)	25,900 (25.9)	12,800 (12.8)	19,300 (19.3)	16,100 (16.1)	28,200 (28.2)	21,600 (21.6)
Platelet, $\times 10^3$/μL ($\times 10^9$/L)	60 (60)	20 (20)	2.0 (2.0)	4.0 (4.0)	4.2 (4.2)	4.2 (4.2)	4.0 (4.0)
Body fluid culture and sensitivity							
Blood		Methicillin-resistant *Staphylococcus aureus* (MRSA)					
Cerebropinal fluid culture	No growth						
Urine culture	No growth						
Purulent matter culture	MRSA			MRSA			
Ultrasonography of the lower limb (Fig 2)	The right common femoral vein, right external iliac vein, and a small part of the common iliac vein show complete thrombus		Resolution of thrombus in femoral and iliac vein. Persistent thrombosis of the left portal vein and umbilical vein		Intramuscular and subcutaneous edema in the right thigh. Collection of 0.5 mL purulent matter around hip joint associated with cortical irregularities of the shaft of the femur		Bilateral lower limb arterial and venous Doppler shows normal flow velocity
Radiography (Fig 3)					Signs of osteomyelitis of right femur with periosteal reaction with cortical irregularity with edema	Antibiotic beads (stimulant) in the right hip joint after arthrotomy and purulent matter drainage and joint lavage	
Ultrasonography of the shoulder	Heterogenous hypoechoic collection of size 5–6 mL just superior to the right spine of the scapula in the infraspinatus muscle and extending through the spine of the scapula	Abscess in the subcutaneous and intramuscular plane of 20–25 mL near the right shoulder		Right parascapular collection in the form of heterogenous hypoechoic (uniquified 20 mL)	An organized thick collection of 0.3 mL near the right scapular region		Resolution of collection, mild inflammation present

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causative infectious agents and pathogenesis of osteomyelitis and septic arthritis.
- Know the clinical and laboratory features and differential diagnosis of osteomyelitis and septic arthritis.
- Know the management and complications of osteomyelitis and septic arthritis.

Acknowledgments

The authors thank Dr Sangeeta Ravat, Dean, Seth GS Medical College, and KEM Hospital, Mumbai, India, for granting permission for publication.

References

1. Sparger KA, Gupta M. Neonatal thrombosis. In: Eric C. Eichenwald, Anne R Hansen, Camilia R.Martin, Ann R. Stark, Navin Jain, eds. *Cloherty and Stark's Manual of Neonatal Care*. South Asia, India: Wolters Kluwer, 2021: 616–634
2. Nowak-Göttl U, von Kries R, Göbel U. Neonatal symptomatic thromboembolism in Germany: two year survey. *Arch Dis Child Fetal Neonatal Ed*. 1997;76(3):F163–7
3. Park CK, Paes BA, Nagel K, Chan AK, Murthy P; Thrombosis and Hemostasis in Newborns (THiN) Group. Neonatal central venous catheter thrombosis: diagnosis, management and outcome. *Blood Coagul Fibrinolysis*. 2014;25(2):97–106
4. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol*. 2013;13(1):34–45 Epub 2012 Dec 7.
5. Greenway A, Massicotte MP, Monagle P. Neonatal thrombosis and its treatment. *Blood Rev*. 2004;18(2):75–84
6. Chan AK, Monagle P. Updates in thrombosis in pediatrics: where are we after 20 years? *Hematology Am Soc Hematol Educ Program*. 2012;2012:439–443
7. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e737S–e801S
8. Saavedra-Lozano J, Falup-Pecurariu O, Faust SN, et al. Bone and joint infections. *Pediatr Infect Dis J*. 2015;36(8):788–799
9. Fisher R. Neonatal osteomyelitis. *NeoReviews*. 2011;12(7):e374–e380
10. McMullan BJ, Campbell AJ, Blyth CC, et al. Clinical Management of *Staphylococcus aureus* bacteremia in neonates, children, and adolescents. *Pediatrics*. 2020;146(3):e20200134
11. Klaassen IL, van Ommen CH, Middeldorp S. Manifestations and clinical impact of pediatric inherited thrombophilia. *Blood*. 2015; 125(7):1073–1077
12. O'Connell AE. Primary immunodeficiency in the NICU. *Neoreviews*. 2019;20(2):e67–e78
13. Kim JH, Lee YS, Kim SH, Lee SK, Lim MK, Kim HS. Does umbilical vein catheterization lead to portal venous thrombosis? Prospective US evaluation in 100 neonates. *Radiology*. 2001;219(3):645–650
14. Dong Y, Glaser K, Speer CP. New threats from an old foe: methicillin-resistant *Staphylococcus aureus* infections in neonates. *Neonatology*. 2018;114(2):127–134
15. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics*. 1995; 96(5 Pt 1):939–943

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INDEX OF SUSPICION

Term Neonate With Macrosomia and Coarse Facies: An Overlapping Etiology of Fetal Overgrowth

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THE CASE

A male infant is born to a 27-year-old gravida 3, para 1 mother with 2 spontaneous abortions and 1 living child from a planned spontaneous pregnancy to nonconsanguineous parents. The cause of 2 spontaneous abortions has not been evaluated and the older child is 3 years old with normal growth and development.

At 38 weeks of gestation, an ultrasonographic evaluation shows polyhydramnios with an amniotic fluid index of 28 and an estimated fetal weight of 4,500 g. There is no history of maternal diabetes, obesity, or exposure to medications, smoking, alcohol, or recreational drugs. No other previous scan reports are available. She is referred to our center for delivery.

The infant is born at 39 weeks via cesarean delivery. His birthweight is 4,314 g, length is 52 cm, head circumference is 36 cm, and the ratio of upper to lower segment is 1.6:1. Apgar scores are 9 and 9 at 1 and 5 minutes, respectively, and he does not require any resuscitation after birth. Birth anthropometry on World Health Organization growth charts suggested macrosomia, with all measurements between 2 and 3 standard deviations (SD).

Physical examination of the head confirms macrocephaly with 1×1.5 cm anterior fontanel without overriding sutures and posterior fontanel admitting the fingertip. The infant has coarse facial features with frontal bossing, bilateral infratemporal hollowing, broad bulbous nose with flat philtrum, hypertelorism, and short broad nasal root, macroglossia with a furrowed tongue, low-set ears, left ear skin tag, thick and everted lower lip, and postaxial polydactyly (left upper and lower limbs) with overlapping toes with a furrow. (Fig 1) There is no hepatomegaly, splenomegaly, or renomegaly, and systemic examination findings are normal. He passes meconium within 24 hours after birth and is exclusively breastfed.

DIFFERENTIAL DIAGNOSIS

- Congenital hypothyroidism
- Fetal overgrowth syndromes:
  A) Beckwith-Wiedemann spectrum
  B) Simpson-Golabi-Behmel syndrome

AUTHOR DISCLOSURES Drs Raghavendra, Goyal, Mhatre, and Haribalakrishna have disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Figure 1. Clinical features noted in the index case: coarse facial features with frontal bossing, bilateral infratemporal hollowing, broad bulbous nose with flat philtrum, hypertelorism, and short broad nasal root, macroglossia with a furrowed tongue, low-set ears, left ear skin tag, thick and everted lower lip, and postaxial polydactyly (left upper and lower limbs) with overlapping toes with a furrow.

C) Sotos syndrome

- Infant of diabetic mother
- Storage disorder:
  A) Mucopolysaccharidosis
  B) Lysosomal storage diseases

ACTUAL DIAGNOSIS

The neonate underwent an extensive evaluation for the cause of fetal overgrowth (Table 1).

FINAL DIAGNOSIS

Although genetic studies for fetal overgrowth and evaluation for inborn errors of metabolism had normal results, based on the temporal findings on examination, antenatal ultrasonography, and abnormal thyroid function test results, a final diagnosis of congenital hypothyroidism with clinical Beckwith-Wiedemann spectrum is made (clinical score of 4—macroglossia [2], polyhydramnios [1], birth weight >2 SD above the mean [1]).

DISCUSSION

Overgrowth syndromes are characterized by excessive postnatal growth and tall stature, which is more than an individual's genetic potential. This can be prenatal, postnatal, or segmental. Prenatal overgrowth, which was seen in this index neonate, refers to those who are born large for

Table 1. Investigations for Fetal Overgrowth in Index Neonate

INVESTIGATION	RESULT
Complete blood cell count	Normal
Blood glucose	Normal
Serum calcium	Normal
Radiographs of long bone (Fig 2)	No other abnormality apart from left upper and lower limb postaxial polydactyly Normal bone age
Ultrasonography of abdomen	No evidence of hepatosplenomegaly or renomegaly
Cranial ultrasonography	Normal
Echocardiography	Normal
Ophthalmologic examination	No cataracts or cherry red spots
Inborn error of metabolism screening	Negative
Karyotype	Normal
Clinical exome sequencing for fetal overgrowth	Normal
Methylation study	Normal
Thyroid function test	
Thyroid-stimulating hormone, μIU/mL (mIU/L)	−17.17 (normal range, 0.72–11)
Free thyroxine, ng/dL (pmol/L)	1.25 (16.09) (normal range, 0.83–3.09 [10.68–39.77)
Free triiodothyronine, pg/mL (pmol/L)	3.710 (0.06) (normal range, 2.3–6.6 [0.04–0.10])
Ultrasonography of the thyroid	Normal
Maternal hemoglobin A1C	Normal
Histopathology of placenta	Normal

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Figure 2. Radiographs of upper and lower limbs demonstrating normal bone age and polydactyl.

gestational age, either macrosomic (>4,000 g) or with length and weight greater than the 97th percentile. (1) These neonates can continue to have accelerated postnatal growth or follow a normal pace. The etiology commonly includes maternal diabetes, Beckwith-Wiedemann spectrum (BWSp), Simpson-Golabi-Behmel, and Sotos syndrome. BWSp is the most common genetic overgrowth syndrome, with a prevalence of 1 in 10,340. (2)

Abnormal proliferation of chondrocytes and differentiation into hypertrophic chondrocytes are seen. These are mediated by hormones such as parathyroid hormone–related protein, growth hormone, insulinlike growth factor 1, fibroblast growth factor, and thyroid. (3) Various key causes of overgrowth syndromes seen in the neonatal period are summarized in Table 2.

Diagnosis of BWSp is made using the European Network of Congenital Imprinting Disorders scoring system (Table 3). (4) If the neonate has BWSp based on the scoring system but has a negative test result, it is reasonable to refer to a BWSp expert for further evaluation and management. The index neonate has a clinical score of 4 (macroglossia [2], polyhydramnios [1], birth weight >2 SD above the mean [1]).

The unique co-occurrence of congenital hypothyroidism and overgrowth has been reported in a few case reports and is often described as primary acquired hypothyroidism. It has been hypothesized that the gene governing the production of thyroxin-binding globulin might be in close proximity to the one that governs the production of thyroxin and also to the gene suppressing the manifestations of BWSp. (5) Congenital hypothyroidism was reported in another case of a neonate with Sotos syndrome. (6)

In infants with suspected BWSp, the first-tier test is a methylation study which may show a gain of methylation on IC1 (maternal), loss of methylation on IC2 (maternal), or both (paternal UPD); or a loss of chromosomal segment on 11p15.5 (along with its proper methylation) in nearly 75% cases. (4) If the methylation study is negative, sequence analysis or gene-targeted deletion-duplication analysis of CDKN1C for loss of function on the maternal allele will detect ~5% of cases with no family history and ~40% of cases with positive family history. (4) Karyotype may pick cytogenetic duplication, inversion, or translocation of 11p15.5 in less than 1% of cases. (4) However, a chromosomal array (single nucleotide polymorphism based) can pick small chromosomal deletions and duplications in ~20% of cases. (4) When peripheral blood sample test results are negative, other tissues such as saliva, skin, or the

Table 2. Important Causes of Overgrowth Syndromes in the Neonatal Period

ETIOLOGY	CLINICAL CHARACTERISTICS	GENETIC BASIS
Beckwith-Wiedemann spectrum	Hemihyperplasia, macroglossia, organomegaly, macrosomia, omphalocele	Chromosome 11p15.5 mutation
Simpson-Golabi-Behmel syndrome	Macrosomia, macrocephaly, coarse facial features, hypertelorism, ear lobe creases, macrostomia, macroglossia, nipple anomalies, postaxial polydactyly	Chromosome Xq26.2 (GPC3 mutation)
Sotos syndrome	Prominent forehead, down slanting palpebral fissures, malar flushing, macrosomia, joint laxity	*NDD1* mutation
Perlman	Macrosomia, macrocephaly, hypotonia, abdominal wall weakness, nephromegaly, cryptorchidism	*DIS3L2* mutation
Weaver syndrome	Broad forehead and face, almond-shaped and down slanting palpebral fissures, wide philtrum, excess loose skin, camptodactyly, stuck-on protruding chin	*EZH2* gene
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, macrocephaly, enlarged penis, supernumerary nipples, joint hypermobility, pectus excavatum	PTEN-related disorders
MOMO syndrome	Macrosomia, obesity, macrocephaly, ocular abnormalities	*LINC00237* gene
Primrose syndrome	Enlarged and calcified external ears, distal muscle wasting, microphthalmia, cataract, hypothyroidism, corpus callosum agenesis	*ZBTB20* mutation

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Table 3. Diagnosis of Beckwith-Wiedemann Spectrum (BWSp) is as per the European Network of Congenital Imprinting Disorders Scoring System (4)

FINDINGS	POINTS
Cardinal features	
Macroglossia	2
Exomphalos	2
Lateralized overgrowth	2
Multifocal and/or bilateral Wilms tumor	2
Persistent hyperinsulinism (>1 wk)	2
Characteristic pathology: adrenal cortex cytomegaly, placental mesenchymal dysplasia, pancreatic adenomatosis	2
Minor findings	
Birthweight >2 standard deviations above the mean	1
Facial naevus simplex	1
Polyhydramnios	1
Ear creases and/or pits	1
Transient hyperinsulinism (<1 wk)	1
Characteristic tumor: Unilateral Wilms tumor, neuroblastoma, rhabdomyosarcoma, hepatoblastoma, adrenocortical carcinoma, or pheochromocytoma	1
Nephromegaly and/or hepatomegaly	1
Umbilical hernia and/or diastasis recti	1
Clinical Score	**Interpretation**
4+	BWSp confirmed
2–3	Diagnosis by genetic testing
0–1	BWSp rejected

hypertrophied tissue may identify low-level mosaic genetic and epigenetic changes within 11p15.5 in up to 10% of affected patients. (7)

Short-term complications include the risk of hypoglycemia and macroglossia-related feeding difficulty, the risk of apnea, and persistent drooling. In the long term, the current guidelines of the American Association of Cancer Research recommend uniform surveillance for all overgrowth syndromes with an increased propensity for Wilms tumor (WT) and hepatoblastoma. (8) The overall risk of malignancy among BWSp patients is approximately 7.5%: 4% WT, 1% hepatoblastoma, 0.5% rhabdomyosarcoma, 0.5% neuroblastoma, and ~1.3% all other tumors. (4)(9) α-fetoprotein (AFP) testing is currently lacking in the international consensus statement as infants with BWSp often have higher AFP levels. (7) The neurocognitive development of BWSp patients is similar to that in the general population, and therefore no additional surveillance is recommended for development. (10)

Further Course

The infant has no complications during the hospital stay, is exclusively breastfeeding at the time of discharge, and receives close follow-up by pediatrics genetics. At 3 months and 6 months of follow-up, the coarse facial features and dysmorphism persist. Repeat abdominal ultrasonography shows no evidence of organomegaly and thyroid function tests have normalized with thyroid supplementation at 10 µg/kg per day. The infant continues to exclusively breastfeed, with weight, length, and head circumference between 2 and 3 SD with normal development and continues to receieve close monitoring.

Lessons for the Clinician

- Fetal overgrowth syndromes such as the BWSp present with inherited health concerns and risk of tumor predisposition necessitating prompt diagnosis at the earliest suspicion.
- The association of congenital hypothyroidism leads to overlapping clinical findings because of the complex interplay of genetic, epigenetic, and hormonal factors in growth, which complicates the diagnosis.
- A combination of methylation studies, karyotype, and clinical exome sequencing might still underdiagnose those with BWSp, and these infants are required to be followed up closely for growth and risk of malignancy.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the diagnostic implications of single vs. multiple anomalies.
- Know the indications, limitations, and techniques for newborn screening for genetic disorders.

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- Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER [vertebrae, anus, trachea, esophagus, and limbs) association and DiGeorge syndrome).
- Know the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis, and how to interpret test results.

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References

1. Yachelevich N. Generalized overgrowth syndromes with prenatal onset. *Curr Probl Pediatr Adolesc Health Care*. 2015;45(4):97–111
2. Mussa A, Russo S, De Crescenzo A, et al. Prevalence of Beckwith-Wiedemann syndrome in north west of Italy. *Am J Med Genet A*. 2013;161a(10):2481–2486
3. Hartmann C, Tabin CJ. Dual roles of Wnt signaling during chondrogenesis in the chicken limb. *Development*. 2000;127(14):3141–3159
4. Shuman C, Kalish JM, Weksberg R, et al. Beckwith-Wiedemann syndrome. In: Adam MP, Feldman J, Mirzaa GM editors. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 2000:1993–2024.
5. Leung AKC, McArthur RG. EMG-syndrome and hypothyroidism. *Clin Genet*. 1989;36(4):269
6. Verma A, Salehi P, Hing A, Curda Roberts AJ. Sotos syndrome with a novel mutation in the NSD1 gene associated with congenital hypothyroidism. *Int J Pediatr Adolesc Med*. 2021;8(3):191–194
7. Brioude F, Kalish JM, Mussa A, et al. Expert consensus document: clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol*. 2018;14(4):229–249
8. Kalish JM, Doros L, Helman LJ, et al. Surveillance recommendations for children with overgrowth syndromes and predisposition to wilms tumors and hepatoblastoma. *Clin Cancer Res*. 2017;23(13):e115–e122
9. Brioude F, Toutain A, Giabicani E, Cottereau E, Cormier-Daire V, Netchine I. Overgrowth syndromes: clinical and molecular aspects and tumour risk. *Nat Rev Endocrinol*. 2019;15(5):299–311
10. Barisic I, Boban L, Akhmedzhanova D, et al. Beckwith Wiedemann syndrome: a population-based study on prevalence, prenatal diagnosis, associated anomalies and survival in Europe. *Eur J Med Genet*. 2018;61(9):499–507

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MATERNAL-FETAL CASE STUDIES

Alloimmunization in Pregnancy: Implications for the Fetus and Neonate

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ABSTRACT

Blood group or red cell alloimmunization occurs when a pregnant patient has produced antibodies to a blood group antigen possessed by the fetus and not possessed by the pregnant patient. Maternal antibodies are usually produced as an immune response to fetal-maternal bleeding or blood product transfusion. Prevention remains the most important strategy to avoid the formation of maternal antibodies or alloimmunization. Maternal alloimmunization may result in transplacental passage of these antibodies into the fetal circulation and the potential for fetal or neonatal hemolysis and anemia. Red cell alloimmunization can result in significant perinatal morbidity and mortality. Management of alloimmunization in pregnant patients should be protocol-driven. Current strategies for assessment and therapies allow for more thorough and less invasive management with risks to mother and fetus.

THE CASE

A 37-year-old gravida 5, para 3-0-2-2-4 pregnant woman who conceived through in vitro fertilization had anti-D antibodies with a titer of 1:1,024 at 10 weeks' gestation. In her last pregnancy, antibody screening had been negative, and she had received antepartum Rh immune globulin at 28 weeks' gestation. Her neonate was Rh positive and also received intravenous immunoglobulin (IVIG) after delivery. Kleihauer-Betke testing performed after delivery to assess for fetomaternal hemorrhage had negative results.

After the detection of anti-D antibodies in her current pregnancy, her husband had D-antigen genotyping and was found to be heterozygous for D antigen. Given that there was a 50% chance of her fetus being Rh positive, she underwent amniocentesis for fetal D-antigen genotyping. The amniocentesis results demonstrated her fetus also to be D positive. In light of the low gestational age with high risk of early-onset hemolytic disease of the fetus, Doppler assessments of the fetal middle cerebral artery peak systolic velocity (MCA PSV), maternal plasmapheresis, and IVIG therapy began at 13 weeks' gestation.

CASE PROGRESSION

Her MCA PSV was initially just below the threshold of 1.5 multiples of the median (MOM), providing reassurance that there was no significant fetal anemia.

AUTHOR DISCLOSURE Dr MacGregor has disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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She received 2 treatments of plasmapheresis and then began weekly IVIG therapy until 26 weeks' gestation. Her antibody titers decreased after plasmapheresis and IVIG treatments. However, after IVIG at 26 weeks' gestation, her anti-D antibody titer again increased to 1:1,024. The MCA PSV was elevated (>1.5 MOM) at 27 weeks, 2 days' gestation, and she was scheduled for fetal blood sampling with possible transfusion. She received betamethasone for fetal lung maturity before her first transfusion. The blood bank, maternal-fetal medicine, and neonatology specialists coordinated a multidisciplinary preparation for a percutaneous umbilical blood sampling (PUBS) procedure.

At the time of her PUBS, a sinusoidal fetal heart rate pattern was noted, consistent with severe fetal anemia (Fig 1). PUBS was performed and the initial fetal hemoglobin concentration was 4.1 g/dL (41 g/L). The fetus was given a transfusion and had a post-transfusion hemoglobin concentration of 13.7 g/dL (137 g/L). The MCA PSV was 91 cm/s before the transfusion and 44 cm/s after the transfusion.

The patient was scheduled to undergo repeat transfusion at 29 weeks, 4 days' gestation because the MCA PSV increased to greater than 1.5 MOM and a decrease in fetal hemoglobin was calculated with advancing gestational age. The patient received a second course of betamethasone before the planned second PUBS. Fetal blood sampling was repeated, and the fetal hemoglobin was 6.5 g/dL (65 g/L). During the procedure (Fig 2), a prolonged fetal bradycardia occurred before transfusion was initiated, which prompted an urgent delivery.

MATERNAL AND NEONATAL OUTCOMES

The pregnant patient underwent an urgent cesarean delivery under spinal anesthesia without complications. Her postpartum course was unremarkable.

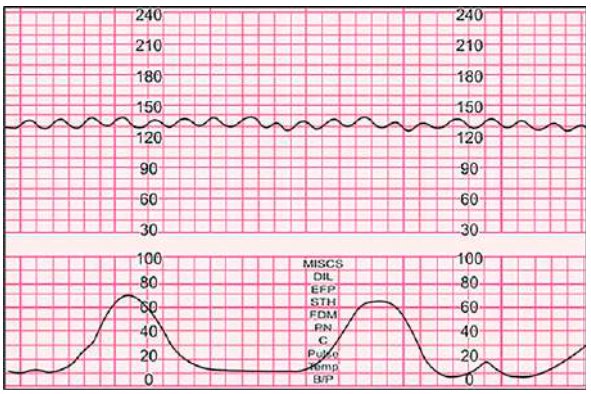


Figure 1. Fetal sinusoidal fetal heart rate at 27 weeks and 2 days' gestation.



Figure 2. Percutaneous umbilical blood sampling with needle inserted into the placental cord insertion of the posterior placenta.

A male infant was born at 29 weeks and 4 days' gestation via cesarean delivery, with Apgar scores of 6 and 8 at 1 and 5 minutes, respectfully. The etiology of the fetal bradycardia was most consistent with fetal vasospasm during the PUBS procedure. He was noted to have respiratory distress that was treated with continuous positive airway pressure. He had a birthweight of 1,788 g (82nd percentile). His admission hemoglobin concentration was 7.0 g/dL (70 g/L).

In the NICU, the newborn received 2 doses of surfactant and was weaned to room air by 24 hours of age. He required 5 packed red blood cell transfusions during his hospitalization in addition to phototherapy. He did not receive IVIG and did not require an exchange transfusion. He was eventually discharged at 41 days of age, with a hemoglobin concentration of 11.2 g/dL (112 g/L).

DISCUSSION

RhD alloimmunization occurs when RhD-positive cells enter the circulation of an RhD-negative person, stimulating an immune response with resulting production of anti-D antibodies. The frequency of RhD-negative blood type varies. The highest incidence is in the Basque region of Spain (30%–35%). The incidence in other populations varies, with an incidence of 15% in white North Americans and Europeans, 8% in African Americans, 5% in Asian Indians, and less than 1% in non-Indian Asians. (1)

Most commonly, RhD alloimmunization occurs from transplacental fetomaternal bleeding during pregnancy, if the pregnant patient is RhD positive and the fetus is RhD negative. Worldwide, the incidence of RhD alloimmunization in pregnancy is 0.4% to 2.7%. (1) The incidence of RhD alloimmunization historically was as high as 13% to 16% in RhD-positive pregnant patients. RhD immune globulin is administered to all RhD-positive pregnant patients to reduce the frequency of alloimmunization by

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decreasing the likelihood of an immune response to RhD-negative red blood cells. (1) Administration of RhD immune globulin to pregnant persons with RhD-positive fetuses reduces the incidence of RhD alloimmunization to 0.4% to 1.8%.(1) The addition of routine antepartum RhD immune globulin administration to all RhD-negative pregnant patients at the beginning of the third trimester further reduces the risk of RhD alloimmunization to 0.12% to 0.2%. (1)

In infants born to pregnant persons with RhD alloimmunization, 50% will be unaffected, 25% will be unaffected prenatally but require postnatal treatment of hyperbilirubinemia (phototherapy or exchange transfusion), and 25% will have severe fetal anemia requiring delivery or fetal transfusion to avoid intrauterine fetal demise. (2) Proper surveillance and treatment during pregnancy have greatly reduced morbidity and mortality associated with RhD hemolytic disease of the fetus and newborn (HDFN). (2)

Screening for red cell alloimmunization in pregnant persons is routinely performed at the initial presentation for obstetric care. (1) If antibodies are present, identification of the specific antibody is routinely performed. If the antibody is against blood group antigens associated with increased risk for HDFN, additional evaluation is required. (3) For pregnant patients, after identification of antibodies associated with HDFN, management involves a stepwise approach to identify whether the fetus is at risk for HDFN and to determine the degree of risk (Table). (3)

ASSESSMENT OF FETAL RISK AND ANEMIA

Paternal Antigen Testing

After identifying antibodies in the pregnant person that may be associated with HDFN, the next step would be to assess for paternal antigen status. If the father of the fetus is homozygous for the antigen, the fetus will inherit the concerning blood group antigen and be at risk for developing HDFN. If the father is heterozygous for the antigen, there is a 50% risk that the fetus will inherit the antigen and be at risk. If the father is negative for the antigen, the fetus will not inherit the antigen and will not be at risk for HDFN. In this case, no further assessment and surveillance is required. (3)

Table. Stepwise Assessment of a Pregnant Person with Blood Group Alloimmunization

Step 1: Antibody screening shows positive finding in the pregnant person
Step 2: If antibody screening result positive, perform antigen genotype testing in partner
Step 3: If partner is antigen heterozygous, determine fetal risk with antigen testing using cell-free DNA or amniocentesis
Step 4: If fetal antigen is positive or unknown, obtain serial antibody titer measurements in the pregnant person
Step 5: If critical fetal antibody titer is reached, assess fetal anemia with weekly MCA PSV Dopplers
Step 6: If MCA PSV >1.5 MOM for gestational age, perform fetal PUBS with possible transfusion

MCA PSV=middle cerebral artery peak systolic velocity, MOM=multiples of the median.

Fetal Antigen Testing

In patients with heterozygous or unknown paternal antigen status, it is possible to assess fetal antigen status using either amniocentesis or noninvasive prenatal screening with fetal cell-free DNA from blood specimens from the pregnant person. Cell-free DNA testing can be performed for D, c, C, E, Kell, and Duffy A antigens. (4) The sensitivity and specificity of cell-free DNA testing is very high. If the pregnant patient desires further confirmation, amniocentesis for fetal genotype can be performed. (4)

Antibody Titer Assessment

If the fetus is at risk based on 1) fetal antigen testing (amniocentesis or cell-free DNA testing), 2) paternal antigen testing without fetal antigen testing, or 3) unknown paternal antigen testing, serial assessment of antibody titers in the pregnant person is performed every 4 weeks. The critical titer, or titer at which the fetus is considered at risk for hemolytic anemia, varies among blood banks and most commonly is 1:16 or 1:32. (3) Fortunately, for most pregnant patients with alloimmunization, the titer does not reach the level at which additional evaluations are required before delivery. (3)

Assessment of Severity of Fetal Anemia

If the titer of the pregnant person reaches the critical level, additional evaluations are required. In the past, serial amniocentesis was performed every 2 to 4 weeks to assess the amniotic fluid δ OD450. The δ OD450 reflects the spectrophotometric deflection due to amniotic fluid bilirubin, which is produced with fetal hemolysis. Doppler measurement of fetal MCA PSVs has replaced amniotic fluid δ OD450 for the assessment of fetal anemia. As the fetal hemoglobin concentration decreases, the fetal blood becomes less viscous, resulting in increased velocity that can be reliably measured with Doppler ultrasonography.(5)(6) MCA PSV has similar or better sensitivity and specificity compared with amniotic fluid δ OD450 and is noninvasive. MCA PSV is considered normal if it is less than 1.5 MOM for gestational age. (5)(6) If the MCA PSV is above 1.5 MOM, there is an increased risk of severe fetal anemia requiring additional diagnostic evaluation. MCA PSV is usually performed weekly. (3)(5)(6)

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Fetal Blood Sampling and Transfusion

The standard approach to suspected fetal anemia with MCA PSV greater than 1.5 MOM at preterm gestational age less than 34 weeks is to perform fetal blood sampling with possible transfusion. (5)(6) Under ultrasound guidance, a spinal needle is introduced, preferably into the umbilical cord at the placental cord insertion, and immediate fetal assessment is performed to determine whether to proceed with transfusion (Fig 2). The procedure is usually performed with local anesthesia and occasionally sedation of the pregnant person. The amount of blood that is transfused is based on a calculation using the estimated fetal weight, the estimated fetoplacental blood volume, hematocrit of the transfused blood, and the initial hematocrit of the sampled fetal blood. The goal of transfusion would be to increase the hemoglobin to approximately 15 g/dL (150 g/L). After 34 weeks' gestation, antenatal steroids should also be considered, as an option for lung maturity (if not already given) and delivery. (3)

Delivery

Timing of delivery for patients with titers remaining below the critical titer is based on routine obstetric management. For patients with a critical titer resulting in weekly MCA PSVs and not requiring fetal transfusion, delivery is usually recommended at 37 weeks' gestation.(3) For patients requiring frequent fetal transfusions, delivery is typically earlier.

UNCOMMON MANAGEMENT CONSIDERATIONS

This case illustrates an uncommon problem in a pregnant patient with blood group alloimmunization. The case required the uncommon use of plasmapheresis and IVIG early in the second trimester given the high risk of early onset of HDFN. Data correlating MCA PSVs in the early second trimester with fetal anemia are limited; however, there have been some extrapolations of these data in unusual and severe circumstances. These values could be used to suggest the risk of fetal anemia before 18 weeks' gestation. (5)(7)

One case series suggested that pregnant patients with risk for, or suspected to have, severe fetal anemia before 18 weeks' gestation could be treated with plasmapheresis and IVIG therapy to reduce the risk of fetal hemolysis and anemia. (8) Plasmapheresis was used to reduce maternal antibody. IVIG was used to bind to the neonatal Fc receptor (FcRn), reducing transfer of antibodies across the placenta, and decreasing circulating antibodies. There is currently a multicenter, open-label study evaluating a monoclonal antibody in pregnant patients at high risk for early-onset severe HDFN. The monoclonal antibody specifically targets the neonatal FcRn with similar actions as suggested for IVIG, specifically, reduced transfer of IgG across the placenta and reduced circulating antibody. The advantage of the monoclonal antibody compared with IVIG is that the monoclonal antibody has greater targeted blockage of the FcRN. (8)

CONCLUSIONS

A systematic approach to the assessment and management of alloimmunization in pregnancy reduces the risk of fetal morbidity and mortality associated with HDFN. In the future, it is possible that plasmapheresis and IVIG or monoclonal antibody–blocking neonatal Fc receptors could be more widely used to reduce the need for, and risks of, invasive procedures including fetal blood sampling and fetal transfusion.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of maternal immunologic diseases and their management.
- Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow measurements, in assessment of fetal conditions and well-being.
- Understand the rationale, interpretation, and limitations of maternal detection of fetal movement, of the biophysical profile, the non-stress test, and the contraction stress test as means of assessing fetal well-being.
- Know the diagnostic evaluation and perinatal management of fetal-maternal blood group incompatibility.

References

1. Prevention of RhD Alloimmunization during pregnancy Practice Bulletin No. 181 American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2017;130:e57–e70
2. Koelewijn JM, Vrijkotte TGM, van der Schoot CE, Bonsel GJ, de Haas M. Effect of screening for red cell antibodies, other than anti-D, to detect hemolytic disease of the fetus and newborn: a population study in the Netherlands. *Transfusion*. 2008;48(5):941–952
3. Management of RhD Alloimmunization during pregnancy: practice bulletin no 192. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2018;113:e82–e89
4. Alford B, Landry BP, Hou S, et al. Validation of a non-invasive prenatal test for fetal RhD, C, c, E, K and Fy^a antigens. *Sci Rep*. 2023;13(1):12786

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5. Mari G, Deter RL, Carpenter RL, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. *N Engl J Med*. 2000;342(1):9–14
6. Oepkes D, Seaward PG, Vandenbussche F, et al. DIAMOND Study Group. Doppler ultrasonography versus amniocentesis to predict fetal anemia. *N Engl J Med*. 2006;355(2):156–164
7. Tongsong T, Wanapirak C, Sirichotiyakul S, Tongprasert F, Srisupundit K. Middle cerebral artery peak systolic velocity of healthy fetuses in the first half of pregnancy. *J Ultrasound Med*. 2007;26(8):1013–1017
8. Ruma MS, Moise KJ, Jr, Kim E, et al. Combined plasmapheresis and intravenous immune globulin for the treatment of severe maternal red cell alloimmunization. *Am J Obstet Gynecol*. 2007;196(2):138.e1–138.e6

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VISUAL DIAGNOSIS

Unusual Dermatologic Findings in an Extremely Low Birthweight Infant: The Genetic Diagnosis

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THE CASE

An extremely low-birthweight (ELBW) preterm neonate presents with unusual dermatologic findings, atypical hair features, and extremity abnormalities.

PRENATAL AND BIRTH HISTORIES

- Born to a 26-year-old gravida 3, para 2 woman with normal results on prenatal laboratory screening.
- Parents are from similar regions in Central America; no known consanguinity.
- The prenatal course is notable for limited prenatal care.
- Female infant born at 28 3/7 weeks' gestation following premature rupture of membranes, fetal bradycardia, and concern for placental abruption.
- Born in a vaginal delivery and had decreased tone and respiratory distress. The infant required positive pressure ventilation initially and then underwent intubation; Apgar score of 2, 4, 6, and 8 at 1, 5, 10, and 15 minutes, respectively.
- Sepsis risk factors: Group B *Streptococcus* status unknown with inadequate treatment.

PRESENTATION (NEWBORN DAY)

Vital Signs

- Heart rate: 170 beats/min
- Respiratory rate: 35 breaths/min
- Blood pressure: 39/24 (mean 31) mm Hg
- Oxygen saturation: 98% on synchronized intermittent mechanical ventilation peak inspiratory pressure of 18 mm cm H_2O, positive end-expiratory pressure of 5 cm Hg, rate of 40 breaths/min, and fraction of inspired oxygen of 0.55
- Temperature: 97.7°F (36.5°C)

Physical Examination

- Birthweight 860 g (20th percentile), head circumference 24 cm (15th percentile)
- Head: Normocephalic with significant bruising; normal, open, flat fontanelles; prominent hyperpigmented eyebrows, scalp alopecia with hyperpigmentation, fused eyes

AUTHOR DISCLOSURE Dr Carter is vice-chair of the American College of Medical Genetics Education Committee. Dr Saxonhouse has attended meetings with the support of Pediatrix. Ms Ricker has disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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- Oral cavity: Pink mucosae, intact palate, natal teeth
- Lungs: Clear, equal breath sounds; moderate retractions, good aeration throughout
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallops
- Abdomen: Soft, nontender, nondistended; no hepatosplenomegaly
- Genitourinary: Normal preterm female genitalia; patent anus
- Skin: Severely friable, gelatinous, and immature skin out of proportion to her level of prematurity
- Extremities: Large broad toes, long fingers
- Neurologic: Active, symmetric Moro reflex, normal strength and tone

Laboratory Studies

- Complete blood cell count: White blood cell count 9.9 × 10^3/μL (9.9 × 10^9/L), hemoglobin 13.7 g/dL (8.5 mmol/L), hematocrit 42%, platelet 170 × 10^3/μL (170 × 10^9/L)
- Blood culture: Sent

Progression

The infant required increased total fluid volume administration for high insensible losses and persistent hypernatremia. Cranial ultrasonography at 1 and 4 days of age did not show any abnormalities. The blood culture had no growth. At 2 days of age, enteral feedings were initiated and she tolerated advancement, though her feedings were later discontinued due to acute illness. Echocardiography was performed at 4 days of age because of increased work of breathing and low blood pressure to rule out a patent ductus arteriosus; the findings were normal except for a small atrial septal defect. Given her worsening skin appearance with standard incubator humidity weaning protocol, she was maintained at high levels of humidity (75%–85%) during the first week after birth. Topical emollients as well as topical and systemic antifungal medications were used to treat advancing erythematous skin changes. Her skin findings at 5 days of age and 15 days of age are shown in Figs 1 and 2.

Differential Diagnosis

- Immature premature skin
- Congenital candidiasis
- Congenital ichthyosis
- Genetic condition

Actual Diagnosis

Given this infant's presentation, an initial working diagnosis of congenital ichthyosis was pursued. Dias et al (1) describe infants with autosomal recessive congenital ichthyosis (ARCI) as often being born prematurely and encased in a collodion membrane that typically transitions to a scaling, erythematous skin within 2 to 4 weeks. Affected infants are at risk for high insensible losses and resulting electrolyte abnormalities. (1)



Figure 1. Infant at 5 days of age demonstrating inflammatory skin changes.

With various forms of congenital ichthyosis and limited documented cases of ELBW infants, the patient did not fit within a specific ARCI type. Thus, the genetics team was



Figure 2. Infant at 15 days of age demonstrating inflammatory skin changes.

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consulted at 7 days of age and a microarray was sent. The single nucleotide polymorphism microarray results were reported at 18 days of age and demonstrated the absence of heterozygosity in an area of epidermal growth factor receptor (EGFR) presence. Given the clinical overlap with her features, autosomal recessive *EGFR* variant was considered as a possible diagnosis. The infant underwent rapid trio exome sequencing.

Trio whole exome sequencing revealed homozygous pathogenic variants in EGFR, c.1631 + 1 G>A, in intron 13 of the gene, which are novel canonical splice site variants. Results confirmed the diagnosis of autosomal recessive EGFR-related inflammatory skin and bowel disease.

During the rest of her hospitalization, the infant's skin underwent various inflammatory changes including scaling, sloughing, seeping, and pustule development (Fig 3), and her once prominent eyebrows began to "peel" off (Fig 4). She underwent multiple courses of systemic antibiotic and antifungal treatment of presumed and identified infections (including *Serratia marcescens* in the blood and tracheal cultures and *Enterococcus fecalis* from a swab of a chest skin lesion). She required increased total fluid volumes (as high as 260 mL/kg per day) for persistent electrolyte derangements but did not have any gastrointestinal issues. She had persistent and profound hypotension that required inotropic support and was found to have adrenal insufficiency treated with hydrocortisone. She had decreased urine output and developed acute renal failure. At 39 days of age, she developed significant bradycardic and apneic events and required intubation. Brain magnetic resonance imaging showed devastating progressive severe encephalomalacia, extensive cystic periventricular leukomalacia, and ventriculomegaly. She ultimately died of multiorgan system failure at 6 weeks of age.



Figure 3. Inflammatory skin changes at 21 days of age.



Figure 4. Inflammatory skin and eyebrow changes at 35 days of age.

What the Experts Say

Neonatal inflammatory skin and bowel disease are associated with homozygous disease-causing variants of the *EGFR* gene. (2)(3)(4)(5) Receptors found along the cellular surface bind to epidermal growth factor and other factors, inducing the processes responsible for cell survival, proliferation, and differentiation. (2)(3) Mutations of this gene are commonly expressed in neoplastic disease. (2)(3)(4)(5) Neonatal inflammatory skin and bowel disease is a rare condition. (2) This presents the challenge of limited amount of literature on the neonatal disease course and management, specifically in the premature ELBW infant.

Lemos et al (2) describe a similar case of a premature female infant born at 28 weeks' gestation with intrauterine growth restriction and subsequent ELBW, failure to thrive, fragile skin with recurrent infections, and distinctive atypical craniofacial features. The infant is described as having

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had "persistently erythematous and friable skin" with electrolyte derangements requiring high total fluid volumes and frequent replacement therapy. This infant had significant congenital heart defects (ventricular disproportion with hypoplastic left ventricle, severe aortic arch hypoplasia, complete atrioventricular septal defect, and a patent ductus arteriosus), as well as nephromegaly and severe brain injury (bilateral ventricular hemorrhage with severe periventricular and subcortical white matter lesion, cerebellum atrophy, and a mega cisterna magna). Genetic testing resulted in a homozygous variant of the *EGFR* gene. The infant ultimately died of related cardiac failure at 3 months of age.

In another report, Alruwaithi and Sherlock (4) describe a 5-year-old female patient born at 27 weeks' gestation with ELBW, similarly fragile skin, recurrent infections, failure to thrive, cardiac defects (large ventriculoseptal defect and mitral valve regurgitation), renal enlargement, and multiple phenotype abnormalities (thick eyebrows, alopecia, arachnodactyly). This child is believed to be the longest living of the few known ELBW patients with this EGFR disease–causing variant with a course notable for failure to thrive and recurrent hospitalizations for skin and gastrointestinal infections at the time her case was documented. (4)

Most recently, Labbouz et al (3) described a 685 g male infant born at 26 4/7 weeks' gestation with a homozygous *EGFR* gene mutation, further delineated as a missense mutation resulting in loss of function. (3) The infant's clinical presentation was similar to the other published cases, however, with necrotizing enterocolitis and rectal perforation as well. This infant developed acute renal failure and subsequent metabolic acidosis, and died at 11 months of age. (3) In their report, Labbouz et al also provide a detailed description of clinical findings in the literature on patients with *EGFR* gene variants for comparison. Only 3 of the 8 clinical cases reviewed were of infants born at less than or equal to 28 weeks' gestation, and all had the same homozygous *EGFR* gene mutation of c. 1283G>A (p. Gly428Asp).

The differential diagnoses of immature premature skin and congenital candidiasis were inconsistent with persistent inflammatory changes found on this infant's examination. *Candida* was also unlikely because the skin did not show improvement with antifungal treatments. Congenital ichthyosis was also determined to be inconsistent with this infant's findings as it describes thick, scaly plates of skin that shed over time.

Lessons for the Clinician

- Neonatal inflammatory skin and bowel disease due to disease-causing variants in EGFR should be included in the differential diagnosis when encountering unusual dermatologic findings in the ELBW infant.
- Early involvement of genetics consultants with rapid whole exome sequencing should be considered in premature infants with obscure inflammatory skin changes.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the indications, limitations, and techniques for newborn screening for genetic disorders.

References

1. Dias JV, Cardoso K, Prado SN, Cavaco H. Congenital ichthyosis: a multidisciplinary approach in a neonatal care unit. *BMJ Case Rep.* 2023;16(2):e250077
2. Lemos M, Gonçalves JS, Correia CR, Maria AT. Neonatal inflammatory skin and bowel disease type 2: a very rare disease associated with EGFR mutation. *JPNIM.* 2021;10(1):e100123
3. Labbouz S, Keegan G, King T. Neonatal cutaneous inflammatory syndrome associated with homozygous epidermal growth factor receptor mutation. *Pediatr Dermatol.* 2023;40(1):171–175
4. Alruwaithi M, Sherlock M. A210 neonatal inflammatory skin and bowel disease caused by a homozygous egfr mutation: a case report and review of the medical literature. *J Can Assoc Gastroenterol.* 2018; 1(suppl_1):367–368
5. Scaltriti M, Baselga J. The epidermal growth factor receptor pathway: a model for targeted therapy. *Clin Cancer Res.* 2006;12(18):5268–5272

ANSWER KEY FOR NOVEMBER 2024 NEOREVIEWS

Disorders of Coagulation in the Newborn:
1. B; 2. E; 3. A; 4. C; 5. D

Thrombotic Disorders in the Newborn:
1. A; 2. E; 3. D; 4. C; 5. D

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COMPLEX FETAL CARE

Pallister-Killian Syndrome

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CASE PRESENTATION

A 27-year-old gravida 6, para 2 woman was referred to our fetal care center at 26 3/7 weeks' gestation because of the presence of multiple fetal anomalies.

The maternal and pregnancy histories were notable for substance use (tetrahydrocannabinol, alcohol, methamphetamines), depression, herpes labialis (on suppressive therapy), exercise-induced asthma, and normocytic anemia. She established late prenatal care at 25 1/7 weeks' gestational age (GA) at which time, anatomic ultrasonography showed sonographic age of 23 3/7 weeks' gestation (estimated fetal weight [EFW], 2nd percentile), polyhydramnios (amniotic fluid index [AFI], 28.6 cm), omphalocele, shortened femurs (measuring 17 2/7 weeks' gestation), concave chest, and stomach positioned above the diaphragm. These findings prompted referral to our fetal care center for further evaluation and multidisciplinary consultation.

Anatomic ultrasonography at our institution at 26 3/7 weeks' gestation revealed multiple congenital anomalies including left-sided congenital diaphragmatic hernia (CDH) containing liver, bowel, and stomach (lung-to-head circumference ratio [LHR], 0.95); small omphalocele containing liver and bowel; severe shortening of the long bones especially the femurs (9 weeks behind dates); right hand deformity; severe polyhydramnios (maximum vertical pocket, 11 cm); small chest cavity; generalized skin thickening; flattened facial profile; interocular distance suggesting hypertelorism; fetal growth restriction (EFW <2nd percentile); and elevated umbilical artery Dopplers (4.7–6.3). Fetal magnetic resonance imaging (MRI) performed the same day showed a large left-sided CDH containing the left hepatic lobe and stomach associated with rightward displacement of the heart and severely diminished fetal lung predictors (LHR 0.76 and observed/expected [O/E] LHR 29.5%). Although severe fetal growth restriction makes predictive interpretation more challenging, calculated total fetal lung volume (TFLV) was 4.3 mL (normal TFLV at this GA is 34.8 mL [range 22.5–44.2 mL]), O/E TFLV was 12%, and no significant left fetal lung tissue was identified. Additional fetal MRI findings included a small omphalocele containing liver; deformity of the right hand; generalized prominence of the extra-axial spaces; and widely spaced eye globes and thick coarseness of the facial soft tissues (Fig 1). Fetal

AUTHOR DISCLOSURES Dr Chock works under grants from Stanford University Global Health, The Cerebral Palsy Alliance Research Foundation and the Harman Faculty Scholars award, The NICHD Neonatal Research Network, and Nationwide Children's Hospital. She has attended meetings with the support of the University of California Los Angeles and the Newborn Brain Society, and is a board member of the Newborn Brain Society. Dr Dahmoush has attended meetings with the support of Stanford University. Dr Matalon works under grants from the NIH Genomics Research to Elucidate the Genetics of Rare Disease Consortium and Stanford MCHRI and Department of Pediatrics. They have delivered paid expert testimony for Dinsmore & Shohl, LLP, and Sutton Pierce, LLC. Ms Smith works under a grant from, and has attended meetings with the support of, Stanford Medicine Children's Health. Drs Chitkara, Barth, Matalon, Herring, and Hintz have disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AFI	amniotic fluid index
CDH	congenital diaphragmatic hernia
EFW	estimated fetal weight
GA	gestational age
LHR	lung-to-head circumference ratio
MRI	magnetic resonance imaging
O/E	observed/expected
PKS	Pallister-Killian syndrome
TFLV	total fetal lung volume

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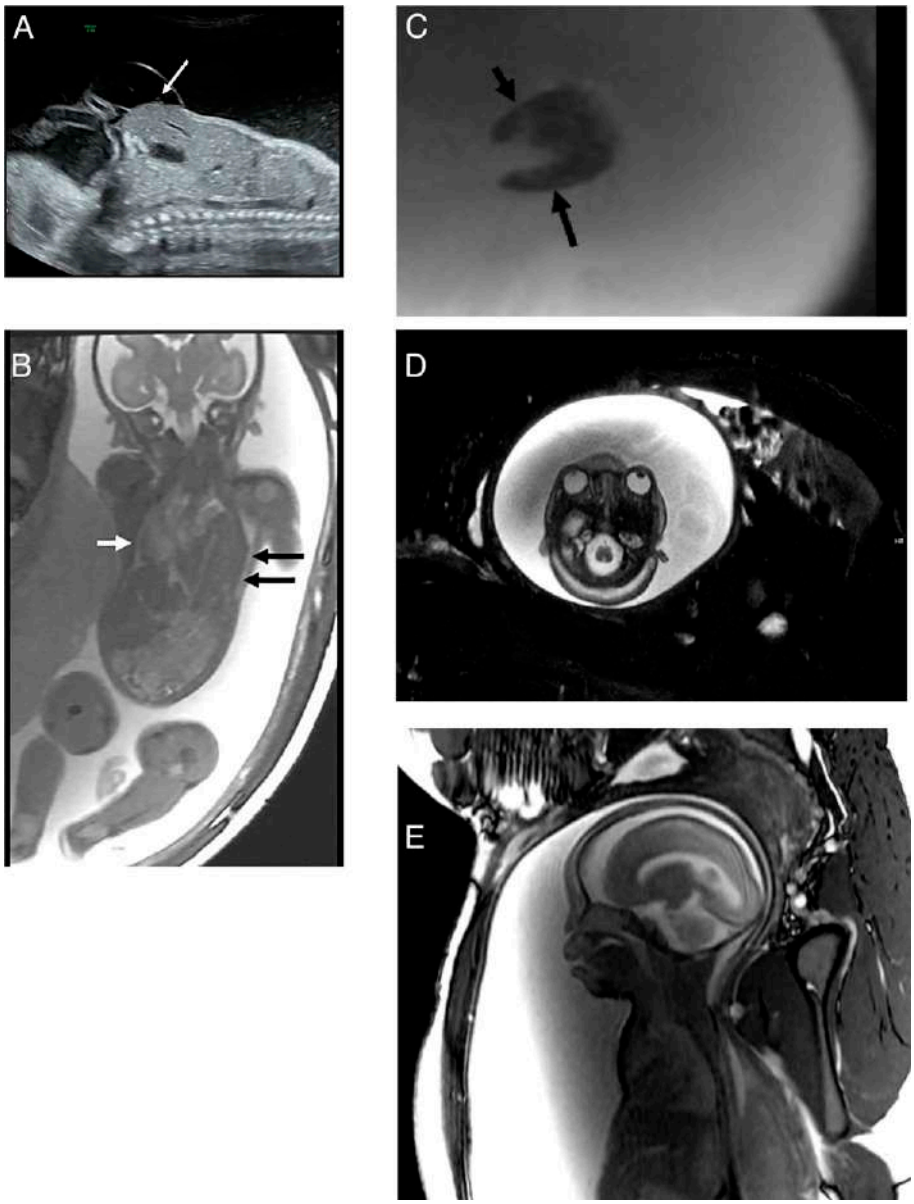


Figure 1. A. Fetal ultrasonography at 26 3/7 weeks' gestation showing a small abdominal omphalocele (arrow). Fetal magnetic resonance imaging scan at 26 3/7 weeks' gestation showing congenital diaphragmatic hernia with liver (black arrows) herniated into left chest and heart displaced into right chest (white arrow) (B); deformed hand (arrows) (C); widely spaced eye globes (D); coarse facial features and prominence of extra-axial spaces (E).

echocardiography at 26 3/7 weeks' gestation showed normal cardiac structure and function with mild hypertrophy of both ventricles. Cell-free DNA screening showed low risk (<1/10,000) for trisomies 21, 18, and 13 and monosomy X as well as low risk for triploidy; a female fetus was predicted. The couple received urgent genetic counseling given the imaging findings and were offered late amniocentesis but declined.

EXPERT OPINION

Given the multiple anomalies, the case was presented at our multidisciplinary fetal care conference to solicit the input of our colleagues from maternal-fetal medicine, neonatology, genetics, and pediatric surgery. From fetal lung predictors for CDH alone, mortality and/or need for extracorporeal membrane oxygenation were estimated to be high. The additional anomalies also predicted a low likelihood of survival. If the infant's respiratory function could be supported, surgical management would remain challenging given both the CDH and omphalocele. The initial focus would be to approach the CDH from the chest because the omphalocele prevented an abdominal approach. There was high suspicion for an underlying genetic etiology. Medical

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genetics would be consulted postnatally with a plan to send a microarray and reflex to exome sequencing if necessary.

The expectant parents were extensively counseled by specialists in neonatology, pediatric surgery, and medical genetics. Social work involvement was vital during counseling and throughout the prenatal course. In-depth discussions focused on delivery room management of the CDH and omphalocele as well as escalation of resuscitative efforts to possibly include chest compressions and intravenous medications should their daughter not respond to initial interventions. The option of solely comfort care was also explained in detail. The couple opted for a trial of intensive care with full attempts at resuscitation.

PRENATAL COURSE

The pregnant patient presented several times over the next few weeks with abdominal pain due to worsening polyhydramnios (AFI 35 cm and then 44 cm). Amnioreduction was offered but the patient declined. She received betamethasone and tocolysis. At 30 5/7 weeks' gestation, she again presented with abdominal pain and contractions (AFI 47 cm), and this time consented to amnioreduction given the severity of her pain. Approximately 2 L of fluid was removed with notable symptomatic relief; an additional 30 mL of amniotic fluid was sent for cytogenetic studies including a karyotype. She was followed closely as an outpatient with serial ultrasonography. Her last ultrasonographic scan performed at 32 2/7 weeks' gestation before ultimately delivering at 32 5/7 weeks' gestation showed an AFI of 44.7 cm. At that time, the EFW was 1,149 g (<2nd percentile) mainly due to severely shortened long bones following a rhizomelic pattern (femur length measuring 20 6/7 weeks' gestation and humeral length measuring 21 2/7 weeks' gestation whereas biparietal diameter and head circumference measured at 34 and 35 4/7 weeks' gestation, respectively). Umbilical artery Dopplers were elevated with systolic/diastolic ratio of 3.9 to 5.4 (95th percentile systolic/diastolic ratio at 32 weeks' GA is 3.79) and the LHR was 0.87 (O/E LHR 26%–28%). The left-sided CDH was again seen with right mediastinal shift as was the omphalocele. There was mild skin edema but no other evidence of hydrops.

OUTCOME AND POSTNATAL COURSE

The pregnant patient presented in active labor at 32 5/7 weeks' gestation. She underwent urgent cesarean delivery in the context of multiple fetal anomalies and a desire for full resuscitation and intensive care support. The infant emerged hypotonic and apneic. The umbilical cord was immediately clamped and cut. The infant was moved to the warmer, placed in a bowel bag to cover the omphalocele, and underwent intubation. A Replogle tube was inserted to aid with gastrointestinal decompression. Auscultation of the heart rate was difficult given the CDH, and the infant briefly received chest compressions in the delivery room. Electrical activity was noted on the cardiac monitors and, while auscultation continued to pose a challenge, a brachial pulse was palpable.

Upon arrival to the NICU, attempts at establishing access proved difficult given the limitations posed by the omphalocele. Both peripheral intravenous access and peripheral arterial access were unsuccessful. Intraosseous access obtained in the right tibia initially functioned but then infiltrated. An emergent umbilical venous catheter was placed through the omphalocele while pediatric surgery attempted femoral access that was unsuccessful.

The infant was placed on high-frequency oscillatory ventilation with a fraction of inspired oxygen of 1.0 and inhaled nitric oxide of 20 parts per million. She was given 1 dose of intratracheal surfactant. Her chest radiograph showed near total opacification of the thorax [Fig 2]. The endotracheal tube was noted to be high and subsequently advanced. Pre- and postductal oxygen saturations demonstrated a 60-point difference. The infant's heart rate slowly

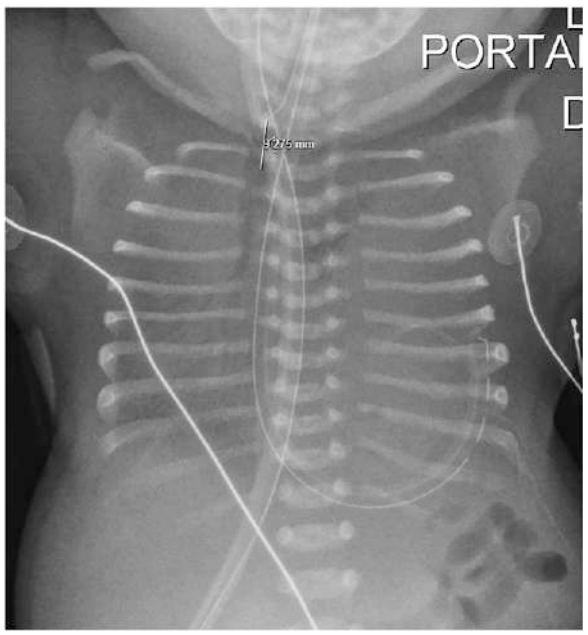


Figure 2. Chest radiograph at approximately 30 minutes of age. Endotracheal tube is in the cervical trachea (subsequently advanced 1 cm). Nasogastric/orogastric tube with tip and side-port projecting over the left lower thorax. There is complete opacification of the thorax with air bronchograms and the cardiomediastinal silhouette is completely obscured by the opacified lungs. Subcutaneous edema is noted as well as 11 ribs bilaterally.

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downtrended to less than 60 beats/min. Chest compressions were provided, and she was given a dose of intravenous epinephrine. She received 1 dose of sodium bicarbonate for profound metabolic acidosis and 60 mL of packed red blood cells for a hematocrit value of 21%. She was given fentanyl boluses for pain and sedation. The mother was brought to the bedside and counseled on the infant's condition. In discussion with the team and given the infant's poor prognosis, the family elected to stop resuscitative efforts. The infant underwent compassionate extubation and was placed in her mother's arms. She died approximately 30 minutes later at 2 hours of age.

Results of the karyotype from the amniocentesis were 48,XX,+i(12)(p10)x2[2]/46,XX[17]. Identification of the presence of 2 i(12p) chromosomes indicated that the fetus was hexasomic for the short arm of chromosome 12. Mosaicism for an isochromosome of the short arm of chromosome 12 is clinically associated with Pallister-Killian syndrome (PKS). While most cases of PKS are the result of tetrasomy 12p, rare cases of hexasomy 12p have been reported. (1)(2)

The parents consented to have an autopsy. Notable findings on autopsy (Fig 3) included abnormal facies (prominent forehead, hypertelorism, sparse eyebrows, flattened nasal bridge, short nose, long philtrum, peaked upper lip, patchy cranial hair, short neck) and skeletal anomalies (short limbs with humerus and radius length fourth percentile for GA; femur, tibia, and fibula length <1st percentile for GA; fused right duplicated first toe; 11 ribs). The omphalocele included intestinal malrotation containing a

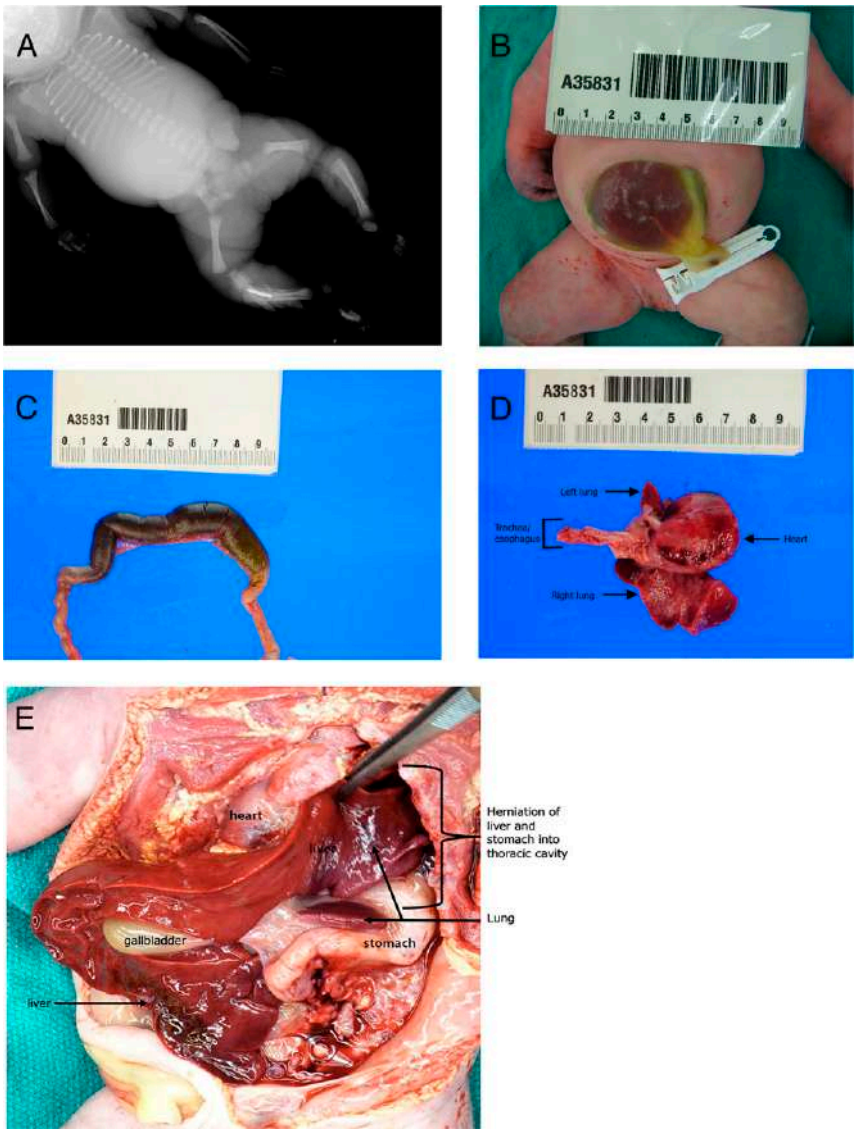


Figure 3. Gross autopsy photographs. A. Skeletal radiograph demonstrating rhizomelic limb shortening. B. Omphalocele. C. Intestinal malrotation containing 10 cm dilated loop of bowel. D. Lung hypoplasia. E. Congenital diaphragmatic hernia containing portion of stomach and liver.

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10-cm segment of dilated bowel. The CDH included herniation of the spleen, a portion of the stomach, and a portion of the liver. The infant's hypoplastic lungs measured less than the 1st percentile for GA, and the cardiac atria were compressed. A tissue culture was performed, and chromosomes were analyzed. Chromosome analysis identified 2 copies of isochromosome 12 in 12 of 20 cells examined, resulting in mosaic hexasomy for chromosome 12p. The presence of this i(12p) was confirmed with fluorescence in situ hybridization and substantiated the abnormal amniocentesis result, consistent with a diagnosis of PKS.

DISCUSSION

PKS is a rare genetic syndrome caused by extra copies of the short arm of chromosome 12 (12p) with an estimated incidence of 5.1 per million live births; however, it is likely underdiagnosed. (3) PKS is due to a spontaneous mosaic duplication event most often resulting in tetrasomy 12p from the formation of an additional 12p isochromosome, (4) however, PKS may also be due to cases of trisomy and hexasomy 12p (as in our case). First described by Dr Pallister in 1977 (5) and subsequently by Drs Teschler-Nicola and Killian in 1981, (6) PKS is a multisystem developmental disorder with significant variability in phenotype owing to the mosaic distribution of the disease. While the mechanism leading to formation of the isochromosome 12p cell lines is still to be determined, most studies suggest maternal meiosis II nondisjunction as the likely mechanism of mosaic tetrasomy 12p. (7) More rarely, paternal nondisjunction has been reported as well. (8)(9) Similar to other autosomal aneuploidy syndromes such as trisomy 21, a maternal age effect is seen in PKS. (10) Reported cases of PKS have all been sporadic; recurrence risk is therefore close to that of the general population.

Prenatal diagnosis of PKS can be challenging because of the variability of associated features and difficulty detecting the isochromosome 12p. (11) The 3 most frequent prenatal ultrasonographic indicators in PKS, all of which were noted in our case, are polyhydramnios, CDH, and rhizomelic shortening. (12) A flat facial profile and thickened nuchal fold can also be seen on ultrasonography. (11) Additional common prenatal findings may include cerebral ventriculomegaly, and congenital heart disease. (13)

Tissue-limited mosaicism for isochromosome 12p is the hallmark of PKS, making diagnosis challenging. The percentage of mosaicism is higher in skin fibroblasts, amniocytes, or chorionic villi cells as opposed to lymphocytes. (13) Often, a buccal smear or skin biopsy is needed for diagnosis after the neonatal period as euploid cells in the blood replace tetrasomic cells. (13)

Postnatally, multiple systems are affected in PKS. Common findings include atypical facial features, differences in pigmentation, intellectual disability, epilepsy, CDH, congenital heart disease, and limb differences. Characteristic facial features include prominent forehead, frontoparietal sparse hair with sparse eyebrows, hypertelorism or telecanthus, long philtrum, depressed nasal bridge, prominent cheeks, low-set and posteriorly rotated ears with ear pits and/or thickened helices, palate differences, accessory nipples, and short neck. (7) "Pallister lip," described as extension of the philtral skin into the vermilion border of the upper lip, is a classic feature. Facial features coarsen over time and the typical pattern of alopecia tends to resolve, making diagnosis more difficult with age.

Multiple organ systems may be affected in patients with PKS. Neurologic manifestations of PKS include severe intellectual disability, epilepsy, and abnormal muscle tone (7) with hypotonia often noted in infancy and variable spasticity and hypertonia in older individuals. (10) Common abnormal MRI findings in patients with PKS include cerebral volume loss, malformations of cortical development, dysgenesis of the corpus callosum, white matter disease, and craniofacial malformations (abnormally shaped skull, hypertelorism, and maxillary hypoplasia). (4) Congenital heart disease, most commonly atrial or ventricular septal defects, can be seen in individuals with PKS. Other cardiac manifestations include bicuspid aortic valve, aortic dilation, patent ductus arteriosus, and patent foramen ovale. Later onset cardiomyopathy is rare but potentially life-threatening. (14)

Ophthalmologic findings in patients with PKS can include strabismus, nystagmus, and/or myopia, with 20% having significant visual impairment and diagnosed as legally blind. (15) Hearing loss of all forms is also common in PKS and is often bilateral. (10) Gastrointestinal involvement ranges from anatomic to functional. Intestinal malrotation, CDH, umbilical hernias, and displacement of the anus are common anatomic findings whereas functional manifestations can include feeding difficulties, dysphagia, constipation, and gastroesophageal reflux disease. (7) The most common genitourinary finding in PKS is cryptorchidism. (7) Musculoskeletal manifestations can include polydactyly, broad thumbs and first toes, joint contractures, and hip dislocations. (7)

Individuals with PKS often show a pattern of prenatal overgrowth followed by growth deceleration over the first few years of age. (7) Developmental delay is common and ranges from mild to profound, most often severe to profound. (7) Behavioral manifestations can include repetitive

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hand and body movements as well as self-injurious behaviors. (10) Life expectancy has never been formally evaluated. One report cites individuals with PKS surviving into their 40s and 50s. (7) However, given the diagnostic challenges, more mild presentations, and individuals who may not have undergone genetics assessment, it is likely that there may be undiagnosed older individuals with PKS. (7)

Summary

This case of PKS fittingly demonstrates this rare, multisystem, sporadic disorder. PKS is due to mosaic supernumerary isochromosome 12p leading to a wide spectrum of possible clinical manifestations. Most often these manifestations include craniofacial, neurologic, cardiac, ophthalmologic, musculoskeletal, dermatologic, and growth and developmental anomalies. Suspicion for PKS should be raised if polyhydramnios, CDH, and/or rhizomelic shortening are seen on prenatal ultrasonography. Cytogenetic diagnosis is challenging with higher diagnostic rates using amniotic fluid or skin fibroblasts. As demonstrated in our case of PKS, coordination of complex care is imperative for fetuses with multiple anomalies of possible genetic etiology, so as to bridge uncertainties in both the prenatal and postnatal periods.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the role and risks of magnetic resonance imaging, as well as other non-ultrasonographic imaging techniques in assessing fetal anatomy.
- Know the importance and limitations of ultrasonographic findings of common fetal anomalies including congenital heart disease.
- Know the significance of polyhydramnios and the management of pregnancy when it is diagnosed.
- Know how specific fetal diagnoses, such as airway abnormalities, abdominal wall defects, myelomeningocele, or severe hydrocephalus might alter prenatal care and intrapartum management (eg fetal intervention "Exit" strategy).
- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.
- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Recognize the imaging features of extrapulmonary causes of respiratory distress.
- Know how mosaicism modifies clinical presentation.
- Recognize the diagnostic implications of single vs. multiple anomalies.

References

1. Toydemir RM, Panza E, Longhurst MC, South ST, Rope AF. Seizures and cardiomyopathy in a patient with Pallister-Killian Syndrome due to hexasomy 12p mosaicism. *Mol Syndromol*. 2020;11(3):125–129
2. Vogel I, Lyngbye T, Nielsen A, Pedersen S, Hertz JM. Pallister-Killian syndrome in a girl with mild developmental delay and mosaicism for hexasomy 12p. *Am J Med Genet A*. 2009;149A(3):510–514
3. Blyth M, Maloney V, Beal S, et al. Pallister-Killian syndrome: a study of 22 British patients. *J Med Genet*. 2015;52(7):454–464
4. Barkovich EJ, Lateef TM, Whitehead MT. Neuroimaging findings in Pallister-Killian syndrome. *Neuroradiol J*. 2018;31(4):403–411
5. Pallister PD, Meisner LF, Elejalde BR, et al. The pallister mosaic syndrome. *Birth Defects Orig Artic Ser*. 1977;13(3B):103–110
6. Teschler-Nicola M, Killian W. Case report 72: Mental retardation, unusual facial appearance, abnormal hair. *Synd Ident*. 1981;7:6–7
7. Izumi K, Krantz ID. Pallister-Killian syndrome. *Am J Med Genet C Semin Med Genet*. 2014;166C(4):406–413
8. Conlin LK, Kaur M, Izumi K, et al. Utility of SNP arrays in detecting, quantifying, and determining meiotic origin of tetrasomy 12p in blood from individuals with Pallister-Killian syndrome. *Am J Med Genet A*. 2012;158A(12):3046–3053
9. Turleau C, Simon-Bouy B, Austruy E, et al. Parental origin and mechanisms of formation of three cases of 12p tetrasomy. *Clin Genet*. 1996;50(1):41–46
10. Wilkens A, Liu H, Park K, et al. Novel clinical manifestations in Pallister-Killian syndrome: comprehensive evaluation of 59 affected individuals and review of previously reported cases. *Am J Med Genet A*. 2012;158A(12):3002–3017
11. Doray B, Girard-Lemaire F, Gasser B, et al. Pallister-Killian syndrome: difficulties of prenatal diagnosis. *Prenat Diagn*. 2002;22(6):470–477
12. Thakur S, Gupta R, Tiwari B, Singh N, Saxena KK. Pallister-Killian syndrome: review of fetal phenotype. *Clin Genet*. 2019;95(1):79–84
13. Salzano E, Raible SE, Kaur M, et al. Prenatal profile of Pallister-Killian syndrome: Retrospective analysis of 114 pregnancies, literature review and approach to prenatal diagnosis. *Am J Med Genet A*. 2018;176(12):2575–2586
14. Tilton RK, Wilkens A, Krantz ID, Izumi K. Cardiac manifestations of Pallister-Killian syndrome. *Am J Med Genet A*. 2014;164A(5):1130–1135
15. Kostanecka A, Close LB, Izumi K, Krantz ID, Pipan M. Developmental and behavioral characteristics of individuals with Pallister-Killian syndrome. *Am J Med Genet A*. 2012;158A(12):3018–3025

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