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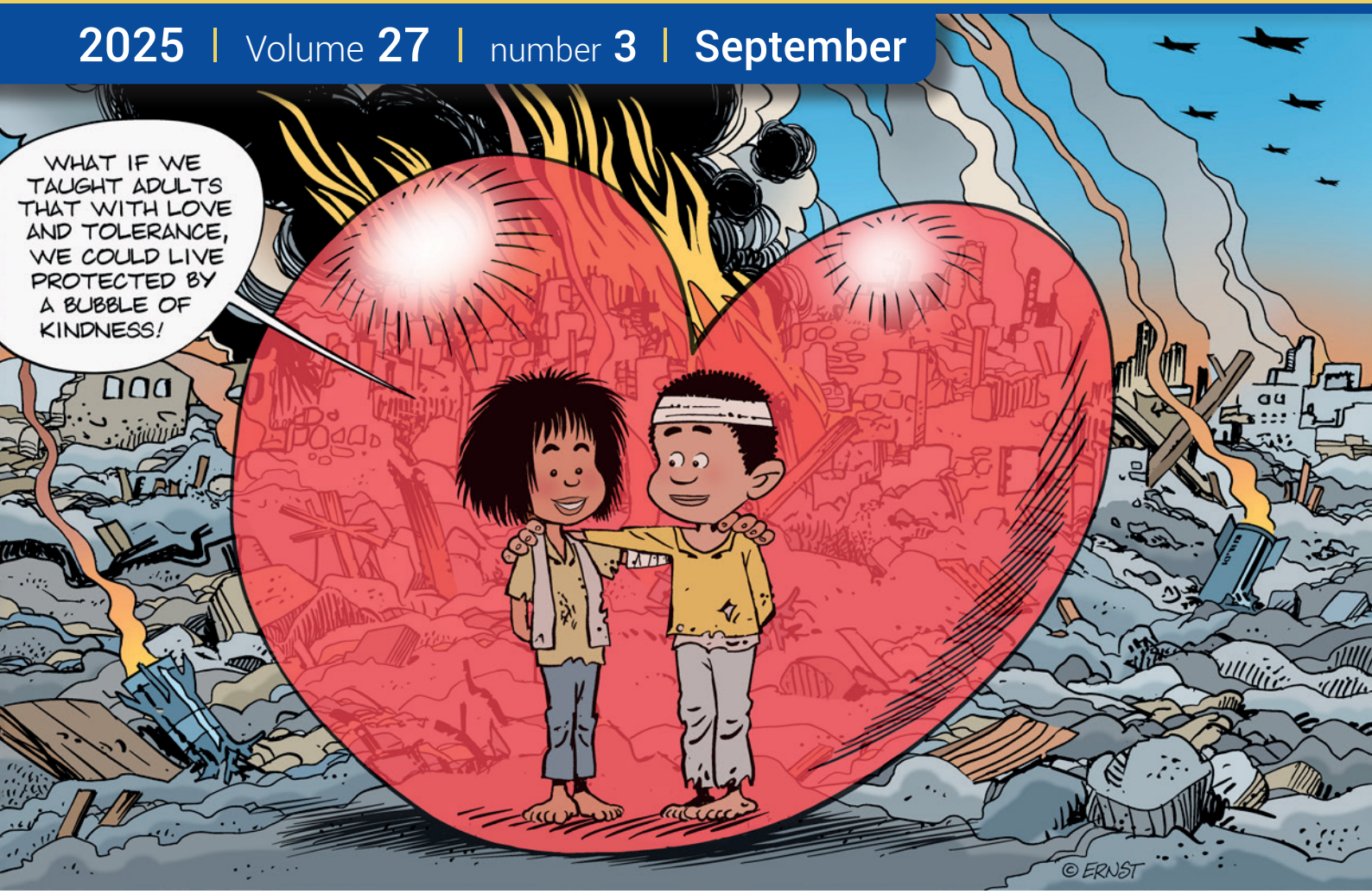

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If you don't recommend MenB vaccination to your patients,

who will?

81% van de ouders beschouwt hun arts als een primaire bron van informatie over vaccinatie voor hun kinderen. (n=800)[2]

BEXSERO
Meningokokken groep B-vaccin
(rDNA, component, geadsorbeerd)

BEXSERO is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B.[1]

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN: Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL:** Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd), EU/1/12/812/001-EU/1/12/812/002-EU/1/12/812/003-EU/1/12/812/004. Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING: Een dosis (0,5 ml) bevat:** Recombinant Neisseria meningitidis groep B NHBAfusieeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B NadAeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B fHbpfusieeiwit[1,2,3]: 50 microgram • Buitenmembraanvesikels (BMV) van Neisseria meningitidis groep Bstam. NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat[2]: 25 microgram • [1] Geproduceerd in E. colicellen door recombinantDNAtechnologie - [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) - [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de volledige SPK. **FARMACEUTISCHE VORM:** Suspensie voor injectie. Melkwitte vloeibare suspensie. **KLINISCHE GEGEVENS: Therapeutische indicaties:** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door Neisseria meningitidis groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **Dosering en wijze van toediening:** Dosering: **Tabel 1. Samenvatting van de dosering: Leeftijd bij eerste dosis:** Zuigelingen van 2 tot en met 5 maanden[a]: **Primaire immunisatie:** Drie doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. - **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. • **Leeftijd bij eerste dosis:** Zuigelingen van 6 tot en met 11 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 12 tot en met 23 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 2 tot en met 10 jaar: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • **Leeftijd bij eerste dosis:** Adolescenten (11 jaar of ouder) en volwassenen*: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • [a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. - [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. - [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld. - [d] Zie rubriek 5.1 van de volledige SPK. - * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening: Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **Contraindicaties:** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **Bijwerkingen:** Overzicht van het veiligheidsprofiel: De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen: Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥ 1/10) - Vaak: (≥ 1/100, < 1/10) - Soms: (≥ 1/1.000, < 1/100) - Zelden: (≥ 1/10.000, < 1/1.000) - Zeer zelden: (< 1/10.000) - Niet bekend: (kan met de beschikbare gegevens niet worden bepaald). De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar):** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Voedings en stofwisselingsstoornissen: Zeer vaak: eetstoornissen. Zenuwstelselaandoeningen: Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn. - Soms: insulten (inclusief febriele insulten). - Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen: Soms: bleekheid (zelden na booster). - Zelden: ziekte van Kawasaki. Maagdarmstelselaandoeningen: Zeer vaak: diarree, braken (soms na booster). Huid en onderhuidaandoeningen: Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster). - Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar). - Soms: eczeem. - Zelden: urticaria. - Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: koorts (≥ 38 °C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid. Soms: koorts (≥ 40 °C). - Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). **Adolescenten (van 11 jaar en ouder) en volwassenen:** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Zenuwstelselaandoeningen: Zeer vaak: hoofdpijn. - Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen: Zeer vaak: misselijkheid. Huid en onderhuidaandoeningen: Niet bekend: huiduitslag. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: myalgie, artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise. - Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België:** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie - Postbus 97 - 1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.be. **Luxemburg:** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië. **DATUM VAN DE GOEDKEURING VAN DE TEKST:** 26/04/2023 (v15). **AFLEVERINGSWIJZE:** Op medisch voorschrift.

References: 1. SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

PM-BE-BEX-ADVR-240003 - Maart 2024 | VU: GlaxoSmithKline Pharmaceuticals s.a./n.v. Avenue Fleming 20 - 1300 Waver Belgium

GSK

Contents

Beyfortus® (nirsevimab)

Prijs Beyfortus® 2025	
Publieksprijs, incl. BTW	777,58 €
Prijs terugbetaald (GZ)	12,50 €
Prijs terugbetaald (PZ)	8,30 €

Bereid u voor op het RSV-seizoen

Beyfortus® is het **eerste** direct langwerkende antilichaam ontwikkeld **voor alle baby's**[1]

Alle kinderen geboren sinds **19/02/2025** komen in aanmerking voor de **terugbetaling** van Beyfortus® voor hun **eerste RSV-seizoen.**

Nieuw: Beyfortus® wordt nu ook terugbetaald tijdens het **tweede RSV-seizoen** voor kwetsbare kinderen*

Voor al uw vragen, contacteer **Beyfortus.Belgium@sanofi.com**

Scan de QR-code voor meer informatie over Beyfortus®.

▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg worden verzocht alle vermoedelijke bijwerkingen te melden. Zie rubriek 4.8 voor het rapporteren van bijwerkingen. NAAM VAN HET GENEESMIDDEL Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit. Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 50 mg nirsevimab in 0,5 ml (100 mg/ml). Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 100 mg nirsevimab in 1 ml (100 mg/ml). Nirsevimab is een gehumaniseerd immunoglobuline G1 kappa (IgG1κ) monoklonaal antilichaam dat geproduceerd wordt uit ovariumcellen van de Chinese hamster (Chinese hamster ovary, CHO) met behulp van recombinant-DNA-technologie. Hulpstoffen met bekend effect: Dit middel bevat 0,1 mg polysorbaat 80 (E433) in elke doseringseenheid van 50 mg (0,5 ml) en 0,2 mg in elke doseringseenheid van 100 mg (1 ml). FARMACEUTISCHE VORM Oplossing voor injectie (injectie). Heldere tot opalescente, kleurloze tot gele oplossing met een pH-waarde van 6,0. THERAPEUTISCHE INDICATIES Beyfortus is geïndiceerd voor de preventie van lagere luchtwegaandoeningen veroorzaakt door het respiratoir syncytieel virus (RSV) bij: - Pasgeborenen en zuigelingen tijdens hun eerste RSV-seizoen. - Kinderen tot 24 maanden oud die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen (zie rubriek 5.1). Beyfortus dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering Zuigelingen tijdens hun eerste RSV-seizoen De aanbevolen dosering is een enkelvoudige dosis van 50 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht < 5 kg en een enkelvoudige dosis van 100 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht ≥ 5 kg. Beyfortus moet worden toegediend vanaf de geboorte voor zuigelingen die tijdens het RSV-seizoen zijn geboren. Voor diegenen die buiten het seizoen geboren zijn, dient Beyfortus idealiter te worden toegediend voorafgaand aan het RSV-seizoen. De dosering bij zuigelingen met een lichaamsgewicht van 1,0 kg tot < 1,6 kg is gebaseerd op extrapolatie. Hiervoor zijn geen klinische gegevens beschikbaar. Naar verwachting zal blootstelling bij zuigelingen van < 1 kg hogere blootstellingen opleveren dan bij zuigelingen die meer wegen. De voordelen en risico's van het gebruik van nirsevimab bij zuigelingen van <1 kg moeten zorgvuldig worden afgewogen. Er zijn beperkte gegevens beschikbaar over extreem premature zuigelingen (zwangerschapsduur < 29 weken) jonger dan 8 weken. Er zijn geen klinische gegevens beschikbaar over zuigelingen met een postmenstruele leeftijd (zwangerschapsduur bij geboorte plus chronologische leeftijd) van minder dan 32 weken (zie rubriek 5.1). Kinderen die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen De aanbevolen dosis is een enkelvoudige dosis van 200 mg intramusculair toegediend als twee injecties (2 x 100 mg). Beyfortus dient idealiter te worden toegediend voorafgaand aan aanvang van het tweede RSV-seizoen. Voor personen die een hartoperatie ondergaan met cardiopulmonale bypass, kan zodra de persoon stabiel is na de operatie een extra dosis toegediend worden om adequate nirsevimab-serumspiegels te garanderen. Als dit binnen 90 dagen na ontvangst van de eerste dosis Beyfortus plaatsvindt, dient de aanvullende dosis tijdens het eerste RSV-seizoen 50 mg of 100 mg te zijn, afhankelijk van het lichaamsgewicht, of 200 mg tijdens het tweede RSV-seizoen. Als er meer dan 90 dagen zijn verstreken sinds de eerste dosis, kan de aanvullende dosis een enkelvoudige dosis van 50 mg zijn, ongeacht het lichaamsgewicht, tijdens het eerste RSV-seizoen of 100 mg tijdens het tweede RSV-seizoen om de rest van het RSV-seizoen te dekken. De veiligheid en werkzaamheid van nirsevimab bij kinderen in de leeftijd van 2 tot 18 jaar zijn niet vastgesteld. Er zijn geen gegevens beschikbaar. Wijze van toediening Beyfortus is alleen voor intramusculaire injectie. Het wordt intramusculair toegediend, bij voorkeur in de anterolaterale zijde van de dij. De gluteale spieren mogen niet routinematig als injectieplaats worden gebruikt vanwege het risico op beschadiging van de ischiaszenuw. Zijn er twee injecties nodig, gebruik dan twee verschillende injectieplaatsen. Zie rubriek 6.6 voor instructies inzake speciale hanteringsvereisten. CONTRA-INDICATIES Overgevoeligheid voor de werkzame stof of voor een van de in rubriek 6.1 vermelde hulpstoffen. BIJWERKINGEN Samenvatting van het veiligheidsprofiel De meest voorkomende bijwerking was rash (0,7%) die binnen 14 dagen na toediening optrad. Het merendeel van deze bijwerkingen was licht tot matig van intensiteit. Aanvullend werden pyrexie en injectieplaatsreacties binnen 7 dagen na toediening gemeld met een prevalentie van respectievelijk 0,5% en 0,3%. Injectieplaatsreacties waren niet ernstig. Lijst van bijwerkingen Hieronder staan de bijwerkingen die zijn gemeld bij 2.966 voldragen en premature zuigelingen (zwangerschapsduur, Gestational Age (GA) ≥ 29 weken) die nirsevimab kregen in klinische onderzoeken en tijdens het toezicht na het in de handel brengen. De bijwerkingen die zijn gemeld in gecontroleerde klinische onderzoeken zijn ingedeeld volgens systeem/orgaanklasse (SOC) van MedDRA. Binnen elke SOC zijn voorkeurstermen gerangschikt op afnemende frequentie en vervolgens op afnemende ernst. De frequenties van optreden van bijwerkingen wordt gedefinieerd als: zeer vaak (≥ 1/10); vaak (≥ 1/100 tot < 1/10); soms (≥ 1/1.000 tot < 1/100); zelden (≥ 1/10.000 tot < 1/1.000); zeer zelden (< 1/10.000) en niet bekend (kan met de beschikbare gegevens niet worden bepaald). Immunsysteemaandoeningen · Niet bekend - Overgevoeligheid a Bijwerkingen uit spontane melding Huid- en onderhuidaandoeningen · Soms – Rash b Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen · Soms – Injectieplaatsreacties ; Pyrexie c Injectieplaatsreactie is gedefinieerd door de volgende gegroepeerde voorkeurstermen: injectieplaatsreactie, injectieplaatspijn, injectieplaatsverharding, injectieplaatsoedeem, zwelling van injectieplaats Zuigelingen met een verhoogd risico op ernstige RSV-ziekte in hun eerste seizoen De veiligheid is onderzocht in MEDLEY bij 918 zuigelingen met een verhoogd risico op ernstige RSV ziekte, onder wie 196 extreem premature zuigelingen (GA < 29 weken) en 306 zuigelingen met chronische longziekte van prematuriteit of hemodynamisch significante aangeboren hartziekte die hun eerste RSV seizoen ingingen, die nirsevimab (n=614) of palivizumab (n=304) kregen. Het veiligheidsprofiel van nirsevimab bij zuigelingen die nirsevimab ontvingen in hun eerste RSV-seizoen was vergelijkbaar met het vergelijkende geneesmiddel palivizumab en consistent met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥ 29 weken (D5290C00003 en MELODY). Zuigelingen die kwetsbaar blijven voor ernstige RSV-ziekte in hun tweede seizoen De veiligheid werd beoordeeld in MEDLEY bij 220 kinderen met chronische longziekte van prematuriteit of hemodynamisch significante congenitale hartziekte die nirsevimab of palivizumab kregen in hun eerste RSV-seizoen en vervolgens nirsevimab kregen in hun tweede RSV-seizoen (180 proefpersonen kregen nirsevimab in zowel seizoen 1 als 2, 40 kregen palivizumab in seizoen 1 en nirsevimab in seizoen 2). Het veiligheidsprofiel van nirsevimab bij kinderen die nirsevimab kregen in hun tweede RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥29 weken (D5290C00003 en MELODY). De veiligheid werd ook onderzocht in MUSIC, een open-label onderzoek zonder controlegroep met enkelvoudige dosis bij 100 immuungecompromitteerde zuigelingen en kinderen ≤24 maanden die nirsevimab ontvingen in hun eerste of tweede RSV-seizoen. Dit omvatte deelnemers met ten minste een van de volgende aandoeningen: immunodeficiëntie (gecombineerd, antilichaam of andere etiologie) (n=33); systemische behandeling met hoge doses corticosteroïden (n=29); orgaan- of beenmergtransplantatie (n=16); gebruik van immunosuppressieve chemotherapie (n=20); andere immunosuppressieve behandeling (n=15) en HIV-infectie (n=8). Het veiligheidsprofiel van nirsevimab was consistent met wat werd verwacht voor een populatie van immuungecompromitteerde kinderen en met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥29 weken (D5290C00003 en MELODY). Het veiligheidsprofiel van nirsevimab bij kinderen tijdens hun tweede RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab dat werd waargenomen tijdens hun eerste RSV-seizoen. Voldragen en premature zuigelingen die hun eerste RSV-seizoen beginnen. De veiligheid van nirsevimab werd ook beoordeeld in HARMONIE, een gerandomiseerd, multicenter open-labelonderzoek bij 8.034 voldragen en premature zuigelingen (GA ≥29 weken) die hun eerste RSV-seizoen begonnen (en niet geschikt waren voor palivizumab), die nirsevimab (n=4.016) of geen interventie (n=4.018) kregen ter preventie van ziekenhuisopname voor onderste luchtweginfectie (lower respiratory tract infection, LRTI) door RSV. Het veiligheidsprofiel van nirsevimab toegediend in het eerste RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab in de placebogecontroleerde onderzoeken (D5290C00003 en MELODY). Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. 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Referentie:
1. Beyfortus® SKP, April 2025.

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CHILDREN IN CONFLICT ZONES: NOTHING BUT VICTIMS

In recent months, many parts of the world have been caught up in intense and destructive armed conflicts. Tragically, young people and the most vulnerable are often those who suffer the most from these situations. According to *Save the Children*, an international organisation that has been defending children's rights worldwide for over 100 years, and the *International Paediatric Association* (IPA), more than 460 million children live in areas affected by armed conflict (1,2). In 2023, over 30,000 verified cases of grave violations against children's rights in conflict zones were reported — but the actual figures are likely much higher, as many cases go unreported. Thirty thousand Ukrainian children have been forcibly deported by Russia, tens of thousands of children have been killed or are dying in Gaza, and countless others have died in Sudan. Those who flee are also affected by violence, as demonstrated by the attitude of certain governments who, without hesitation, separate immigrant families, taking children away from their parents.

Our country and the Belgian paediatric community are trying to respond and take a stand on these issues. In August 2025, the *Belgian Society for Paediatric Haematology and Oncology* (BSPHO) coordinated the evacuation of four young cancer patients from Gaza in collaboration with the Ministries of Health, Foreign Affairs and Defence. A similar humanitarian operation for four young cancer patients and their relatives had already occurred in July 2024, following a request from Egypt and the *World Health Organization* (3). The BSPHO also coordinated the arrival of 14 Ukrainian children for treatment in Belgium in 2022 and 2023. The *Belgian Academy of Paediatrics* (BAoP) recently established a "Disaster Medicine" working group, led by our colleagues Els Duval and Gerlant van Berlaer, set up to understand, monitor and better anticipate the impact of disasters on children. In this way, we aim to prepare the paediatric community in Belgium for the growing challenges of the 21st century. This new issue of the *Belgian Journal of Paediatrics* (BJP) features a cover and editorial relaying the statement which was made by BAoP in June 2025. It advocates for the protection of all children worldwide and clearly expresses the profound and lasting impact of conflict and war on children and future societies (4):

- **Death and injury**: thousands of children are killed or maimed each year.
- **Forced recruitment**: children are forced into armed groups as soldiers and human shields.
- **Sexual violence**: heightened risk of rape, exploitation and abuse.
- **Displacement**: loss of home and family as children are torn from their communities.
- **Psychological trauma**: PTSD, depression, anxiety and lifelong emotional scars.
- **Disruption of education**: schools destroyed, education halted, compromising children's future.
- **Severe malnutrition and disease outbreaks**: due to food shortages, poor sanitation, lack of clean water, and attacks on hospitals and health workers.
- **Cycle of hatred and revenge**: children who lose parents, siblings, relatives or classmates may grow into adults filled with hatred towards perceived perpetrators, further delaying hopes for world peace.

Our role as paediatricians is to stand firm, not aligning with any party but guided by humanity and universal rights. We know that the roots of conflicts are sometimes very complex and historical. However, as human beings, we have also learned from history that the law of the strongest is not necessarily the right. In his book Sapiens: *A Brief History of Humankind*, historian Yuval Noah Harari explains how *Homo Sapiens* became the dominant species on Earth. This was not because they were the fastest, the strongest or the best at night vision…. Thanks to their cognitive abilities, our ancestors were able to develop complex and nuanced communication, uniting around shared narratives and values. While certain civilisations have dominated the world at times, it is societies that are capable of uniting, innovating, and adapting to change that ultimately lead the way. Let us keep this in mind and try to pass it on to our children through our daily choices and actions!

In this issue, we are also very proud to publish several research articles. Laura Noppe and colleagues report on a qualitative study investigating parental perspectives on children with bedwetting. Dorian Deroo and his team study the impact of the COVID-19 lockdown on the oral ingestions of toxic substances in children. Loes Tanghe and colleagues review the effectiveness of the Buzzy device in managing needle pain in children. Sidney Van Leynseele and colleagues analyse the clinical outcomes of Belgian children following kidney transplantation from 2005 to 2022. Several case reports illustrate the dynamism of Belgian paediatric teams. We round off the issue with a State-of-the-Art article edited by the *Vlaams Netwerk Zeldzame Ziekte/Epilepsy* (VNZZ) members on the top 10 guidelines for following up a person with epilepsy.

On behalf of the editorial team, we hope this issue offers reflection and inspiration and we wish you a pleasant autumn season.

Christophe Chantrain and Marc Raes

Sources: (1) https://www.unicefusa.org/stories/protect-children-conflict-unicefs-call-action-2025?utm_source=chatgpt.com"nearly. (2) https://childrenandarmedconflict.un.org/wp-content/uploads/2025/06/Secretary-General-Annual-Report-on-Children-and-Armed-Conflict-Covering-2024.pdf. (3) https://bspho.be/en/news/gaza-patients-august25. (4) https://baop.be/en/information/item/statement-baop-children-conflict-zones-nothing-victims.

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Top 10 Guidelines for Following up a Person with Epilepsy

Edited by The Vlaams Netwerk Zeldzame Ziekten / Epilepsy members

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Keywords
Epilepsy ; child ; adult ; guideline.

Abstract

The "Vlaams Netwerk Zeldzame Ziektes / Epilepsy (VNZZ)" has in recent years worked on a number of guidelines that can be used in the follow-up of a person with new or already known epilepsy. The VNZZ/epilepsy consists of representatives of first (Domus Medica), second (regional hospitals) and third line (university centres and epilepsy centres), with also members of the Flemish Epilepsy League and patient associations (RadiOrg, Ikaros). The guidelines should improve the cooperation between the different lines in medical care, so that every person with epilepsy can be followed correctly by the general practitioner, paediatrician and (paediatric) neurologist. It will also allow the difficult-to-treat patient to be referred adequately and quickly enough to the more specialised third line, for expert diagnosis and treatment. Although these guidelines are made both for children and adults with epilepsy, we believe also the paediatrician can benefit from the insights more specifically relevant for adults.

1. The Epilepsy Patient at the General Practitioner / Paediatrician

Annual Routine Check-up

Although the follow-up of individuals with active epilepsy is primarily carried out by a (paediatric) neurologist, they should also be seen at least once a year by their general practitioner (GP) or paediatrician.

During routine check-ups, inquiries should be made about seizure frequency, medication adherence, side effects, and other epilepsy-related problems. The GP or paediatrician should also review the individual seizure management plan, which has been drawn up in collaboration with the (paediatric) neurologist.

In individuals whose epilepsy has been well-controlled for several years, care and follow up may be managed by the GP or paediatrician. This may be less applicable to young children with epilepsy, where treatment adjustments may be needed more frequently. Even then, it is advised to schedule at least an annual structured check-up.

Referral back to the (paediatric) neurologist is recommended in the event of seizure recurrence, medical problems interfering with seizure control, major life events (such as start anticonceptive

medication, pregnancy), or consideration of tapering anti-seizure medication.

Measuring Serum Levels of Anti-Epileptic Drugs

Routine monitoring of anti-seizure drug (ASM) serum levels is not recommended. Measurements should only be done when clearly indicated and interpreted within the clinical context. Reference values for "therapeutic levels" are population-based averages and may differ for individual patients. It is therefore not always necessary to adjust the dose for slight sub- or supra-therapeutic levels in the absence of seizures or side effects.

Situations where serum level measurement may be useful:

- Suspected non-adherence
- Expected pharmacokinetic changes (e.g., starting/stopping interacting medications, renal/hepatic disease, changes in ASM formulation, pregnancy).
- Treatment-resistant epilepsy (persistent seizures despite usually adequate dosage or recurrence after a seizure-free period).
- Suspected side effects (especially nonspecific symptoms or when communication about side effects is limited, such as in children or individuals with cognitive impairments or altered consciousness).
- Monitoring phenytoin, which has non-linear kinetics; small absorption differences or interactions may lead to loss of efficacy or toxicity.

If possible, measure trough levels (blood sample taken just before the next dose).

Certain life stages with increased pharmacokinetic variability may justify more frequent monitoring to allow dosage adjustments:

- Children: age-dependent variability in absorption/metabolism.
- Pregnancy: increased metabolism can lower serum levels.
- Elderly: less predictable pharmacokinetics, large inter-individual variation. Laboratories usually determine the total plasma concentration, but only the unbound fraction is pharmacologically active. This is especially relevant for protein-bound drugs like valproate and phenytoin. Changes in blood protein (e.g., due to liver disease, old age) can alter the free drug fraction.

Blood Tests for General Chemical and Hematologic Parameters

Various ASMs can induce chemical or hematologic abnormalities (e.g., elevated liver enzymes, blood cell changes like thrombocytopenia with valproate, or hyponatremia with oxcarbazepine). Routine monitoring is not indicated. Extended testing is warranted when side effects are suspected.

A one-time baseline check several weeks after starting ASMs may be helpful for drugs like phenytoin, phenobarbital, valproate, lamotrigine (complete blood count (CBC) and liver enzymes), or carbamazepine and oxcarbazepine (CBC, liver enzymes, sodium). For valproate, clotting parameters and bleeding time should be checked prior to surgery.

Screening for Osteoporosis

People with epilepsy have an increased fracture risk. This is due to seizures, medication-induced sedation or ataxia, or underlying disability (e.g., wheelchair use). ASMs - especially carbamazepine, phenytoin, phenobarbital, topiramate, and valproate - can reduce bone mineral density. The first four induce vitamin D metabolism; valproate and topiramate may also increase osteoporosis risk via unknown mechanisms.

Patients on these ASMs should be advised to get adequate exercise and consume sufficient calcium and vitamin D. Annual vitamin D level checks and supplementation as needed are also recommended (1).

2. When to Refer to a (Paediatric) Neurologist

New Diagnosis of Epilepsy

A diagnosis of epilepsy must be made by a (paediatric) neurologist. This involves a (hetero)anamnesis about seizure episodes, review of any home videos, EEG, brain MRI, and possibly genetic or immunologic tests (2). Additional exams like cardiac evaluation, polysomnography, or seizure recording may be needed to differentiate epilepsy from mimics such as migraine, syncope, parasomnias, psychiatric disorders, etc.

Follow-up

Once epilepsy is diagnosed, the medical record should include the seizure type, syndrome classification, underlying etiology, last seizure date, and seizure frequency, current treatment and also co-morbidities. Changes in frequency or seizure characteristics require prompt referral.

Most patients with active epilepsy should have at least annual follow-up with a (paediatric) neurologist. This consultation addresses seizures, medication side effects, and the psychosocial/societal impact (including fitness to drive). Children, individuals with intellectual disabilities, or those with significant comorbidities often require more frequent follow-up.

The treatment goal is seizure freedom without side effects and with good quality of life. If seizure freedom is not achieved after two adequately dosed ASM trials, referral to a specialized epilepsy centre is necessary. Non-drug treatments (surgery, vagus nerve stimulation, deep brain stimulation, ketogenic diet) should then be considered.

Additional consultations may be warranted in case of:

- Pregnancy or pregnancy planning – short-term referral to a neurologist.
- Newly emerging comorbidities (e.g., anxiety, depression, cognitive decline, behavioural problems) – may be related to the condition or medication.
- Severe allergic or idiosyncratic reactions within 6–12 weeks of starting ASMs (especially lamotrigine, phenytoin, carbamazepine, oxcarbazepine, cenobamate):
  - Painful skin rash with blisters or peeling and fever
  - Bleeding or bloody crusts on lips, tongue, gums, palate, or inside cheeks
  - Genital mucosal bleeding
  - Red, burning eyes (conjunctivitis)
  - Malaise, confusion, cognitive impairment
  - Fever
  - Swollen lips, mouth, throat, or face
  - Swollen lymph nodes
  - Leukopenia or aplastic anaemia – urgent recognition required
- After 2 years of seizure freedom – medication tapering can be considered (especially in children) and should be discussed with a (paediatric) neurologist.

3. Epilepsy and Pregnancy

See also review paper (3).

There are several important risk factors related to epilepsy and pregnancy requiring a multidisciplinary approach involving GP, gynaecologist, and neurologist.

Seizure frequency can change significantly during pregnancy:

- In 30%: increased frequency (check adherence).
- In 20%: decreased frequency.
- In 50%: no change.

There is an increased risk of birth defects due to ASM use during pregnancy. The risk of major congenital malformations in the general population is 2–3%, with ASM use 3–10% Preconception counselling for optimal treatment is essential. The priority is seizure control, preferably with the lowest effective ASM dose. Women should not enter pregnancy unmedicated. Monotherapy is preferred. Divide the daily dose over 3–4 intakes.

Risk of major malformations by ASM:

- Valproate: 10% at ≥700 mg/d, 23–24% at ≥1500 mg/d
  → should be avoided
- Lamotrigine: ~2–3% at <300 mg/d, 4% at ≥300 mg/d
- Phenobarbital: ~4% at <150 mg/d, 10% at ≥150 mg/d
- Carbamazepine: ~3–5% at <1000 mg/d, 8% at ≥1000 mg/d
- Levetiracetam: ~3%

Lamotrigine and levetiracetam appear to carry the lowest risk and are well-studied.

Folic Acid Supplementation

Start ≥1 month before conception and continue through the first trimester:

- 0.4 mg/day (standard)
- 4 mg/day in case of: known deficiency, neural tube defect in a previous pregnancy, or folate-related disorders

During Pregnancy

- Long seizures, repeated seizures, or seizure-related trauma
  → consult a gynaecologist to assess foetal status
- New tonic-clonic seizures in the third trimester
  → urgent gynaecologic evaluation to exclude eclampsia

ASM Serum Levels in Pregnancy

Hormonal changes can significantly affect drug levels.

- Lamotrigine: clearance may double
  → dosage may need to be increased 2–3×
- Oxcarbazepine: up to 36% lower levels
- Levetiracetam: up to ~50% lower levels
- Phenobarbital: up to 50% lower levels
- Valproate, phenytoin, carbamazepine: little change

Recommendation: For lamotrigine, oxcarbazepine, and levetiracetam, check serum levels monthly preconception and throughout pregnancy; adjust dosage if levels drop substantially.

Breastfeeding

No absolute contraindication.

However, monitor the infant for sedation if the mother is using phenobarbital or benzodiazepines. Avoid abrupt weaning, as it may cause withdrawal symptoms in the baby (e.g., irritability, tremors, insomnia).

4. Epilepsy and Psychological and/or Cognitive Problems

Due to the interplay of seizures, the stigma and social consequences of an epilepsy diagnosis, possible side effects of medication, and especially the underlying causes of epilepsy, the risk of psychological issues such as anxiety, depression, and low self-esteem is significantly increased in people with epilepsy. The likelihood of developing a psychiatric disorder or suicidal behaviour is 2.5 to 5 times higher than in the healthy population. Cognitive problems such as concentration difficulties, ADHD, memory problems, and executive dysfunction are also more frequent for these reasons. In addition, developmental issues such as intellectual disability and autism are common comorbidities. Conversely, up to 25% of individuals with intellectual disabilities develop epilepsy. Many of these comorbidities result from a complex interaction of factors and not solely from medication, as patients often believe.

Routine and repeated screening for and early treatment of psychological problems are therefore of paramount importance. Supporting appropriate self-care, coping mechanisms, and stress management can also have a beneficial effect on seizure frequency. It is important to promote a healthy lifestyle with sufficient physical and social activity, a regular sleep-wake rhythm with adequate sleep, healthy nutrition, and avoidance of alcohol and drugs. Timely referral to a psychologist or psychiatrist is recommended. For cognitive complaints impacting functioning, a neuropsychological assessment can help identify strengths and weaknesses and suggest appropriate interventions. This type of assessment is offered to people with refractory epilepsy during evaluation in an epilepsy surgery centre. Individuals with well-controlled epilepsy may also benefit from such an assessment.

In children with epilepsy, an increased risk of learning difficulties, ADHD, and other behavioural problems has been shown, particularly when epilepsy begins at an early age, seizure frequency is high, and multiple anti-seizure drugs are required. Again, the cause is multifactorial. The importance of neuropsychological diagnostics and initiating the right support or medication should be particularly emphasized in this group.

There is no contraindication to initiating antidepressants or other psychotropic medications when clinically indicated. SSRIs are the first choice for moderate to severe depression (4). However, some combinations of anti-epileptic drugs and antidepressants may increase the risk of sedation, hyponatremia, cardiac arrhythmias, sexual dysfunction, urinary retention, and osteoporosis. Benzodiazepines are used in epilepsy for seizure control or as part of therapy in complex epilepsy. For other indications, their use should be avoided.

Several anti-seizure drugs may have negative effects on mood, anxiety, and cognitive functioning. An increased risk of suicide has also been described, particularly during the initial treatment phase. Cognitive issues may sometimes be alleviated through better seizure control or by selecting more appropriate anti-seizure medications. Close consultation with a (paediatric) neurologist is therefore always indicated.

Psychogenic or functional non-epileptic seizures (PNES or FNES) are episodes of altered awareness and/or perception and/or signs of neurological dysfunction that are not caused by hypersynchronous abnormal brain activity as seen in typical epileptic seizures. These can be categorized as symptoms of conversion, psychosomatic, or dissociative disorders. Such episodes can closely resemble epileptic seizures, and misdiagnosis is common. Due to their sometimes long duration, abnormal movements, and high frequency, these episodes can have a significant impact on quality of life. Positive and supportive psychoeducation is the first step, and anti-epileptic medication generally has no effect on these types of seizures. Coordinated communication within the treatment team leads to better long-term outcomes. Given the complex differential diagnosis and challenging treatment, referral to a specialized epilepsy centre for diagnosis and care is recommended. Psychological treatments such as cognitive behavioural therapy have shown a positive impact on quality of life, even independently of their effect on seizure frequency (5).

5. Acute Seizure Management in Convulsive Seizures

The convulsive (motor) phase of most epileptic seizures usually lasts no longer than 1 to 2 minutes, as the inhibitory systems in the brain are capable of neutralizing excessive excitation. A short convulsive seizure in itself does not cause brain damage. However, secondary injuries can occur during this phase (such as head trauma, traffic accidents, burns, drowning, etc.).

If a seizure lasts longer than 5 minutes (T1 in the definition by the International League Against Epilepsy, ILAE), the risk increases that the brain's protective mechanisms will fail and the seizure will not stop spontaneously. This condition is called status epilepticus. In status epilepticus, there is a higher risk of brain damage from the seizure itself, which typically occurs after about 30 minutes (T2 in the ILAE definition). The development of cerebral oedema can cause additional morbidity. It is therefore important to prevent prolonged convulsive seizures as much as possible and to act appropriately during a convulsive episode.

In non-convulsive seizures, the time frame in which brain damage occurs is less clear, and likely takes longer. Nevertheless, it is generally accepted that the chance of spontaneous resolution also decreases after 5 minutes in these cases.

Various products are available on the market to rapidly stop epileptic seizures, all of which belong to the benzodiazepine class. The most commonly used medications include lorazepam, midazolam (buccal Buccolam® 2.5, 5, 7.5, and 10 mg or compounded intranasal Dormicum®), clonazepam (Rivotril® drops), and rectal diazepam.

For every patient known to experience convulsive seizures or prolonged epileptic episodes, an individualized treatment plan should be discussed. In addition to chronic medication management, the approach to potential acute seizures must also be reviewed. This acute management is highly patient-specific.

The following guidelines may be helpful (6, 7):

- An acute seizure plan is primarily necessary for recognizable convulsive seizures. These are seizures with a clear motor component (such as tonic-clonic seizures).
- It should be agreed upon when to administer a benzodiazepine: usually after 5 minutes of convulsive activity, but in certain severe epilepsy syndromes (e.g., Dravet syndrome), where seizures frequently last longer, this may be earlier (at onset or after 1 minute). Time indications always refer to the convulsive phase of the seizure (not to postictal confusion, sleep, etc.).
- Type of medication and dosage should be agreed upon in advance. This should preferably be recorded in an epilepsy "passport" that the patient carries at all times.
- It must also be clarified who is authorized to administer the seizure medication (parents, grandparents, partner, school or workplace staff, etc.).
- A single adequate dose of benzodiazepines very rarely causes respiratory depression.
- A prolonged epileptic seizure should always be considered a serious medical event. Therefore, it is recommended to contact emergency services after administration of benzodiazepines, especially if the seizure does not resolve after 3–5 minutes. A second dose (preferably intravenous or intramuscular) should only be given under medical supervision due to the increased risk of respiratory depression.

6. Interaction Between Anti-Epileptic Drugs and Other Medications

Most interactions between ASM's and other medications occur with enzyme-inducing ASMs such as:

Carbamazepine (Tegretol®), phenobarbital (Gardenal®), phenytoin (Diphantoine®), oxcarbazepine (Trileptal®), primidone (Mysoline®), topiramate (Topamax®) at doses >200 mg/day, felbamate (Taloxa®), rufinamide (Inovelon®), and perampanel (Fycompa®).

A key issue is the interaction with contraceptive treatments, particularly enzyme-inducing ASMs and the oral contraceptive pill (OCP) (8).

Enzyme-inducing ASMs reduce serum levels of ethinylestradiol and progesterone, thereby lowering the effectiveness of OCPs.

Recommendations:

- Use a higher-dose progestin OCP (e.g., doubling the regular pill dose).
- Continuous use of pills during the "pill-free" week offers better protection when using enzyme-inducing ASMs and lamotrigine (avoids partial ovulation during the break).
- After switching from enzyme-inducing to non-enzyme-inducing ASMs, continue the high-dose pill for at least 1 month due to the "carryover effect" of enzyme induction.
- Combining the pill with condoms increases protection.
- Depo-Provera ("injection contraceptive"): Lacks strong evidence for effectiveness when used with enzyme-inducing ASMs. Consider more frequent administration every 6–8 weeks instead of every 12 weeks. Not a first-choice method.
- Progestin-only pills ("minipill") are not recommended.
- NUVA ring: Releases oestrogen; presumed interaction with enzyme-inducing ASMs and lamotrigine (limited studies); not recommended.
- Morning-after pill: Consider 1.5 tablets (2.25 mg) of levonorgestrel. Intrauterine copper device placement within 5 days is preferred.
- Hormonal IUDs are likely the safest contraceptive option with enzyme-inducing ASMs and lamotrigine.

Interaction with other medications

Enzyme-inducing ASMs can reduce serum concentrations of various drugs, including traditional oral anticoagulants, calcium channel blockers, corticosteroids, and benzodiazepines.

Enzyme-inhibiting drugs can increase concentrations of several ASMs. For example:

- Ketoconazole and fluconazole can raise levels of phenytoin, valproic acid, and phenobarbital.

– Erythromycin, grapefruit juice, and fluoxetine inhibit CYP3A4, potentially increasing carbamazepine levels.

Avoid using meropenem and valproic acid together, as meropenem can reduce valproic acid blood levels by 60–100% within two days.

To check drug interactions, you can use tools such as the Medscape Drug Interaction Checker.

7. Fitness to Drive

When a diagnosis of a first epileptic seizure or epilepsy is made, a person is legally deemed unfit to drive. A distinction is made between Group 1 driving licences (categories AM, A1, A2, A, B, BE, G) and Group 2 licences (categories C1, C1E, C, CE, D1, D1E, D, and B for remunerated transport). The duration of being unfit to drive depends on various factors.

If someone is declared unfit to drive, they must surrender their driving licence and have it medically suspended by the competent authority within four working days of the diagnosis. For this purpose, the doctor provides a 'Model VII certificate' confirming unfitness to drive. This certificate can be issued by any doctor, including a general practitioner.

Below is an overview of the minimum period of driving disqualification for Group 1 (Table 1). More detailed information can be found in the brochure on driving fitness from the Epilepsy League (https://www.epilepsieliga.be). When the patient is deemed fit to drive again, the doctor issues a new 'Model VII certificate' specifying the duration and any restrictions of the driving fitness. The validity period for the first issuance is 1 year, then up to a maximum of 5 years after the last seizure, and after that, fitness to drive may be granted without a time limit. For subcategories 6 and 7 in the table: four times for 1 year first, and then possibly for an unlimited duration.

TABLE 1: Group 1 : overview of the minimum period of driving disqualification

Condition	Earliest Possible Declaration of Fitness to Drive
First provoked seizure (e.g., due to alcohol withdrawal, sleep deprivation, acute illness)	After 6 months if the provoking factor is clear and not repeated
First unprovoked seizure	After 6–12 months seizure-free, based on neurological evaluation
Epilepsy diagnosis (i.e., two or more unprovoked seizures)	After 1 year seizure-free
Seizure relapse due to medication adjustment	After 6 months seizure-free following dose change
Seizures occur only during sleep	After 3 years of purely nocturnal seizures
Seizures without loss of awareness (e.g., focal aware seizures)	After 1 year, if these remain the only seizure type
Seizure-free patient after stopping anti-epileptic medication	After 6 months of continued seizure-freedom

Interpretation: You can interpret the table as follows: A person with a … can be declared fit to drive again after … seizure-free period.

For Group 2, the regulations are stricter and the disqualification period is longer. Driving fitness can only be regained if all investigations are normal and the patient has been seizure-free for at least 10 years without anti-epileptic drugs. In Belgium, the occupational physician makes the final decision about Group 2 driving fitness, in consultation with the neurologist.

See also:

https://werk.belgie.be/nl/themas/welzijn-op-het-werk/het-gezondheidstoezicht-op-de-werknemers

8. Epilepsy and Sports

Adequate physical activity and active participation in sports have a proven positive impact on seizure control in people with epilepsy, in addition to the broader benefits of sports for health and general well-being. Physical exercise is associated with a reduction in epileptiform discharges on EEG and increases the seizure threshold. However, sports are often discouraged in people with active epilepsy, usually due to fear, overprotection, and lack of knowledge about the specific benefits and risks of such activities.

Many people with epilepsy are less physically active than their peers, and this more sedentary lifestyle negatively affects psychosocial development, independence, and mental well-being. Of course, some sports do carry an increased risk for people with epilepsy. When providing advice about sports, the benefits and risks must be weighed, considering the type of sport, type and severity of seizures, existence of prodromal symptoms, known seizure-provoking factors, and the possibility of supervision during the activity.

The assessment of risks involved in participating in sports is a shared responsibility between physicians, the person with epilepsy, and/or parents/guardians.

For most sports, there is no specific regulation regarding medical fitness to participate for individuals with epilepsy. The International League Against Epilepsy (ILAE) has published guidelines to help physicians discuss risks with patients or their parents. It is helpful to distinguish three categories of sports (9):

1. *Sports with minimal risk* to the person with epilepsy and/or bystanders (e.g., ball sports, most athletics disciplines, dancing, cross-country skiing, most contact sports). These are generally allowed for all people with epilepsy, unless the neurologist believes the seizures are triggered by specific sports.
2. *Sports with moderate risk* to the individual but not to bystanders (e.g., swimming, cycling, skiing, high jump, gymnastics, horse dressage, high-impact contact sports such as boxing). These are generally allowed after 12 months of seizure freedom but can sometimes be permitted earlier in consultation with the (paediatric) neurologist if certain conditions are met (e.g., continuous supervision possible, only nocturnal seizures, or seizures without loss of awareness).
3. *Sports with high risk* to the individual and/or bystanders (e.g., scuba diving, windsurfing, motocross, skydiving, flying, mountaineering, solo sailing). Here, risks must be clearly discussed with the patient, and a minimum of 1 year seizure freedom is generally recommended—especially if there is potential danger to bystanders. Some organizations, like diving clubs, require a medical assessment and may not permit people with epilepsy to participate regardless of seizure-free duration, while others may allow participation after 5 years of seizure freedom without medication.

9. Epilepsy and Work

Some professions are not accessible to people with epilepsy, such as active duty in the fire department, police or military, pilot, maritime occupations, professional drivers (taxi, bus, and truck drivers,

ambulance personnel, driving instructors), and train operators. Generally, one must be seizure-free for at least 10 years (sometimes with at least 5 years without medication) before being eligible for these professions. For individuals with a one-time (provoked) seizure, slightly less strict rules usually apply. Regulations may change over time, so it is best to consult the most recent laws when making career choices.

Well-controlled epilepsy does not necessarily affect a person's ability to work. For active epilepsy, a risk assessment should ideally be performed, considering the type of seizure, postictal phase, severity of epilepsy, job content, and work environment. Certain professions pose risks for people with active epilepsy. In consultation with the occupational physician, (temporary) restrictions may be imposed, such as restrictions on working at heights (e.g., construction workers, painters), operating machinery (e.g., forestry), or working with hazardous materials (e.g., chemicals, gas fitting).

The occupational physician may also, with input from the neurologist, recommend workplace adjustments to ensure safety, such as exemption from night shifts, flexible working hours post-seizure, availability of a quiet recovery space, or delegation of riskier tasks (e.g., working on high ladders) to colleagues.

See also:

https://werk.belgie.be/nl/themas/welzijn-op-het-werk

10. Sudden Unexpected Death in Epilepsy Prevention (10)

People with epilepsy are at a slightly higher risk of sudden death. This is referred to as SUDEP, or Sudden Unexpected Death in Epilepsy. The estimated incidence is 1 in 4500 patients per year for children and 1 in 1000 patients per year for adults. The incidence is highest in people aged 20 to 45 years.

It is suspected that problems with the autonomic nervous system during seizures lead to cardiac arrhythmias and/or respiratory disturbances that cause death.

Studies have shown that certain patient groups are at increased risk:

- Patients with nocturnal generalized (tonic-clonic) seizures
- Patients with long-standing refractory epilepsy
- Patients with poor seizure control (e.g., due to poor medication adherence)
- Patients whose epilepsy began before the age of 10

To reduce the risk of SUDEP, achieving and maintaining seizure freedom is crucial. Medication adherence is essential. For patients with refractory epilepsy, trying new anti-seizure drugs and considering alternative treatments (such as epilepsy surgery or neurostimulation) remains important.

Sometimes monitoring is used for patients with frequent nocturnal seizures. It is important to stress that no monitoring system is foolproof, and reliance on them should not create a false sense of security.

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A Qualitative Study to Investigate the Parental Perspectives on Children with Bedwetting

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Nocturnal enuresis ; taboo ; parental perspectives.

Abstract

Objective
Nocturnal enuresis (NE) is a common condition in children. It is clinically defined as the involuntary urination of children aged five years or older, occurring at least twice per week over the past three months, in the absence of an identifiable somatic cause. NE affects not only the child with the condition, but also their wider environment and the well-being of their parents. This qualitative study aims to examine the repercussions of NE for parents and identify the specific daily life challenges they face as a result of their child's condition.

Methodology
We conducted semi-structured interviews with parents of children experiencing NE. Participants were recruited after providing informed consent following paediatric nephrology consultations at University Hospitals Leuven or Regional Hospital Heilig Hart Leuven, both of which are located in Flanders, Belgium.

Results
The study included interviews with 11 parents of children aged between 6 and 13 years old. Of these children, 64% were boys (n = 7) and 36% were girls (n = 4). Parents identified the impact of bedwetting on their children across three key domains: emotional well-being, social interactions and triggering factors. Furthermore, the effects on parents were categorised into five dimensions: parental concerns; the parent–child relationship; family dynamics; advice for other parents; and the influence of societal taboos.

Conclusion
NE can affect various aspects of life for both children and their parents, potentially impacting their overall quality of life. It is therefore crucial for healthcare providers to openly discuss this issue to deliver comprehensive, holistic care.

Introduction

Bedwetting, clinically termed 'nocturnal enuresis' (NE), is a common condition in children. NE occurs when a child older than 5 years involuntarily voids urine at night at a frequency of at least twice per week over the past three months, in the absence of an identifiable somatic cause. About 10 percent of 7-year-olds and 5 percent of 10-year-olds have bedwetting incidents more than three times a week. With increasing age, the prevalence of NE decreases by approximately 15% per year (1,2).

It is important to recognise the effect of bedwetting on the child's well-being and the positive effects of treatment. The health-related quality of life (HRQoL) is higher in the treated children with enuresis than in untreated children and a higher treatment response is associated with a higher HRQoL (3).

The level of depression experienced by children with NE increases in line with their social anxiety (4). Parental opinions regarding bedwetting often exert a greater influence on the child's psychological state than the child's own concerns. A sense of optimism often correlates positively with managing enuresis (5).

The social impact of bedwetting is not confined to the child itself, but also its immediate environment. The QoL of mothers of children with NE is negatively affected (6).

Parents of children with NE experience increased levels of anxiety (7). Fewer studies have been conducted on the impact of NE on parents. Parents of children with NE are more isolated and have more stress, but it is particularly related to child characteristics. The following stressors are experienced by parents: interrupted sleep, bedwetting related laundry and potential bullying directed to their child (5). Secrecy is very important for all the young people.

Parents have frustration and want the bedwetting to stop. They feel embarrassed when they need to tell other people that their child is not dry.

A perceived lack of support from healthcare professionals can leave parents feeling powerless and isolated. They feel left alone when the healthcare professionals run out of ideas to help them or when they re-offer methods that had not worked before. Many parents feel the worst about the inability to help their child when they went through all the methods to try to stop the bedwetting (8).

A holistic approach in the treatment of children and their families by health care professionals improves the outcome of therapy (9,10). It is crucial to treat psychosocial aspects in addition to physical ones to achieve the best quality of care. It is important to treat and prevent psychosocial damage of the child and to support the family (6).

This study aims to evaluate the perspectives of parents who have a child with NE. Despite the prevalence of NE, few studies have systematically explored its impact on parents, and the consequences for family members are frequently underestimated. This gap in literature underscores the need for a deeper investigation into the effects of paediatric NE on family well-being.

TABLE 1: Participant characteristics.

Age child (years)	Gender of child	Gender of parent	Total number of children
12	male	female	2
13	male	female	2
11	male	male	2
10	female	female	3
8	male	female	3
7	male	female	3
7	male	female	1
7	female	female	3
8	female	female	2
6	female	female	2
6	male	female	2

Methodology

Study design

This research used a qualitative study design with semi-structured interviews. An interview guide was developed in advance to ensure consistency in the topics covered, allowing the questions to serve as a structured framework. Initially, a preliminary question list was generated with the assistance of ChatGPT to establish a foundational guideline aimed at exploring parental perspectives on paediatric bedwetting. This guideline was subsequently refined to align with the specific research objectives of this study. All participants were asked the same set of questions, facilitating the comparability of responses. This approach enabled a detailed examination of individual experiences, providing insight into the participants' emotions, thoughts, and perspectives.

Participants

Parents of paediatric patients attending the nephrology clinics at University Hospitals Leuven (academic centre) or Heilig Hart Hospital Leuven (regional centre) in Flanders, Belgium, were invited to participate in the study between March and October 2024. Interested parents were subsequently contacted by e-mail or telephone, through which they received a detailed explanation of the study and were scheduled for an interview. Prior to the interview, all participants were provided with an informed consent form, which they signed to indicate their agreement to participate. Approval from the UZ KU Leuven Ethics Committee was received before the start of the study. (MP028323)

The inclusion criteria for the study were NE in children without significant comorbidities. Exclusion criteria encompassed the presence of identifiable underlying somatic conditions that could explain the NE, such as neurological disorders.

Interviews

At the outset of each interview, the interviewer introduced themselves and provided an overview of the study's design. Prior to commencing the interview, the rationale for audio recording was explained to participants, and their consent to record was obtained. The use of audio recordings facilitated the interviewer's full engagement in the discussion, with the recordings later transcribed for analysis.

The interview guide comprised nine thematic sections, each containing 2–4 questions. All interviews were conducted in Dutch via Microsoft Teams by the same interviewer, ensuring consistency across sessions. Interviews took place from March to October 2024.

Data-analysis

The audio recordings of the interviews were transcribed in full. During the transcription process, potential quotes were identified for later use in the presentation of results. An open coding approach was applied to identify specific themes recurring across interviews. These themes were subsequently organised through axial coding into broader, overarching concepts.

Results

Demographics

The study sample consisted of 11 parents (out of 18 contacted parents), including one father and ten mothers, each having between one and three children. The ages of the children experiencing enuresis ranged from 6 to 13 years, with a median age of 8 years. Among the affected children, boys exhibited a higher prevalence of bedwetting, accounting for 64% (n = 7), compared to girls, who constituted 36% (n = 4) (Table 1).

Of the 11 children included in the study, 8 had primary monosymptomatic nocturnal enuresis (NE), 1 had secondary monosymptomatic NE, 1 had primary NE with encopresis, and 1 initially presented with daytime incontinence, which was subsequently controlled, although the child continued to experience NE. In the selected population there was one child who was treatment naïve, all others (n=10) were already under treatment with medication, bedwetting alarm or TENS (transcutaneous electrical nerve stimulation).

TABLE 2: Illustrative quotes reflecting the impact on children.

Impact on children
Emotional
• Yes, he was still wearing diapers, but at a certain point, it started to become more challenging because he no longer wanted to wear them; he felt he was too old for that.
• She doesn't admit it often, but sometimes she says, "Yes, I am different from the others."
• It's very strange, but I think he must realize it on some level; however, he seems to ignore it quite deliberately.
Social
• Two identical sleeping bags and two identical pyjamas, so that if one got wet, it could be replaced without the other children asking, "Why do you have a different one now?"
• Because there are certainly others as well, he doesn't really mind it himself or anything like that.

Impact on children

The impact of NE on children, as described by their parents, can be categorised into three key domains: emotional well-being, social interactions, and triggering factors. Table 2 presents illustrative quotes that reflect these aspects of the impact.

Emotional well-being

Children frequently experience feelings of shame associated with bedwetting. At a certain age, they may become reluctant to wear diapers, recognising that their peers no longer do so. They often express to their parents a sense of being different from friends or siblings. When diapers are not worn, or when they fail to contain urine fully, bedwetting results in disturbed sleep as children wake up during the night. Parents report that disrupted sleep can lead to increased irritability or decreased concentration in their children during the day. Additionally, some parents note that bedwetting negatively impacts their child's self-confidence and induces stress, particularly when sleeping away from home. In such situations, children may experience poorer sleep quality, often waking more frequently to use the bathroom to avoid bedwetting incidents.

Social interactions

Some parents report that their child experiences minimal social limitations due to bedwetting. However, other parents note that their child refrains from participating in overnight activities with friends or youth organisations. In instances where children do attend overnight events, specific precautions are often taken, including informing supervising adults beforehand, arranging for the child to change in a private space, and packing extra clothing and bedding in case of accidents. Most children occasionally stayed overnight with family members, such as grandparents, who were aware of the bedwetting issue. School-organised overnight trips frequently caused anticipatory stress, sometimes beginning several months in advance, as parents and children hoped for improvement before the event. Additionally, some children took medication during camps or holidays to help prevent bedwetting while away from home. This concern about school trips, in addition to the child's age, was a common motivator for parents to seek professional intervention.

Triggering factors

In response to inquiries regarding potential triggers for variations in their child's frequency of bedwetting, most parents reported an inability to identify specific precipitating factors. A small subset, however, observed an increased incidence of bedwetting associated with heightened stress at school, periods of fatigue, or in anticipation of particularly stimulating events.

Impact on parents

The domains most frequently discussed in this study by parents of children with NE included concerns about the condition, the parent-child relationship, and broader family dynamics. Parents also offered advice for other caregivers and addressed the societal taboo surrounding the issue. Table 3 provides representative quotes from parents illustrating these concepts.

Concerns

Parental concerns regarding childhood bedwetting are widespread, often accompanied by a strong desire to maintain secrecy about the issue. This reticence is frequently motivated by fears that disclosure might lead to social repercussions, such as bullying or stigmatization among peers. While many parents anticipate that the condition will resolve naturally over time, uncertainty regarding the duration of the issue remains a significant source of stress. Additionally, some parents harbour concerns that the problem might persist into adolescence, potentially causing further challenges, including social isolation or discomfort as their child grows older. Fear of judgment from other adults also contributes to this silence, leading many parents to avoid discussing the topic unless necessary.

Parent-child relationship

All parents reported engaging in open communication with their child regarding bedwetting. They consistently refrained from expressing anger when incidents occurred, recognizing that bedwetting is beyond the child's control. Nonetheless, some parents acknowledged that when bedwetting persisted over several consecutive nights, they occasionally responded to their child in a gruff manner, a reaction they later regretted. Children exhibited varied responses to bedwetting episodes. Some woke their parents during the night to inform them of the incident or reported it the following morning. Others managed the situation independently, covering the wet area with a towel and resuming sleep without disturbing their parents.

Family dynamics

Communication about bedwetting tends to remain within the confines of the family. Siblings are typically aware of the condition and approach it with discretion, rarely using it as a basis for teasing. Older siblings may express concern when a younger sibling participates in overnight activities away from home. Within the family, mothers often take a central role in managing practical aspects of the condition, such as maintaining a bladder diary. Parents frequently report that balancing the demands of addressing bedwetting with the needs of other children poses a significant challenge. Caring for a child who experiences bedwetting requires significant organizational effort. In addition

TABLE 3: Illustrative quotes reflecting the impact on parents.

Impact on parents
Concerns
• There are other things you can share, but the personal ones, just keep them to yourself. • Because today they are your friends, and tomorrow they might not be. • For me personally, the most exhausting part is worrying about the future. • As she gets older and it remains difficult, the chance also becomes a bit greater that negative reactions may occur.
Parent-child relation
• Don't hide it somewhere, that was the case at the beginning, and then it started to smell, so we made agreements about it. • It's not that I get angry with her, but you do become a bit curt, and I can't be all "oh, poor thing, it's nothing." It's more like, "Come on, get out of bed, I'll change your sheets, and then I'm gone."
Family
• Brother: make sure to say something when that happens, because other kids might not want to sleep next to you.
Advice
• What I try to do most of all is not to make it a problem or a big issue ... but to approach it in a positive way, just like learning to read it's something she needs to learn. And just like with some things at school, some children simply need a bit more time. • It's just nice to talk about it in the sense that you know others who have a child like that, and then you don't feel so alone.
Taboo
• It's part of her privacy, and I don't think it's something I need to broadcast to everyone. So, in that sense, it might be a bit of a taboo subject. • Just handle it discreetly; no one needs to know. It's fine if someone knows you have to take medication, but don't say what it's for.

to tasks such as changing bedding and laundry, parents may also need to attend medical or physiotherapy appointments. Nevertheless, all parents interviewed in this study reported finding these demands manageable and expressed a strong willingness to take extensive measures to address bedwetting as quickly as possible.

Advice

When parents were asked to provide advice for others managing a child with bedwetting, many emphasized the importance of fostering open communication about the issue. A substantial number of parents advised against problematising bedwetting, believing that doing so was counterproductive in resolving the condition. Some parents recommended seeking professional assistance without delay, reflecting on their own experiences of waiting too long and noting that an evaluation could help identify any underlying causes. Conversely, other parents expressed reluctance to seek medical intervention, as they wished to avoid framing the issue as a medical problem.

Societal taboo

When parents were asked whether they considered bedwetting a taboo subject, most responded that they did not, as they were aware of other families facing the same issue. However, many acknowledged that initiating a conversation about bedwetting for the first time could be challenging. Some parents noted that when they began discussing the topic in the presence of other parents, it often encouraged others to share their own experiences with a bedwetting child. Similarly, some parents stated that they were more likely to discuss the topic if others initiated the conversation. Parents described such discussions as gratifying, though certain factors deterred them from talking about the issue. For instance, many respected their child's preference for privacy and refrained from discussing the matter if the child objected. Additionally, some parents avoided the subject due to the social stigma surrounding bedwetting at certain ages, as they wished to shield their child from potential judgment. One parent admitted to concealing the truth by claiming their child did not bed wet when, in fact, they did.

Discussion

NE has a complex and multidimensional impact on both the affected children and their parents, necessitating a clear understanding of its psychosocial consequences. The findings of this study highlight the emotional and social challenges faced by children with NE, as well as the underestimated burden placed on parents. This dual impact should alert physicians to approach NE not only as a medical condition but as a phenomenon with extensive psychosocial ramifications that require holistic management.

Participants

In assessing the demographics of our participant group, the study involved 11 parents, predominantly mothers, which reflects common trends in volunteer research related to paediatric health issues, where mothers are typically more represented (11). The number of participants in this qualitative study is adequate to generate meaningful insights into the psychosocial aspects of managing nocturnal enuresis (bedwetting) in children, aligning with recommended practice for qualitative research, which prioritises depth over breadth of data (12). The children, ranging from 6 to 13 years with a median age of 8 years, fall within the typical clinical range for presenting symptoms of enuresis. Notably, the higher prevalence of bedwetting among boys (64%) compared to girls (36%) in our sample parallels existing literature, indicating that nocturnal enuresis is more commonly reported among males (13).

Emotional and social impact on children

Children with NE often experience feelings of embarrassment and shame, which can lead to secrecy and social withdrawal. This

aligns with previous research, such as the study by Morison et al., which emphasises the central role of secrecy in the management of NE. At a certain age, children tend to refuse to wear diapers, a decision that parents generally respect in our study by no longer putting their child in a nappy. This finding contrasts with the observations of Morison et al., who described instances where children older than four years were required to wear diapers, a practice deemed humiliating (8). Previous research has indicated that the sleep quality of children with NE improves when they wear a diaper at night (14).

Our study provides additional insight by documenting specific coping strategies employed by children in social situations, such as changing clothes in private or avoiding sleepovers altogether. While these behaviours serve as protective mechanisms, they may inadvertently reinforce feelings of 'being different' and isolation, further undermining the child's self-esteem.

The anticipation of spending a night away from home, including school trips and camps, was identified as a major source of stress for both children and their parents. While some children adopted precautionary measures to participate in these activities, others opted to avoid them entirely, highlighting a spectrum of social limitations linked to NE. This finding aligns with existing evidence that the psychosocial burden of NE is pronounced in social contexts and increases with age (15). Ring et al. previously reported diminished self-esteem in children with NE (16). In our study, parents occasionally noted reduced self-esteem in their children; however, distinguishing this from other potential contributors to lower self-esteem proved challenging.

Impact on parents

Parents in this study reported experiencing considerable stress and frustration, often driven by feelings of helplessness and concern for their child's well-being.

In contrast to the findings of previously conducted research, which identified heightened parental anxiety as a prominent theme, parents in this cohort primarily expressed moderate, situationally dependent concerns (7,17). Spending a night away from home was in this study was a common cause for concern in this study and this was often a reason to seek medical advice, alongside the increasing age of the child. This divergence may reflect cultural or contextual variations in the perception and management of NE, or it could be linked to the open communication strategies employed by parents in this study.

In addition to the psychosocial impact, parents consistently reported logistical challenges associated with managing NE, including increased laundry demands, disrupted sleep, and the need to attend medical appointments. Despite these difficulties, parents exhibited notable resilience and a strong willingness to prioritize their child's needs. This underscores the importance of providing holistic support to families coping with NE.

The parental burden associated with NE parallels that experienced by parents of children with chronic dermatological conditions, such as atopic dermatitis or psoriasis (18,19). The quality of life (QoL) of parents of children with atopic dermatitis or psoriasis is negatively impacted across multiple domains. Both cases illustrate how chronic conditions affecting children can profoundly influence various aspects of family life, emphasising the need for interventions that address both the medical and psychosocial dimensions of care.

Addressing the Societal Taboo

The existing literature provides limited insights on the social taboo associated with NE. As mentioned above, the concept of secrecy is important in the child's emotional well-being, but it also plays a role regarding social taboo (8).

The perception of NE as a societal taboo emerged as a nuanced theme among participants in our study. While most parents recognized NE as a common condition, many expressed discomfort discussing it outside close family circles. This hesitation was primarily motivated by a desire to protect their child's privacy and shield them from potential stigma or judgment. However, parents who engaged in discussions about NE - particularly in supportive and understanding environments - frequently found these interactions to be therapeutic and empowering.

These findings highlight the importance of addressing the stigma associated with NE. Normalising conversations about the condition can foster a more supportive atmosphere for affected families. It is important to communicate openly with the parents and the child and determine whether the impact on the child and parents on both mental and physical levels is important to initiate therapy (20).

Implications for Healthcare Providers

Previous research has demonstrated that treatment of NE is associated with an improvement in health-related quality of life and psychological functioning of children (3,21).

The findings of this study underscore the necessity of adopting a family-centred approach to the management of NE. It is essential for medical professionals to address not only the illness itself but also the uncertainty and psychological impact experienced by parents (6,22). Additionally, fostering open communication between healthcare professionals and patients is crucial for building trust, addressing patient concerns, and delivering comprehensive clinical information. This patient-centred approach has the potential to empower parents to disclose their concerns more effectively (23).

Limitations and strengths

This study has several limitations. The sample size was relatively small, consisting of a limited number of parents. Even though it aligns with qualitative methodology, the small cohort, which includes exclusively Flemish parents, limits the generalizability of the findings. Additionally, all participants were recruited during a nephrology consultation by the same physician (who works both at an academic and regional centre), which may have introduced selection bias, as these parents might already have been more inclined to discuss and address bedwetting. Parents who do not seek professional help might perceive the topic as even more taboo and may refrain from seeking assistance due to feelings of shame or other negative emotions.

A notable strength of this study is the inclusion of parents with children across a range of ages, enabling the collection of information about both younger and older children. Additionally, the use of semi-structured interviews allowed for the generation of rich, detailed narratives, providing valuable insights into both the emotional and practical aspects of managing NE.

Conclusion

This study examined the impact of bedwetting on various aspects of the lives of parents.

Addressing this topic openly is essential to ensure that parents do not feel isolated and are encouraged to seek the necessary support. Breaking the taboo and fostering discussions can empower parents to share their experiences more freely. Gaining insight into parents' perspectives enables caregivers to engage in conversations with sensitivity and openness. Furthermore, understanding the diversity of parental experiences allows caregivers to provide personalized care tailored to each unique

parent-child relationship. Future research could qualitatively investigate non-monosymptomatic enuresis associated with daytime incontinence or encopresis. It is hypothesized that these conditions may have a more significant impact on parents, thus justifying further exploration of this aspect. Additionally, the influence of family dynamics, such as parental separation, on NE represents another area worthy of further investigation, as it was not examined in detail in the present study.

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INTRODUCING WATER INTO INFANT FEEDING:

how to improve the transition and avoid pitfalls

Despite clear recommendations from the World Health Organization (WHO) and UNICEF advocating exclusive breastfeeding for the first six months of life, many infants around the world are given water before this age. Although discouraged, this practice remains widespread in various settings, often driven by cultural beliefs or concerns about dehydration. Yet, breast milk alone is sufficient to meet the hydration needs of a healthy infant.[1-5]

A systematic review[1] published in 2023 highlights the wide variability in water introduction rates among infants aged 0 to 6 months, ranging from 2.5% to 85% depending on the country, cultural context, and family awareness. This early introduction of water contributes to the gradual decline in exclusive breastfeeding rates, which are already low in many regions — globally, only 38% of infants under six months are exclusively breastfed.[6-13]

The aim of the study was to gain a deeper understanding of water consumption practices in infants and to identify the associated factors. Thirteen quantitative studies published between 2002 and 2022 were analyzed to provide a comprehensive overview of the current situation and to inform potential intervention strategies.[1]

PRACTICES ROOTED IN CULTURAL BELIEFS AND SOCIOCULTURAL CONTEXT

The study reveals that the introduction of water is often driven by deeply rooted cultural beliefs: many families consider water to be essential for quenching an infant's thirst or preventing dehydration. However, this perception is inaccurate in the context of exclusive breastfeeding. Breast milk contains approximately 85% water, along with all the nutrients required to support optimal development during the first six months of life.[1-14]

Moreover, water consumption in infancy — especially when the water is not specifically adapted for babies (such as low-mineral-content water, which is recommended) — is associated with tangible risks: reduced breast milk intake, insufficient caloric supply, impaired growth, increased risk of neonatal jaundice, and weakened immune function. In addition, when introduced prematurely, water can serve as a vector for infectious agents, particularly in areas with limited access to safe drinking water.[1]

FACTORS INFLUENCING THE EARLY INTRODUCTION OF WATER[1]

Several factors are associated with water consumption in infants under six months of age. Among the most frequently reported determinants are maternal education level, employment status, and socioeconomic conditions.

It has been shown that mothers with lower levels of education are more likely to introduce water during the first six months, compared to more educated mothers. The latter are also more likely to boil water before giving it to their infant, whereas less educated mothers more frequently use tap water. A statistically significant association was found between maternal education level and the type of water given to the infant ($p = 0.026$), as well as between education level and the early introduction of water before six months ($p = 0.001$).

Maternal employment status was also identified as an influencing factor: unemployed mothers were more likely to give water to their infants before six months of age than those who were employed. Furthermore, a significant relationship was observed between household income and the use of tap water, with low-income families more frequently resorting to it (p = 0.020).

Finally, some studies emphasized that water was not always introduced for nutritional or medical reasons, but also for cultural or personal ones. According to one study, 34.2% of mothers reported giving water to their infants for reasons unrelated to complementary feeding or the introduction of infant formula. Other studies included in the review reported high rates of water use from the earliest days of life, often based on the belief that the infant was thirsty or that breast milk alone was insufficient to meet hydration needs.

RECOMMENDATIONS TO IMPROVE THE TRANSITION AND AVOID PITFALLS

To address the continued early introduction of water in infant feeding, the review emphasizes the essential role of healthcare professionals in guiding families through evidence-based practices. As trusted figures, nurses are well positioned to correct misconceptions and provide clear information on exclusive breastfeeding. Routine healthcare encounters, such as growth monitoring, immunization appointments, and postnatal follow-ups, should be systematically used to reinforce the recommendation to avoid giving water to infants under six months of age. These moments of contact are also opportunities to explain that breast milk alone is sufficient to meet infants' hydration needs, even in hot climates.[1]

The review also highlights the importance of context-specific educational strategies. Interventions should extend beyond the mother-infant dyad and actively engage family members, particularly grandmothers and elder relatives, who often play a decisive role in feeding decisions. Cultural norms and generational beliefs — such as the idea that water is necessary to quench a baby's thirst — remain powerful drivers of behavior. As shown in several studies included in the review, a significant proportion of mothers acted based on traditional practices or family advice, even when they were aware of exclusive breastfeeding guidelines.[1]

Programmatic efforts that begin during pregnancy, continue in the maternity ward, and are sustained through home-based counseling have proven effective in reducing unnecessary water intake. For example, randomized controlled trials included in the review demonstrated that structured support programs, including prenatal education and postpartum follow-up, significantly increased exclusive breastfeeding rates and reduced the introduction of water and herbal teas in the first months of life.[1]

The review further underscores the need for high-quality, culturally diverse research to better understand the behavioral and social determinants of early water introduction. Notably, few studies investigated who initiates the decision to give water (e.g., mothers vs. family elders), or whether healthcare workers were ever the source of such recommendations. Moreover, most of the available data relied solely on maternal self-reporting, without biochemical validation. To strengthen public health interventions, future research should examine the impact of caregiver beliefs, community norms, and health provider training on feeding practices.[1]

A clearer understanding of these influencing factors will help refine educational messages, develop culturally sensitive materials, and ultimately support global efforts — such as the WHO's 2025 target — to raise the rate of exclusive breastfeeding to at least 50% during the first six months of life.[1,15]

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COVID-19 Lockdown and its Effects on Pediatric Oral Ingestions with Toxic Substances: A Retrospective Study of the Belgian Poison Center Reports

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Keywords

COVID-19, Child, Hand Sanitizers, Anti-infective Agents, Detergents, Poisons, Belgium, Emergencies, Incidence, Public Health.

Abstract

Background:

The COVID-19 lockdown led to significant changes in household behaviors, including an increase in the use of disinfectants, hand sanitizers, and cleaning agents. These changes may have raised the risk of pediatric intoxications. This study examines the impact of lockdown measures on the incidence of the reports of oral exposures to toxic products in children obtained from the Belgian Poison Center.

Methods:

A retrospective analysis was conducted of all pediatric cases of oral ingestion with hand sanitizers, bleach, detergents, or medicines reported to the Belgian Poison Center during the first lockdown (March 1–May 31, 2020) and compared to data from the same period in 2019, 2021, and 2022. Descriptive and comparative statistical analyses were performed to evaluate the frequency, characteristics, and trends in exposure cases.

Results:

A total of 2591 pediatric ingestion cases were reported during the lockdown in 2020, compared to 2657, 2406, and 2644 cases in 2019, 2021, and 2022, respectively. In 2020, the number of calls related to hand sanitizers increased by 329% compared to 2019, with continued elevated numbers in the following years. Bleach and detergent exposure cases also increased by 163% and 30%, respectively, while cases involving human medicines decreased by 20%. Most cases involved young children, with those under six years consistently accounting for over 75% of exposures throughout the study period. During the lockdown, children aged 2–6 years were significantly overrepresented, while adolescent cases were underrepresented. Exposure cases from educational institutions and hospitals decreased and were significantly underrepresented. Referrals to emergency departments decreased slightly during the lockdown, with non-referrals increasing correspondingly.

Conclusion:

The COVID-19 lockdown period saw a marked increase in reports of pediatric oral ingestions to hand sanitizers and household chemicals, highlighting the unintended consequences of public health measures on child safety. These findings underscore the need for targeted public health interventions, including public awareness campaigns and stricter product safety regulations, to mitigate the risk of pediatric poisoning during future public health emergencies.

What is already known on this topic

International studies have reported a surge in poison control center cases linked to cleaning agents and hand sanitizers during the lockdown measures in the early months of the pandemic. However, the specific impact of lockdown measures on acute intoxication trends among children in Belgium has not yet been thoroughly investigated.

What this study adds

The study investigates the impact of the COVID-19 lockdown and Its effects on pediatric oral Ingestions with toxic substances and underscores the need for targeted public health interventions, including public awareness campaigns and stricter product safety regulations, to mitigate the risk of pediatric poisoning during future public health emergencies.

Introduction

The COVID-19 pandemic, which became global in early 2020, brought about unprecedented changes to daily life as governments worldwide implemented different lockdown measures to curb the spread of the virus. In Belgium, the first strict lockdown measures, which began on March 18, 2020, and lasted until May 2020, included strict stay-at-home orders, the closure of schools, catering and non-essential businesses, and restrictions on social interactions (1). While these interventions were deemed vital for public health, they also created significant shifts in household behaviors and routines.

Among these changes was a dramatic increase in the use of disinfectants, bleach, hand sanitizers, and other cleaning agents (2, 3). This surge was driven by widespread fears of transmission of SARS-CoV-2, as in the pandemic's early stages, it was unclear whether the virus spread exclusively through respiratory droplets or also via contaminated surfaces (4). Alongside this, the COVID-19 pandemic also influenced medication use, with a notable trend of global drug stockpiling observed during its early months, particularly in developed countries (5). These behavioral shifts, reinforced by public messaging and individual differences, combined with extended time spent at home, inadvertently heightened the risk of unintentional exposure to hazardous substances, especially in children (6, 7). With children spending more time indoors and driven by their natural curiosity, the likelihood of accidental ingestion increased. Young children are especially vulnerable to accidental exposures, which are a leading cause of poisoning and intoxication incidents in this age group (8).

International studies have reported a surge in poison control center cases linked to cleaning agents and hand sanitizers during the pandemic's early months (9-13). However, the specific impact of lockdown measures on acute poisoning trends among children in Belgium has not been thoroughly investigated. The Belgian Poison Center is a national public service organization available 24/7 to provide advice and assistance in cases of poisoning and toxic exposure. It is dedicated to responding to emergency calls regarding harmful substances, supporting both the public and healthcare professionals; it receives approximately 65,000 calls annually. The Center also documents all cases in detail for administrative and research purposes.

This study aims to assess the oral ingestion cases with hand sanitizers, bleaching agents, detergents, and human medicines in children that have been reported to and documented by the Belgian Poison Center before, during, and after the first lockdown period. By examining the frequency and characteristics of these reported incidents, we seek to highlight the unintended consequences of lockdown measures on child safety and identify opportunities for public health interventions.

Methods

Study design

This retrospective review analyzed all oral ingestion cases in children of (a) hand sanitizers (biocidal products for human hygiene), (b) bleaching products for cleaning, (c) detergents and (d) human medicines that were reported to the National Belgian Poison Center during an equal period before (March 1st , 2019, through May 31st, 2019), during (March 1st , 2020, through May 31st , 2020) and after (March 1st , 2021, through May 31st , 2021 and March 1st , 2022, through of May 31st , 2022) the COVID-19 lockdown.

Data source and data collection

We report on anonymized data that we obtained from the Belgian Poison Center through a formal data request process. This dataset comprises information gathered from exposure calls received between 2019 and 2022. Each call was handled in accordance with internal operating procedures and documented using a standardized data collection form. Exposures were identified using the European Product Categorization System (EuPCS). We included only cases that met following criteria: firstly, we included only cases with oral exposures, excluding other routes such as dermal, ocular, or inhalation. Secondly, the product types included were restricted to biocidal products for human hygiene (hand sanitizers), bleaching products for cleaning, detergents and human medicines, all other product categories were excluded. Finally, only data on children aged 0-18 years were included, as this age group was the target population for our investigation. Subject-identifying information was already removed from the dataset provided by the Belgian Poison Center and was not accessible to investigators. All missing data was removed. As all data that were handled by the researchers consisted of an anonymized data collection without any identifying characteristics, no approval from an Ethics Committee was required. There are no conflicts of interest to declare.

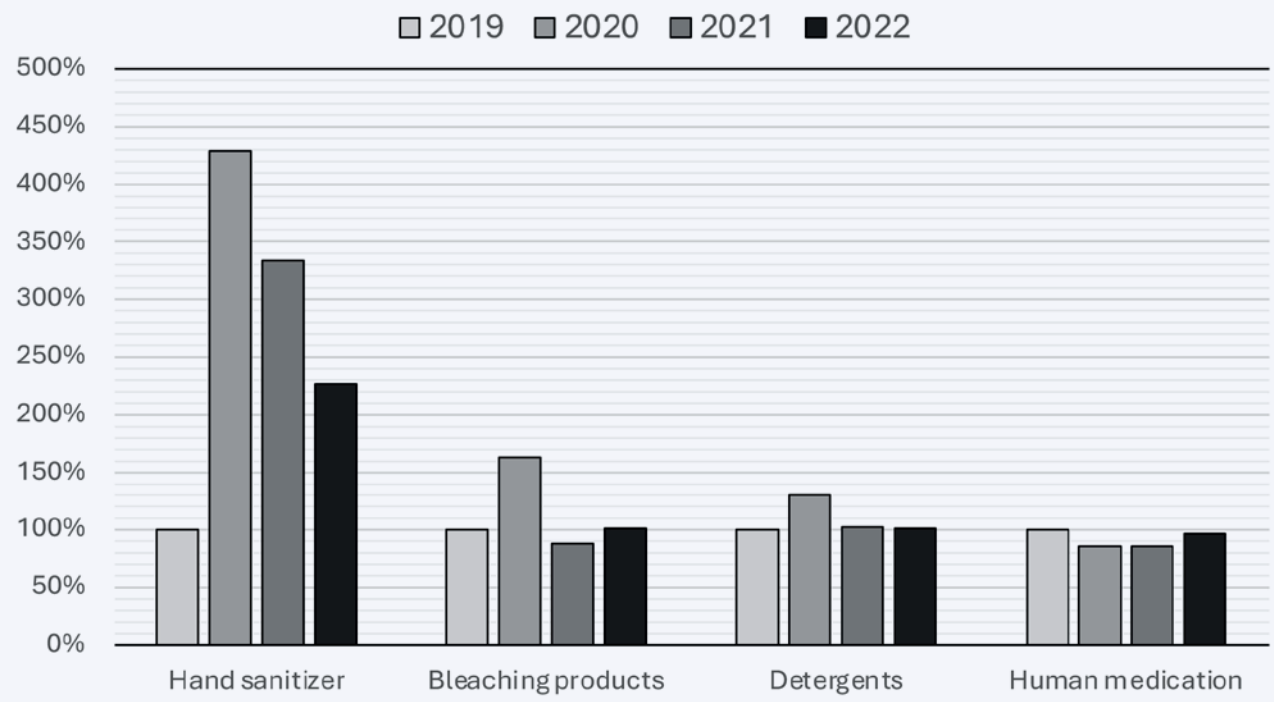
Statistical analysis

The primary objective of this study was to evaluate the number of reports of oral exposure to (a) hand sanitizers, (b) bleaching products for cleaning, (c) detergents and (d) human medicines in children received in the period of lockdown (from the 1st of March 2020, through the 31st of May 2020) and the same period before

TABLE 1: The frequency of calls regarding oral intoxications in children with household cleaning products, hand sanitizers and human medication received in 2019, 2020, 2021 and 2022 (1st March – 31st May).

Product	2019 n	2020 n	2021 n	2022 n
Total	2657	2604	2440	2644
Hand sanitizer	44	189	147	100
Bleaching product	49	80	43	50
Detergent	310	404	320	312
Human medication	2254	1931	1930	2182

FIGURE 1: Year-to-year percentage change (2019-2022).



(2019) and after (2021 and 2022) lockdown. Descriptive statistical analysis was used for all the products identified in the study. We also performed comparative statistical analysis using chi-square tests to determine whether a change in frequencies of cases was statistically significant. A year-to-year percentage change was calculated for each product between 2019 and 2022. The secondary objective of this study was to compare the characteristics of the calls between all periods of interest. We considered the following categorical variables: (i) age group, (ii) victim location and (iii) recommended location of treatment. Comparative statistical analysis was performed using Pearson chi-square tests for categorical variables. When statistically significant ($p < 0.05$), post-hoc analysis using adjusted residuals with a Bonferroni correction was conducted. We used IBM SPSS® Statistics version 29.0 for the data analysis. Ninety-five percent confidence intervals for raw counts and proportions were calculated using a Poisson distribution and using the Clopper-Pearson method.

Results

Frequency of calls for oral ingestions by product type

The Belgian Poison Center received a total of 2591 calls reporting oral exposures with analyzed toxic products in children during the lockdown period in 2020 (1st March – 31st May), whereas 2657, 2406 and 2644 calls were received during the same period in 2019, 2021 and 2022 respectively (Table 1). Of these 2591 calls in 2020, 189 (95% CI, 162.1- 215.9) calls were related to hand sanitizers, 80 (95% CI, 62.5 - 97.5) were related to bleaching products, 404 (95% CI, 364.6 - 443.4) were related to detergents and 1901 (95% CI, 1815.5 - 1986.5) were related to human medication (Table 1). The distribution of cases among the product categories varied significantly across the 4 years ($\chi2(9, N=10,434) = 176.385$ ($p<0.001$)). During lockdown, when compared to 2019, we observed a percentage increase of 329% for reports of exposure with hand sanitizers. For the number of exposures with bleaching products and detergents we observed a 163% increase and a 30% increase respectively. Whilst for the number of exposures with human medication, we observed a 20% decrease (Figure 1). Additionally, for hand sanitizers we observed a persistent increase in 2021 (+234%) and 2022 (+127%) compared to 2019 (Figure 1).

Monthly trends of reported oral ingestions

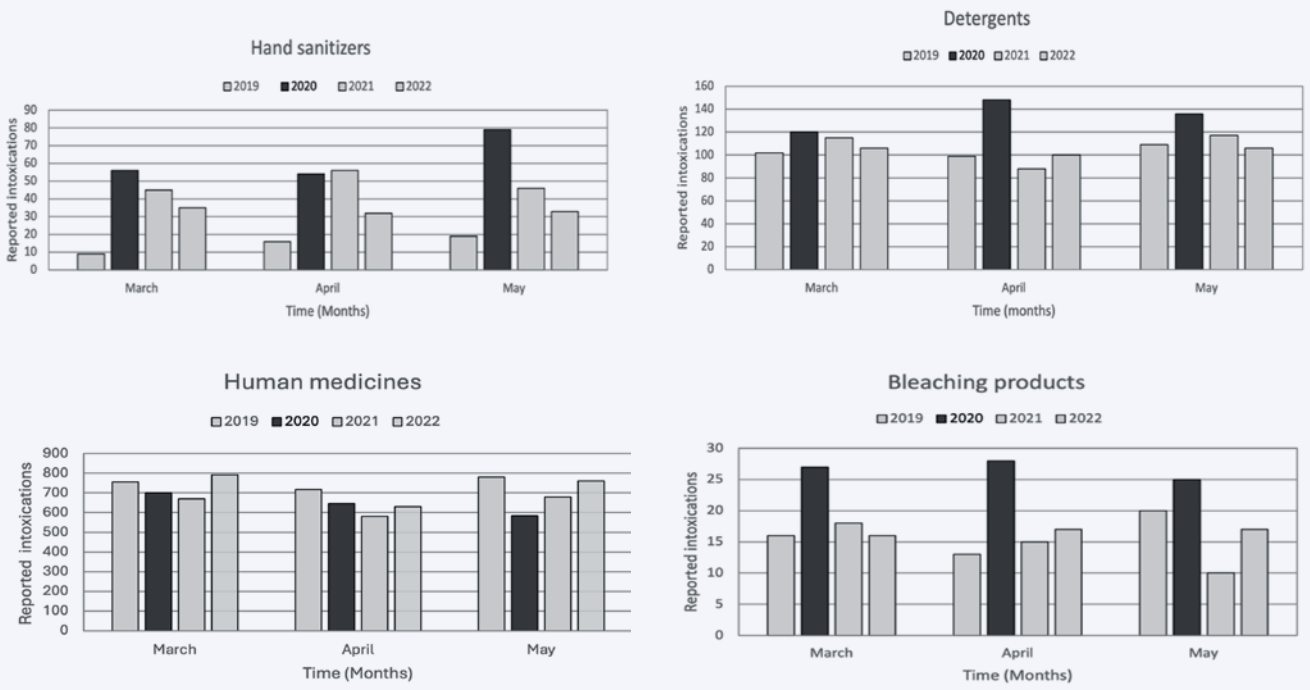
When analyzing the monthly numbers of reported intoxications related to hand sanitizers, during lockdown, we observed 56 reported exposures in March, 54 reports during April and 79 reports during May (Figure 2. Upper left). Compared to 2019, this is an increase of 522%, 238% and 316% for March, April, and May respectively. In 2021 and 2022, we observed a steady decrease in the number of reports compared to 2020 for March with 45 reports (-17%) and 35 reports (-35%) respectively and for May with 46 reports (-42%) and 33 reports (-58%) respectively, while for April we initially observed a slight increase in 2021 with 56 reports (+4%) followed by a considerable decrease in 2022 with 32 reports (-41%).

When we look at the monthly numbers of reported intoxications related to detergents, during lockdown, we observed 120 reported exposures in March, 148 exposures in April and 136 exposures in May (Figure 2. Upper right). Compared to 2019, this is an increase of 18%, 50% and 25% for March, April, and May respectively.

When evaluating the monthly numbers of reported intoxications related to bleaching products, during lockdown, we observed 27 reported exposures in March, 28 exposures in April and 25 exposures in May (Figure 2. Lower right). Compared to 2019, this is an increase of 69%,115% and 25% for March, April, and May respectively. In 2021 and 2022, we observed an important decrease for all 3 months compared to 2020.

Regarding the reported intoxications of human medication, during lockdown, we observed 700 reported exposures in March, 636 exposures in April and 575 exposures in May (Figure 2. Lower left). Compared to 2019, this is a decrease of 12%, 9% and 34% for March, April, and May respectively. In 2021, compared to lockdown we observed a further decrease of reports for March (-4%) and April (-9%), while for May we already observed an increase of reports

FIGURE 2: Monthly numbers of reported oral intoxications in children made to the Belgian poison center regarding household cleaning products, hand sanitizers and human medication in 2019, 2020, 2021 and 2022 (1st March to 31st May).



(+18%). In 2022, we observed an increase of reports compared to lockdown for all 3 months.

Characteristics of reported oral ingestions

Most cases involved young children, with children under the age of 6 consistently representing more than 75% of exposures throughout the study period (Table2). We observed a statistically significant change of age distribution over the different years ($\chi 2$= 78.353, $p < 0.001$). Notably, during lockdown, a statistically significant overrepresentation was observed in early childhood and preschool children with 1044 (40.3% (95% CI, 38.4%-42.2%)) and 329 (12.7% (95% CI, 11.4%-14.0%) cases respectively, as well as a statistically significant underrepresentation of adolescents with 172 (6.6% (95% CI, 5.6%-7.6%) cases (Table2). We noticed a statistically significant change of victim location over the different years ($\chi 2$=76.870, $p < 0.001$). During lockdown, we observed a statistically significant overrepresentation of exposures occurring at home with 2282 (88.0% (95% CI, 86.7%-89.3%) cases reported, as well as a statistically significant underrepresentation of reported exposures occurring at educational institutions and hospitals with 17 (0.7% (95% CI, 0.4%-1.0%) and 240 (9.3% (95% CI, 8.2%-10.4%) cases respectively (Table2). Furthermore, we also observed a statistically significant overrepresentation of exposures occurring in hospitals in 2021 (Table2). We observed a decrease of referrals to the emergency department/hospital during lockdown, compared to 2019 (300 (11.6% (95% CI, 10.4%-12.8%) vs 352 (13.3% (95% CI, 12.0%-14.6%)), as well as an increase in non-referrals during lockdown compared to 2019 (2219 (85.6% (95% CI, 84.2%-87.0%) vs 2224 (83.7% (95% CI, 82.3%-85.1%))

Discussion

This retrospective analysis of pediatric oral exposures reported to the Belgian Poison Center during the COVID-19 lockdown provides critical insights into the unintended consequences of public health measures on child safety. Our findings demonstrate significant changes in exposure patterns to hand sanitizers, bleaching agents, and detergents, coinciding with the heightened preventive behaviors associated with the pandemic. The true exposure remains difficult to assess as only the documented reports could be studied. Misinformation disseminated by the media regarding hygiene practices may have also contributed to these changes though we did not explicitly assess its impact on our data (14, 15). These results contribute to the growing body of evidence highlighting the need for targeted interventions to reduce the risks of accidental oral ingestions in children during public health crises (16, 17). Opportunities to strengthen the current product safety standard to further reduce exposures exist and have been proposed even before the COVID-19 pandemic, as well as possible natural alternatives to chemical-based hand sanitizers (18, 19).

The most striking finding in this study is the dramatic surge in oral ingestion cases with hand sanitizers, which increased by 329% during the lockdown period compared to 2019. The rapid adoption of hand hygiene measures during the early stages of the pandemic, driven by fears of SARS-CoV-2 transmission via contaminated surfaces, likely contributed to this sharp rise. The persistence of elevated hand sanitizer ingestion cases in the following years (234% increase in 2021 and 127% in 2022) underscores the continued risks associated with these products. Additionally, our study identified notable increases in cases of oral ingestion with bleaching products and detergents, with an overall increase of 163% and 30%, respectively, during the lockdown. These increases are likely reflective of the expanded use of cleaning agents driven by stricter sanitation measures during the lockdown. These findings are consistent with other international studies, which reported significant increases in calls to poison centers regarding hand sanitizers and household products during the pandemic's early months (9-13). Interestingly, despite a notable global trend of drug stockpiling during the pandemic, cases of oral ingestion involving human medications decreased by 20% during the same

TABLE 2: Characteristics of the studied exposure calls received by the Belgian Poison Center in 2019, 2020, 2021 and 2022 (1st March– 31st May).

	2019 n (%)	2020 n (%)	2021 n (%)	2022 n (%)	p
All cases	**2657**	**2591**	**2406**	**2644**	
Age group (years)					<0,001
Infant/Toddler (<2 years)	792 (29.8)	779 (30.1)	716 (29.8)	771 (29.2)	
Early childhood (≥2 and <4 years)	1068 (40.2)	1044 (40.3)*	872 (36.2)	937 (35.4)§	
Preschool (≥4 and <6 years)	291 (11.0)	329 (12.7)*	254 (10.6)	304 (11.5)	
Schoolchild (≥6 and <12 year)	289(10.9)	267 (10.3)	277 (11.5)	329 (12.4)	
Adolescent (≥12 and <18 years)	217 (8.1)§	172 (6.6)§	287 (11.9)*	303 (11.5)*	
Victim location					<0,001
Educational institutions	73 (2.8)*	17 (0.7)§	50 (2.1)	56 (2.1)	
Home	2187 (82.3)	2282 (88.0)*	1968 (81.8)	2201 (83.2)	
Hospital	332 (12.5)	240 (9.3)§	325 (13.5)*	290 (11.0)	
Other	65 (2.4)	52 (2.0)§	63 (2.6)	97* (3.7)	
Referred treatment location					<0,001
Emergency/hospital	352 (13.3)*	300 (11.6)	284 (11.8)	275 (10.4)	
GP	67 (2.5)	51 (2.0)	59 (2.5)	62 (2.3)	
Intensive care	6 (0.2)	12 (0.5)	9 (0.3)	2 (0.0)	
Non referral	2224 (83.7)	2219 (85.6)	2044 (85.0)	2298 (86.9)	
Specialist	8 (0.3)	9 (0.3)	10 (0.4)	7 (0.3)	

* Statistically significant positive adjusted residuals with Bonferroni correction (Critical value Z depending on significance threshold) (p<0.001)
§ Statistically significant negative adjusted residuals with Bonferroni correction (Critical value Z depending on significance threshold) (p<0.001)

period. This finding aligns with reports from other international studies, further supporting the observed decrease (9, 20). Further research is needed to fully understand the relationship between drug stockpiling and changes in drug ingestion cases during the pandemic

The age distribution of exposures in this study also warrants significant attention. Consistent with previous literature, children under the age of six accounted for most oral ingestion cases, with a disproportionately high number of incidents in the early childhood (40.3%) and preschool (12.7%) age groups during the lockdown (21, 22). The increased time spent indoors during the lockdown, coupled with changes in household routines, likely provided more opportunities for young children to come into contact with hazardous substances. On the other hand, the decrease in adolescent exposures (from 8.1% in 2019 to 6.6% in 2020) may reflect a combination of factors, including increased awareness of safety precautions and reduced environmental exposure, as schools were restricted.

This analysis also revealed a significant shift in the location of exposures, with a significant increase and disproportionately high number of incidents occurring at home during the lockdown (88.0% of all cases in 2020), compared to 2019 (82.3%). On the other hand, the study revealed a significant decrease of incidents occurring in schools and hospitals. This shift reflects the closure of schools and highlights the home environment as a key area for prevention efforts during lockdowns. Additionally, the decrease in hospital-related exposures could be attributed to the fear of contracting COVID-19 in healthcare settings, leading families to contact poison control centers instead of seeking emergency care.

Another finding of this study is the decrease in referrals to the emergency department/hospital during the lockdown, compared to 2019, with non-referrals increasing correspondingly. This is a trend that has already been described by other international studies and may have been explained by a climate of fear for COVID-19 infection when visiting a hospital or emergency room (23, 24).

The strengths of this study include its large sample size and the timely collection of data during an unprecedented global health crisis, providing valuable insights into the impact of the COVID-19 lockdown on pediatric toxic oral ingestion patterns. However, our study also has limitations. First, the retrospective nature of the data restricts our ability to establish causal relationships. Second, we were unable to assess the effectiveness of specific preventive measures implemented during the pandemic, which warrants further research. Additionally, our analyses rely on reports submitted to the Belgian Poison Center, which likely capture only a fraction of total exposures, as some cases may have been managed independently at home or treated through in-person medical attention. Moreover, poison center specialists rely on reported information to manage and treat exposures, meaning that the data in their case management systems is influenced by the accuracy of the description of the caller, potentially leading to underreporting or misclassification of cases.

Conclusion

This study provides valuable evidence of the significant shifts in pediatric oral ingestion patterns with hand sanitizers, bleaching agents, detergents, and human medication during the COVID-19 lockdown. These findings highlight the need for sustained public health efforts to ensure the safe use of household products and to mitigate the risks of unintentional exposures in children, especially during public health emergencies. Future research should evaluate the effectiveness of preventive interventions, including public awareness campaigns and product safety regulations, to mitigate pediatric toxic oral ingestion risks during such crises.

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Effectiveness of the Buzzy Device in Managing Needle Pain in Children: A Systematic Review

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Keywords
Procedural analgesia ; pain relief ; paediatric.

Abstract

Background:
Needle procedures often cause pain and anxiety in children, highlighting the necessity for effective pain management strategies. This systematic review aimed to evaluate the effectiveness of the Buzzy® device, a non-pharmacological intervention combining cold and vibration, in managing paediatric needle pain using a standardized pain assessment tool.

Methods:
A systematic search was conducted in December 2024 using PubMed, CINAHL, Embase, and Google Scholar databases to identify randomized controlled trials. Inclusion criteria were studies involving children aged 2–18 years undergoing needle-related procedures, employing the Faces Pain Scale-Revised (FPS-R), and comparing the Buzzy® device against control groups or alternative interventions like topical anaesthetics, distraction techniques, or other non-pharmacological methods. Study quality was assessed using the Risk of Bias 2 (RoB 2) tool.

Results:
8 RCTs comprising 1.569 paediatric participants were included. Studies consistently demonstrated significant pain reduction with Buzzy® compared to no intervention. Comparisons with topical anaesthetics showed mixed results: Buzzy® provided rapid analgesia advantageous in emergency settings but was commonly less effective in pain reduction than topical anaesthetics like EMLA cream. Buzzy® persistently outperformed other non-pharmacological methods, such as ShotBlocker® and DistrACTION® Cards, and was most effective when combined with distraction techniques. Risk of bias was moderate across studies, primarily due to the inability to blind participants and practitioners.

Conclusion:
Our work provides nuanced support for the claim that the Buzzy® effectively reduces needle-related procedural pain in children, particularly in acute clinical settings where a rapid onset of analgesia is required. Further research employing standardised methodologies is recommended to strengthen the evidence base for multimodal paediatric pain management strategies.

What is already known on this topic
Children often undergo painful procedures when they visit or stay in a paediatric hospital.

What this study adds
Procedural analgesia using a Buzzy device significantly relieves pain sensation in children who undergo a needle procedure.

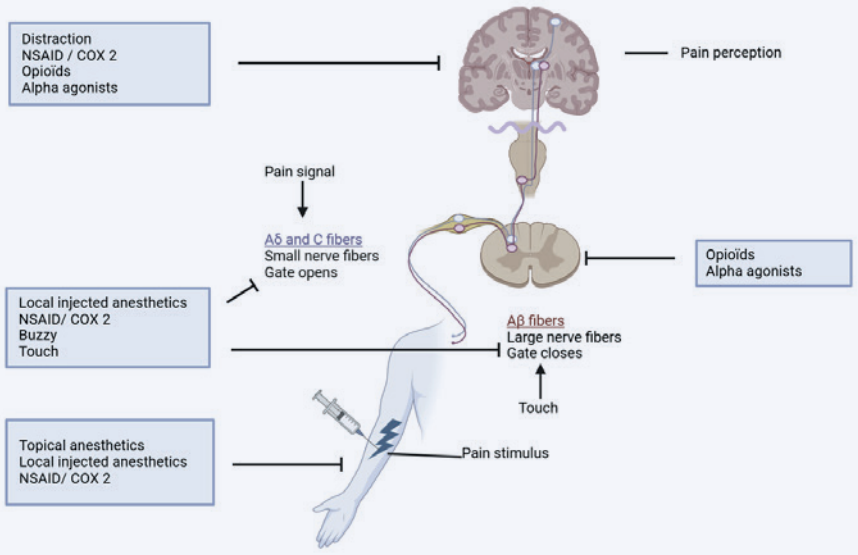
Introduction

Children are frequently exposed to various needle-related procedures, including routine vaccinations, peripheral catheterisation and venipunctures. These procedures, commonly performed during emergency department visits, outpatient clinics or hospital admissions, can induce considerable distress in paediatric patients (1–3). Despite the existence of evidence-based pain management strategies, their implementation in clinical practice remains insufficient (4). Needle pain and injection fear are highly prevalent among children. Effective pain management techniques can improve procedure outcomes and reduce the need for repeated attempts (5,6).

Pain modulation in the spinal cord occurs through interactions between C-, Aδ-, and Aβ-fibres, as described by the Gate Control Theory (7). When a painful stimulus occurs, the signal travels through C- and Aδ-fibres (small fibres), which open the pain gate by transmitting nociceptive input to second-order neurons in the dorsal horn. In contrast, Aβ-fibres (large fibres), responsible

FIGURE 1: Pain mechanism.

Overview of pharmacological and non-pharmacological strategies targeting pain perception in paediatric patients. Various interventions—ranging from topical and locally injected anesthetics, NSAIDs/COX-2 inhibitors, opioids, and alpha agonists to non-pharmacological techniques such as distraction, tactile stimulation, and the use of devices like Buzzy®—act at different levels to modulate the child's pain experience. Several of these strategies influence the transmission of nociceptive signals via A-delta and C fibers, either by inhibiting signal conduction or by modulating central pain processing



for touch and vibration, help close the gate and reduce pain perception. This explains why non-pharmacological interventions, such as vibration and cold therapy, can effectively relieve pain by stimulating Aβ-fibres. Additionally, topical anaesthetics reduce pain signals transmitted by (Aδ and C-fibres and simultaneously stimulate Aβ-fibres through touch or massage, enhancing pain relief (8,9).

Evidence-based multimodal strategies, including pharmacological and non-pharmacological approaches, are essential for effective paediatric pain management, particularly during needle-related procedures (10). Currently, various pain management strategies are employed in paediatric care to minimize discomfort and distress during medical procedures. These methods include non-pharmacological techniques like distraction cards and virtual reality, which divert attention from pain, and pharmacological options both local and systemic (e.g. vapo-coolant sprays, topical anaesthetics, sucrose solutions and analgetic drugs). Their effectiveness and tolerability in children make them valuable tools, with selection based on the procedure, age, and clinical context (11–13). An overview of the pain pathways and the possible pain relief approaches are given in Figure 1.

Non-pharmacological interventions can be categorized into three main groups: behavioural methods, supportive methods, and physical methods. Behavioural methods include techniques such as relaxation and distraction, which focus on modifying the patient's pain perception and response. Supportive methods encompass interventions like the presence of a family member, watching videos, or listening to music, providing emotional comfort and reassurance to the patient. Lastly, physical methods involve sensory-based approaches such as deep touch, vibration, and thermal stimulation through the application of cold or heat, all of which act by altering pain perception through the gate control principle (14,15).

Among the pharmacological options available for pain reduction during needle-related procedures, Eutectic Mixture of Local Anaesthetics (EMLA) composed of 2.5% lidocaine and 2.5% prilocaine, is considered the gold standard (16,17). Topical aesthetic creams, such as EMLA, are commonly used to reduce pain during needle procedures but require 30 to 60 minutes to achieve analgesic effect (18,19). This delayed onset makes them impractical for use in acute settings, such as the emergency department, where rapid pain management is often required.

The Buzzy® device (MMJ Labs, Atlanta, Ga) is a compact medical device consisting of a cold pack designed as wings and a central component that produces vibration. Developed by paediatrician Amy Baxter, it uniquely combines cold application with tactile vibration, effectively reducing procedural pain through dual sensory stimulation. It represents one of the more recent developments in non-pharmacological pain management techniques (20,21). The proposed mechanism behind its analgesic effect is based on the Gate Control Theory of pain, which describes how simultaneous stimulation of sensory nerves (e.g., through vibration and cold) will reduce pain perception as mentioned above (21).

Compared to traditional methods (topical anaesthetics), vibration and cold therapy may provide faster analgesic effects and is associated with fewer side effects, making it particularly suitable for use in acute clinical settings, such as emergency departments, where rapid pain relief is essential (19).

There is a need for a new systematic review on the effectiveness of the vibration and cold therapy, as a substantial amount of new literature has emerged in recent years. While several recent systematic reviews have been published (20,22,23), they often compare studies that use different pain measurement tools or lack a non-active control group, limiting the comparability and overall conclusions.

Our systematic review provides a meaningful contribution to the current literature as it exclusively includes randomized controlled trials (RCTs) that use a consistent pain assessment tool across all studies. Furthermore, each included RCT compares the Buzzy® device to either a non-active comparator or a control group receiving the standard of care, ensuring a more robust and clinically relevant evaluation of its effectiveness.

The aim of the study is to evaluate the evidence on the efficacy of the Buzzy® device, which combines cold and vibration, in managing needle-related procedural pain and associated outcomes in the paediatric population up to 18 years old , using a well-validated and standardized assessment tool.

Materials and methods

Protocol

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24). To clearly define the research question, the PICO (Population, Intervention, Comparison, Outcome) framework was utilized. Specifically, the review focused on evaluating the effectiveness of the Buzzy® device among children undergoing needle-related procedures. The effectiveness was assessed by comparing observed pain levels, measured with

the Faces Pain Scale-Revised (FPS-R), between the intervention group and a control group receiving either standard care or no intervention.

Faces pain scale-revised

The Faces Pain Scale – Revised (FPS-R) is a self-report instrument designed to assess pain intensity in children. It consists of six facial expressions ranging from no pain (score 0) to severe pain (score 10). The FPS-R is a validated and widely used pain assessment tool, demonstrating strong reliability and validity across paediatric populations. Research suggests that it is most effective for children aged 4 to 12 years, as it aligns well with their cognitive and emotional development, allowing for an accurate representation of their pain experience (24,25). We chose the use of FPS-R over the Wong-Baker Faces Pain Scale because the latter may confound pain with emotions, as it features a smiling face for no pain and a crying face for severe pain. In contrast, the FPS-R uses neutral expressions, making it a more objective and reliable tool for paediatric pain assessment (24).

Eligibility criteria

This systematic review included only randomized controlled trials (RCTs). Articles were deemed eligible for inclusion if they met the following criteria: participants aged 2–18 years, study design classified as an RCT, use of the Faces Pain Scale – Revised (FPS-R), involvement of needle-related procedures (e.g., single injections, intravenous therapy, vaccinations, or blood sampling), compared the experimental group to control subjects receiving either no intervention or standard of care, and publication in English or Dutch. Studies were excluded if they focused on dental procedures, involved children with cognitive impairments, or included participants with conditions that could affect sensitivity to cold.

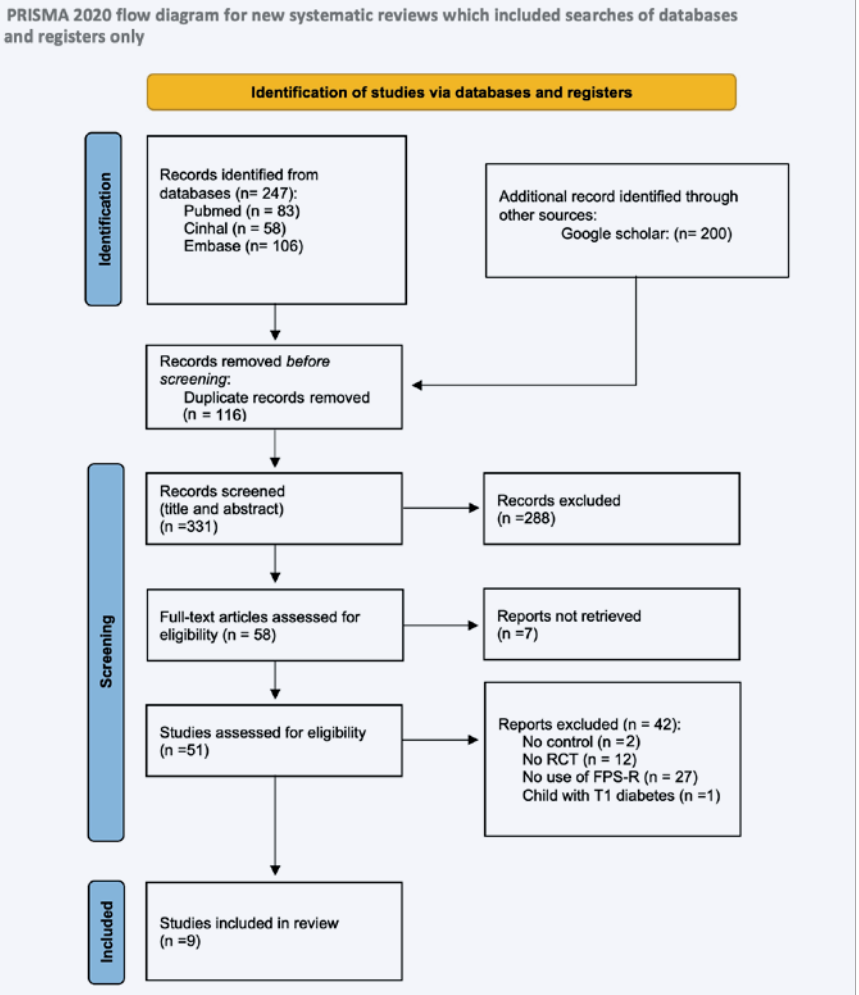
Search strategy and study selection

Searches were conducted between December 14 and December 18, 2024 using several databases, including PubMed, CINAHL, and Embase. Search terms consisted of a combination of relevant keywords and search terms. The search strategy was customized for each database. The complete study selection is detailed in figure 2. The initial screening was based on titles and abstracts. Each study was assessed for its eligibility based on the inclusion criteria. If studies appeared to meet the eligibility criteria, their full texts were analysed.

Data extraction

Data extraction was performed manually by the researchers. The following information was collected from the included studies: pop-

FIGURE 2: PRISMA flow diagram.
RCT indicates randomized controlled trial. FPS-R indicates Faces pain scale revised.



* Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

TABLE 1: Risk of bias assessment of the included studies.

Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Nasser A. Haidar et al. (2024)	+	-	+	-	+	-
Sivri B. B., Feng. Y. S. et al. (2023)	+	-	+	-	+	-
Sivri B. B., Balci S. et al. (2023)	+	-	+	-	-	-
Lescop, K et al. (2021)	+	X	+	-	+	-
Inal, S. et al. (2020)	+	-	+	-	+	-
Sivri B. B., Balci S. et al. (2019)	+	-	+	-	-	-
Potts, D et al. (2019)	-	-	+	-	-	X
Inal, S et al. (2012)	+	-	+	-	+	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

TABLE 2: Studies that compare Buzzy® versus topical anaesthetics.

Title	Author(s)	Year	Journal	Mean age/ Sex	Number of participants	Comparison/ Control
Efficacy of Buzzy Device Versus EMLA Cream for Reducing Pain During Needle-Related Procedures in Children: A Randomized Controlled Trial(21)	Nasser A. Haidar et al.	2024	Pediatric Emergency Care	Mean age: 6.5 ± 3.1 years Sex distribution: 49% male: -EMLA: 49.4 % -BUZZY®: 48.6 %	N= 300 154: Buzzy® group 146: EMLA group	Buzzy® device vs EMLA cream (control)
A Vibrating Cold Device to Reduce Pain in the Pediatric Emergency Department: A Randomized Clinical Trial(29)	Potts, D et al.	2019	Pediatric Emergency Care	Mean age: 8.17 years (IQR: 6.2–11.9) Sex distribution: -119 males (53.1%) - 105 females (46.9%)	N= 224 114: Buzzy® (VCD) group 110: Topical Lidocaine (TL) group	VCD group (Buzzy® device) vs TL group (4% topical lidocaine cream = standard of care)
The effectiveness of the Buzzy® device to reduce or prevent pain in children undergoing needle-related procedures: The results from a prospective, open-label, randomized, non-inferiority study(28)	Lescop, K et al.	2021	International Journal of Nursing Studies	Mean age: 9 +- 3.15 years Sex distribution: -113 (52.6%) female -106 male (47.4%)	N= 219 randomized 215 included 108: Buzzy® 107: Lidocaine patch)	Buzzy® vs Control group: Lidocaine patch applied 1 hour before procedure

TABLE 3: Studies that compare Buzzy® versus DistrACTION® cards (DC).

Title	Author(s)	Year	Journal	Mean age/ Sex	Number of participants	Comparison/ Control
The Effect of External Thermomechanical Stimulation and Distraction on Reducing Pain Experienced by Children during Blood Drawing(31)	Inal, S. et al.	2020	Pediatric Emergency Care	Mean age: Control: 9.3 ± 2.1 years -Buzzy®: 9.1 ± 2.0 years Distraction Cards: 9.5 ± 1.8 years Combi: 9.2 ± 1.7 years Sex distribution: -108 female (49.5%) -110 male (50.5%)	N= 218: 56: control, no intervention 55: Buzzy® 55:distraction Cards 52: Buzzy® + DistrACTION Cards	Group 1 (control): No intervention vs Group 2: Buzzy® vs Group 3: DistrACTION Cards vs Group 4: Combination of both methods
The effect of Buzzy® and DistrACTION® cards on reducing pediatric pain and fear during blood collection in the rheumatology polyclinic: A randomized controlled trial(30)	B. B. Sivri et al.	2023	Journal of Pediatric Nursing	Mean age: 9.21 ± 2.15 years Sex distribution: - 45 male (46.9%): - Buzzy®: 53.1% - DC: 59.4% - Control: 53.1%	N= 224 114: Buzzy® (VCD) group 110: Topical Lidocaine (TL) group	Buzzy® device vs DistrACTION® Cards vs Control: no intervention

ulation characteristics (e.g., mean age, gender distribution, and sample size), details of the intervention, reported outcomes, and key findings. The extracted data were summarized and structured according to the intervention used for comparison with the Buzzy® Device.

Risk of Bias assessment

All included studies were systematically assessed for their risk of bias. To evaluate the methodological quality of the randomized controlled trials (RCTs), the Risk of Bias 2 (ROB-2) tool was used (26). This tool allows for a structured assessment of potential biases that could influence study outcomes. The risk of bias assessment for all included articles can be found in Table 1. For each included study, the risk of bias was assessed for deviations from intended interventions (performance bias), missing outcome data (attrition bias), the measurement of the outcome (detection bias), the selection of the reported result (reporting bias), and the randomization process (allocation bias), after which an overall risk of bias was calculated for each study.

Primary outcome

The primary outcome of this systematic review was to evaluate the efficacy of the Buzzy® device in reducing pain during needle-related procedures in the paediatric population compared to a control group receiving either no intervention or standard of care. The outcome parameter specifically assessed was the pain experienced by the child during or immediately after the

	Outcome	Key findings
	Pain, anxiety	EMLA cream = more effective in reducing pain and anxiety for needle procedures with observer assessment (not with self-assessment) Buzzy® device offers rapid action (valuable in emergency departments) *Needle Procedure:* *Venipuncture and intravenous (IV) cannulation*
	Pain, anxiety	Pain scores = similar between Buzzy® and TL. IV procedure time = significantly shorter with VCD (3.0 min vs. 40.5 min, p < 0.0001) *Intervention*: Intravenous (IV) catheter insertion
	Pain	Buzzy® did not meet non-inferiority criteria for pain relief. 43% of children removed the cold wings due to discomfort. Buzzy® is a cheaper but less effective alternative. *Interventions*: Vaccinations (93.5%) and venipuncture (6.5%)

	Outcome	Key findings
	Pain, anxiety	All intervention groups = significantly lower pain than control (p < 0.001). The Buzzy® + DistrACTION combination = most effective Buzzy® outperformed distraction alone. *Intervention*: Venipuncture
	Pain, anxiety	Buzzy® = most effective for reducing pain and fear during venipuncture DistrACTION® Cards : less effective than Buzzy®. *Intervention* : Venipuncture

intervention. This outcome was assessed through a descriptive comparative analysis. The efficacy of the device was determined by measuring pain using the Faces Pain Scale-Revised (FPS-R), a validated assessment tool.

Results

Study selection

The initial search across the three databases (including PubMed, CINAHL, and Embase) yielded a total of 247 articles. In addition to the primary search strategy, Google Scholar provided an additional source to identify relevant articles. A total of 560 results were retrieved using general search terms. Due to feasibility constraints, only the first 200 articles were screened for potential inclusion. The procedures for article selection within these databases are outlined in the PRISMA flowchart (Figure 2) (27). After applying the inclusion criteria and assessing the quality of the studies, a total of 8 articles met the eligibility requirements and were included in this systematic review. These studies collectively involved 1569 participants. The selection process ensured that only studies of the desired methodological quality were incorporated.

Characteristics of the studies

A total of eight studies were included in this review, comprising a total of 1569 children. All studies were conducted between 2010 and 2022. Each study utilized the Faces Pain Scale - Revised to assess pain outcomes. All included studies incorporated a control group for comparison. The control condition consisted of either no intervention or the application of topical anaesthesia, using lidocaine or EMLA cream. The mean age of participants across studies ranged from 6.5 to 10.45 years, with relatively balanced sex distributions. The studies investigated the effectiveness of the Buzzy® device in various needle-related procedures, including venipuncture, intravenous (IV) cannulation, blood specimen collection, and intramuscular injections. Comparators included topical anaesthetics (e.g., EMLA cream, lidocaine patch, see Table 2), distraction techniques (e.g., DistrACTION® Cards, see Table 3), other non-pharmacologic pain mitigation strategies (e.g., ShotBlocker®, see Table 4), and negative controls (see Table 5). Of the 8 included studies, three focused on comparing Buzzy® with topical anaesthetics, two evaluated Buzzy® against distraction-based methods, two examined its efficacy relative to other non-pharmacologic pain relief techniques and one compared the Buzzy® device with no intervention. These studies collectively provide insights into the effectiveness and limitations of Buzzy® across different procedural contexts.

Risk of Bias assessment

The risk of bias in the included RCTs was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool. As shown in Table 1, most studies presented "some concerns" in several domains, particularly in deviations from intended interventions (D2) and measurement of the outcome (D4). The concerns in D2 were mainly due to the lack of blinding across all studies, which could have influenced participants' or personnel's behaviour and, consequently, the study outcomes. One study was rated as having a high risk of bias in the domain D2 (deviations from intended interventions) as participants could remove refrigerated wings, potentially affecting the efficacy of the intervention (28). Additionally, the study by Potts et al. was judged to have a high overall risk of bias due to concerns across multiple domains (29). These findings reflect moderate methodological quality across studies and should be considered when interpreting the overall results.

Buzzy® vs. Topical Anaesthetics

Three studies evaluated the comparative effectiveness of the Buzzy® device against topical anaesthetics such as EMLA cream and lidocaine patches. Haidar et al assessed 300 paediatric patients undergoing venipuncture or IV cannulation (19). Observer-assessed pain and anxiety scores indicated superior efficacy of EMLA cream compared to Buzzy®, although self-reported pain scores showed no statistically significant differences. The rapid onset of Buzzy® was highlighted as a clinically relevant advantage in high-acuity settings. Similarly, Potts et al found that while pain scores between Buzzy® and 4% topical lidocaine cream were comparable, the procedural duration was significantly shorter with Buzzy® (3.0 min vs. 40.5 min, p < 0.0001), underscoring its practicality in time-sensitive environments (28). However, Lescop et al reported that Buzzy® failed to meet non-inferiority criteria relative to lidocaine patches for pain relief, with 43% of children requesting removal of the cold wings due to discomfort, indicating potential limitations in tolerability (29) .

TABLE 4: Studies that compare Buzzy® versus Shotblocker®.

Title	Author(s)	Year	Journal	Mean age/ Sex	Number of participants	Comparison/ Control
The Effect of 3 Methods (Buzzy, ShotBlocker, and DistrACTION Cards) Used While Taking Blood Samples From Children with Pain and Anxiety: A Randomized Controlled Trial(32)	B. B. Sivri et al.	2023	Pediatric Emergency Care	Mean age: 9 –12 years -ShotBlock: 10.34 ± 1.45 years -Buzzy®: 10.45 ± 1.55 years -Distraction Cards: 10.45 ± 1.32 years -Control: 10.38 ± 1.28 years Sex distribution: -131 female (54.1%) - 111 male (45.9%)	N=242 60: Buzzy® 61: ShotBlocker 60: Distraction Cards 61: No intervention	Buzzy® vs ShotBlocker vs DistrACTION Cards vs Control group: No intervention
The Effect on Pain of Buzzy® and ShotBlocker® during the Administration of Intramuscular Injections to Children: A Randomized Controlled Trial(33)	B.B. Sivri et al.	2019	Journal of Korean Academy of Nursing	Mean age: 8.92 ± 1.87 years Sex distribution: -69 female (46%) -81 male (54%)	N= 150 50: Control group 50: Buzzy® group 50: ShotBlocker	Control: no intervention vs ShotBlocker® vs Buzzy®

TABLE 5: Studies that compare Buzzy® versus control (no intervention).

Title	Author(s)	Year	Journal	Mean age/ Sex	Number of participants	Comparison/ Control
Relief of pain during blood specimen collection in pediatric patients(34)	Inal, S et al.	2012	MCN (Maternal Child Nursing)	Mean age: 9.3 +- 2.02 years Sex distribution: -56.7% male -43.3% female	N= 120 60: Buzzy® 60: Control no intervention	Buzzy® vs Control group: no intervention

Buzzy® vs. Distraction Methods

Two studies compared the Buzzy® device with distraction techniques such as DistrACTION® Cards. Inal et al and Sivri et al both examined the impact of Buzzy® and DistrACTION® Cards on procedural pain and anxiety (30) (31). Inal et al. found that all intervention groups had significantly lower pain levels than controls ($p < 0.001$), with the combination of Buzzy® and DistrACTION® Cards being the most effective. Similarly, Sivri et al. demonstrated that Buzzy® alone resulted in the lowest procedural pain and fear scores across all evaluative measures, including self-report, parental assessment, and researcher evaluation. Both studies conclude that while Buzzy® is effective as a standalone intervention, its pain and anxiety-reducing effects are enhanced when combined with distraction techniques.

Buzzy® vs. Other Pain-Relief Devices

Two studies compared the Buzzy® device with alternative non-pharmacologic pain relief methods. Sivri et al and Sivri and Balci both found that Buzzy® was more effective than ShotBlocker® in reducing procedural pain during venous blood collection and intramuscular injections, respectively (32) (31). Additionally, Sivri et al. showed that Buzzy® and DistrACTION® Cards provided comparable pain relief, both outperforming ShotBlocker®. These findings indicate that Buzzy® is a superior non-pharmacological intervention for pain management in paediatric needle-related procedures, particularly when compared to ShotBlocker®.

Buzzy® vs. Control (no intervention)

Inal and Kelleci investigated the effect of Buzzy® on blood specimen collection in 120 children, finding significantly lower pain and anxiety levels in the Buzzy® group compared to controls ($p < 0.001$) (33).

Anxiety Outcomes

Several studies also examined the impact of Buzzy® on procedural anxiety. While pain relief was the primary focus, anxiety reduction was frequently assessed as a secondary outcome. Studies comparing Buzzy® with topical anaesthetics found that EMLA cream generally led to greater anxiety reduction, particularly in observer-assessed measures. However, Buzzy® demonstrated significant advantages in settings requiring rapid intervention, where prolonged preparation time for topical anaesthetics was not feasible. In comparisons with distraction techniques, Buzzy® was often found to be more effective at reducing both pain and anxiety, with the combination of Buzzy® and DistrACTION® Cards yielding the lowest anxiety scores.

Discussion

Poorly managed pain in children can result in significant psychological effects, including increased anxiety and, in some cases, the development of needle phobia (34). Pain experienced by children during medical procedures can significantly influence their subsequent healthcare behaviours, potentially leading to avoidance of medical care or decreased compliance with future treatments (35) (36). Consequently, effective pain management in paediatric care is crucial not only to address immediate physical comfort but also to mitigate long-term psychological effects and reduce the risk of developing procedure-specific anxieties.

The aim of this study was to evaluate the evidence regarding the effectiveness of the cold and vibrations device in managing needle-related procedural pain in children utilizing a well-validated and standardized assessment instrument. This review synthesizes

	Outcome	Key findings
	Pain, anxiety	Buzzy, ShotBlocker, and DistrACTION Cards significantly reduced pain and anxiety. Buzzy and DistrACTION Cards were the most effective. ShotBlocker was less effective but better than no intervention. The control group experienced the most pain and anxiety. *Intervention*: Venipuncture
	Pain	Control group = significantly higher pain than the ShotBlocker® and Buzzy® groups. Buzzy® group = significantly less pain than the both the ShotBlocker® and control groups (p<.001) *Intervention*: IM injections with procaine penicillin

	Outcome	Key findings
	Pain, anxiety	Buzzy® = significantly lower pain and anxiety levels (p<0.001) No significant effect on venipuncture success *Intervention*: Venipuncture

findings from 8 RCTs assessing the efficacy of the Buzzy® device in reducing pain in children undergoing needle-related procedures compared to alternative methods, such as topical anaesthetics and distraction techniques, as well as to no intervention. The primary findings from the reviewed RCTs indicated variable efficacy of the Buzzy® device. While some studies demonstrated equivalence or superiority of Buzzy® in comparison to distraction techniques alone or no intervention, other studies concluded inferior or equivalent efficacy compared to topical anaesthetics. Specifically, EMLA cream consistently outperformed Buzzy® in observer-rated pain scores, though self-reported scores were sometimes comparable between groups. Notably, Buzzy® provided faster analgesic action, an important advantage in settings such as emergency departments where waiting times are critical. Buzzy® outperformed distraction techniques and other non-pharmacologic devices (e.g., ShotBlocker®) in reducing procedural pain. Its effectiveness in anxiety reduction was notably enhanced when combined with distraction methods.

Effectiveness of Buzzy® Versus Alternative Interventions

The findings of this review largely confirm previous literature which highlighted mixed results regarding Buzzy®'s effectiveness. Similar to prior studies the current systematic review found that topical anaesthetics generally offer superior pain reduction compared to cold and vibration therapy in paediatric needle-related procedures (37,38). However, topical anaesthetics have a slower onset of action and additional practical barriers, such as longer application time, whereas cold and vibration therapy provides benefits like rapid application and ease of use. The present systematic review demonstrates that combined cold and vibration therapy significantly reduces pain during needle-related procedures compared to no intervention. Multiple RCTs -using other pain scales such as the Wong-Baker Face Pain Scale- consistently support this finding. For example, Redfern et al. showed reduced pain scores with cold and vibration during paediatric vaccinations (mean pain score 3.56 vs. 5.92, p=0.015) (39). Similarly, Canbulat et al. found significant pain and anxiety reduction during paediatric immunizations and intravenous cannulation (14). Additionally, Simoncini et al confirmed these results in venipuncture procedures (mean pain scores 2.5 vs. 4.7, p<0.001) (40). The consistency of these results highlights cold and vibration therapy as an effective and practical non-pharmacological approach for managing procedural pain in clinical settings.

However, it should be noted that not all studies confirm these findings. A recent RCT by Yılmaz et al. reported no significant difference in pain and anxiety levels with the use of cold and vibration therapy (Buzzy® device) compared to no intervention during peripheral intravenous cannulation in children (mean pain score 1.36 vs. 1.33, p>0.05) (41). The lack of a significant effect of the Buzzy® device in this study may be partially explained by the relatively higher mean age of the participants (12.8 ± 3.0 years). Previous studies that reported a significant reduction in pain and anxiety often included younger children, who may be more receptive to the Buzzy® due to its visual appeal and distracting features. In older children and adolescents, these sensory stimuli may be less engaging, thereby reducing the device's effectiveness. Furthermore, the sample size in this study (n = 60) was relatively small compared to other trials, which may have limited the statistical power to detect subtle differences in pain and anxiety levels between groups. Together, these factors could explain the discrepancy between the findings of the Yilmaz study and the previous ones. This discrepancy indicates that, while generally effective, the benefits of cold and vibration therapy may vary depending on the clinical context or specific patient characteristics. Further research is needed to assess these variations in more detail.

Additionally, a recent RCT by Erdogan and Ozdemir compared the Buzzy® device with distraction cards and virtual reality in children undergoing venipuncture (42). The Buzzy® device showed a higher effectiveness, achieving the lowest mean pain and anxiety scores compared to the other methods. These findings further support the efficacy of combined cold and vibration therapy, highlighting its advantage over alternative distraction methods in paediatric clinical practice. On top of that, in our systematic review, the ShotBlocker device appeared to be less effective than the Buzzy® in reducing procedural pain in children. However, there is currently a limited number of studies directly comparing these two interventions. Another systematic review that included four studies on this topic reported mixed results, suggesting that the relative effectiveness of these methods may vary depending on the clinical context (23). Interestingly, the study by Canbulat Sahiner et al. found that ShotBlocker was more effective than Buzzy® in reducing pain during insulin injections in children with type 1 diabetes (43). This discrepancy may be attributed to differences in procedure type (repetitive insulin injections versus single venipuncture), which can alter pain perception over time (44). Overall, Buzzy® is effective in managing paediatric procedural pain and anxiety, particularly when integrated with complementary distraction strategies. At present there are no trials available that directly compare Buzzy® to nitrous oxide, a common and effective analgesic and anxiolytic.

Strengths and Limitations

A strength of this systematic review is that all included randomized controlled trials (RCTs) featured a control group and employed the same validated instrument for assessing pain. Although several recent systematic reviews have evaluated the effectiveness of Buzzy® in reducing pain during needle-related procedures, this is, to our knowledge, the first review specifically focused on pain outcomes assessed using a consistent measurement tool.

However, this review also has several limitations. Firstly, considerable heterogeneity existed among the interventions evaluated in the included studies. Additionally, none of the included RCTs employed blinding, primarily due to the inherent nature of the intervention, making participant and practitioner blinding impractical. Another limitation is the absence of a meta-analysis, mainly due to the insufficient number of comparable studies evaluating similar intervention strategies. Therefore, the conclusions of this review are based solely on qualitative assessments, potentially limiting the robustness and generalizability of the findings.

Clinical implementation

Clinically, the results suggest that while Buzzy® may not universally outperform established topical anaesthetics, it holds substantial value in specific contexts, particularly where rapid pain relief is required, such as emergency or outpatient settings. The immediate onset of analgesic effects and ease of use make it an attractive option for healthcare providers, especially in environments demanding swift procedural actions, like emergency departments. However, clinicians should balance the convenience of Buzzy® against the superior analgesic efficacy of topical anaesthetics in settings where procedural delay is feasible. Currently, pain management techniques are still underutilized in clinical practice, indicating a clear need for greater integration of effective pain relief strategies into standard care. Therefore, although Buzzy® presents clear advantages for reducing procedural pain, its application should be carefully considered depending on the specific clinical circumstances.

Conclusion

In conclusion, the review provides nuanced support for the Buzzy® device as a practical, although sometimes less effective, alternative to topical anaesthetics in managing paediatric needle-related procedural pain. Buzzy® offers notable advantages such as rapid onset, ease of use, and superior performance compared to distraction alone or other non-pharmacologic devices like ShotBlocker®. The clinical decision to use Buzzy® should consider the specific context, urgency, and procedural environment. Recommendations for practice include utilizing multimodal approaches combining Buzzy® with distraction techniques to optimize pain and anxiety relief outcomes.

All authors certify that they have no conflicts of interest (COIs), including financial or other relationships with the product or its manufacturer. Moreover the manufacturer had no influence on the design, methodology or reporting of this review.

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- ✔ **Fibres** (0,4g/100ml)
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* En ligne avec les nouvelles recommandations ESPGHAN 2024. ESPGHAN position paper on the diagnosis, management, and prevention of cow's milk allergy. JPGN. 2024;78(2):386-413.

Clinical Outcomes of Belgian Children Following Kidney Transplantation, Comparative Analysis from 2005 to 2022

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Keywords
End stage renal disease ; kidney transplantation ; renal replacement therapy ; hypertension ; growth stunting.

Abstract

The aim of this study was to analyze the annual cross-sectional data on the outcome of all patients followed after pediatric kidney transplantation in Belgium, as collected for the Convention of Pediatric Nephrology from 2018-2022. During this period, a total of 569 entries of individual follow-up data were included in the registry with a mean of 113.8 entries annually, mean follow-up time was 5.6 years post-transplantation. Most patients were classified as having chronic kidney disease (CKD) stage 2 or 3 (36.4% and 41.3% respectively). The mean estimated glomerular filtration rate (eGFR) was lower compared to the 2005 cohort (61.8 + 25.4 ml/min/1.73 m2 vs. 68.1 + 17 ml/min/1.73 m2, respectively ($p<0.05$)). eGFR decreased with the number of years of follow-up, which was particularly evident in boys but not in girls. We compared our findings to the Belgian registry cohort of 2005 and to the recently published data from North-American and European registries. Overall, we observed a positive evolution in growth and cardiovascular outcomes, with mean height and blood pressure standard deviation scores (SDS) significantly improving compared to both the 2005 and the international cohorts.

Introduction

Chronic kidney disease affects approximately 9% of the global population and causes approximately 1,2 million deaths annually (1). The incidence of kidney failure (KF) in the general population is approximately 144 cases per million people (pmp) (2).

In contrast, KF affects only 5 to 15 per million children (pmc) annually, worldwide. However, it is associated with significant morbidity, including cardiovascular disease and growth stunting (3). Moreover, children with KF face a mortality risk 30 times higher than that of the general pediatric population (4, 5). Kidney transplantation (KTx) is the preferred kidney replacement therapy (KRT) for both adults and children with KF, offering a significant survival advantage over dialysis (6). In Europe, the median incidence rate of pediatric KTx is 5.7 pmc, while in Belgium, the incidence exceeds 10.5 pmc, with approximately 24 pediatric KTx performed annually (7). Over the last few decades, there have been significant improvements in patient and graft survival rates among children receiving kidney transplants, largely due to advances in immunosuppressive therapy, surgical techniques, organ allocation policies and increased rates of living donor transplantation (6).

KF is a rare condition in children compared to adults, making evidence-based conclusions about optimal treatment and outcome parameters more challenging. To gather valuable data on pediatric KTx, several (inter)national retrospective data registries have been established, such as the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) and the Cooperative European Pediatric Renal Transplant Initiative Registry (CERTAIN) (8, 9). However, the CERTAIN registry does not include data from all six centers currently involved in pediatric KTx in Belgium.

In 2001, the Belgian Pediatric Nephrology Registry (BPNR) was established to collect comprehensive data on all children diagnosed with chronic kidney disease (CKD) in Belgium. The goal was to monitor and analyze outcomes before and after the diagnosis of pediatric KF in Belgium, as described by Hiep et al.

in 2010 (10). Unfortunately, this registry has not been continued. In 2009 the "Convention for Pediatric Nephrology" was introduced as a collaboration between the government, health insurance companies and pediatric nephrology centers (11). This convention aims to enable children with severe kidney diseases to live "as normal as possible" and "in the best feasible health condition" by offering additional financial support to the centers, enabling them to deliver tailored multidisciplinary care. To comply with the convention, each center is required to conduct regular face-to-face contact, provide individual medical reports to healthcare workers and provide outcome parameters for children receiving care under the convention. An interim analysis of the data was performed by Knops et al. (12).

This study aimed to analyze the data collected for the Convention of Pediatric Nephrology and provide information on the outcomes of all patients who underwent pediatric KTx in Belgium between 2018-2022. This study will report their clinical characteristics and outcomes and compare them with previously gathered data from 2005, as well as data from larger international registries.

Materials and Methods

In this multicenter, retrospective cross-sectional study, data were collected from the six academic centers in Belgium that perform KTx in children: CHU (Liege), HUDERF and UCL (Brussels), UZ Antwerp, UZ Ghent and UZ Leuven. The study included patients with CKD under 19 years of age who underwent KTx between January 1, 2018, and December 31, 2022, as described in the registry (the Convention of Pediatric Nephrology). According to national protocol, children under 19 years of age should receive a kidney transplant in pediatric and not adult centers. Each pediatric nephrology department was represented by at least one local investigator responsible for the patient inclusion and annual follow-up data. The principal investigator conducted a general audit to ensure data completeness. The following information was collected annually: sex, age, date of transplant, time since transplant, length, weight, systolic and diastolic blood pressure and serum creatinine levels. This assembly took place by circulating the same request to provide these data on the individual patients in current follow-up to all centers by the principal investigator at the same time of the year in relation to an annual convention meeting. Informed consent was not required given the anonymity of the data. Estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation (13). Creatinine was, depending on the center, measured by either the photometric or enzymatic method and has its known limitations in estimating the eGFR such as dependency on age and muscle mass (14). CKD stages were defined according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) (15).

TABLE 1: general characteristics of the study population

Characteristic	Study population
Sex (N (%))	Male: 349 (61.3%) Female: 220 (38.7%)
Age at follow-up (mean + SD) - Male population - Female population	12.8 ± 4.2 years - 13.0 ± 4.3 years - 12.7 ± 4.0 years
Age at transplant (mean + SD) - Male population - Female population Age categories (N (%))	7.4 ± 4.6 years - 7.4 ± 4.6 years - 7.5 ± 4.6 years 0-1 years: 27 (4.7%) 2-5 years: 244 (42.9%) 6-12 years: 193 (33.9%) 13-17 years: 104 (18.3%) > 18 years: 1 (0.2%)
Years of follow-up after transplant (mean + SD) - Male population - Female population	5.6 ± 4.3 years - 5.7 ± 4.3 years - 5.4 ± 4.3 years
Center of follow-up (N (%))	HUDERF: 133 (23.4%) UZL: 99 (17.4%) UZGent: 115 (20.2%) UZA: 104 (18.3%) Liege: 57 (10.0%) UCL: 61 (10.7%)
Entries per year of report (N (%))	2018: 121 (21.3%) 2019: 117 (20.6%) 2020: 116 (20.4%) 2021: 109 (19.2%) 2022: 106 (18.6%)
BMI SDS (mean + SD) - Male population - Female population	0.0 ± 1.2 - 0.1 ± 1.3 - -0.1 ± 1.0
Height SDS (mean + SD) - Male population - Female population	-1.2 ± 1.4 - -1.2 ± 1.5 - -1.2 ± 1.4
eGFR (mean + SD) - Male population - Female population	61.8 ± 25.4 mL/min/1.73m2 - 57.6 ± 25.7 mL/min/1.73m2 - 68.6 ± 23.5 mL/min/1.73m2
CKD stage (N (%))	1: 77 (13.5 %) 2: 207 (36.4 %) 3: 235 (41.3%) 4: 27 (4.7%) 5: 23 (4.0%)
Systolic blood pressure SDS (mean + SD) - Male population - Female population	0.7 ± 0.9 - 0.7 ± 0.9 - 0.7 ± 0.9
Diastolic blood pressure SDS (mean + SD) - Male population - Female population	0.6 ± 0.8 - 0.7 ± 0.8 - 0.5 ± 0,8

Hypertension was determined based on the clinical guidelines by Flynn et al., with hypertension defined as systolic or diastolic blood pressure above the 95th percentile for the patients' age, sex and height (16). Stunting was defined as a height standard deviation below -1,96 according to age and sex (17). Statistical significance was defined as a two-sided p-value <0.05. Data analysis was performed using SPSS version 29.0 for Windows (SPSS, Chicago, IL) and the results were compared with the previously published data by Hiep et al. (10).

TABLE 2: number of patients in follow-up per center, listed per year of report

	CHU (Liege)	HUDERF (Brussels)	UCL (Brussels)	UZ Antwerp	UZ Ghent	UZ Leuven	Total
2018	13	34	9	22	24	19	121
2019	12	28	10	23	23	21	117
2020	12	26	14	20	24	20	116
2021	12	21	13	21	23	19	109
2022	8	24	15	18	21	20	106

Results

Demographics of study population

The characteristics of the study population are shown in Table 1. Between 2018 and 2022, 569 entries of individual follow-up data were recorded in the registry, with an average of 113.8 annually. Of these, 61.3% were male. The children were aged 2 - 18 years, with a mean of 12.8 years at the last follow-up visit. The mean age at the time of transplant was 7.4 years, with no significant differences between the centers included in the registry. Only 4.7% of the population underwent transplantation before the age of 2 years. The mean follow-up time after transplant was 5.6 years. The number of patients in follow-up at each center remained stable over the years, although with a slight annual decrease, as shown in Figure 1 and Table 2, with HUDERF following the largest number of patients overall.

Height and weight

The mean height SDS was -1.2 SDS ± 1.4 SD. More than a quarter (27.4%) of the study population demonstrated growth stunting, but the mean height SDS was significantly better compared to the population in 2005: -1.9 SDS ± 1.5 SD (p<0.01) (Figure 2). The entire population had a normal BMI (0.0 SDS ± 1.2 SD), with 3.1% of the population having a BMI SDS of 2.0 or higher, and 4.4% having a BMI SDS of -2.0 or lower. Overall height and weight SDS scores were not significantly correlated with the number of years of follow-up after transplantation. However, in female patients, there was a significant negative correlation between age at follow-up and height or weight SDS (Pearson correlation coefficient respectively -0.138 and -0.220 (p<0.05)).

Blood pressure

Mean reported BP measurements were slightly higher than reference values for normal children with a mean systolic score of 0.7 SDS ± 0.9 and

FIGURE 1: number of patients in follow-up per center, listed per year of report

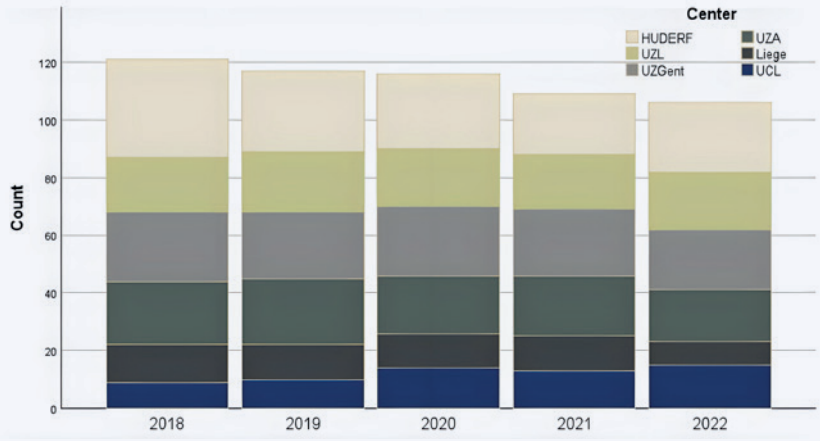


FIGURE 2: comparison of mean height SDS between 2005 and 2018-2022

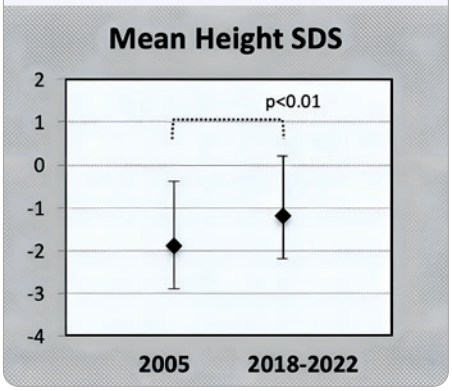


FIGURE 3: comparison of mean systolic blood pressure SDS between 2005 and 2018-2022

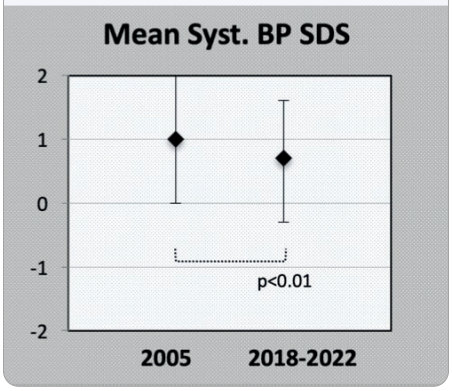


FIGURE 4: comparison of mean diastolic blood pressure SDS between 2005 and 2018-2022

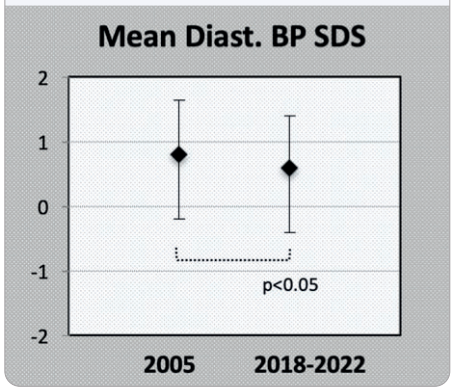


TABLE 3: CKD stages per year of report

	CKD stage 1 N (% of total)	CKD stage 2 N (% of total)	CKD stage 3 N (% of total)	CKD stage 4 N (% of total)	CKD stage 5 N (% of total)	Total
2018	12 (9.9%)	36 (29.8%)	61 (50.4%)	6 (5.0%)	6 (5.0%)	121
2019	18 (15.4%)	47 (40.2%)	41 (35.0%)	8 (6.8%)	3 (2.6%)	117
2020	20 (17.2%)	46 (39.7%)	42 (36.2%)	4 (3.4%)	4 (3.4%)	116
2021	10 (9.2%)	42 (38.5%)	46 (42.2%)	4 (3.7%)	7 (6.4%)	109
2022	17 (16.0%)	36 (34.0%)	45 (42.5%)	5 (4.7%)	3 (2.8%)	106

FIGURE 5: CKD stages per year of report

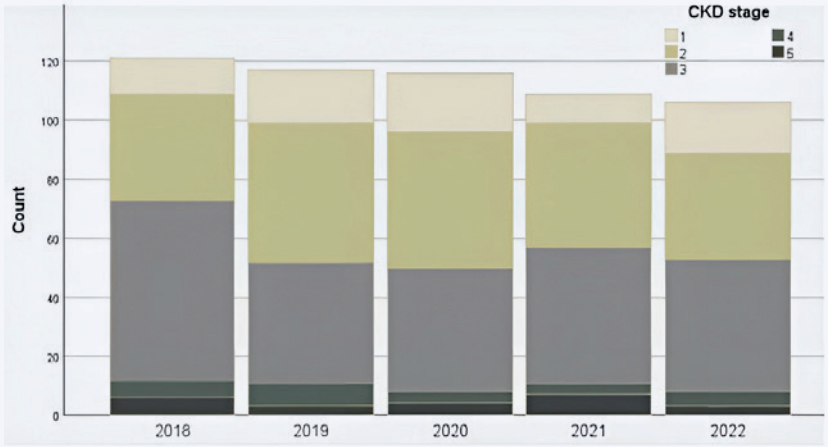
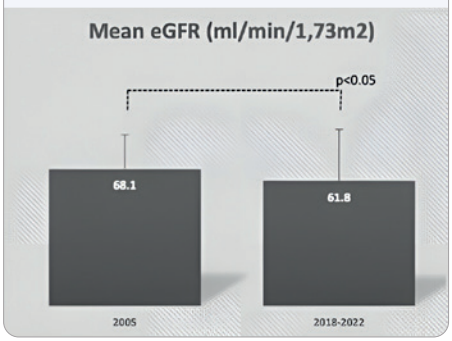


FIGURE 6: comparison of mean eGFR between 2005 and 2018-2022



a mean diastolic score of 0.6 SDS ± 0.9. In this population 9.1% had systolic hypertension and 7.7% had diastolic hypertension. However, the mean systolic and diastolic blood pressures were significantly lower compared to those recorded in 2005 (+1.0 SDS ($p<0.01$) for systolic and +0.8 SDS ($p<0.05$) for diastolic blood pressure) (Figures 3 and 4). Additionally, there was a significant difference in the mean diastolic SDS between boys and girls (+0.7 versus +0.5 SDS ($p<0.01$)), while the mean systolic pressure SDS did not differ significantly between the sexes. Blood pressure SDS was not significantly correlated with the number of years of follow-up after transplantation. However, both systolic and diastolic blood pressure SDS scores were negatively correlated with age at follow-up (Pearson correlation coefficient respectively -0.142 and -0.107 ($p<0.01$)). When analyzed by sex, this negative correlation remained significant for male subjects but not for females. Additionally, systolic blood pressure SDS, but not diastolic blood pressure SDS, was significantly correlated with BMI SDS (Pearson correlation coefficient 0.108 ($p<0.05$)). 17.8% and 17.6% of the population had systolic and diastolic pressure SDS < 0.0, respectively.

Glomerular filtration rate and CKD stages

Mean eGFR was 61.8 + 25.4 ml/min/1.73 m2. Most patients were classified as having CKD stage 2 or 3 (36.4% and 41.3%, respectively), and this distribution remained stable over the follow-up period, as shown in Figure 5 and Table 3. Only 12.8% of the population had an eGFR of 90 ml/min/1.73 m2 or higher. The eGFR was significantly lower in males compared to females ($p <0.01$). At one year post-transplantation, the mean eGFR was higher (71.2 + 27.3 ml/min/1.73 m2). The mean eGFR in the years 2018-2022 was significantly lower than in 2005 (68.1 + 17 ml/min/1.73 m2 ($p<0.05$)) (Figure 6).

There was a strong negative correlation between eGFR and both age at follow-up and number of years post-transplantation (Pearson correlation coefficient respectively -0.135 and -0.211, $p<0.01$). When corrected for sex, this strong negative correlation persisted for male patients (Pearson correlation coefficient respectively -0.165 and -0.282 ($p<0.01$)), but not for females. There was a positive, but not statistically significant correlation between age at transplant and eGFR (Pearson correlation coefficient 0.078, $p=0.062$). The eGFR was significantly negatively correlated with both systolic and diastolic blood pressure SDS (Pearson correlation coefficient respectively -0.120 and -0.127 ($p<0.01$)).

Discussion

In this multicenter, retrospective cross-sectional study, we collected data from the Belgian Convention of Pediatric Nephrology, which contains all patients followed after pediatric KTx in Belgium during the years 2018-2022. In the following, we compared our results with the Belgian 2005 cohort, as well as data from two major

registries: the 2018 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) publication, who followed 11870 pediatric patients post-transplantation between 1987 and 2017, and the 2019 CERTAIN (European) registry publication, which followed 336 children transplanted between 1996 and 2012 (3, 10, 18). The mean age at transplant was lower in our cohort (mean age at transplantation 7.4 ± 4.6 years in our cohort versus 10.1 ± 5.2 years in the CERTAIN study), with the largest proportion of Belgian patients transplanted in the age categories of 2-5 years (42.9%), whereas the most common age at transplantation in the NAPRTCS study was 13-17 years (38.8%). The difference in age may be due to differences in protocols for KRT treatment, experience and availability of donor organs (living versus deceased donor) concerning young children between different countries and centers. Sex distribution was very similar in all three cohorts (male-to-female ratio 61.7/38.3 in our cohort, 60/40 in the NAPRTCS cohort, 62/38 in the CERTAIN cohort).

Height and weight

Although we still reported growth stunting in more than a quarter of our patients, the mean height SDS was significantly higher than that in the 2005 cohort. This improvement is probably due to changes in post-transplantation immunosuppressive therapy over the decades, particularly the decreased use of systemic glucocorticoids (3, 6, 19). Difference in practices regarding the use of growth hormone before and after transplantation might have contributed to this positive trend, although our registry data lacked detailed information regarding the use of both treatments. Overall, growth outcomes in Belgian children with renal transplants appear to be better than those reported in other registries. Our reported mean height SDS (-1.2 SDS ± 1.4 SD) was higher compared to the 2018 NAPRTCS population (mean deficit of -1.62, SD not reported) and the 2019 CERTAIN study (-1.5 SDS ± 1.8 SD), although it is important to mention that the NAPRTCS reported at time of transplant and CERTAIN at discharge within 30 days of transplantation (3, 18). In our female patients, we observed a significant negative correlation between height SDS and age at follow-up, indicating that younger children in our cohort had a higher mean height SDS. This aligns with previous reports suggesting that younger children with CKD who experience growth stunting tend to show greater growth recovery post-transplantation (6). Similarly, the NAPRTCS registry reported the most significant improvement in height post-transplantation among the youngest children in their cohort (3). The observed correlation between height SDS and age at follow-up in our female population might be related to the earlier onset of adolescent growth spurt in girls, providing a shorter window for catch-up growth post-transplantation. We have no data indicating differences in growth hormone or corticosteroid treatments between the sexes. Although obesity and overweight are commonly reported after kidney transplantation in children, our population showed a median BMI SDS of 0.0, with only a small proportion classified as overweight or underweight (19). This could be attributed to improved multidisciplinary care with better nutritional practices and, as mentioned previously, reduced use of systemic glucocorticoids. In comparison, the European registry reported a mean BMI SDS of −0.11 ± 1.31 at discharge within 30 days post-transplantation, while the NAPRTCS registry did not provide a mean BMI SDS (3, 18).

Kidney function

We found a lower mean eGFR in our cohort than in the population of 2005. One possible explanation is that over recent decades, improvements in care have enabled the transplantation of more complex patients, including younger patients with more comorbidities, as suggested by other authors (20, 21). Consistent with this, our cohort included patients transplanted at a younger age than those in the CERTAIN and NAPRTCS cohorts, with nearly 5% of our population being transplanted before the age of 2 years. Younger recipients in the NAPRTCS cohort experienced greater absolute decline in eGFR over time (3). In our patients, eGFR decreased with both older age at follow-up and longer time since transplantation, although we did not find a statistically significant correlation between eGFR and age at transplantation. Poor medication adherence is a common problem among adolescents and young adults and may contribute to this decline (6). Moreover, the underlying disease could play a role: glomerulopathy, which is more prevalent in older age groups, is associated with a faster decline in eGFR compared to patients with congenital anomalies of the kidney and urinary tract (CAKUT), although our data lacked information on CKD etiology (22). The mean eGFR at one year post-transplantation was also lower in our cohort compared to the CERTAIN study (mean eGFR respectively 71.2+27.3mL/min/1.73m2 versus 80.6 ± 29.0 ml/min/1.73 m2) although the CERTAIN study measured eGFR at 30 days post-transplantation (18). Donor characteristics were not collected in this registry, but differences in donor criteria between Belgian and international pediatric nephrology centers, such as living versus deceased donor, age, size and HLA mismatch, could provide useful insight for future studies.

Blood pressure

We observed significantly better systolic and diastolic blood pressure SDS than the 2005 cohort. Only 9.1% and 7.7% of our patient population had systolic and diastolic hypertension, respectively. In comparison, Belgian children performed better than those in the CERTAIN registry, where 77% of children were diagnosed with hypertension at three years post-transplant (18). We hypothesize that this improvement may also be due to improved multidisciplinary care within the convention, better therapy compliance and reduced use of systemic glucocorticoids. They observed higher systolic blood pressure (SBP) SDS in younger patients with a shorter time since transplantation, and in male patients with higher BMI and non-CAKUT cause of CKD. We also found a higher SBP SDS in younger patients and patients with higher BMI. Only the diastolic blood pressure (DBP) SDS was significantly higher in males compared to females. Arterial hypertension contributes to progression of kidney dysfunction and negatively affects graft survival and studies have shown that improved blood pressure control can slow CKD progression (23, 24). Undiagnosed hypertension in infants and young children is a common problem and other studies have also highlighted the undertreatment of hypertension in younger children undergoing KRT (25, 26). Given the correlation between higher BMI and hypertension, increased focus on healthy diet and exercise in patients with CKD could further optimize blood pressure control.

Limitations to this study include the cross-sectional nature of the data and the lack of data on CKD etiology, medication use, type of transplantation and donor characteristics. Methodology in creatinine assay differed between the centers. The number of entries gradually declined each year, without provided reasons, and patient mortality was not recorded. All individual entries were collected per year and merged; therefore, it is possible that a patient with multiple records had a greater influence on the population average.

Conclusion

In conclusion, this study offers insights into the clinical outcomes of pediatric patients at follow-up after kidney transplantation in Belgium. Compared to the 2005 Belgian cohort and larger

European and American registries, we observed better growth and cardiovascular outcomes, which could be the result of improved post-transplant care made possible by a special funding program for multidisciplinary follow-up. However, the mean eGFR has not benefitted, particularly in older male patients, and efforts should be made to tackle eGFR decline during longer follow-up periods. All centers in the registry will continue to collect follow-up information as of 2023 and beyond.

Conflicts of Interest

The authors declare no conflicts of interest.

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E-Cigarette or Vaping-Associated Pneumomediastinum: A Case Report and Pathophysiological Explanation

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Spontaneous pneumomediastinum ; e-cigarette ; vaping ; pathophysiology ; adolescent health.

Abstract

We report the case of a 16-year-old male who presented to the emergency room with chest pain, fever and shortness of breath. Upon physical examination Hamman's sign was positive. The patient was diagnosed with spontaneous pneumomediastinum, most probably caused by e-cigarette use and/or asthma exacerbation. He was treated with nebulizations with salbutamol, corticosteroids and antibiotics and made a full recovery.

This case adds to the evidence of e-cigarette or vaping-associated pneumomediastinum in adolescents. We identified three mechanisms by which vaping can cause pneumomediastinum: the act of smoking itself, through alveolar damage as part of e-cigarette or vaping product use-associated lung injury or, in a secondary way, by triggering an asthma exacerbation.

This case highlights the importance for pediatricians to ask about the use of e-cigarettes in adolescents presenting with chest pain, gastro-intestinal, constitutional and/or respiratory complaints. It also shows that we must educate our patients about the risks of e-cigarette use whenever the opportunity is there. Spontaneous pneumomediastinum should be considered in the differential diagnosis of adolescents with chest pain who use e-cigarettes.

Introduction

Pneumomediastinum is a pathological condition characterized by free air in the mediastinal space. It can be categorized as spontaneous or traumatic. Spontaneous pneumomediastinum (SPM) is a rare condition, particularly in children and adolescents. The reported incidence in this population (under 18 years old, excluding newborns with SPM) presenting to the emergency department ranges from 1 in 8.000 to 1 in 15.000 in retrospective studies (1). However, one study found an incidence of 1 in 368 when routine screening was performed on young adults (14-29 years old) admitted for unexplained chest pain or dyspnea (2). This suggests that SPM may often go undiagnosed in children and adolescents presenting with chest pain.

In adolescents, SPM is most commonly triggered by an asthma exacerbation (3). However, recent case reports suggest a potential risk of SPM in otherwise healthy adolescents who use e-cigarettes (4-11). This case adds to the evidence of e-cigarette or vaping-associated pneumomediastinum in adolescents.

A recent survey conducted in 2023 among adolescents living in Curaçao, found that 16% of teenagers on the island owned an e-cigarette, with 41% of them having used the device in the past six months. The youngest users were just 10 years old, highlighting the urgency of this issue in pediatric care (12).

In Belgium, a similar survey conducted in 2018 showed that 7.4% of adolescents had used an e-cigarette in the 30 days preceding the survey. When the survey was repeated in 2022 within the Flemish community, the percentage had risen to 11.9% (13). These findings indicate a growing trend in e-cigarette use among adolescents, emphasizing the need for clinicians to be aware of its dangers and the importance of educating young people about the associated health risks.

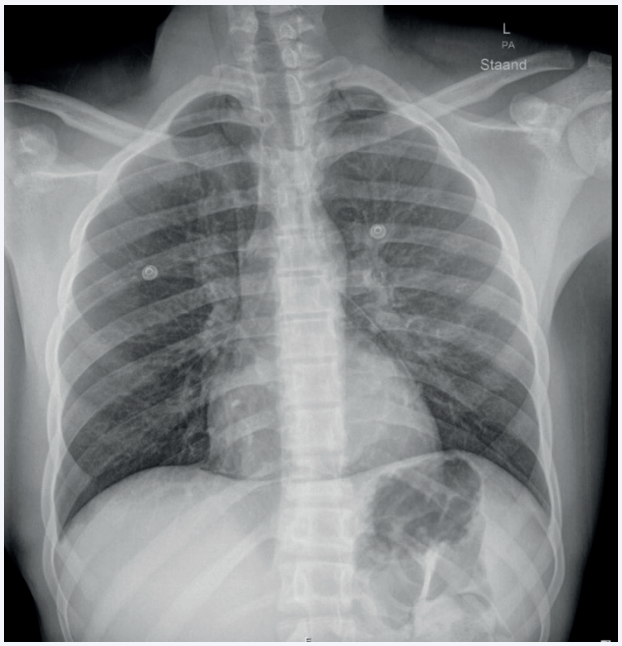
Case

A 16-year-old male presented to the emergency department with chest pain, fever, and shortness of breath. The pain began the night before, predominantly on the left side of his chest, spreading to his left arm. He attributed the pain to muscle strain sustained from lifting a goat earlier that day. The following morning, he developed shortness of breath and a fever, which led him to seek medical attention. The pain intensified with respiration. Additionally, he reported abdominal discomfort and a loss of appetite in de days prior to his presentation. His medical history is notable for bronchial hyperreactivity at four years of age and amphetamine intoxication at ten years of age.

His vitals upon arrival: temperature of 38.3 degrees Celsius, respiratory rate 36/min with a saturation of 91% in room air, heart rate 109/min and blood pressure 136/79 mmHg.

Significant physical assessment findings: in- and expiratory wheezing over all lung fields with crepitations over the right lower lung field as well as crepitations synchronous with the heart beat (Hamman's sign).

FIGURE 1: Thoracic X-ray at moment of presentation



Thoracic X-ray was obtained (Figure 1) and showed pneumomediastinum with suspicion of pneumopericardium. Computed tomography (CT) of the thorax (Figure 2, 3) confirmed the presence of pneumomediastinum with associated emphysema in the neck. Pneumopericardium and pneumothorax were ruled out. There was also bronchial wall thickening visible, especially in the lower lobes, which was attributed to the use of e-cigarettes and/or underlying asthma.

Laboratory results showed leukocytosis (white blood cell count of 13.2 x10 /L [reference range 3.5 - 11.0] with neutrophilia and a CRP of 26 mg/L [normal <10]. D-dimer was negative. Blood cultures were obtained and remained negative.

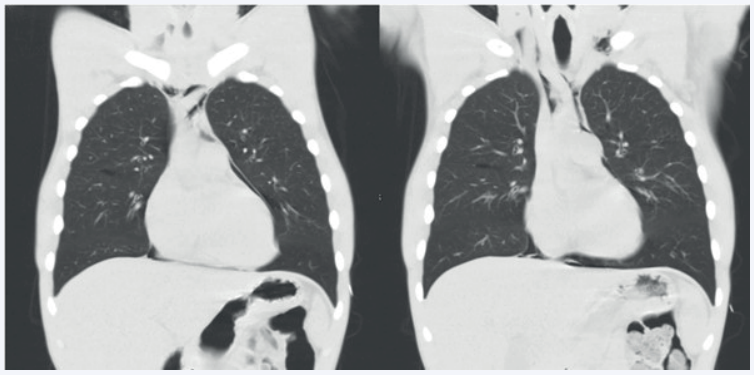
Electrocardiogram, performed to look for signs of cardiac ischemia or arrhythmias, was normal.

Given the patient's medical history and presenting symptoms, asthma exacerbation was our primary differential diagnosis.

The patient was treated with non-steroidal anti-inflammatory drugs and acetaminophen, frequent nebulizations with salbutamol and oxygen suppletion through a venturi mask. Given the severity of his presentation, the treatment regimen was intensified with the addition of oral prednisone (20mg twice daily) to manage an asthma exacerbation and intravenous amoxicillin/clavulanic acid (1000/200mg four times daily) to address a possible underlying lung infection.

During his admission, we learned that he used e-cigarettes with nicotine on a regular basis. He denied smoking combustible cigarettes or using other drugs. E-cigarette associated lung injury was considered as a potential cause of his pneumomediastinum (see discussion). No further investigations were conducted.

FIGURE 2: Chest CT, frontal plane

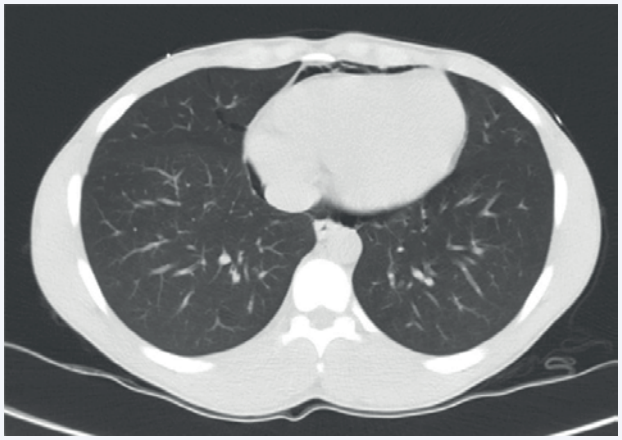


His clinical condition gradually improved. On the fifth day, a follow-up thoracic X-ray showed normalization of the mediastinum. The course of amoxicillin/clavulanic acid was completed over five days, while prednisone was continued for seven days. Oxygen therapy was discontinued after six days.

After eight days, the patient was discharged with a tapering schedule for salbutamol puffs and maintenance therapy with formoterol/beclomethasone. He also received counseling on the potential impact of vaping on his lung health.

Although follow-up was arranged, the patient did not attend his scheduled appointments.

FIGURE 1: Chest CT, transverse plane



Discussion

Causes of spontaneous pneumomediastinum linked to e-cigarette use

SPM is most commonly caused by alveolar rupture that allows air to enter the surrounding bronchovascular sheath and flow down a pressure gradient from the alveolus to the mediastinum as demonstrated by Macklin and Macklin in 1939. Alveolar rupture occurs when the pressure gradient between the alveoli and the surrounding structures reaches a critical level and can therefor occur by increased intra alveolar pressure and/or by decreased pressure in the interstitial space (14). Abnormalities of the alveolocapillary membrane can contribute to the occurrence of alveolar rupture (15).

This mechanism explains how asthma exacerbation and Valsalva maneuver when lifting heavy objects can cause SPM. As previously stated, the use of e-cigarettes has also been associated with the occurrence of SPM in adolescents and young adults.

We propose two mechanisms by which e-cigarette use may directly result in alveolar rupture.

TABLE 1: Results from retrospective cohort study of 44 adolescents by Kopsombut G et al. (22)

Content of vape	90% delta-9-tetrahydrocannabinol containing products
Presenting symptoms at time of admission	Most common: vomiting, fever, cough 84% constitutional symptoms (fever, weight loss, fatigue, chills, headache) 81% gastro intestinal symptoms (nausea or vomiting, diarrhea, abdominal pain) 74% respiratory symptoms (cough, shortness of breath, chest pain or tightness, congestion, hemoptysis)
Laboratory findings (average and CI)	Elevated white blood cell count of 14.300/µL (CI, 13.7–15.0) with neutrophilic predominance CRP of 25.2 mg/dL (CI, 22.1–28.2) Erythrocyte sedimentation rate of 66.7 mm/hour (CI 26.9–76.4) Abnormal coagulation studies were observed in all 21 patients who underwent such testing: PT of 17.7 seconds (CI, 16.4–19.1), INR of 1.54 (CI,1.43–1.66)
Imaging studies	Chest radiograph: - 20% normal - 26% abnormal with hyperinflation, pneumomediastinum or pneumothorax - 54% lung field haziness or multifocal opacities Chest CT scan: - 100% lung parenchymal pathology: bilateral ground glass opacification with sub pleural sparing. The lower lobes were more affected than the upper lobes
Pulmonary function testing	21% of tested individuals (n=14) had signs of airway obstruction (forced expiratory volume in 1 second/forced vital capacity <85% of predicted value) This normalized after hospitalization (within 6 weeks)
BAL	3 out of the 4 BAL samples exhibited the presence of red blood cells, while all 4 demonstrated the presence of lipid-laden macrophages

The first mechanism pertains to the act of smoking itself and is also the proposed mechanism by which inhalation of smoking related drugs can cause SPM. In individuals who smoke cocaine or marijuana, a specific breathing pattern has been observed that may result in alveolar trauma. This pattern involves a forced exhalation, followed by inhalation against a closed airway (Muller's maneuver) which creates a negative intrapleural pressure. It is hypothesized that the narrow lumen of the e-cigarette may cause the user to inhale even more strongly, thereby enhancing the effect of Muller's maneuver (11). Additionally, exhalation against a closed glottis (Valsalva maneuver) is a common occurrence during smoking, representing another way by which smoking may lead to SPM (16-19).

The second mechanism is through alveolar damage as part of the acute lung injury seen in e-cigarette or vaping product use-associated lung injury (EVALI). The first large case series covering 98 cases of EVALI was published in 2019 by Layden et al. as a result of a public health investigation initiated by the Wisconsin Department of Health Services and the Illinois Department of Public Health (20).

Subsequently, a case definition of EVALI was proposed by the Centers for Disease Control and Prevention (CDC) in America. A case must meet three criteria: a history of vaping within 90 days prior to symptom onset, pulmonary infiltrate on imaging and the absence of an alternative diagnosis such as infection (i.e., diagnosis of exclusion). Presenting symptoms may be respiratory, gastrointestinal or constitutional (21).

Table 1 summarizes the clinical characteristics of EVALI in adolescents (12 to 18 years of age) based on a retrospective cohort study performed by Kopsombut et al (n=44) (22).

Although the coagulopathy observed in this patient group does not align with the clinical presentation defined by the American Thoracic Society—which is based on literature review and expert opinions from both adult and pediatric specialists—all other findings described above are consistent (23). The authors could not identify the exact causation for the observed coagulopathy in their cohort and suggest further studies on this subject (22). In our patient, no coagulation studies were performed apart from D-dimers, which were within normal limits.

The exact pathophysiology of EVALI is not yet fully understood, but it is thought that inhaled chemicals cause direct cell damage and disrupt immune responses, leading to lung inflammation. E-cigarettes can contain various harmful substances, but vitamin E acetate has been strongly implicated as a key factor in the 2019 outbreak. A pivotal study by Blount et al. found vitamin E acetate in 94% of bronchoalveolar lavage (BAL) fluid samples from EVALI patients, while none was detected in healthy controls, including smokers and e-cigarette users without lung injury (24). This additive, used as a thickening or diluting agent in delta-9-tetrahydrocannabinol (THC)-containing vaping liquids, became common on the illicit market in late 2018 and gained popularity in 2019, coinciding with the surge in EVALI cases.

Vitamin E acetate can alter surfactant properties, making it less effective at maintaining normal surface tension in the lungs (24). It also causes cytotoxic effects in various lung cells and activates macrophages that cannot break it down, leading to cell death and an exaggerated inflammatory response (25). This explains the frequent finding of lipid-laden macrophages in BAL fluid from EVALI patients (22). Animal studies have since confirmed that inhaled vitamin E acetate can reproduce lung damage similar to that seen in human EVALI cases (26, 27).

These findings led the CDC to issue a warning against using vitamin E acetate in vaping products in 2020 (28). Following increased public awareness, removal of vitamin E acetate from many THC e-liquids, and enforcement against illicit products, EVALI cases peaked in September 2019 and declined sharply afterwards, prompting the CDC to end national surveillance in February 2020. However, isolated cases still occur (29).

While vitamin E acetate accounts for most THC vaping–associated cases, approximately 14% of EVALI patients during the CDC's national surveillance period reported using only nicotine-containing e-cigarettes (28). This indicates that additional causative agents may contribute to EVALI, including flavoring additives, solvents such as propylene glycol and glycerol, manufacturing contaminants, or nicotine itself. Notably, nicotine vapor exposure directly increases pulmonary endothelial permeability, disrupts endothelial barrier integrity, and promotes inflammation and oxidative stress in a dose-dependent manner (27, 30-32).

In addition to the aforementioned mechanisms, e-cigarettes can also indirectly contribute to SPM by precipitating an asthma exacerbation. As e-cigarette use is a known risk factor for developing asthma and increases the frequency of exacerbations in asthma patients, this provides a secondary pathway through which e-cigarettes may lead to SPM (33).

Literature cases of spontaneous pneumomediastinum attributed to e-cigarette use

A literature search yielded eight case-reports describing in total nine cases of SPM attributed to e-cigarette use in adolescents aged 18 years or younger (4-11). Of those nine cases, five were reported as part of EVALI (4, 8-10) and two were believed to be due to forceful inhalation (act of smoking) and/or secondary to coughing (7, 11). In two of the cases, no suspected causative mechanism was mentioned (5, 6). It is our hypothesis that both of these cases were due to the act of smoking.

Table 2 provides an overview of the characteristics of these nine cases.

All of the listed cases attributed to EVALI, were users of THC containing e-cigarettes, adding to the evidence of the strong link between THC containing e-cigarettes and EVALI. These cases were published/occurred in the years 2019-2020, when vitamin E acetate was still used as additive to THC containing e-liquids. Unfortunately, in only one case was the patient's e-liquid analyzed, revealing a vitamin E acetate concentration of 66%.

Cases that were attributed to the act of smoking used nicotine containing e-cigarettes or did not specify which specific product was used nor investigated what substances it contained.

Application and integration of the above information into the case

In this case, e-cigarette use and asthma exacerbation are likely contributors to the patient's spontaneous pneumomediastinum (SPM). While non-vape-related causes such as heavy lifting, respiratory infection, or an asthma flare from another trigger were considered, none fully explain the full symptom profile.

The patient presented with the typical EVALI triad—gastrointestinal, respiratory, and constitutional symptoms—and lab findings aligned with previous adolescent EVALI cases, including bronchial wall thickening on CT (22, 34). However, failure to meet CDC criteria (no pulmonary infiltrate on chest imaging, infectious causes could not be ruled out) argue against a definitive EVALI diagnosis (21).

Given the patient's history of childhood bronchial hyperreactivity, undiagnosed or reactivated asthma remains a plausible cause, possibly triggered by regular e-cigarette use, which is known to exacerbate asthma (33).

Lifting a goat, potentially involving a Valsalva maneuver, may have contributed by increasing the intrathoracic pressure, but this does not explain the systemic symptoms. Similarly, while lower respiratory infections can cause SPM, the lack of radiographic evidence makes pneumonia unlikely.

In conclusion the SPM diagnosed in our patient is most likely caused by e-cigarette use and/or asthma exacerbation.

TABLE 2: Characteristics of nine reported cases of SPM directly related to e-cigarette use in adolescents

	Age	Sex	Nicotine or THC containing vape	Vit E acetate containing liquid	Reported mechanism			Mechanism based on our interpretation
					EVALI	Act of smoking	No mechanism reported	
Case 1 (4)	18	Male	Both	Not specified	x			EVALI
Case 2 (4)	17	Female	Both	Not specified	x			EVALI
Case 3 (5)	17	Male	Not specified	Not specified			x	Smoking
Case 4 (6)	17	Male	Nicotine and flavoring additives	Not specified			x	Smoking
Case 5 (7)	18	Male	Not specified	Not specified		x		Smoking
Case 6 (8)	15	Male	THC	Not specified	x			EVALI
Case 7 (9)	16	Female	Both	Not specified	x			EVALI
Case 8 (10)	Teenage	Male	Both, "off-brand", mint-flavored nicotine product	The most recently vaped THC cartridge contained 66% tocopheryl acetate (Vitamin E)	x			EVALI
Case 9 (11)	18	Male	Not specified	Not specified		x		Smoking

Treatment and outcome of spontaneous pneumomediastinum

Spontaneous pneumomediastinum (SPM) is generally a benign and self-limiting condition that typically resolves within 3 to 15 days. Management usually consists of analgesia, rest, avoidance of activities that increase intrathoracic pressure and treatment of any identified underlying condition (35). Although high-concentration oxygen therapy is frequently employed—based on the proposed "nitrogen washout" effect, which may accelerate resorption of free air into surrounding blood vessels — the supporting evidence is limited (36). A recent review by Grasmuk-Siegl et al. highlighted the absence of adequately randomized controlled trials validating oxygen therapy in normoxemic patients with pneumothorax (37). For the treatment of SPM, evidence is even more limited. Consequently, routine oxygen administration in children and adolescents with SPM is not universally recommended and should be individualized.

Our patient was managed in line with these general principles, receiving analgesics, bed rest, and treatment for an asthma exacerbation—presumed to be the underlying cause—as previously described. Empirical antibiotics were initiated to cover potential pneumonia. Following admission, the patient disclosed a history of e-cigarette use, prompting consideration of EVALI as a differential diagnosis. According to CDC guidelines, EVALI management includes corticosteroids and cessation of e-cigarette use (21). However, there are no randomized clinical trials establishing the efficacy of specific therapeutic interventions for EVALI. Reported treatment is largely supportive and comprises oxygen therapy, (non-) invasive ventilation, corticosteroids and empiric antibiotics. Dose and duration of corticosteroid therapy vary considerably across cases (23).

In practice, the management of EVALI overlaps substantially with that of asthma exacerbation, particularly in the use of supportive care, oxygen supplementation, and corticosteroids to reduce inflammation—whether due to inhaled toxins in EVALI or allergic airway hyperresponsiveness in asthma. Key differences include the routine use of bronchodilators in asthma, which are not commonly indicated in EVALI unless bronchospasm is present. Moreover, while antibiotics are often empirically prescribed in suspected EVALI until infection is excluded, they are generally reserved for asthma exacerbations only when bacterial infection is suspected. Importantly, while smoking and vaping cessation is advisable in both conditions, it is of primary importance in the treatment of EVALI.

In this case, the initial treatment effectively addressed both possible diagnoses. Given the patient's steady clinical improvement and the substantial overlap in treatment approaches, no additional diagnostic investigations or changes to the management plan were deemed necessary.

Long-term health effects of e-cigarette use on previously non-smokers

Given the growing prevalence of e-cigarette use among adolescents, understanding potential long-term health effects is essential for counseling and follow-up. In this section, we provide a brief overview of what is currently known about these long-term effects. Because e-cigarettes were only introduced about 20 years ago, and widespread use has emerged mainly in the past decade, there is still limited clinical and experimental evidence regarding their long-term impact (27). Nevertheless, several worrisome findings have already been reported in the short and medium term, indicating negative effects of e-cigarette use on the cardiovascular and respiratory systems.

A recent review by Izquierdo-Condoy et al. on the health implications of e-cigarette use indicates that while switching to e-cigarettes may offer some health benefits for smokers, their use in a non-smoking, healthy population is associated with several adverse effects (38). These include increased heart rate, elevated mean arterial blood pressure, greater arterial stiffness and various changes in the respiratory system such as altered transcriptomes of small airway epithelium cells and alveolar macrophages, as well as signs of airway obstruction on lung function tests. Many of these effects are linked to the harmful impact of nicotine, although current evidence is conflicting, and further research is needed to determine whether nicotine is solely responsible.

Studies investigating the long-term effects of e-cigarette use in healthy populations remain limited. Regarding cardiovascular risks, e-cigarette use has been associated with higher odds of myocardial infarction compared to non-users (39, 40). Concerning respiratory health, a longitudinal analysis of the adult PATH (Population Assessment of Tobacco and Health) study found a statistically significant link between former or current e-cigarette use at baseline and the development of respiratory diseases—such as COPD, chronic bronchitis, emphysema or asthma—about two years later (41). Additionally, in vitro experiments and animal studies indicate that e-cigarette exposure increases oxidative stress, protease activity, inflammation, and DNA damage, suggesting a potential elevated risk for COPD and lung cancer (42). Although these findings point toward possible long-term harm, more robust research is essential to clarify the overall long-term health effects of e-cigarette use.

Beyond these direct health impacts, it is important to highlight the additional risks for young people due to the so-called gateway effect: evidence suggests an association between e-cigarette use and subsequent combustible cigarette smoking (43). Children and adolescents, often attracted by the appealing designs and flavors, may develop nicotine addiction and transition to other tobacco products. Furthermore, youth e-cigarette use has been linked to increased use of other substances, such as alcohol, marijuana and other illicit drugs (44).

Strengths and weaknesses of this case report

This case served as a foundation for generating hypotheses regarding the pathophysiology of e-cigarette-associated SPM in adolescents. It provided an opportunity to explore the various potential triggers for SPM in this instance and reflects the diagnostic reasoning clinicians regularly navigate.

However, the diagnostic limitations of this case should be addressed. In future cases, it would be valuable to perform microbiological analyses to rule out infectious causes of SPM and to support the diagnostic workup for EVALI.

Furthermore lung function testing might be useful. There is no place for lung function testing in the acute diagnostic workup of SPM since forceful in-and exhalation could aggravate the condition. In follow-up however it might be useful for two reasons: first, to identify underlying asthma, which requires appropriate treatment and monitoring; and second, in case of EVALI, to monitor the residual lung damage. Lung function abnormalities have been described in pediatric EVALI patients, which may persist despite clinical improvement. It is on the other hand not useful as a retrospective diagnostic measure for EVALI since there is no clear lung function signature of EVALI. Reported abnormalities include both airflow obstruction as restriction or a combination of both, with our without impaired diffusion capacity (34, 45, 46).

The lack of follow-up in this case is suboptimal because of the suggested adverse health effects of vaping and the long-term respiratory, cognitive and vaping behavior outcomes patients with EVALI face, as described by Blagev et al. (47). In their cohort of seventy-three adult patients diagnosed with EVALI they found that 39% of them had cognitive impairment, 48% reported respiratory limitations, 59% had mood disorders (anxiety and/or depression) and 62% had post-traumatic stress symptoms after 1 year of follow-up.

Unfortunately most of them continued vaping, with only 38% quitting all vaping and smoking behaviors with younger age being associated with reduced vaping behavior after EVALI.

In future cases, we recommend a structured, multidisciplinary follow-up in accordance with the guidelines of the CDC and the American Thoracic Society. An initial follow-up visit should take place within 48–72 hours after discharge to assess clinical stability, reinforce abstinence from e-cigarette use, ensure medication adherence and address any comorbidities as well as social or behavioral health needs. A second follow-up visit approximately two months after discharge is advisable to evaluate for persistent abnormalities on pulmonary function tests and imaging. Additionally, the CDC recommends an interim follow-up within 2–4 weeks—often coinciding with completion of corticosteroid tapering—to assess pulmonary function and radiographic resolution. Further long-term follow-up is equally important to monitor for the aforementioned long-term effects (23, 48).

Conclusion

By outlining the various pathophysiological pathways through which vaping can lead to pneumomediastinum, this case underscores that vaping should be considered a potential cause of SPM in adolescents. It adds to the growing evidence linking e-cigarette use to adverse respiratory outcomes in this age group. Given the rising prevalence of e-cigarette use, the unclear long-term health risks, and its potential role as a gateway to other substance use, there is an urgent need for increased awareness and preventive education targeting this vulnerable population.

Statements

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NUTRICIA

Belangrijk: Borstvoeding is de beste voeding. Informatie uitsluitend bestemd voor het (para)medisch korps. **Referenties: 1.** Bruzzese E et al. Clinical Nutrition, 2009;28:156–61. **2.** Arslanoglu S et al. Journal of Nutrition, 2007;137:2420–4. **3.** Chatchatee P et al. J Pediatr Gastroenterol Nutr, 2014;58(4):428–37. **4.** Arslanoglu S et al. J Nutr, 2008;138:1091–5. **5.** Chua M et al. JPGN, 2017;65:102–6. **6.** Reverri EJ et al. Nutrients, 2018;10,1346.
*Vitamine C & D, ondersteunen de ontwikkeling van het immuunsysteem **structuuridentieke Human Milk Oligosacharides ***Meer lijkend op de darmmicrobiota samenstelling van vaginaal geboren baby's. Op basis van onderzoek naar de combinatie van prebiotische oligosachariden scGOS:lcFOS (9:1) en Bifidobacterium breve M16-V. ****Op basis van onderzoek naar prebiotische oligosachariden scGOS:lcFOS (9:1). *****Op basis van onderzoek naar prebiotische oligosachariden scGOS:lcFOS (9:1) of 2'-FL • **8/2025 V.U.: Danone Belux nv -Werkhuizenkaai 160 - 1000 Brussel**

Protecting Every Child: A Global Call for Action amid Humanitarian Crises

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Keywords

Health inequities ; adverse childhood experiences ; child advocacy; children's rights; ethics; humanitarian crises; violence on children; child protection.

The Belgian Academy of Paediatrics strongly highlights the affirmation of the universal right of all children to protection under international humanitarian law and medical ethics by the European Academy of Paediatrics (EAP) and stated by the EAP on 16 July, 2025:
No child, adolescent, or caregiver should suffer or die due to war, displacement, terrorism, sexual abuse, sexual and gender-based violence, systemic sexual violence, or denial of essential resources or care. Such violations are grave breaches of children's rights and must be unequivocally condemned. Around the world, children are the most vulnerable victims of conflict, disaster, and neglect, facing displacement, hunger, injury, and trauma. Paediatric professionals have a duty to protect and advocate for their rights, everywhere and without exception.

The EAP Calls For:

Immediate and Sustained Humanitarian Access

- All parties to all conflicts must uphold their obligations under international humanitarian law to allow safe, unimpeded access to children and civilian populations.
- Humanitarian corridors must be protected, and aid workers must be guaranteed safe operational environments, and guarantee unimpeded delivery of food, clean water, vaccinations, medical care, and psychological support.
- Healthcare personnel and humanitarian workers must be protected as neutral actors, and the neutrality of medical facilities and aid convoys must be upheld at all times.

Universal and Consistent Child Protection

Every child deserves protection from violence, exploitation, and deprivation, and these rights must be protected under international law. In armed conflict and humanitarian crises, children and their caregivers continue to face grave violations, including:

- Injury, death, and disfigurement
- Hunger and malnutrition
- Denial of access to medical care and essential vaccinations
- Psychological trauma and chronic mental health conditions
- Displacement due to violence and destruction of homes
- Family separation and orphanhood
- Recruitment by armed groups and use as human shields
- Abduction and sexual violence
- Disruption of education and the loss of safe learning environments

Children must be recognised and protected as non-combatants

Ceasefires and de-escalation must prioritise the safety of children. Wherever conflict continues, access to life-saving services must be guaranteed, and children's dignity, safety, and rights must be respected under international law.

A Global Commitment to Peace and Prevention

The EAP is a non-political organisation focused on children's health and well-being. While humanitarian crises often have political roots, EAP is only focused on children's lives, safety, and rights. This statement reflects an exceptional convergence of global humanitarian concerns affecting child health.

The EAP remains committed to advancing a culture of child protection in Europe and globally - rooted in medical ethics, compassion, and universal human rights.

It joins international partners in calling for diplomatic efforts and conflict prevention strategies that prioritise children and safeguard the rights of future generations.

Moving forward, the EAP aligns itself with the child-focused advocacy and humanitarian reporting of agencies such as the World Health Organization (WHO), United Nations (UN) and United Nations Children's Fund (UNICEF) and supports their work as a reference for its members and partners.

A Worldwide Emergency for Children: Selected Humanitarian Contexts

Many crises unfold in silence. The following are just some of the most urgent humanitarian contexts currently affecting children:

- Afghanistan: 22.9 million people require humanitarian aid, including 3.5 million acutely malnourished children and over 8 million internally displaced. Children face chronic hunger, limited access to healthcare and education, rising disease outbreaks, and collapsing services. Restrictions on female aid workers have further impeded relief efforts, disproportionately affecting women and children. Many children are exposed to child labour, early marriage, and psychological distress, with minimal access to mental health or protection services.
- Armenia: Armenia currently hosts approximately 115,000 refugees, including 36,000 children, who fled to the country in late September 2023 or were escorted through the Lachin corridor between December 2022 and September 2023 following the displacement from Nagorno-Karabakh. These arrivals joined 26,700 individuals already displaced since the 2020 conflict. Many fled without warning, resulting in severe disruption to education, healthcare, and social support systems. Host communities and national health services remain under considerable pressure. Children face heightened risks of trauma, food and housing insecurity, interrupted vaccination schedules, and limited access to routine and psychosocial care.

- Democratic Republic of Congo (DRC): Over 28 million people need humanitarian assistance, including 4.75 million malnourished children under five and 7.8 million internally displaced. Children face hunger, displacement, conflict, and gender-based violence — especially in eastern provinces. Attacks on schools, health centres, and aid workers are common. Thousands of children risk recruitment by armed groups, trafficking, or family separation.
- Gaza: More than 2 million people are affected by the ongoing crisis in Gaza. UNICEF's Situation reports state that up to 1.9 million people (≈90% of Gaza's population, estimated at 2.2 million) are internally displaced in the ongoing crisis. Multiple humanitarian agencies cited that 17,000 children have been killed in Gaza since October 2023, with approximately 37,000 injured. The number of malnourished children is estimated as 65,000 and the UN reports 57 children having died from the effects of malnutrition since May 2025. Children face severe food and water insecurity, with many infants lacking access to infant formula and appropriate nutrition. The crisis is further compounded by the widespread destruction of civilian infrastructure - including schools and hospitals, some of which have reportedly been used for military purposes - as well as acute shortages of shelter, overcrowding, and the collapse of health and sanitation systems.
- Haiti: An estimated 5.7 million people face acute food insecurity, including 277,000 malnourished children. Over 1 million people, many of them children, have been displaced due to gang violence and institutional collapse. Armed groups control large areas, restricting access to schools, healthcare, and aid. Children are at risk of violence, abduction, exploitation, and recruitment. Health systems are overwhelmed, and essential services—vaccinations, maternal care, and mental health support — are severely disrupted.
- Israel: Since the October 2023 attacks, thousands of children have experienced severe trauma due to bereavement, displacement, and ongoing violence. Infants and children were among those tortured, killed, or abducted on October 7, in acts of extreme and systemic violence. As of June 2025, 50 hostages remain in captivity, those still alive are held without access to medical care. More than 58,000 rockets and UAV alerts have disrupted daily life, exposing children to persistent fear, sleep disturbances, and emotional distress.
- Sudan: More than 14 million children require aid amid civil conflict, famine risk, and mass displacement. Children face acute malnutrition, disrupted health and vaccination services and armed violence — particularly in Darfur. Twelve million girls and women are at risk for sexual and gender-based violence.

Attacks on hospitals and aid convoys further restrict access to care. Thousands have been separated from their families and are at risk of exploitation or recruitment by armed groups.

- Syria: 16.7 million people need humanitarian aid, including over 7 million children affected by prolonged conflict. Children endure chronic displacement, malnutrition, disrupted education, and limited health and psychosocial support. Since December 2024, over 330 children have been killed or injured by unexploded ordnance. Attacks on infrastructure and overcrowded camps increase the risk of disease, exploitation, and trauma.
- Ukraine: More than 4 million children have been impacted by war, with over 2,500 confirmed casualties. According to the UN, since February 2022, the UN Human Rights Monitoring Mission in Ukraine (HRMMU) has reported the deaths of at least 716 children and 2,173 children injuries, but considers that the actual number of child casualties may be much higher, since entire regions of Ukraine remain inaccessible. Many children face repeated displacement, the loss of family members, and destruction of schools, homes, and hospitals. Medical facilities have been attacked, limiting care. Children endure daily air raid sirens, prolonged sheltering, and ongoing disruptions to their education. Seventy percent of children in Ukraine (3.5 million) lack essential goods and services, including nutritious food, appropriate clothing, heating at home, and access to education. In frontline areas, students have missed up to 85% of classes.

Humanitarian corridors are frequently compromised. The psychological and developmental consequences for children are deep and long-lasting.

The crises highlighted here are not exhaustive. Many other regions - including Yemen, Myanmar, the Sahel, Venezuela, and parts of the Horn of Africa - face equally urgent humanitarian emergencies affecting children. Their omission reflects no judgment or prioritisation, but rather the limitations of scope within this statement. The EAP recognises that every crisis is shaped by complex, deeply rooted historical and political factors that cannot be fully explored here. We acknowledge that no conflict can be fully understood without its context.

Nevertheless, these and all other affected regions, whether at this point and any point in the future, are fully included in the EAP's call for the protection, care, and rights of every child.

Peace is a prerequisite for child health.

Political actors must commit to ending cycles of violence and investing in systems that safeguard children before, during, and after conflict including mental health, education, and resilience-building. This is the only sustainable foundation for child health and development.

We call on the international community, humanitarian actors, and all sides in conflict to *put children first. Everywhere. Always.*

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Diagnostic Challenges and Novel Insights in Kawasaki Disease, a Case Report

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Keywords
Kawasaki disease ; coinfection ; diagnostic challenges ; case report.

Abstract

This report highlights the case of a 3-year-old girl with Kawasaki disease and concurrent *Mycoplasma pneumoniae* infection. Treatment with intravenous immunoglobulin, high-dose aspirin and corticosteroids led to clinical remission and resolution of cardiac abnormalities. This case highlights the need for timely recognition of KD and co-infection, and stresses the role of early, tailored management in preventing serious complications. Co-infection, pathophysiological hypotheses and pharmacogenetics are briefly explored.

Background

Kawasaki disease (KD) is a leading cause of acquired heart disease in children, characterised by acute vasculitis (1, 2). Classic symptoms include prolonged fever, conjunctivitis, changes in oral mucosa, oedema of the hands and feet, cervical lymphadenopathy, and polymorphous rashes. Atypical KD may lack these hallmark features, making diagnosis more challenging and often reliant on laboratory findings. A resurgence in KD has been reported following the relaxation of SARS-CoV-2 pandemic restrictions, highlighting the need for clinical vigilance (3). This case report aims to raise awareness of KD.

Case description

We present the case of a 3-year-old girl who developed a severe rash, refusal to bear weight, and systemic symptoms following an acute infection with parotitis epidemica. She initially presented to the emergency department with fever and a neck swelling accompanied by torticollis, but was otherwise well. Initial investigations showed a normal complete blood count and mildly elevated CRP (41 mg/L [<5 mg/L]), along with locoregional inflammation on echography. Antibiotics were administered for presumed lymphadenitis colli and discontinued once serology confirmed parotitis epidemica. She was discharged with an expected recovery. However, 11 days after fever onset, she re-presented with persistent fever, irritability, a severe desquamating rash with superinfection in the groin and sacral region, eyelids and perioral area, bilateral foot swelling with refusal to bear weight, anorexia, and mild conjunctivitis (Figure 1). She had no relevant medical history.

Upon closer clinical examination, the patient had bilateral submandibular lymphadenopathy and cracked lips. Nikolsky's sign was negative. Laboratory investigations showed elevated CRP (92 mg/L), thrombocytosis (546,000/µL [150,000-400,000/µL]), neutrophil-predominant leucocytosis (18,770/µL [6,000-17,000/µL]), hyperferritinaemia (1,100 ng/mL [4.6-200 ng/mL]), normocytic normochromic anaemia and hypoalbuminaemia (25.5 g/L [38.0-54.0 g/L]). Liver enzymes, synthetic functions (other than albumin), high-sensitivity troponin, and electrolytes were within normal limits. Lactate dehydrogenase was only mildly elevated. The clinical and laboratory findings were most consistent with KD. Differential diagnosis included Lyell syndrome, Stevens-Johnson syndrome, toxic shock syndrome (TSS), TSS-like syndrome, staphylococcal scalded skin syndrome, and hyperinflammatory conditions. Given the severity of her presentation and potential alternative diagnoses, high-dose flucloxacillin was initiated and she was admitted for further evaluation.

Transthoracic echocardiography (TTE) on the first day revealed coronary artery dilation with increased echogenicity, measuring 4.5 mm in the left and 3.4 mm in the right coronary artery, along with mild pericardial effusion (Figure 2). Chest X-ray showed mild bronchitis, and abdominal echography revealed mesenteric lymphadenopathy. Nasal swab PCR was positive for *Mycoplasma pneumoniae*, while serology ruled out acute viral infections. These findings made alternative diagnoses unlikely. Treatment was adjusted for KD, with a Kobayashi score of 1 indicating a low risk of resistance to intravenous immunoglobulin (IVIG).

IVIG at 2g/kg body weight was administered, and the patient was started on high-dose aspirin and a course of azithromycin. Other antibiotics were discontinued. Despite clinical and biochemical improvement, the fever persisted. On day 3, intravenous methylprednisolone was initiated at 1mg/kg body weight twice daily. She became afebrile by day 5, after which the aspirin dose was reduced. TTE on day 7 showed normalisation of coronary artery diameter (<3 mm bilaterally), with persistently increased echogenicity and no pericardial effusion. Intravenous treatment was switched to oral therapy with a tapering corticosteroid schedule, and the patient was discharged. At six-week follow-up, cardiac abnormalities had fully resolved and the patient remained symptom-free.

FIGURE 1: Patient presented with a severe desquamation of the urogenital region. A small patch suspicious of superinfection is visible in the right groin.

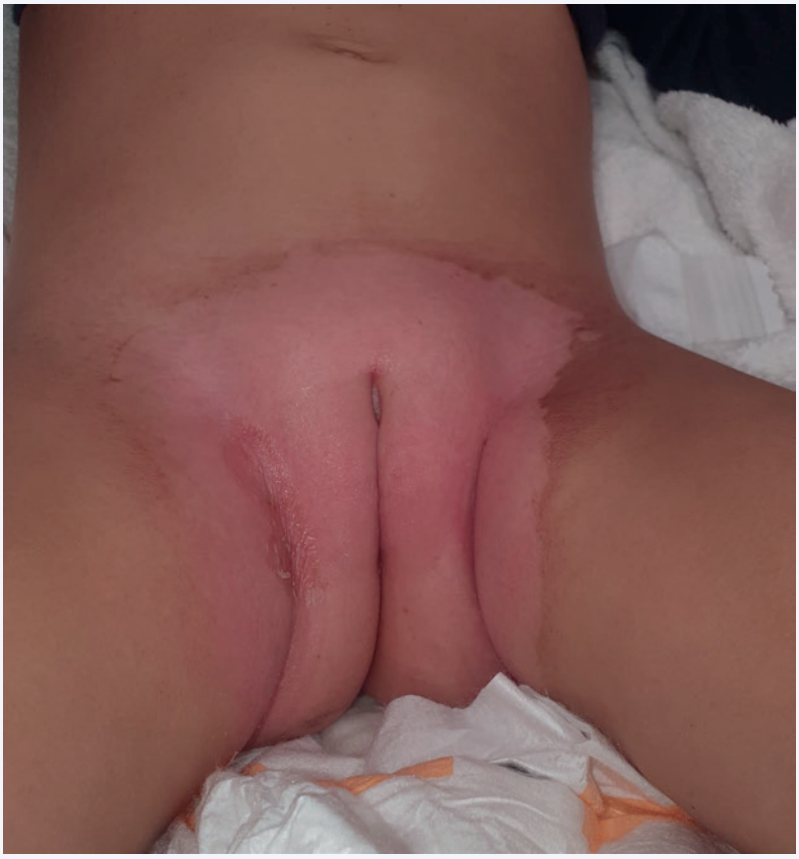
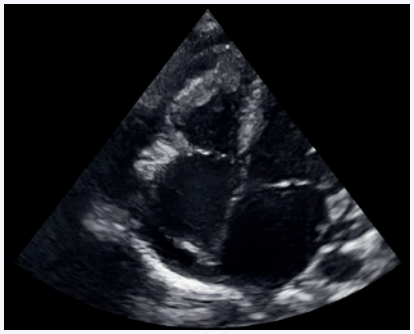


FIGURE 2: Transthoracic echocardiography, apical four chamber view. Mild pericardial effusion is visible.



Discussion

In this case, a high suspicion of KD was maintained while treating for several less likely but potentially serious differential diagnoses. The case illustrates the diagnostic complexity of KD, even when key features are present, particularly in the context of co-infections with uncertain relevance. Treatment was adjusted based on TTE findings, which strengthened the suspicion of KD and allowed for the discontinuation of antibiotics. It is important to note that TTE findings may be normal in the early stages of KD. This diagnosis should still be considered in patients who do not respond to initial treatment for alternative conditions.

Further investigations identified a co-infection with *Mycoplasma pneumoniae*. While co-infections, particularly pulmonary infections, have been associated with KD, the significance of *Mycoplasma pneumoniae* has only recently been recognised. One study reported that such an infection may aggravate the risk of coronary aneurysm formation (4). Clinicians should therefore consider PCR testing for co-infections and initiate appropriate treatment when identified.

Infections are thought to play a primary role in the pathophysiology of KD by activating the immune system. However, the American Heart Association notes that a definitive causative agent has yet to be identified (1). The innate immune response involves the release of proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor, which are nonspecific. Furthermore, the adaptive immune system modulates both proinflammatory and regulatory T cells, which may explain the effectiveness of IVIG therapy, as it promotes regulatory T cell upregulation. Notably, the recurrence rate of KD is very low, possibly due to the protective role of B cell memory.

Most children do not develop KD despite the presence of proinflammatory cytokines during infection, underscoring that the disease's pathophysiology remains poorly understood. This aligns with one report, which found that the incidence pattern in Japan does not support person-to-person transmission as the sole cause (2). An alternative hypothesis proposes that airborne transmission of an infectious agent may contribute to the disease's occurrence, perhaps explaining its geographical distribution. Indeed, several studies have linked KD incidence to tropospheric wind currents (1, 2). Additionally, the marked decline in KD cases during the COVID-19 pandemic further supports a connection with transmissible agents (2).

Recent studies suggest that a subset of KD patients may share a common disease trigger. In one study, Rowley et al. identified a protein epitope recognised by antibodies that develop during KD (5). Using plasmablasts isolated from confirmed KD cases, they generated monoclonal antibodies to detect a specific antigen, which was then cross-tested with sera from other patients. A subsequent study used amino acid substitution matrix analysis to identify a variant of the epitope that enhanced binding to KD monoclonal antibodies (6). This led to the discovery of a convergent antibody response, supporting the hypothesis of a predominant causative agent. Given that such responses are typically associated with infection, a respiratory pathogen is considered the most likely candidate. These findings further our understanding of KD pathophysiology and may contribute to the development of a disease-specific diagnostic test.

Host genetic factors may influence susceptibility to KD. This was first suggested when individuals of Japanese ancestry living in Hawaii, located along the same tropospheric wind path as Japan, were found to have a risk of KD similar to that of native Japanese individuals. In addition, siblings of a KD patient have a 10- to 30-fold higher risk of developing the disease compared to the general population (7). While a detailed discussion of implicated genes is beyond the scope of this report, insights into patients' genetic backgrounds may help explain differences in susceptibility. Notably, certain gene associations appear population-specific. For example, human leukocyte antigen determinants have been linked to KD susceptibility in individuals of Japanese or Taiwanese ancestry, but not in those of European descent (3). Identifying these differences may inform tailored treatment and prevention strategies. Expanding our knowledge of KD-related genes could also support the use of next-generation sequencing (NGS) to refine prognosis and guide therapy.

Some polymorphisms have already shown clinical relevance, informing current treatment approaches in KD. Variants in *ITPKC* and *CASP3* genes have been associated with IVIG-refractory KD, in which corticosteroids are sometimes used (7). While a randomised trial found no overall benefit of corticosteroids over IVIG, subgroup analysis showed reduced coronary artery abnormalities in refractory cases (8). This finding was supported by a trial targeting patients with a high Kobayashi score, which predicts IVIG resistance (9). Genetic insights have also guided the development of novel therapies. For instance, *ITPKC* and *CASP3* variants downregulate a calcineurin-mediated pathway, exacerbating inflammation. Cyclosporine, a calcineurin inhibitor, may restore immune regulation and has prompted trials for its use in IVIG-refractory KD (7). Additionally, pharmacogenomics has driven interest in statins. Their pleiotropic effects may help prevent complications, and they appear to be safe in children (10). Their efficacy is under investigation.

Conclusion

KD remains a leading cause of acquired heart disease in children, making prompt recognition and treatment essential. With rising post-pandemic incidence, renewed clinical awareness is needed. Despite decades of research, our understanding of its aetiology and pathophysiology remain incomplete. Recent findings suggest that concurrent infections may influence outcomes, supporting the need to consider co-infection testing during diagnosis. Genetic factors likely contribute to both disease susceptibility and treatment response, and novel therapies are under investigation. Integrating clinical, genetic, and infectious insights may ultimately improve diagnosis, stratify risk, and personalise treatment for children with KD.

Statements

Written informed consent was obtained from the parents to publish the case report and figures.

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

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Growth delay in infants: ensuring optimal care

Faltering growth in infants and young children under the age of two is a common concern in clinical practice. This condition is associated with various adverse health and developmental outcomes, highlighting the importance of implementing strategies to promote catch-up growth when indicated. However, some healthcare professionals may be reluctant to intervene optimally, often due to the misconception that addressing faltering growth could lead to excessive growth acceleration. Challenging these misconceptions and promoting an evidence-based approach are therefore essential to ensuring the healthy development of affected children.[1-4]

Faltering growth in infants is characterized by a slower-than-expected weight gain relative to age, sex, and current weight. According to the World Health Organization (WHO) criteria, it is defined as a decrease of ≥ 1.0 in the weight-for-age z-score. Experts recommend assessing such a decrease over a period of at least one month.. This definition excludes the first two weeks of life, during which physiological weight loss is expected.[2,3]

Standard management is typically focusing on nutritional support and behavioral guidance to enhance overall energy intake and ensuring an appropriate protein-to-energy ratio. Essential anthropometric measurements - including weight, length, and head circumference - are fundamental for tracking a child's growth trajectory. Screening tools such as STRONGkids, PYMS, STAMP, and iNEWS aid in the identification and assessment of children at risk.[4]

Faltering growth can have immediate consequences on a child's health and may indicate an underlying medical condition. It is therefore crucial for healthcare professionals to identify and appropriately manage growth concerns. Routine growth monitoring, along with parental or professional observations, plays a key role in early detection.[2]

Consequences of faltering growth: a socioeconomic perspective[1,2]

Faltering growth in early childhood can have significant and lasting consequences, both in hospital settings and beyond. In high-income countries, malnutrition in hospitalized children has been associated with increased risk of complications, longer hospital stays, and higher vulnerability to infections. Even when not linked to an underlying disease, growth faltering may negatively affect cognitive development and academic performance. Behavioral and communication difficulties are also more common in these children, including a higher prevalence of attention deficit disorders and hyperactivity. In the long term, faltering growth has been associated with a smaller adult stature and potential socioeconomic disadvantages.

Over time, the effects of early-life growth faltering can persist into adulthood. These include reduced physical work capacity, impaired educational attainment, and lower earning potential — ultimately contributing to a cycle of social disadvantage and diminished human capital. Without timely and adequate intervention, faltering growth can entrench health and economic inequalities across generations, particularly in contexts where access to healthcare and nutrition is limited.

Nutritional management of faltering growth: considerations for infants[1,2,5]

The nutritional management of faltering growth, whether associated with an underlying medical condition or not, requires a balanced intake of energy, proteins, and micronutrients to support optimal catch-up growth. According to WHO recommendations, an adequate protein-to-energy ratio, ranging from 8.9% to 11.5% of total energy intake, is advised to ensure effective and safe recovery without compromising metabolic balance.

Breastfeeding should be encouraged in all cases, ensuring that appropriate techniques are used to provide adequate intake. In specific cases where additional support is needed, fortification, cup feeding, or mixed feeding strategies may be considered.

For infants receiving formula, ready-to-use, high-energy and appropriate protein-energie ratio, medically specialized nutritional products with proven efficacy should be used whenever available. Locally available powdered formulas with appropriate nutritional composition can be utilized, following WHO hygiene guidelines for reconstitution.

The use of modular additives consisting solely of fats and carbohydrates should be avoided, as they increase energy intake without a corresponding increase in protein, thereby lowering the protein-to-energy ratio. This can lead to excess fat gain rather than balanced growth, which ideally consists of approximately 70% lean mass and 30% fat mass.

A structured catch-up growth plan should be integrated into the nutritional strategy, with progress monitored at an appropriate rate, as determined by healthcare professionals. The level of medical supervision and intervention should be tailored to the severity of the growth delay and the healthcare resources available.

Evolution of nutritional management of hospitalized children in Belgium: comparison 2014-2021[6,7]

In Belgium, the nutritional management of hospitalized children has evolved over the past decade, but certain challenges persist. A 2014 survey revealed that only half of pediatric departments conducted nutritional screening (39.5% Flemish speaking and 71.4% Walloon speaking). The main methods used were weight and height measurement (92.7%) and clinical assessment (74.7%), while more specific tools, such as mid-upper arm circumference measurement or skinfold thickness assessment, were rarely employed (19.7%). Furthermore, 60.5% of Flemish-speaking and 28.6% of French-speaking departments had no established protocol for managing malnutrition. The primary barriers to systematic screening were lack of training (46.9%), lack of awareness of nutritional screening tools (42.2%), and time constraints (29.7%).

By 2021, some progress had been made. A dietician was present in 80.3% of all responding units compared to 46.5% in the 2014 survey. However, systematic nutritional screening remains limited to 30.4% of Flemish-speaking and 40% of French-speaking centers, marking a decline from 2014 levels. In French-speaking centres, a positive screening result most often led to referral to a dietitian (86.7%), whereas in Flemish-speaking centers it more frequently resulted in a discussion with the paediatrician about nutritional management (54.3%) than referral to a dietician (34.8%). Post-discharge nutritional follow-up is still primarily handled by a physician with or without a dietician (95.1%) rather than a dietitian alone (3.3%).

Despite these advancements, barriers to nutritional management have remained largely unchanged since 2014. Time constraints (59%), lack of knowledge on the subject (47,5%) and lack of staffing (42,6%), continue to be major obstacles for conducting nutritional screening. Malnutrition treatment barriers included «no barriers» (50.8%), lack of knowledge (34.4%), lack of reimbursement (24.6%) and lack of time (24.6%).

While awareness, paramedical resources, and more systematic screening practices have improved since 2014, nutritional screening remains inconsistently implemented across Belgian pediatric hospitals, and overall, the barriers identified a decade ago persist.

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Bridging the gaps: a call for action on faltering growth

Faltering growth in infants remains a widespread clinical concern with significant long-term consequences. Early identification and nutritional intervention are essential but remain inconsistently applied, particularly in hospital settings. While some progress has been made in Belgium over the past decade, persistent barriers such as lack of time, training, and resources continue to hinder systematic screening. Ongoing professional education and structured protocols are key to improving the quality of care and outcomes for affected children.

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Nasal Dermoid Sinus Cyst in a 17-Year-Old Female: A Case Report

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Keywords
Midline nasal lesion ; dermoid sinus cyst ; congenital malformation ; magnetic resonance imaging ; case report.

Abstract

Introduction
Nasal dermoid sinus cysts are rare congenital anomalies that account for 1% of dermoid cysts. They typically present as midline nasal lesions and may involve intracranial structures.

Observation
A 17-year-old female presented with a congenital midline nasal bridge nodule, which became noticeable during adolescence due to coarse dark hairs. Clinical examination revealed a well-defined nodule with a hyperpigmented patch inferiorly. MRI confirmed the absence of intracranial extension. The lesion was surgically excised, resulting in satisfactory cosmetic and functional outcomes.

Conclusion
This case highlights the importance of including nasal dermoid sinus cysts in the differential diagnosis of midline nasal lesions. Imaging is essential for preoperative planning to assess intracranial involvement and guide safe surgical management.

Introduction

Nasal dermoid sinus cysts are rare congenital anomalies arising from developmental defects during embryogenesis. They represent approximately 1% of all dermoid cysts and 3–12% of those in the head and neck region (1). Intracranial extension occurs in approximately 10-45% of cases and may lead to complications such as meningitis or cerebrospinal fluid leakage if inadequately managed (2, 3). Accurate diagnosis and preoperative imaging are crucial to guide treatment and prevent complications.

Case Presentation

A 17-year-old female presented with a congenital nodule on the nasal bridge, stable since birth but with the recent emergence of coarse dark hairs. Her medical and developmental history was unremarkable.

Clinical examination showed a well-defined nodule on the midline of the nasal bridge with an overlying hyperpigmented patch containing a small tuft of dark hair (Figures 1A, 1B). There were no signs of infection, drainage, or associated congenital anomalies.

Magnetic resonance imaging (MRI) of the head and neck confirmed the absence of any communication with intracranial structures.

Although laser hair removal was offered as an initial treatment for the hyperpigmentation and coarse hairs, the patient opted for surgical excision. The lesion was removed through a direct approach, with satisfactory aesthetic results an uneventful recovery.

Discussion

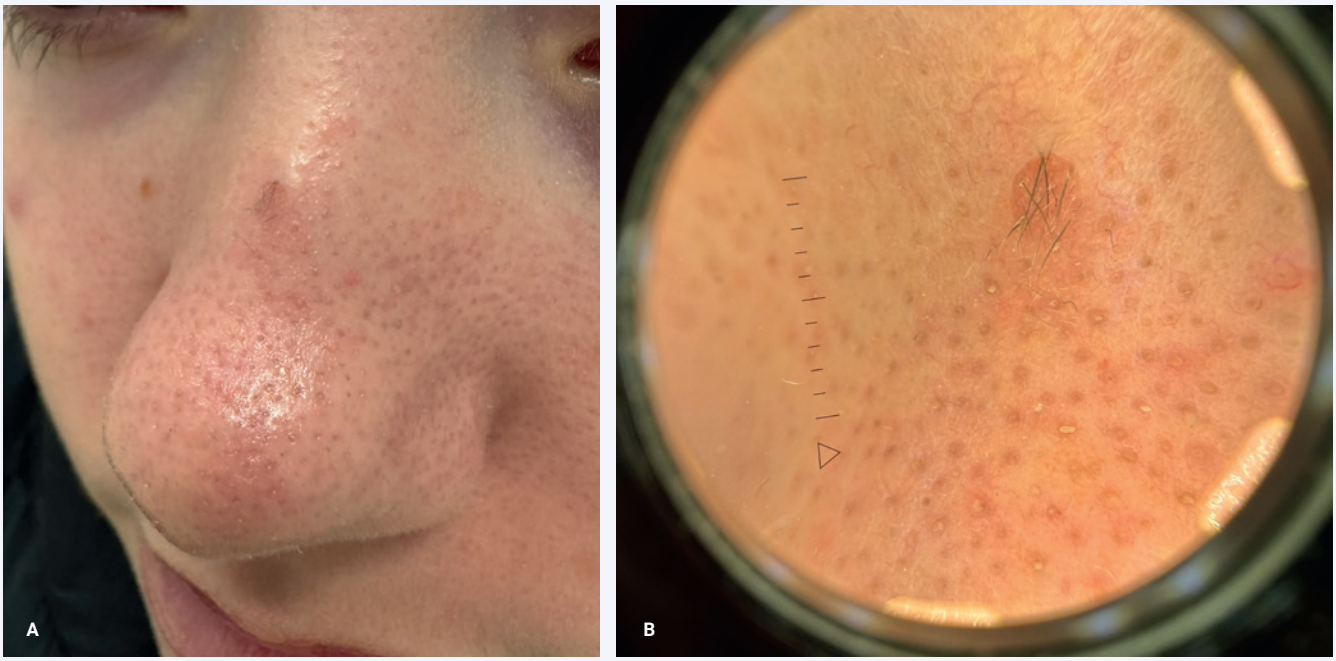
Nasal dermoid sinus cysts are rare congenital midline lesions that usually present during childhood or adolescence (4). Their pathogenesis is attributed to either incomplete regression of the dura mater or ectodermal trapping during embryological fusion of the nasal processes. Although uncommon, familial cases with an autosomal dominant inheritance pattern have been reported (3).

These cysts typically appear as firm, midline nasal dorsum masses, which may be pale, flesh-coloured, or erythematous. A characteristic midline punctum or pit may discharge sebaceous material or contain protruding hairs. Deeper lesions may extend to the cribriform plate and are often asymptomatic unless infected or draining. In up to 40% of cases, other congenital anomalies such as clefting or hydrocephalus may be present (5).

The differential diagnosis includes nasal glioma, encephalocele, epidermoid or sebaceous cyst, haemangiomas, and neuroglial heterotopia (1)

Advanced imaging is essential to exclude intracranial involvement. MRI, with its superior soft tissue resolution, is the preferred modality for detecting intracranial extension and visualizing tracts to the dura mater or cribriform plate. It is particularly valuable for presurgical planning, as it identifies any communication with critical intracranial structures (4). Computed tomography (CT) complements MRI by effectively detecting bony defects, such as foramen cecum erosion or widening, and together they provide detailed insights into skull base involvement (4, 5). This imaging is essential because surgical removal carries the risk of creating an open communication with the brain, potentially causing cerebrospinal fluid leakage or meningitis.

FIGURE 1: A well-defined nasal bridge nodule (A) with adjacent hyperpigmented macule containing dark hairs (B).



In paediatric cases where MRI or CT scans may not be feasible due to concerns about sedation or radiation, high-resolution ultrasound offers a valuable non-invasive alternative to assess lesion depth and vascularity (6). However, ultrasound has limitations in detecting deeper or intracranial extension.

Surgical excision remains the gold standard to prevent complications such as infection, recurrence, or intracranial extension (2). Lesions without intracranial involvement are treated with simple excision, achieved by direct incision or an open rhinoplasty approach, ensuring complete removal while minimizing cosmetic concerns. Lesions with intracranial involvement require a multidisciplinary approach. Surgeons may perform a craniotomy or a combined endoscopic and open procedure to safely remove the cyst and associated tracts.

Although our patient presented at the age of 17, most cases are diagnosed earlier. The optimal time for surgery is between 18–24 months of age, allowing for easier dissection and reducing the risks of cyst growth or infection. Laser therapy can be considered for cases where cosmetic issues such as residual hair or pigmentation are the primary concern. This is suitable for children from the age of 5–6 years, when they can better tolerate the procedure and cooperate with treatment.

Conclusion

This case underscores the importance of considering nasal dermoid sinus cysts in the differential diagnosis of midline nasal lesions, especially when a hair tuft is present. Preoperative imaging, particularly MRI, is essential for assessing intracranial involvement. Early identification and surgical excision optimize outcomes and reduces complications, while laser therapy can be reserved for cosmetic refinements later in childhood.

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An Unusual Skin Reaction after Bexsero® Vaccination in a Paediatric Patient: A Case Report

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Keywords
Meningococcal vaccines ; infant ; injection site reaction ; case report.

Abstract

Bexsero® is a multicomponent vaccine protecting against *Neisseria meningitidis* serogroup B, a major cause of meningococcal disease. Common side effects include injection site reactions (pain, redness, swelling) and systemic symptoms (fever, irritability, fatigue), while rarer complications like febrile seizures and Kawasaki disease occur in less than 1%. This case report describes a previously undocumented reaction in a twelve-week-old infant who developed immediate pale spots on the leg after vaccination, later progressing to a necrotic lesion. Possible hypotheses, including an immune response, intra-arterial injection with embolization, and vasospasm, are discussed.

Introduction

In 2023, Belgium recorded 104 cases of invasive meningococcal disease, with 83 confirmed by the National Reference Centre. The overall incidence was 0.71 cases per 100,000 inhabitants, with the highest rates observed in children between zero and four years (3.4 per 100,000), particularly infants under one year (8.8 per 100,000), as well as adolescents aged 15-19 (1.0 per 100,000) and adults over 80 (1.7 per 100,000). For the first time, serogroups W and Y were dominant (51.8%), followed by serogroup B (43.4%). Although serogroup B was the most prevalent in most age groups, serogroups W and Y were more common in adults aged 25-49 and those aged 65 and older. Among people over 65, serogroup Y was the most frequent. Among infants under one year, serogroup B accounted for six out of nine cases. Three deaths were reported, two from serogroup B and one from serogroup W (1).

Bexsero® is a vaccine given to individuals aged two months and older to protect against invasive disease caused by *Neisseria meningitidis* serogroup B. This bacterium is a gram-negative, aerobic microorganism responsible for severe illnesses such as meningitis and sepsis, collectively known as meningococcal disease. *N. meningitidis* is transmitted from person to person through aerosols or direct contact with the respiratory secretions of infected individuals or asymptomatic carriers, typically via coughing or sneezing (2).

Bexsero® is a multicomponent, recombinant, non-live vaccine specifically targeting meningococcal group B. To stimulate an immune response, it includes four antigenic proteins from the *N. meningitidis* bacterium: Neisseria Heparin Binding antigen, Neisserial adhesion A, factor H binding protein and outer membrane vesicles from Neisseria meningitidis group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4. Apart from these proteins, it also contains inactive ingredients, such as aluminium hydroxide, histidine, sodium chloride, sucrose and water for injection (3).

In Belgium Bexsero® is not part of the routine immunization schedule, but it is advised at individual level (4). The vaccine is administered via intramuscular injection. For children until two years of age, it is injected into the anterolateral thigh muscle (musculus vastus lateralis), while for older children and adults, it is given into the deltoid muscle region of the upper arm (5).

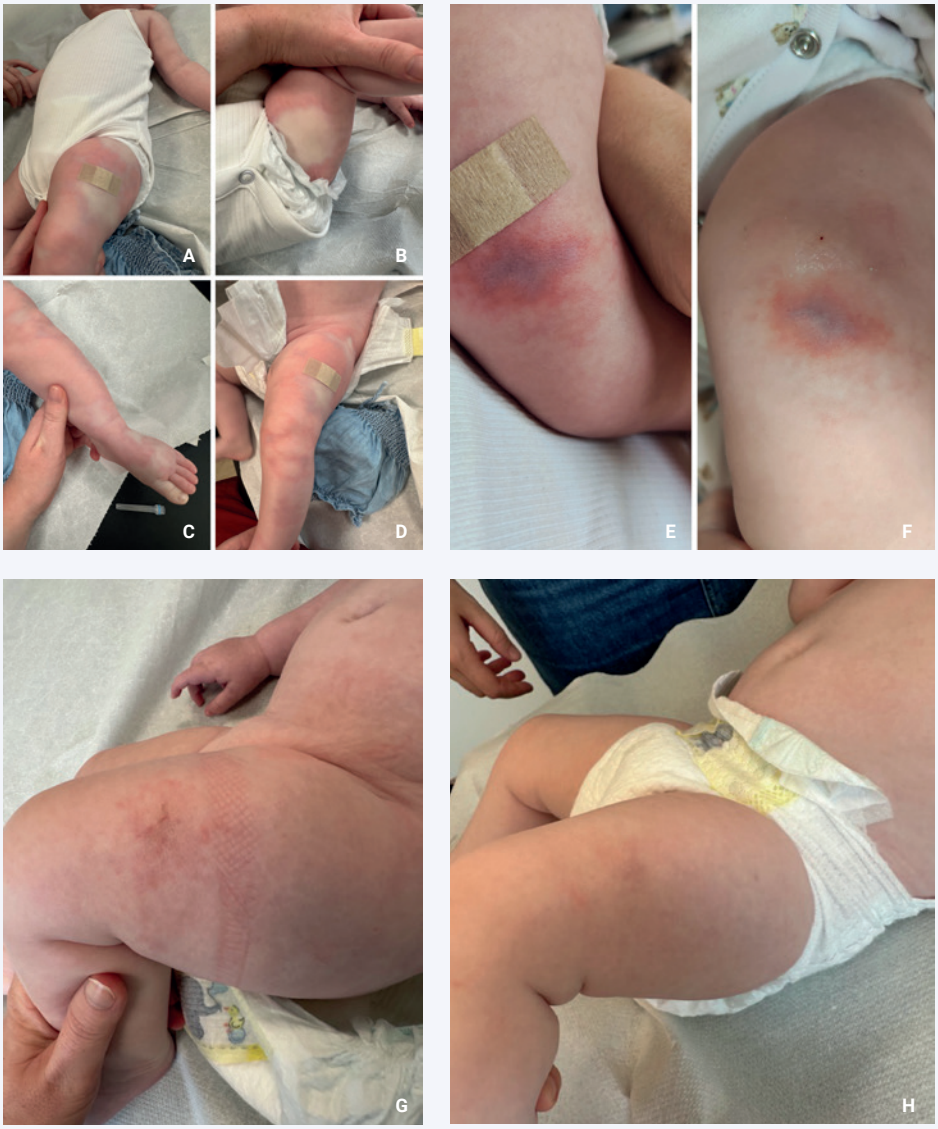
Skin reactions following Bexsero® vaccination, as documented in spontaneous suspected adverse vaccine reaction reports received up to and including 15/03/2022, range from mild and transient to more persistent and concerning manifestations. Common injection site reactions include erythema, swelling, induration and pain. More extensive skin reactions, such as rash, urticaria, pruritus, and dermatitis have also been reported. In some cases more severe presentations, like ecchymosis, skin discoloration, extensive limb swelling, necrosis or ulceration have been observed, though the exact causality remains uncertain (3,6).

Case report

A twelve-week-old girl (87 days) with an unremarkable medical history except for a one-day hospital admission for mild respiratory distress, visited the paediatric outpatient clinic to receive her first dose of the Bexsero® vaccine as a preventive measure. The vaccine was administered according to guidelines, intramuscularly in the anterolateral thigh of the left leg using a 23Gx1" needle. To ensure there was no intra-arterial placement, the paediatrician aspirated before administering the injection, and no blood was aspirated. Based on the latest studies, the Centres for Disease Control and Prevention state there is no evidence supporting the need for aspiration before intramuscular injections because no large blood vessels are present at the recommended injection sites (7).

Immediately after the vaccination unusual circular pale spots appeared on the girl's leg, without any apparent signs of discomfort.

FIGURE 1: Clinical presentation at the paediatrician (a-d), home on the same day (e,f), 5 days (g) and 2 months after onset (h).



Initially, a pale spot appeared directly distal to the injection site and spread down to the foot within seconds. A few minutes later, a purplish band formed around the various spots (Figure 1A). Several minutes after that, most of the spots disappeared, leaving only the initial one distal to the injection site.

Once stabilized, the child was sent home, with the mother sending pictures to monitor the progression of the leg. That same day, the pale spots completely disappeared, but a purplish area with surrounding redness developed at the injection site. While it appeared necrotic, this could not be definitively confirmed, as no dermatologist was consulted and no skin biopsy was taken (Figure 1B). Despite this, the girl remained otherwise healthy with no further complaints following the Bexsero® vaccination.

When the necrotic area appeared, a plastic surgeon was consulted for advice. She recommended treatment with a paraffin gauze dressing. Once the redness had resolved, a soothing and skin-repairing balm enriched with madecassoside, panthenol and antibacterial agents (Cicaplast®), was advised to support skin recovery (8).

After five days, only a light spotty area and a palpable hard zone of induration remained (Figure 1C), but showed gradual improvement over time (Figure 1D).

On the same day as the Bexsero® vaccination, the girl did not receive any other injections. However, later on, she received additional injections in both legs, including the standard twelve-week vaccinations. She had also previously received her eight-week vaccinations, none of which caused a similar reaction. After discussing the situation with the parents, the paediatrician decided not to administer the second Bexsero® vaccination.

Discussion

This reaction to the Bexsero® vaccine has not been previously documented in medical literature or reported to the Federal Agency for Medicines and Health Products. To understand this phenomenon, the following hypotheses must be considered.

Peripheral vasoconstriction is a rare but documented adverse effect of the Bexsero® vaccine, likely caused by a reaction to one of its components (6). In this case, the unusual circular pale spots could indicate a temporary local vascular response, such as vasospasm. This narrowing of the blood vessels, caused by contraction of the vascular smooth muscle, restricts blood flow to specific skin areas and explains the observed discoloration.

A possible link can also be drawn with Raynaud's phenomenon, a condition characterized by episodic vasospasms and skin discoloration due to reduced blood supply. Raynaud's phenomenon has been reported as a rare side effect of various vaccines. Lisy et al. for instance, described its occurrence after COVID-19 vaccination, illustrating how vaccines can sometimes provoke vascular reactions through mechanisms that are not yet fully understood. The tissue necrosis observed in this case may have been caused by prolonged vasospasm, leading to ischemia and subsequent tissue damage (9).

While vasospasm remains the most plausible explanation, it is important to consider other potential mechanisms. One of these mechanisms is an acute local vasoconstriction, possibly triggered by an inadvertent intra-arterial injection of the vaccine, although the exact process remains unclear. Noradrenaline plays a central role in this response. When the injected substance enters the bloodstream, crystal formation may occur, which triggers the local release of noradrenaline. This release induces vasospasm, followed by thrombosis, impaired blood flow and potential tissue damage (10).

In terms of vascular anatomy, the descending branch of the lateral circumflex femoral artery is the artery most likely affected during a lateral thigh injection. This artery, which originates from the profunda femoris artery, supplies the vastus lateralis and rectus femoris muscles, as well as the overlying skin (11). Normally, penetrating a large artery like this would result in a positive

aspiration test, which was not observed in this case, making an unintended intra-arterial injection unlikely. Additionally, if a smaller artery had been punctured, the pressure required for an intramuscular injection would likely have caused arterial rupture and a subsequent hematoma. Since no hematoma was observed, the likelihood of intra-arterial injection is further reduced.

Another possible hypothesis explaining the pale spots is a rare immune-mediated reaction. While this hypothesis is unlikely, it is included to be complete. In this case, an overreaction of the immune system to one of the components of the vaccine might cause a localized inflammatory response and vascular damage, leading to both the initial pale spots and the subsequent necrotic lesion. According to Donaldson et al. aluminium salts, often used as vaccine adjuvants, can cause severe local reactions, including necrosis, particularly when injected incorrectly into subcutaneous fat. The case study describes an adult patient who developed a necrotic ulcer after receiving the Tdap and Pneumovax vaccinations, likely due to the inflammatory response triggered by these adjuvants (12,13).

However, this immune-mediated hypothesis is less likely in this case because of the timing of the reaction. Immune-mediated responses generally develop over several hours or days, while the symptoms in this patient appeared rapidly. The immediate onset of the pale spots and the quick progression to necrosis make this hypothesis highly unlikely (12,13). While it is important to consider all possibilities, the immune-mediated reaction does not align with the observed clinical timeline and therefore remains an unlikely explanation for the lesion.

Conclusion

Although the exact cause of this reaction remains unclear, these hypotheses suggest that both vascular and immune-mediated mechanisms could be involved. Further observation and research are necessary to understand this reaction better. This case highlights the importance of documenting and researching new and unusual reactions to vaccines to make sure the safety and effectiveness of vaccination remain guaranteed.

Acknowledgment

We would like to thank the patient and her parents for their help with this case, and for sharing their medical history. We would also like to thank all the medical staff who contributed to the diagnosis, treatment and follow-up of this case.

Declaration of patient consent

The authors certify that they obtained all appropriate patient consent forms. The parents gave their consent to publish the photos and other clinical information in this article. They understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Conflicts of interests

The authors declare that they have no conflict of interest and no financial disclosures.

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NIEUW
VANAF NU BESCHIKBAAR

UITSLUITEND VERKOCHT IN DE APOTHEEK

Nestlé NAN RICE

1ste lijnsaanbeveling in geval van koemelkeiwitallergie*

- ✔ **Gehydrolyseerde rijsteiwitten**
- ✔ **Zonder lactose**
- ✔ **Maïszetmeel** (1,4g/100ml)
- ✔ **Vezels** (0,4g/100ml)
- ✔ **HALAL en 100% vegetarisch**
- ✔ **Zonder palmolie**

4901-849

* In lijn met de nieuwe ESPGHAN-aanbevelingen. ESPGHAN position paper on the diagnosis, management, and prevention of cow's milk allergy. JPGN. 2024;78(2):386-413.

Dit document is voorbehouden voor gezondheidsspecialisten. Belangrijke informatie voor (para)medici: de Wereldgezondheidsorganisatie (WHO) heeft aanbevolen om zwangere vrouwen en moeders van zuigelingen te informeren over de voordelen en de superioriteit van borstvoeding. In het bijzonder dat borstvoeding de beste voeding is en de beste bescherming tegen ziektes biedt. Moeders moeten ook begeleid worden met de voorbereiding op en de verderzetting van borstvoeding, met de nadruk op het belang van de kwaliteit van hun eigen voeding tijdens de zwangerschap en na de geboorte. Onnodige introductie van gedeeltelijke flesvoeding of andere voedingsmiddelen of dranken zou ontmoedigd moeten worden omdat het een negatieve invloed op borstvoeding kan hebben. Bovendien moeten moeders gewaarschuwd worden dat zij niet terug kunnen komen op hun beslissing om geen borstvoeding meer te geven. Voordat een moeder besluit om flesvoeding te geven, zou ze geadviseerd moeten worden over de sociale en financiële gevolgen van haar beslissing, bijvoorbeeld als een baby exclusief flesvoeding krijgt, dan is meer dan 450 gram per week nodig, dus de familiale omstandigheden en de kosten moeten in overweging worden genomen. Moeders moeten eraan herinnerd worden dat borstvoeding niet alleen de beste voeding, maar ook de meest economische voeding is. Wanneer toch wordt besloten om flesvoeding te geven is het belangrijk om de juiste instructies mee te geven omtrent het gebruik van deze voeding en erop te wijzen dat ongekookt water, niet gesteriliseerde zuigflessen of een onjuiste bereiding de baby ziek kan maken. **Met vriendelijke groeten, Nestlé Babyvoeding.** V.U : Karlien Desmedt, Nestlé Belgilux SA/NV, rue de Birminghamstraat 221-1070 Bruxelles/Brussels, BCE/KBO 0402.231.383. PID3788 September 2025

NONO-Associated Syndrome: A Rare Case Report in a 2-Month-Old Belgian Male Infant

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Keywords

NONO-associated syndrome ; hypotonia, neonatal ; left ventricular noncompaction ; frameshift variant ; syndromic intellectual disability.

Abstract

We report the first Belgian case of *NONO*-associated syndrome, which was identified in a male infant presenting with hypotonia, macrocephaly, dysmorphic features, and severe non-compaction cardiomyopathy. A likely pathogenic *NONO* variant was identified through whole exome sequencing. While cardiac monitoring was guided by clinical findings, the genetic diagnosis allowed for personalised care and counselling. This case highlights the importance of combining phenotype recognition with molecular testing for early diagnosis. Continued case reporting is essential to improve our understanding of this rare X-linked disorder, and to guide future management and family planning strategies.

Case report

A boy born at 40 weeks of gestation was admitted to the NICU 24 hours after birth due to respiratory distress. His head circumference was 34.5 cm (–0.5 SD), his weight was 3032 g (–1.5 SD), and his length was 47.2 cm (–1.9 SD). On admission, the clinical examination revealed tachypnoea (88 breaths/min), generalized hypotonia, glandular hypospadias, and facial dysmorphism, including a broad forehead, hypertelorism, and microretrognathia (Figure 1). He was the first child of healthy, unrelated parents. Malformative assessment, including cardiac, abdominal, and transfontanellar ultrasounds, identified no major abnormalities except slight cardiac ventricular asymmetry. Genetic testing, including molecular karyotype analysis via Shallow Whole Genome Sequencing, was inconclusive. Because of the hypotonia, Prader Willi syndrome, congenital myotonic dystrophy, and spinal muscular atrophy were ruled out with dedicated tests. The patient's condition improved during hospitalization, and he was discharged on day 9 with scheduled follow-up care.

At home, persistent polypnea and hypotonia were observed, with no feeding difficulties or excessive sweating. At 2 months and 2 weeks of age, a cardiac ultrasound was performed as part of the follow-up for ventricular asymmetry. This revealed severe left ventricular enlargement and dysfunction (ejection fraction <20%, left ventricular (LV) end-diastolic diameter 37 mm (> 2 SD)) with a trabecular left ventricle and no intracardiac thrombus (Figure 2). Elevated cardiac biomarkers (troponin T: 180.8 ng/L; NT-proBNP: 17,244 ng/L) led to admission to the intensive care unit to manage congestive heart failure associated with left ventricular dilated cardiomyopathy. Treatment with an ACE inhibitor (enalapril) and fluid restriction resulted in stabilization, allowing for transfer to the paediatric unit for further evaluation.

At admission, a rapid increase in head circumference was noted, shifting from –0.5 SD to +1.28 SD. Transfontanellar ultrasound revealed a slightly increased Evans index (0.32-0.34), suggesting hydrocephalus.

During hospitalization, the patient received thiamine, riboflavin, and L-carnitine as substitute treatments while awaiting the results of metabolic investigations. Carvedilol (1 mg/day, increased to 1.5 mg/day) was introduced along with enalapril (gradually increased to a maximum of 1.5 mg/day). Fluid intake was restricted to 110 ml/kg/day. Regular cardiac monitoring confirmed the diagnosis of non-compaction cardiomyopathy (NCC). The most recent ultrasound scan revealed stable, severely impaired left ventricular function (ejection fraction (EF) 25%) and consistent dilatation (LV end-diastolic diameter 33-38 mm), as well as a reduction in NT-proBNP levels (8701 ng/L).

Axial hypotonia persisted throughout the hospitalization. After obtaining informed consent from the parents, whole exome sequencing (WES) in trio was performed, identifying a likely pathogenic variant (class 4) in the hemizygous state of the *NONO* gene (NM_007363.5, GRCh38):c.441dup p.(Ala148Cysfs*36). This de novo variant causes a premature STOP codon at exon 5/12. Loss-of-function variants in *NONO* are well-known pathogenic mechanisms responsible for X-linked syndromic intellectual developmental disorder-34 (MRXS34) (OMIM: 300967), consistent with a diagnosis of *NONO*-associated syndrome.

Given the patient's stable condition, good treatment tolerance, and overall well-being, he was discharged at 3 months and 3 weeks of age. At discharge, he was prescribed oral ACE inhibitors and beta-blockers, with plans for continued follow-up care by general paediatricians, paediatric cardiologists and a geneticist.

Discussion

Left ventricular non-compaction cardiomyopathy (LVNC) is a rare congenital heart disease characterized by prominent trabeculations and deep intertrabecular recesses in the left ventricle, resulting from arrested myocardial compaction during embryogenesis. In paediatric populations, LVNC ranks as the third most prevalent cardiomyopathy after dilated and hypertrophic cardiomyopathy. Its clinical presentation in children varies widely, ranging from asymptomatic cases to severe heart failure, arrhythmias, and thromboembolic events. Notably, LVNC in children is more frequently associated with genetic syndromes, neuromuscular disorders, and other congenital anomalies compared to adults. Genetic factors play a significant role in paediatric LVNC, with up to 41% of cases attributed to genetic mutations (1) Most familial cases follow an autosomal dominant inheritance, often involving mutations in sarcomeric protein genes (e.g., *MYH7*, *MYBPC3*, *TNNT2*). X-linked forms are also known – for example, mutations in the *TAZ* gene on the X chromosome cause Barth syndrome, a metabolic disorder that includes LVNC as a feature (2).

Among these, loss-of-function variants in the *NONO* gene have been identified as a cause of X-linked syndromic intellectual developmental disorder-34 (MRXS34), which includes features such as developmental delay, intellectual disability, hypotonia, macrocephaly, and LVNC.

The *NONO* gene, located at Xq13.1, consists of 13 exons and encodes the non-POU domain-containing octamer-binding protein *NONO* (also known as p54NRB). This protein belongs to the DBHS (Drosophila behaviour/human splicing) family and plays a crucial role in gene expression by regulating transcription, RNA processing, transport, and DNA repair (3). It also actively regulates synaptic transcript expression across a substantial number of connections within the central nervous system (4). In 2015, a study by Mircsof et al. first implicated *NONO* in cognitive impairment by showing that *NONO*-deficient mice exhibited impaired neuronal connectivity (5). The protein's deficiency disrupts GABA-ergic inhibitory synapses, potentially contributing to the cognitive deficits.

Loss-of-function variants in *NONO* are responsible for X-linked syndromic intellectual developmental disorder-34 (MRXS34; OMIM: 300967), a rare condition that predominantly affects males. This condition is marked by haploinsufficiency due to hemizygous loss-of-function variants in the *NONO* gene. It is characterized by developmental delay, intellectual disability, macrocephaly, anomalies of the corpus callosum, and left ventricular non-compaction cardiomyopathy (LVNC).

Over the past decade, 27 cases of *NONO*-associated syndrome have been reported, contributing to a better delineation of its phenotypic spectrum (6-8). Consequently, our case represents the 28th reported in the literature and the first in Belgium.

Among this limited cohort, 7 prenatal cases were reported, all diagnosed due to cardiac malformations. All patients were male, aged between 78 days and 29 years, with an average age of 9 years.

Individuals with *NONO*-associated syndrome exhibit a broad range of phenotypes, summarized in Table 1. All surviving patients presented with neurodevelopmental delay (27/27), with 23 experiencing moderate to severe intellectual disability. Cerebellar structural abnormalities were reported in 20/23 cases, most frequently involving abnormal corpus callosum development (17/22) (4,6,9).

Cardiac anomalies were identified in 22/26 patients, primarily non-compaction cardiomyopathy (18/22) (6,7). 7 patients showed prenatal cardiopathies (7/7), including 5 cases of left ventricular non-compaction (LVNC) (10). The incidence of LVNC in patients with pathogenic *NONO* variants is significantly higher than in the general population (4,9,11). Indeed, LVNC is considered a rare form of non-compaction cardiomyopathy, with a prevalence of less than 1% among young individuals. This rarity underscores its potential as an early diagnostic indicator of *NONO*-associated syndrome (7). Other cardiac anomalies are also frequent in patients with pathogenic *NONO* variants, including ventricular and atrial septal defects. In 2023, in vitro studies demonstrated that the *NONO*-knockout H9c2 cell line exhibited reduced proliferation and adhesion capacity, along with impaired mitochondrial function and altered energy metabolism. This condition may adversely affect cardiomyocyte development in rodent models (12).

The most common musculoskeletal feature was muscle hypotonia, observed in 19/25 cases. Nearly half of the patients experienced failure to thrive associated with feeding difficulties. Regarding craniofacial features, macrocephaly was the most prevalent (24/27), followed by a prominent forehead and abnormalities of the eyes, nasal tip, or external ear. Additional features include cryptorchidism and strabismus or more rarely, renal anomalies and haematological issues such as thrombocytopenia (9,13).

FIGURE 1: Pictures showing the patient's facial dysmorphia: broad forehead, hypertelorism, micrognathia, a broad nasal bridge and bulbous nasal tip (A: aged 1 month; B and C: at birth).

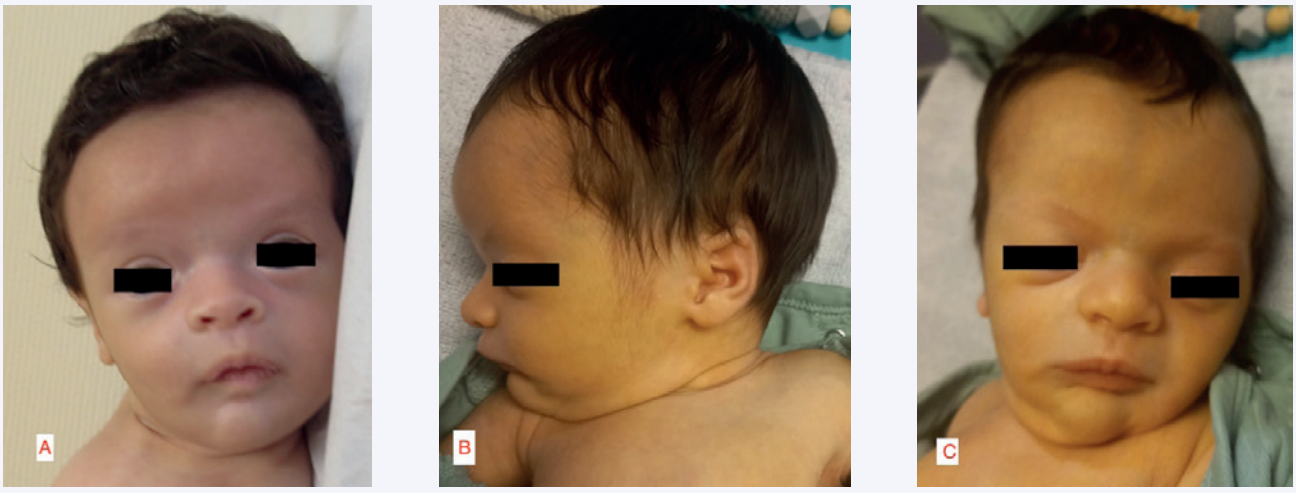
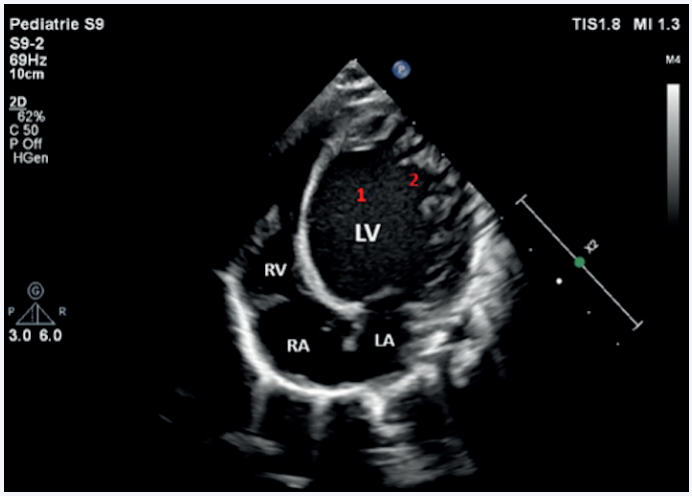


FIGURE 2: Echocardiogram of the patient aged two months and three weeks revealed left ventricular non-compaction (LVNC) with severe left ventricular (LV) dilatation (end-diastolic diameter 37 mm (>2SD)) and LV dysfunction (ejection fraction (EF) <20%) (1). The left ventricular apex appeared trabeculated (2).



Similarities and differences of our case compared to the literature

The literature reports a total of twenty-one distinct variants in the *NONO* gene implicated in the *NONO*-associated syndrome (7). We report a novel likely pathogenic variant (class 4) identified in our patient in *NONO* gene (NM_007363.5, GRCh38):c.441dup p.(Ala148Cysfs*36), in the hemizygous state and occurring de novo. This variant is responsible for a frame shift with a premature STOP codon at exon 5/12 and the absence of the production of a functional protein resulting in a loss-of-function mechanism. This mechanism is known to be responsible for *NONO*-associated disorder.

Our clinical case is consistent with the phenotype previously described in the literature and underscores the importance of a comprehensive malformative assessment in the presence of dysmorphic features and minor anomalies, such as hypotonia, hypospadias and asymmetry of the cardiac ventricles. These findings may serve as an early indicator of a genetic syndrome characterized by macrocephaly and cardiomyopathy. As observed in other reports, our patient presented with generalized hypotonia, progressive macrocephaly, low weight for gestational age, and left ventricular non compaction cardiomyopathy (LVNC). He exhibited well known dysmorphic features, including a prominent forehead and nasal abnormalities (nasal ensellure, broad nasal base, bulbous nasal tip). He also displays characteristics that are rarely described, such as hypertelorism and microretrognathia. Additionally, glandular hypospadias—although not definitively linked to *NONO*-associated syndrome—has been observed in other case reports (Table 1).

What can we learn from our case?

This case highlights the challenges in diagnosing malformative syndromes associated with neonatal hypotonia. A structured diagnostic pathway is essential for the early identification and management of genetic conditions in infants presenting with facial dysmorphism and hypotonia (14). Facial dysmorphic features, when combined with other clinical signs, facilitate the formulation of differential diagnoses for syndromes such as Down syndrome, Prader-Willi syndrome, and Cornelia de Lange syndrome. In our patient, midline abnormalities—including hypertelorism and hypospadias—prompted consideration of Opitz G/BBB syndrome (15). However, genetic testing plays a pivotal role in this context. A retrospective study involving 324 hypotonic infants reported diagnostic yields of 19% for chromosomal microarray analysis (CMA) and 31% for exome sequencing (ES) (16). Notably, combining CMA and ES provided the highest diagnostic yield, underscoring the complementary nature of these methods in identifying genetic causes of hypotonia. Due to the rarity of some syndromes, broad phenotypic variability, and clinical overlap, ES is the test of choice, as targeted testing for individual causes often leads to unnecessary delays and costs. Early genetic diagnosis confirms clinical suspicions and allows for targeted interventions, thereby improving patient outcomes. It also guides further investigations, management, and genetic counselling for affected families.

Although the patient does not exhibit entirely novel features, this case report provides a detailed description of both rare and common manifestations of the disease. These findings corroborate previous observations and highlight the phenotypic variability of the disease. Documenting these rare characteristics can help clinicians recognize atypical presentations, leading to improved diagnosis and patient management. Furthermore, collecting additional data on these traits may encourage further research into the underlying mechanisms. Even without newly identified features, our report contributes to a more comprehensive and nuanced understanding of the disease.

For paediatricians, the key message is that male infants presenting with macrocephaly, cardiac anomalies, and developmental delay—including hypotonia—should raise suspicion for a broad range of rare genetic conditions. Although each of these findings can occur in many disorders, their coexistence warrants early and comprehensive investigation. In this context, agnostic whole exome sequencing is the test of choice, as it allows for the identification of numerous rare syndromes, including *NONO*-associated syndrome. Recognizing this pattern early enables appropriate genetic evaluation and the timely implementation of targeted cardiac and neurodevelopmental interventions, ultimately improving patient care and outcomes.

How did this diagnosis influence the patient's follow-up?

This case presents an opportunity to understand the implications for patient management. The molecular diagnosis of a de novo, likely pathogenic variant in the *NONO* gene (OMIM: 300967) in our 2.5-month-old patient confirmed the cause of his severe LVNC. Although sustained cardiac monitoring was initiated based on his baseline cardiac dysfunction (ejection fraction <20%), the genetic diagnosis was instrumental in establishing a personalized care plan. It enabled us to define clear protocols for emergency intervention, resuscitation, and intensive care in case of decompensation.

Additionally, this diagnosis emphasized the need for early developmental support, as hypotonia observed at birth may predict future delays. Early intervention programs could help mitigate these outcomes (12).

The identification of a de novo *NONO* variant also had important implications for genetic counselling. Despite the de novo nature of the variant, the recurrence risk was estimated at approximately 1%, which led to a prenatal diagnosis during the couple's subsequent pregnancy. This highlights the critical role of molecular diagnostics in both clinical decision-making and reproductive planning. Regular follow-up is recommended for affected children, including monitoring of growth, development, vision, and hearing, with supportive therapies as appropriate (6,7).

TABLE 1: Clinical characteristics and proportions of all reported cases (4-9,11,13,17-19)

Human phenotype ontology (HPO)	Postnatal phenotypes	Prenatal phenotypes
Abnormality of the nervous system		
Cerebral anomalies (corpus callosum (17/22) and/or cerebellum anomaly, ventriculomegaly or polymicrogyria)	20/23	5/24
Seizures	5/25	
Neurodevelopmental delay	27/27	
Intellectual disability	23/23	
Behavioural disorders	11/20	
Cardiopathies	22/26	7/7
NCC (non-compaction cardiomyopathy, including LVNC)	18/22	5/7
VSD	9/22	4/7
ASD	7/22	1/7
Abnormality of the musculoskeletal system		
Muscular hypotonia	19/25	
Skeletal malformation	11/26	
Craniofacial Features		
Macrocephaly	24/27	
Prominent forehead	13/25	
Abnormality of the nasal tip	10/26	
Abnormality of the outer ear	12/24	
Hearing impairment	6/19	
Strabismus	10/24	
Visual impairment	9/22	
Deep set eyes	8/26	
Hypertelorism	2	
Micro/retrognathia	4	
Other abnormalities		
Failure to thrive	13/25	
Urinary tract malformation	2	
Cryptorchidism	9/24	
Thrombocytopenia	4	

Conclusion

The *NONO*-associated phenotype represents a complex neurodevelopmental and cardiac disorder, often accompanied by multisystem malformations.

This case reinforces the known clinical spectrum of the syndrome, particularly its association with hypotonia, macrocephaly, non-compaction cardiomyopathy (NCC), low birth weight, and craniofacial dysmorphism. Although the phenotype is consistent with previous reports, the *NONO* variant identified in this patient is novel and adds to the growing genotypic data available for this condition.

Careful phenotypic observation, including the recognition of facial dysmorphism, remains essential for guiding clinical suspicion. A structured diagnostic approach incorporating Whole Exome Sequencing is critical for confirming the diagnosis when a syndromic association is suspected.

In this case, the molecular diagnosis of a de novo *NONO* variant confirmed the aetiology of the cardiac pathology and helped guide a personalized management plan, including protocols for intensive care if decompensation occurred. It also had a direct impact on genetic counselling, allowing the family to benefit from prenatal testing in a subsequent pregnancy.

As the first case reported in Belgium and the 28th globally, this case emphasizes the importance of early recognition and comprehensive follow-up. It highlights the need for vigilant cardiac and developmental monitoring, as well as well as regular genetic follow-up and counselling.

Continued case reporting and research are essential to further refine the phenotype, improve genotype–phenotype correlations, and optimize long-term outcomes for patients with *NONO*-associated syndrome.

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BEXSERO
Vaccin méningococcique groupe B
(ADNr, composant, adsorbé)

BEXSERO est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B.[1]

RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT : Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT :** Bexsero suspension injectable en seringue préremplie. Vaccin méningococcique groupe B (ADNr, composant, adsorbé) ; EU/1/12/812/001 ; EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004. Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine recombinante NadA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine de fusion recombinante fHbp de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Vésicules de membrane externe (OMV) de Neisseria meningitidis groupe B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4[2] : 25 microgrammes • [1] produite dans des cellules d'E. coli par la technique de l'ADN recombinant - [2] adsorbée sur hydroxyde d'aluminium (0,5 mg Al^{3+}) - [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **FORME PHARMACEUTIQUE :** Suspension injectable. Suspension liquide blanche opalescente. **DONNÉES CLINIQUES : Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par Neisseria meningitidis de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose :** Nourrissons de 2 à 5 mois[a]. **Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c] - Primovaccination : Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. **Age lors de la première dose :** Nourrissons de 6 à 11 mois. **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année de vie avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose :** Enfants de 12 à 23 mois. **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose : Adolescents (à partir de 11 ans) et adultes*. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. - [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 mois. - [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. - [d] Voir rubrique 5.1 du RCP complet. - * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et Haemophilus influenzae de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000). Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée. Peu fréquent : convulsions (y compris convulsions fébriles). Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). Peu fréquent : eczéma. Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l.,Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 26/04/2023 (v15). **MODE DE DELIVRANCE :** Sur prescription médicale.

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Don't Forget the Forgotten Disease: Lemierre Syndrome. Case Report

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Keywords
Lemierre syndrome ; group A Streptococcus ; child ; case report.

Abstract

We present the case of a three-year-old boy with Lemierre syndrome. He presented with the typical symptoms of an oropharyngeal infection, followed by bacteraemia and thrombophlebitis of the internal jugular vein. However, the infection was atypically caused by group A *Streptococcus*. The patient underwent surgical drainage of the abscess and received intravenous antibiotics and subsequently anticoagulation therapy. This case report highlights the importance of early recognition and initiatiniation of appropriate antibiotics with coverage for both gram-positive and anaerobic bacteria to prevent adverse outcomes. The indications for anticoagulation therapy in paediatric patients remain controversial, but in general, it should only be administered if the thrombus involves critical areas or if septic emboli occur or the thrombus progresses despite antibiotic therapy.

Introduction

Lemierre syndrome (LS) is a rare but serious condition first described by André Lemierre in 1936 (1). There is no standardized definition of LS, but it is usually characterized by a recent history of an oropharyngeal infection followed by bacteraemia, septic thrombophlebitis of the internal jugular vein (IJV) and at least one focus of septic metastasis. While *Fusobacterium necrophorum* remains the most common causative pathogen, recent reports suggest an increasing role for group A *Streptococcus* (GAS) (7). The rising incidence of severe GAS infections, particularly in children, raises concerns about its impact on presentation, treatment, and outcomes of LS. Compared to LS cases caused by *Fusobacterium necrophorum*, those caused by GAS may differ in terms of metastatic risk and response to treatment (2-4). This case of GAS-induced LS in a young child underscores the diagnostic challenges and evolving therapeutic considerations, highlighting the importance of early recognition and appropriate management.

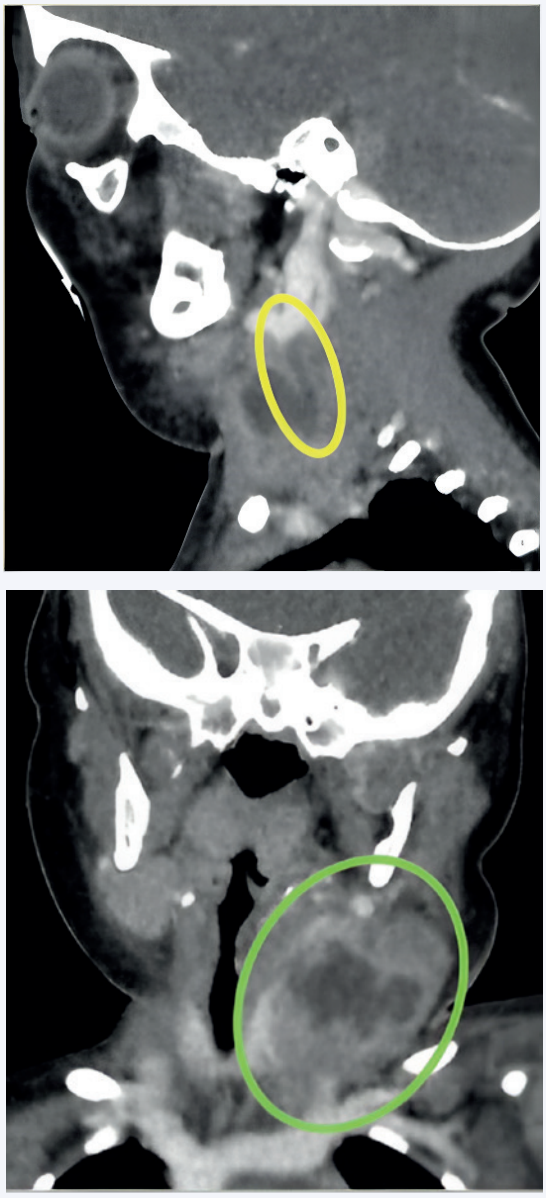
Case Presentation

A 3-year-old boy presented at the emergency department with a three-day history of fever, left neck swelling, vomiting, and decreased intake. He had been diagnosed with possible scarlet fever one week earlier but had not received antibiotics. On examination, he was non-ill appearing and had a temperature of 38.5°C, an erythematous pharynx, and a 4 x 4 cm firm, painful mass on the left side of the neck (figure 1). Further clinical examination was unremarkable. Laboratory results showed a white blood cell count of 21.5 x10³/mm³ [N 5.5-15.5 x10³/mm³], with 87.5% neutrophils , a haemoglobin level of 10.9 g/dL [N 12.5], a platelet count of 336 x10³/mm³ [N 150-350 x10³/mm³] and elevated erythrocyte sedimentation rate (>120 mm/h [N < 10 mm/h]) and C-reactive protein (189 mg/L [N 5 mg/L]). Urine culture was sterile. Serology for Epstein-Barr virus, *Toxoplasma* and cytomegalovirus were negative. Blood cultures were positive for GAS. Doppler ultrasound (US) of the neck revealed unilateral lymphadenopathy of 1.4 x 2 cm, with (?) secondary abscess formation, along with a thrombus in the IJV. He was admitted and treated with intravenous (IV) clindamycin, amoxicillin-clavulanic acid, and metronidazole. Subsequently, a contrast-enhanced computed tomography (CT) scan of the neck confirmed an abscess beneath the left mandible and IJV thrombosis, consistent with LS without lung emboli (Figure 2). The abscess was surgically drained, and culture of the puncture fluid grew GAS, which was sensitive to penicillin, ceftriaxone, and clindamycin. Given the polymicrobial nature of LS, with frequent involvement of anaerobes, we switched to monotherapy with IV amoxicillin-clavulanic acid. Anticoagulation therapy was not started due to the lack of progression of the thrombus and the absence of septic lung emboli. The patient showed progressive clinical improvement. After 10 days, the patient was discharged with oral clindamycin for another 10 days.

Follow-up imaging after 3 weeks showed insufficient thrombus reduction leading to initiation of low molecular weight heparin. Gradual thrombus regression and development of collateral circulation were subsequently observed. Initial follow-up included monthly ultrasounds and multidisciplinary consultation by ENT and haematology. This was later extended to every 6 months, and at 2.5 years post-discharge, follow-up could be fully discontinued given the stable partial thrombosis and well-developed collateral circulation.

FIGURE 1: clinical presentation of swelling on the left side of the neck.

FIGURE 2 AND 3: CT scan of neck. On the left side confirmation of thrombosis of the internal jugular vein. On the right side unilaterally enlarged lymphadenopathy (1.7 x 1.7 x 1.2cm) with possible abscess.



Discussion

LS was common before the advent of antibiotics, incurring a high mortality rate. With the introduction of antimicrobials and the routine use of penicillin in treating oropharyngeal infections, the incidence began to decline, and LS became the "forgotten disease" (2,3,6). Unfortunately, there has been an increase in reported cases over the past 10 years, particularly in the paediatric population. This is likely due to the accumulation of antibiotic resistance, the increasingly judicious use of antibiotics for pharyngitis in recent years and the rise in GAS infections (6,7). The worldwide incidence of LS varies, with reports ranging from 3.6 cases to 14.4 cases per million persons per year (3,5).

Clinical suspicion for LS arises when patients with any ENT infection show signs of IJV thrombophlebitis, sepsis, or organ failure due to septic emboli (2). Diagnosis is confirmed through laboratory studies, with a positive blood culture for *Fusobacterium necrophorum*, the main pathogen, often being the initial clue. Diagnostic delays can lead to metastatic spread by the time of official diagnosis (2). The initial clinical presentation usually involves oropharyngeal, dental, middle ear, or sinus infections, accompanied by fever (80%), sore throat (50%), nausea, vomiting, and neck pain, stiffness, or swelling. During this stage, there are no pathognomonic symptoms for LS. The second stage may manifest various clinical symptoms depending on the site of invasion, including IJV vascular involvement or cranial nerve palsies. IJV thrombophlebitis typically presents as painful unilateral swelling at the mandible angle, sometimes with trismus and dysphagia, serving as an initial indication of LS. The final stage leads to septic emboli development, often in the lungs or central nervous system (CNS), causing pleural effusions, abscesses, or cavitary lesions in the lungs, and meningitis or epidural abscess in the CNS, causing high morbidity and mortality (2). Other possible metastatic locations include joints, liver, spleen, muscles, kidneys, bones, and heart (5). In our case, the combination of pharyngitis, neck tenderness/swelling, and left IJV thrombosis raised suspicion for LS.

In 70-80% of cases, *Fusobacterium necrophorum* is the main pathogen (2). About 20-30% of patients have polymicrobial infections involving other organisms, including *Bacteroides* spp., *Staphylococcus* and *Streptococcus* spp., *methicillin-resistant Staphylococcus aureus* (MRSA), *Enterococcus* spp., and Candida spp. (3,7). Polymicrobial infections typically present as a monophasic, progressive, and pyogenic illness, differing from the typical triphasic presentation of LS caused by *Fusobacterium* infection (5). In our case report, cultures from blood, throat swab, and puncture fluid from the abscess, showed positive results for GAS only, which is rarely the solitary pathogen in LS (7). Similar to other paediatric LS cases caused by GAS, there was no progression to septic emboli. Although GAS is a highly invasive pathogen capable of causing severe infections, cases of GAS-associated LS tend to have a lower incidence of septic emboli compared with cases of *F. necrophorum*-associated LS. This may be due to differences in virulence factors. Another hypothesis is that the robust immune response that GAS infections often elicit leads to earlier clinical recognition and intervention (7).

To confirm IJV thrombosis and assess its extent and size, the gold standard is a contrast-enhanced CT scan of the neck. This scan is also useful for evaluating additional complications in the head and neck. The typical findings in LS are distended neck veins, enhancing vessel walls, low-attenuation intraluminal filling defects, and soft tissue swelling. US utility is limited due to poor imaging quality in the mandibular and clavicular regions and the risk of missing a thrombus with low echogenicity. MRI and magnetic resonance venography remain the preferred modalities for tracking the progression or regression of thrombosis, particularly in the intracranial space (9).

In suspected LS cases, prompt initiation of high dose IV antibiotic therapy is essential. The choice of antibiotics is primarily directed toward gram-positive and anaerobic bacteria to target the most common microorganisms (5-7). As soon as cultures become available, antibiotic therapy can be adjusted accordingly, with treatment typically lasting 4 to 6 weeks, which is longer than standard duration for other ENT-abscesses. Transitioning from IV to oral antibiotics can be considered upon clinical improvement (5). The initiation of anticoagulation therapy in paediatric patients remains controversial due to the lack of randomized controlled trials evaluating its risks and benefits. The existing evidence and recommendations rely on anecdotal case reports, theoretical assumptions, and extrapolation from the adult population (6).

Anticoagulation therapy is usually used only in cases involving thrombus extension into the cerebral sinuses, large or bilateral clots, or ongoing sepsis and disease progression despite antibiotic therapy, provided there are no contraindications (5). Although there was no clear evidence of thrombus progression or septic emboli in our case, anticoagulation therapy was started one month after diagnosis of LS. Given the slow and incomplete resolution of the thrombus in our case, one could argue that anticoagulation was started too late, or that this would have been the outcome regardless of its use. The most documented anticoagulant in children is low molecular weight heparin (LMWH), due to its predictable pharmacokinetics and favourable safety profile (3). If used, anticoagulation is typically continued for three months, assuming resolution of the septic thrombophlebitis (9).

Conclusion

As LS is becoming more prevalent, clinicians should consider it in paediatric patients presenting with fever and unilateral neck swelling. In parallel with the rising incidence of invasive GAS infections in children, there is an increasing number of cases of GAS-associated LS. Although these cases tend to have a lower incidence of septic emboli, prompt diagnosis and the initiation of antibiotic treatment are essential for preventing complications and improving outcomes. The use of anticoagulation therapy in the treatment of paediatric LS is controversial and requires further study.

All authors state that they have no conflict of interest to declare in relation to the realization of this case report.

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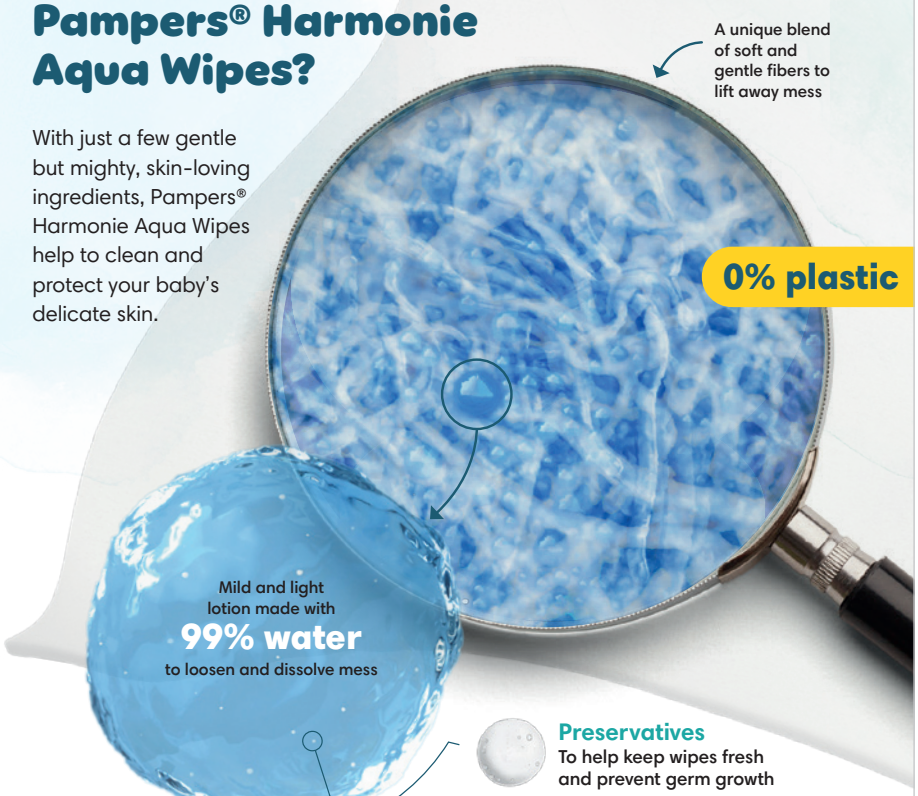

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Syndromic Meningoencephalitis Panels – Multiplex PCR : the Limits of an Innovative Tool

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Keywords
Meningitis ; meningoencephalitis ; multiplex PCR ; syndromic meningoencephalitis panel ; Haemophilus influenzae ; false positive.

Abstract

The main challenge in a clinical presentation of meningoencephalitis lies in the early detection of pathogens in the cerebrospinal fluid. Owing to their rapid results and imperviousness to prior antibiotic use, syndromic panels using multiplex PCR have emerged as an innovative tool for the etiological diagnosis of meningoencephalitis.

However, this test presents limitations, as illustrated by two patient cases: one with questionable results and another strongly suggestive of likely false-positive result for *Haemophilus influenzae* on multiplex PCR.

This case report highlights the importance of interpreting the results provided by this technique by integrating the patient's clinical and biological data.

Introduction

Central nervous system infections, although rare and of diminishing prevalence for bacterial etiologies, thanks to the introduction of conjugate vaccines into vaccination programs, remain a significant cause of morbidity and mortality in the pediatric population (1).

In high-income countries, the main responsible germs in the neonatal period are *Escherichia coli*, *Streptococcus agalactiae*, and, more rarely, *Listeria monocytogenes*. In older children, *Streptococcus pneumoniae* and *Neisseria meningitidis* remain the most frequently encountered pathogens (2). Finally, although historically responsible for a significant number of bacterial meningitis cases, *Haemophilus influenzae* type B has been rarely observed in Belgium since the introduction of vaccination against this strain in 1993 (3).

The recent advent of new diagnostic techniques using molecular biology, such as multiplex PCR syndromic panels for meningoencephalitis, has enabled significant progress in the management of patients suspected of bacterial meningitis.

Easier to use and significantly faster than conventional methods, with an average turnaround time of less than 2 hours (compared to 1 to 5 days for cultures), these tools simultaneously detect 90% of pathogens (bacteria, viruses, and fungi) involved in meningoencephalitis using only 200 µL of cerebrospinal fluid (CSF). This allows early treatment adaptations and helps to reduce the duration of antibiotic therapy when found negative for bacterial etiologies, compared to relying solely on conventional diagnostic methods (4,5). Moreover, prior use of antibiotics does not affect the panel's performance (unlike cultures), as it detects bacterial DNA rather than live bacteria (5).

Currently, two meningoencephalitis panels are available: BioFire® FilmArray® (FA) as from 2015 and, more recently, QIAstat-Dx® (QIA) as from 2022. The former detects 14 targets, including 6 bacterial (*E. coli K1, S. agalactiae, L. monocytogenes, S. pneumoniae, N. meningitidis,* and *H. influenzae*), 7 viral, and 1 fungal pathogen. The latter additionally detects *Mycoplasma pneumoniae* and *Streptococcus pyogenes* while omitting one viral target, totaling 15 targets.

While providing undeniable advantages, these new diagnostic tools demonstrated certain limitations in clinical practice, particularly in terms of diagnostic accuracy. Indeed, false-negative results have been reported, particularly for herpes simplex virus, as multiplex panels tend to be less sensitive than most singleplex PCR assays. In case of strong clinical suspicion of herpetic encephalitis, diagnostic sensitivity can be enhanced by employing singleplex assays and by repeating the PCR later in the disease course (4,6).

Moreover, false-positive results have also been observed. Through two clinical cases, we highlight the importance of interpreting positive multiplex PCR findings with caution.

Case report

Case 1

A 3-year-old boy, presented to the emergency department with headache, fever, vomiting, anorexia, rhinorrhea, apathy, irritability, and left otorrhea. History taking revealed prior hospitalizations for enteroviral meningitis at 3 months and severe rotavirus gastroenteritis at 18 months. He had received all recommended vaccinations. His vital signs were normal, and clinical examination identified a decline in general condition, neck stiffness, and bilateral acute otitis media, for which oral amoxicillin 80 mg/kg/day was initiated 24 hours prior.

Given this clinical picture, meningitis was suspected. Bloodwork revealed a severe inflammatory syndrome with neutrophilic leukocytosis: CRP 290 mg/L [reference: <5 mg/L], 16.75x10³/mm³ white blood cells [reference: 4-12x10³/mm³], including 14.9x10³/mm³ neutrophils [reference: 1.5-8.5x10³/mm³]. A small amount of CSF was collected via traumatic lumbar puncture, revealing 1654/mm³ red blood cells (with 4.18x106/mm³ in peripheral blood), 12 nucleated cells (reported to 5.37 after correction factor for contaminated CSF) [reference: <5], with negative direct examination and culture. CSF protein, glucose, and multiplex PCR could not be performed due to insufficient sample volume.

In the context of an unidentified etiology and persistent lack of clinical improvement, a second lumbar puncture was performed after three days of intravenous cefotaxime therapy. The multiplex PCR (FA panel) returned positive for *H. influenzae*. Cytology and chemistry results were normal, and direct examination was negative. Blood and CSF cultures returned negative. A diagnosis of *H. influenzae* meningitis was made in a fully vaccinated child. The patient had a favorable outcome with intravenous cefotaxime for 10 days. Subsequent immune testing was normal.

Case 2

A 17-day-old female newborn, born at term with no notable history, presented with fever, nasal congestion, and blood-streaked diarrhea. Vital signs were normal except for T° 38.8°C [reference: 36.5-37.5°C]. Clinical examination was unremarkable. A complete infectious workup was performed due to her age. Blood analysis revealed a mild inflammatory syndrome (CRP 29 mg/L) and normal leukocytes with mixed formula. Nasopharyngeal aspiration was positive for SARS-CoV-2 and catheterized urine showed pyuria (336 white blood cells/µL, [reference: <13]), along with a positive culture for *Klebsiella pneumoniae* (> 100,000 CFU/mL). Blood cultures and stool analysis (culture and rotavirus/adenovirus antigens) were negative.

Lumbar puncture showed no pleocytosis, with normal glucose, protein, and lactate levels, along with negative direct examination and culture results (15 days of incubation). Surprisingly, the multiplex PCR (QIA panel) was positive for *H. influenzae*. A subsequent analysis on the same sample using the FA panel returned negative, suggesting a false positive for *H. influenzae* on the QIA panel.

Discussion

While interpretation is challenging due to prior antibiotic use, our first case demonstrated discordant microbiological results warranting further analysis. This raised doubts about the positive result for *H. influenzae* on the FA panel.

If a false positive is considered, it's not an isolated case. Despite the FA panel's good sensitivity and specificity (90% and 97% respectively, per Tansarli and Chapin), false positives — mainly for *S. pneumoniae* and *S. agalactiae*, but also some for *H. influenzae* — have been reported (4). Zanella et al. identified an alarming likely false-positive rate for *H. influenzae* on FA (78% of tested cases). Most of positive cases for *H. influenzae* had alternative diagnoses, and only a third were treated as bacterial meningitis, reflecting discordance between positive panels and non-suggestive clinical presentations. Given careful sample handling and low false positives for *S. pneumoniae* (which in theory, could be a contaminant as often as *H. influenzae*), it likely stems from pre-analytical issues or analytical artifacts rather than contamination (7).

Additionally, FA assays target multiple genetic sequences per pathogen; for *H. influenzae*, two specific gene targets are typically analyzed. Concurrent positivity for both targets significantly increases the likelihood of a true positive result, given the low probability of simultaneous false positives. Conversely, detection of only one target should be interpreted with caution, as it may reflect a low-level or non-specific signal. Our patient's PCR was retrospectively found to be positive for both targets, suggesting a true-positive result nonetheless.

As mentioned, the child received appropriate antibiotic therapy despite initial diagnostic uncertainty. Indeed, he exhibited clinical signs consistent with meningitis, and inflammatory markers suggested a bacterial origin. Correction factors for CSF white blood cell counts are not sufficiently reliable to definitively exclude pleocytosis, and mild or even absent pleocytosis can occasionally be found in cases of bacterial meningitis (8). Considering this, and more broadly, even when the likelihood is low, the threshold for initiating appropriate treatment should remain low, as the consequences of untreated disease are more serious than the potential adverse effects of overtreatment.

Our second case leaves less room for doubt. Although clinical assessment may be more challenging due to the patient's young age, samples collected prior to any antibiotic administration showed no evidence of CSF infection. Moreover, two other infectious foci — SARS-CoV-2 (respiratory) and *K. pneumoniae* (urinary) — were identified. The QIA panel's result, discordant with other findings, was quickly considered as likely false positive by the negative FA panel's result. This limited the potential consequences of a false positive, such as unnecessary additional tests, prolonged antibiotic therapy, extended hospital stays, epidemiological overestimation, and undue concern.

Beyond PCR amplification curves, QIA offers enhanced analytical detail compared to FA, including cycle threshold (Ct) values, which provide useful insight when assessing whether a positive result reflects a true infection or a potential false positive. Retrospective analysis of our case revealed a normal amplification curve, but the elevated Ct value (36.2, i.e. very little target genetic material detected) suggested a likely false positive.

Also, we could have decided not to perform the panel test immediately, given its cost and the lack of supporting evidence for meningoencephalitis following the initial laboratory results. It could instead be carried out at a later stage and in a more targeted manner in cases where meningoencephalitis is genuinely suspected.

Finally, false positivity could have been confirmed through specific (singleplex) PCR, a test requiring technical expertise, but capable of accurately detecting a single bacterial pathogen (e.g., *H. influenzae*) and useful in discordant cases like ours.

Conclusion

With the roll-out of syndromic panels as an additional tool for diagnosing bacterial meningitis, these cases highlight their limitations, particularly pertaining to false positives.

To minimize their impact, clinicians must carefully select candidates for multiplex PCR as well as understand and interpret the results it provides, including PCR amplification curves and cycle threshold (Ct) values if available, while integrating clinical context and other laboratory findings.

Consulting with experts in microbiology and infectious diseases is recommended for discordant or complex cases to ensure proper follow-up testing, including specific PCR, and to determine the best course of care for patients while balancing the potential consequences of misinterpreting a result as false.

The authors have no conflicts of interest to declare about the topic discussed in this manuscript.

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Mycoplasma Pneumoniae Associated Reactive Infectious Mucocutaneous Eruption (RIME). Case Report

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Keywords

Mycoplasma pneumoniae ; RIME ; rash ; mucocutaneous lesions.

Abstract

Mycoplasma pneumoniae is a well-known cause of community-acquired pneumonia. In a subset of patients, it causes mucocutaneous eruptions with prominent mucositis, termed as "*Mycoplasma pneumoniae* induced rash and mucositis" (MIRM). Recently, "Reactive infectious mucocutaneous eruption" (RIME) has been proposed as the umbrella term for MIRM as other pathogens than *Mycoplasma* species can cause rash and mucositis. In this report, we describe a case of *M. pneumonia*-associated RIME. This article is intended to raise disease awareness and provide diagnostic tools for differentiating *M. pneumoniae*-associated RIME from other, more severe mucocutaneous diseases.

Introduction

Mycoplasma pneumoniae is a common cause of atypical, community-acquired pneumonia in school-aged children. The clinical presentation varies from asymptomatic to multiple extrapulmonary complications. Approximately 25% of patients experience extrapulmonary complications, with mucositis and dermatologic manifestations being the most common (1-5).

For many years, mucocutaneous manifestations associated with *M. pneumoniae* were considered among the spectrum of erythema multiforme (EM) and the potentially life-threatening Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN). EM minor presents with typical target lesions, while EM major includes severe mucosal erosions. In SJS and TEN, skin and mucosae are affected by vesicular and bullous eruptions followed by erosions. In 2014, "*Mycoplasma pneumoniae* induced rash and mucositis" (MIRM) was described as a distinct clinical entity (3, 4, 6-8). Recently, reactive infectious mucocutaneous eruption (RIME) has been proposed as the umbrella term for MIRM as also non-*Mycoplasma pneumoniae* pathogens may cause similar rash and mucositis. RIME emphasizes that mucocutaneous eruptions result from a variety of infectious triggers. Other pathogens reported to cause a similar clinical picture are *Chlamydophila pneumoniae,* human metapneumovirus, human parainfluenza virus 2, rhinovirus, enterovirus, influenza B virus and SARS-CoV-2 (3, 8-11).

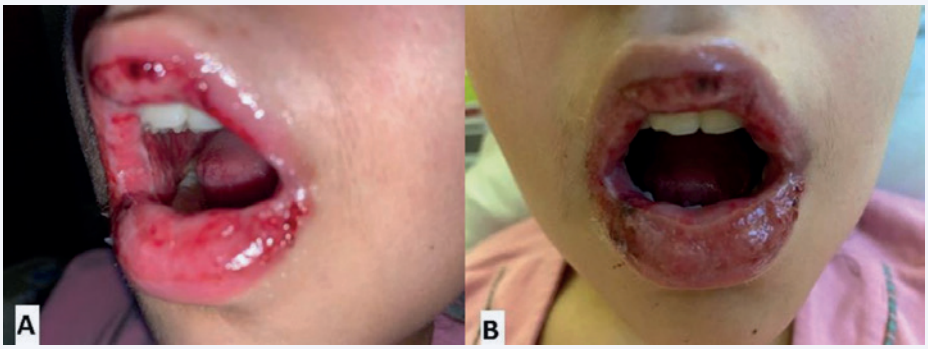
Due to the low incidence of RIME, distinguishing it from SJS/TEN can be challenging. Recognizing RIME as an infection-triggered condition allows for targeted treatment and avoids unnecessary drug restrictions.

Case description

A previously healthy, overweight fourteen-year-old girl (68kg – BMI 26) presented at the emergency department with respiratory problems. She had a sore throat, productive cough, and high fever for five days. Two days before admission, she received oral amoxicillin (500mg TID). After the first dose, she developed painful mucosal ulcerations on her buccal mucosa, palate, and tongue, causing difficulty eating. Blood analysis revealed normal white blood cell (WBC) count (7600 cells/µL; ref. 4300-9640 cells/µL), high C-reactive protein level (CRP 266 mg/l; ref. < 5 mg/l), and normal liver and renal function. Chest X-ray showed bilateral pneumonia. She was treated with intravenous cefuroxime (1,5g TID) and high-flow oxygen (40L 25%). Supportive care, including intravenous hydration and pain management, was provided. Two days later, antibiotic was switched to ceftriaxone (2g BID) and azithromycin (500mg QD) due to persistent fever and a further CRP increase of 403 mg/l. The WBC count was 7800 cells/µL (ref. 4300-9640 cells/µL), with a lymphopenia of 600 cells/µL (ref. 1230-3420 cells/µL). The next day, she developed oral bleeding and macroscopic hematuria. Urine microscopy revealed 277 white blood cells/µL,140 red blood cells/µL and proteinuria of 1.54 g/l. Urine culture was negative. Referral for tertiary care was made.

Upon arrival at our tertiary hospital, she exhibited edema, bleeding, exudation, and hemorrhagic crusts on the lips, with erosions on the buccal mucosa and tongue extending to the pharyngeal cavity (Figure 1a, b). Genitalia were unaffected and no other skin lesions were observed. Ophthalmologic examination was normal. Lung auscultation revealed bilateral crackles and opening snaps. The lymphocytes

FIGURE 1: Erosions on the buccal mucosa and tongue. B: Edema, bleeding and hemorrhagic crusts on the lips.



were normalized. Chest CT showed alveolar opacities with incident bronchiectasis, tree-in-bud configuration in right middle and inferior lobe, and bilateral ground-glass opacification, especially in both inferior lobes (Figure 2). Given its resemblance to granulomatosis with polyangiitis, additional tests were performed, showing positive antinuclear antibody (ANA) (1/1280), negative complement 3 and 4, anti-neutrophil cytoplasmic antibodies (ANCA), and anti-double stranded DNA (dsDNA) antibodies. Polymerase chain reaction (PCR) of a nasopharyngeal swab and a serum immunoglobulin M (IgM) antibody test were positive for *M. pneumoniae*. Tuberculin skin test was negative. Methylprednisolone (40 mg/day) was initiated due to severe oral lesions. High-flow oxygen was replaced by low-flow oxygen for two days. Hematuria and proteinuria resolved, and renal ultrasound was normal. Three days following referral, she became afebrile and resumed eating. Blood cultures remained negative. After five days of ceftriaxone, azithromycin and methylprednisolone, significant improvement in oral lesions and CRP (17 mg/l) was noted. She was discharged with inhaled corticosteroids (ICS) and inhaled long-acting beta 2-agonists (LABA).

Two months post-discharge, auscultation improved with persistent opening snaps and crackles. The cough was absent and pulmonary function remained normal, though prolonged fatigue persisted. A chest CT five months after discharge showed significant improvement with a single bronchiectasis in the lingula and resolution of previous lesions (Figure 3). She had been asymptomatic for weeks without medication. ANA titers decreased (1/320).

Discussion

M. pneumoniae infections are generally mild and self-limiting, with pneumonia being the most common manifestation in school-age children. Extrapulmonary manifestations may occur without respiratory symptoms such as pericarditis, hepatitis, hemolytic anemia, thrombosis, arthritis, glomerulonephritis, mucositis, and varying dermatologic manifestations. MIRM presents with respiratory symptoms such as cough, pharyngitis, malaise, and fever, typically one week before mucocutaneous symptoms. Skin involvement is typically scant, varies from vesiculobullous, to targetoid, macular, papular, or morbilliform and can affect the extremities, trunk, and face. The most affected mucosal areas are oral and ocular, followed by genital and anal mucosa. Mucosal lesions are ulcerative or hemorrhagic and painful. Ocular involvement manifests as bilateral conjunctivitis, photophobia, ulceration, pseudomembrane formation, and eyelid edema (1, 2, 4, 7, 12, 13).

MIRM is associated with prolonged fever, higher CRP level, greater likelihood of hospitalization and oxygen need. Diagnostic criteria include clinical and laboratory evidence of *M. pneumoniae* infection, involvement of at least two mucosal sites, and skin involvement < 10% of body surface area. As in our case, approximately one third of cases present with absent or scarce skin involvement (3-5, 14, 15). The pathological mechanism remains unknown. It is hypothesized that polyclonal B-cell proliferation and antibody production result in skin damage due to immune complex and complement deposition (1, 4, 7, 12, 13).

Detection of *M. pneumoniae* is required to diagnose MIRM. Confirmatory laboratory tests include a PCR of oropharyngeal swabs and measurement of serum-specific immunoglobulin (Ig) G and IgM. The prevalence of *M. pneumoniae* carriage in children is high; up to 56% (2, 14). While PCR is highly sensitive and specific, it cannot distinguish between an acute infection and an asymptomatic carriage. Furthermore, it is unable to differentiate between a past and current infection, as PCR remains positive for up to four months following infection. IgM titers start to increase seven to nine days after infection, reach its peak at three to six weeks and persist for months. IgG titers begin to rise and peak approximately two weeks after IgM titers and persist for years. In the acute phase, both IgM and IgG may be within the normal range. Moreover, there is a significant probability of false positive and false negative results, necessitating repetitive testing (2 to 4 weeks following the acute phase) to document a titer increase for an accurate serologic diagnosis. Once antibiotics are started, the PCR may become negative after 2 days (16).

FIGURE 2: The bronchiectasis (blue arrow), ground-glass opacification (green arrow) and tree-in-bud configuration (red arrow) on chest CT.

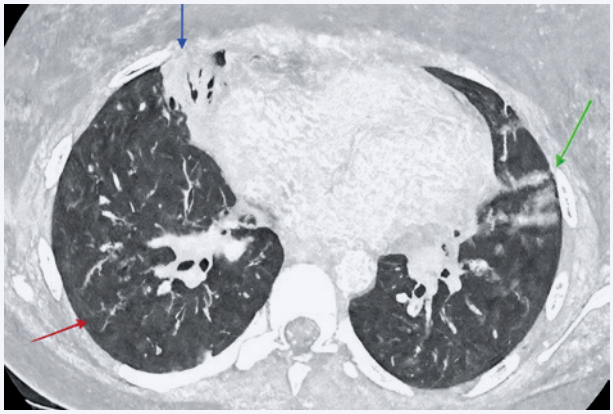
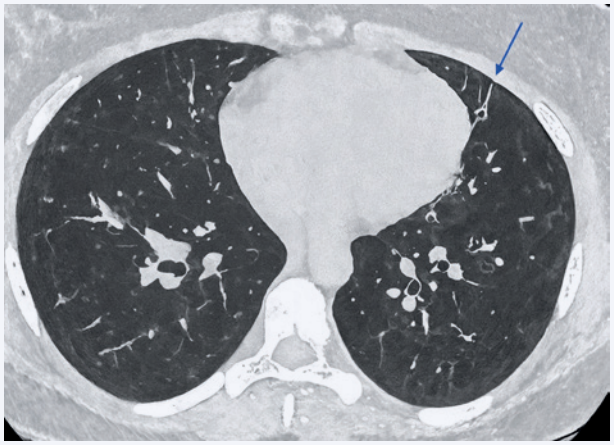


FIGURE 3: One residual bronchiectasis in the lingula (blue arrow) on a control chest CT.



There are no evidence-based guidelines for MIRM treatment. Antibiotics and supportive treatment, which includes pain management, mucosal care and intravenous hydration, appear to be the most universally accepted therapies. Macrolides are the most commonly used antibiotics sharing a combined antibiotic and immunomodulatory effect. While antibiotics reduce pulmonary disease severity, their effect on mucocutaneous symptoms remains unclear. Severe mucocutaneous involvement may require corticosteroids or intravenous immunoglobulin, though strong evidence is lacking (1, 2, 8, 17, 18).

The overall prognosis of *M. pneumoniae*-associated mucositis is good. Long-term sequelae are rare but included mucosal pigmentary changes, orbital complications (corneal ulceration, conjunctival shrinkage, ocular synechiae, xerophthalmia, or blindness), genital adhesions, epiglottitis, and chronic phimosis (1-4, 13). Recurrence of MIRM is usually milder and affects fewer mucosal sites (9, 16). ANA positivity, as observed in this case, have been previously reported as part of the immunological response to *M. pneumoniae* (12). Chest CT abnormalities in this case align with previous reports on MIRM (13, 14). Radiographic findings are variable and nonspecific, including ground glass opacities, air bronchograms, atelectasis, tree-in-bud patterns, peri-bronchial thickening, single or multiple infiltrates, bronchiectasis, pleural effusion, and necrotizing pneumonia. These chest CT abnormalities can persist for months to over a year, despite clinical recovery. In exceptional cases, *M. pneumoniae* infection can lead to bronchiolitis obliterans, characterized by airway obstruction and fibrosis of the bronchioles (19-22).

It is important to differentiate RIME from other mucocutaneous diseases as it requires a less aggressive intervention. A misdiagnosis of SJS/TEN as RIME could result in inadequate and delayed treatment of these potentially life-threatening conditions, that may need immediate withdrawal of the causative drug. TEN is the more severe form of SJS, covering more surface of the body (SJS has skin detachment of < 10%, TEN >30% and 10-30% indicates SJS/TEN overlap). Additional features that help to distinguish between EM/SJS/TEN are patient's age and pathophysiology. Most patients with RIME are young (mean age 12 years). Pathophysiologically, RIME is triggered by an acute infection, whereas SJS/TEN is predominantly triggered by drug exposure. However, the coexistence of both triggers can complicate the diagnostic process. Prominent mucositis, especially oral involvement, with variable though relatively scarce cutaneous involvement is nearly universal for RIME. Nevertheless, prominent mucositis accompanied by minimal cutaneous involvement has been documented in cases of SJS. Similarly, extensive skin detachment as observed in TEN may – though being extremely rare – occur in RIME. SJS and TEN remain important diagnostic considerations (1-4, 6-9, 13).

Conclusion

Children and adolescents suffering from respiratory symptoms accompanied by a prominent mucositis, especially oral involvement, with minimal or absent cutaneous involvement should raise clinical suspicion of RIME/MIRM. Treatment is based on antibiotics and supportive care, with an overall favorable prognosis.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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A Novel X-linked Variant in Congenital Nephrogenic Diabetes Insipidus. Case Report

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Keywords

Congenital nephrogenic diabetes insipidus ; arginine vasopressin receptor 2 gene variant ; case report ; novel variant ; water reabsorption.

Abstract

Congenital nephrogenic diabetes insipidus (NDI) is a rare hereditary renal disorder caused by variants in the arginine vasopressin receptor 2 (*AVPR2*) or aquaporin 2 (*AQP2*) genes, resulting in the kidney's inability to concentrate urine.
We report the case of a 52-day-old boy presenting with feeding difficulties and poor weight gain. Laboratory findings revealed hypernatremia and hyperchloremia, associated with a marked disparity between high serum osmolality and low urine osmolality. Genetic analysis identified a novel missense variant in the *AVPR2* gene. The therapeutic approach consisted of nasogastric free water supplementation and oral hydrochlorothiazide therapy, with good clinical response.
This case highlights the importance of early recognition and genetic testing in infants with suspected diabetes insipidus and expands the phenotypic spectrum of *AVPR2*-related NDI.

Introduction

In recent years, there has been a growing initiative—supported by both the scientific community and patient advocacy groups—to adopt the term "arginine vasopressin resistance (AVP-R)" instead of nephrogenic diabetes insipidus (NDI). This nomenclature better reflects the underlying pathophysiology and aims to reduce confusion with diabetes mellitus or central (pituitary) diabetes insipidus, now often referred to as "arginine vasopressin deficiency". While this terminology has not yet been formally incorporated into international classifications such as ICD-11, we have chosen to acknowledge it here in response to recent consensus efforts. For clarity and continuity, however, we will continue to use the term NDI throughout this report to describe the condition of renal unresponsiveness to vasopressin.

In this case report, we use the term variant instead of mutation in accordance with current genetic nomenclature guidelines. The term mutation has historically been used in clinical contexts to imply pathogenicity; however, it scientifically encompasses all types of genetic variation, regardless of clinical consequence. To avoid ambiguity and to align with the recommendations of the American College of Medical Genetics and Genomics (ACMG), we therefore adopt the term variant, which can be further specified by adjectives such as benign, likely pathogenic, or pathogenic.

Congenital nephrogenic diabetes insipidus (NDI) is a rare hereditary tubular dysfunction characterized by the kidney's inability to concentrate urine in response to vasopressin (antidiuretic hormone, ADH). This results in the excretion of large volumes of diluted urine (1,2).

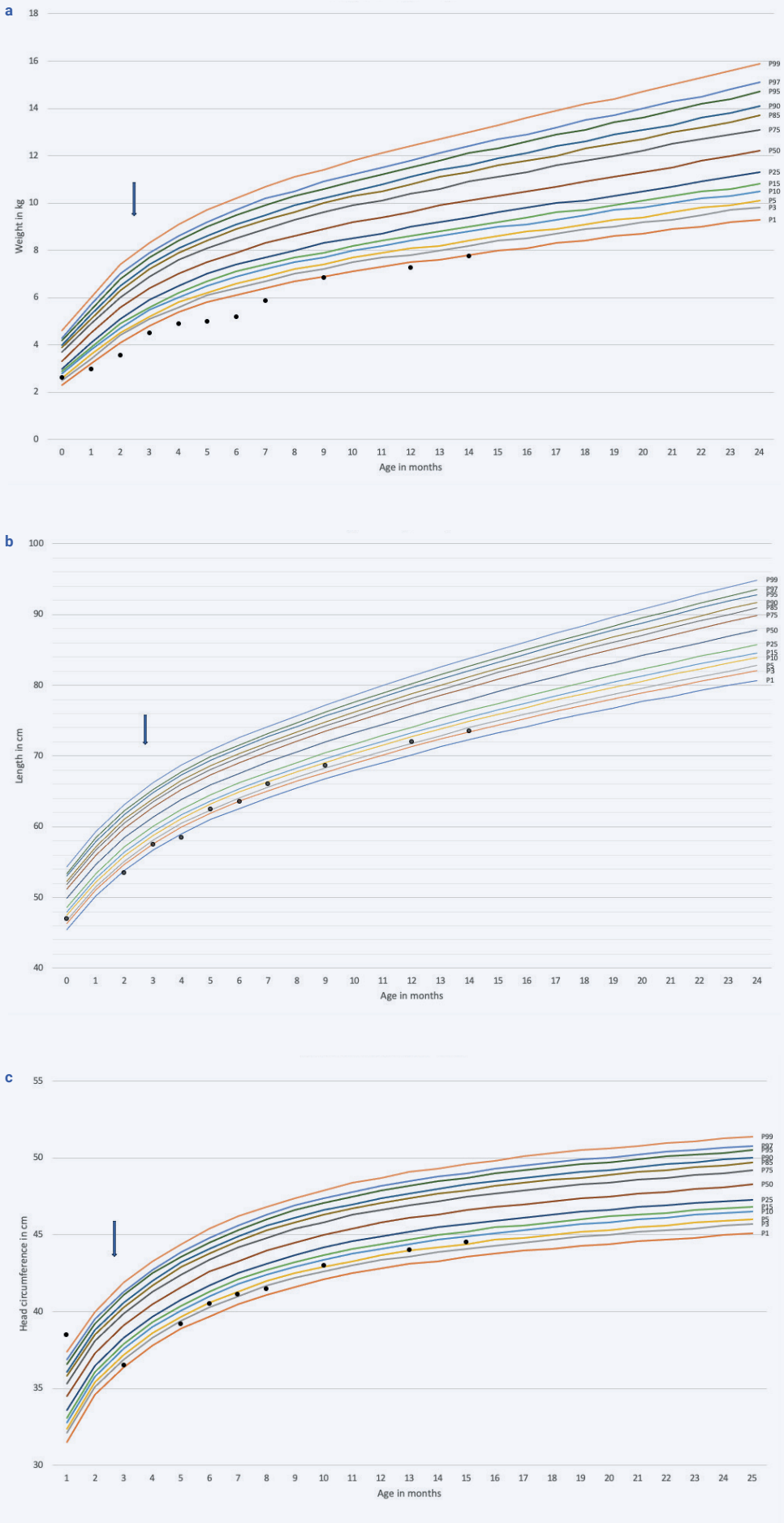
Clinical signs may include polyuria, polydipsia, electrolyte disorders (hypernatremia, hyperchloremia), dehydration, constipation, irritability, and developmental delay (2,4).

Approximately 90% of NDI cases are caused by variants in the *AVPR2* gene, transmitted in an X-linked pattern of inheritance. The remaining 10% are due to variants in the *AQP2* gene (9% autosomal recessive and 1% autosomal dominant) (2,3).

The incidence of NDI due to *AVPR2* variants is 4 to 8 boys per million with over 250 types of mutations reported (5).

Here, we would like to report a case of NDI in a male infant caused by a novel *AVPR2* gene variant. We will discuss the diagnostic and management challenges associated with this condition,

FIGURE 1 a, b, c: Auxological parameters of the patient. Weight (a), height (b), and head circumference (c) are plotted on WHO growth charts. The arrow indicates the time at which treatment was initiated (oral hydrochlorothiazide and free water supplementation).



highlighting the importance of early recognition and treatment to prevent severe dehydration episodes. Such episodes can lead to neurological complications, acute kidney injury, or growth impairment if not promptly managed.

Case Report

A 52-day-old European boy was admitted to the pediatric ward for feeding difficulties and failure to thrive.

He was the first child of the family, born with a history of intrauterine growth retardation of undetermined origin (weight: 2.63 kg, height: 47 cm, head circumference: 38 cm at 39 4/7 weeks of gestation). There was no polyhydramnios and the parents were non-consanguineous. Family history was unremarkable. At the one-month checkup, the pediatrician noted a lack of weight gain (below the 3rd percentile). At 5 weeks of age, due to persistent poor weight gain, several formula changes were attempted—including those aimed at increasing caloric density and managing potential gastroesophageal reflux. Despite these adjustments, the parents reported ongoing feeding difficulties, and the child was referred to our clinic for further evaluation.

Upon admission, the child had normal hemodynamic and respiratory parameters. His body weight was 3.58 kg (<P3), height was 53.5 cm (<P3), and head circumference was 36.5 cm (<P3) (Figure 1). Clinical examination was unremarkable except for plagiocephaly. Notably, there were no signs of dehydration, irritability, lethargy, or other neurological abnormalities.

A series of investigations was performed because of persistent poor weight gain and reduced appetite.

Laboratory findings revealed severe hypernatremia (162 mmol/L [N 130-145]) and hyperchloremia (126 mmol/L [N 97-108]), with a corresponding elevated serum osmolality (317 mOsm/kg [N 275-295]). Urine osmolality was markedly decreased (115 mOsm/kg), demonstrating a clear dissociation between concentrated plasma and diluted urine. The association of polyuria (>8 mL/

kg/h), significant hypernatremia, and inappropriately low urine osmolality raised the suspicion of diabetes insipidus. Abdominal ultrasound showed normal-sized kidneys with preserved corticomedullary differentiation and no pelvic dilatation. Heart and brain ultrasounds were normal. The metabolic assessment—including serum creatinine, bicarbonate, and glucose—was unremarkable, confirming preserved renal function and excluding other common metabolic disorders.

A DDAVP (desmopressin) trial (administered as an intranasal spray at a dose of 10 µg) was conducted to differentiate between central and nephrogenic diabetes insipidus (12). DDAVP is a synthetic analogue of arginine vasopressin (AVP) that selectively stimulates type 2 receptors in the kidney, without activating type 1 receptors involved in vascular vasoconstriction. As shown in Figure 2, the child's weight, blood pressure, urine output, serum osmolality, urine osmolality, and serum sodium levels remained unchanged during the 8 hours following administration.

Exome sequencing identified a hemizygous A>C substitution at nucleotide 610 in the *AVPR2* gene (Figure 3), resulting in a missense variant : threonine was substituted by proline at amino acid position 204 (Thr204Pro). This variant was initially classified as a variant of uncertain significance (class 3), but given the strong clinical phenotype and elevated copeptin levels, it can be considered likely pathogenic. This interpretation aligns with ACMG criterion PP4 applied at a moderate level. Given the phenotype and the very high serum copeptin level (294 pmol/L, which—although not pathognomonic—supports the diagnosis in the context of hyperosmolality and hypotonic urine, reference range: 1–28.2 pmol/L), the variant is considered likely pathogenic in this context. Although copeptin thresholds >21.4 pmol/L are validated in adults for diagnosing nephrogenic diabetes insipidus, pediatric reference data are limited (12). Further studies are needed to assess the reliability of copeptin in infants. The authors encourage further research into the utility of plasma copeptin in pediatric diagnostic workups.

In silico analysis using polymorphism prediction tools such as PolyPhen was not conducted but could further support pathogenicity evaluation. Early genetic testing is essential not only to confirm the diagnosis and guide management, but also to enable genetic counseling and family planning. Maternal analysis demonstrated a healthy heterozygous carrier status.

The therapeutic approach consisted of gradually correcting hypernatremia using free water administered via a nasogastric tube. Gradual correction is important to avoid rapid shifts in serum sodium that may lead to cerebral edema. Enteral administration is preferred over intravenous hydration when possible. After confirming the diagnosis through lack of response to DDAVP, oral hydrochlorothiazide (1 mg/kg/day) was started. At discharge, the patient was prescribed 60 mL of oral water three times daily and continued hydrochlorothiazide therapy. Prior to treatment, the patient had a urine output estimated at approximately 10–12 mL/kg/h, based on diaper weight and fluid balance records. Following the initiation of hydrochlorothiazide and fluid management, urine output progressively decreased to 4–5 mL/kg/h, remaining within a physiologically acceptable range for age (generally considered <4–6 mL/kg/h in infants). Although urine osmolality was not re-measured during follow-up, the progressive weight gain, normalization of serum sodium (from 162 to 141 mmol/L), and reduction in fluid intake requirements (from 300 to approximately 140 mL/kg/day) support the effectiveness of the therapeutic strategy. These objective markers were used to define clinical improvement and therapeutic response in this case.

FIGURE 2 a, b: Results of laboratory examinations before and after administration of desmopressin (administered as an intranasal spray; the time of administration is indicated by the arrow). We show via these figures that urinary osmolality (a) and urinary volume (b) remain unchanged after the administration of desmopressin. Plasma osmolality remained stable throughout the test (data not shown).

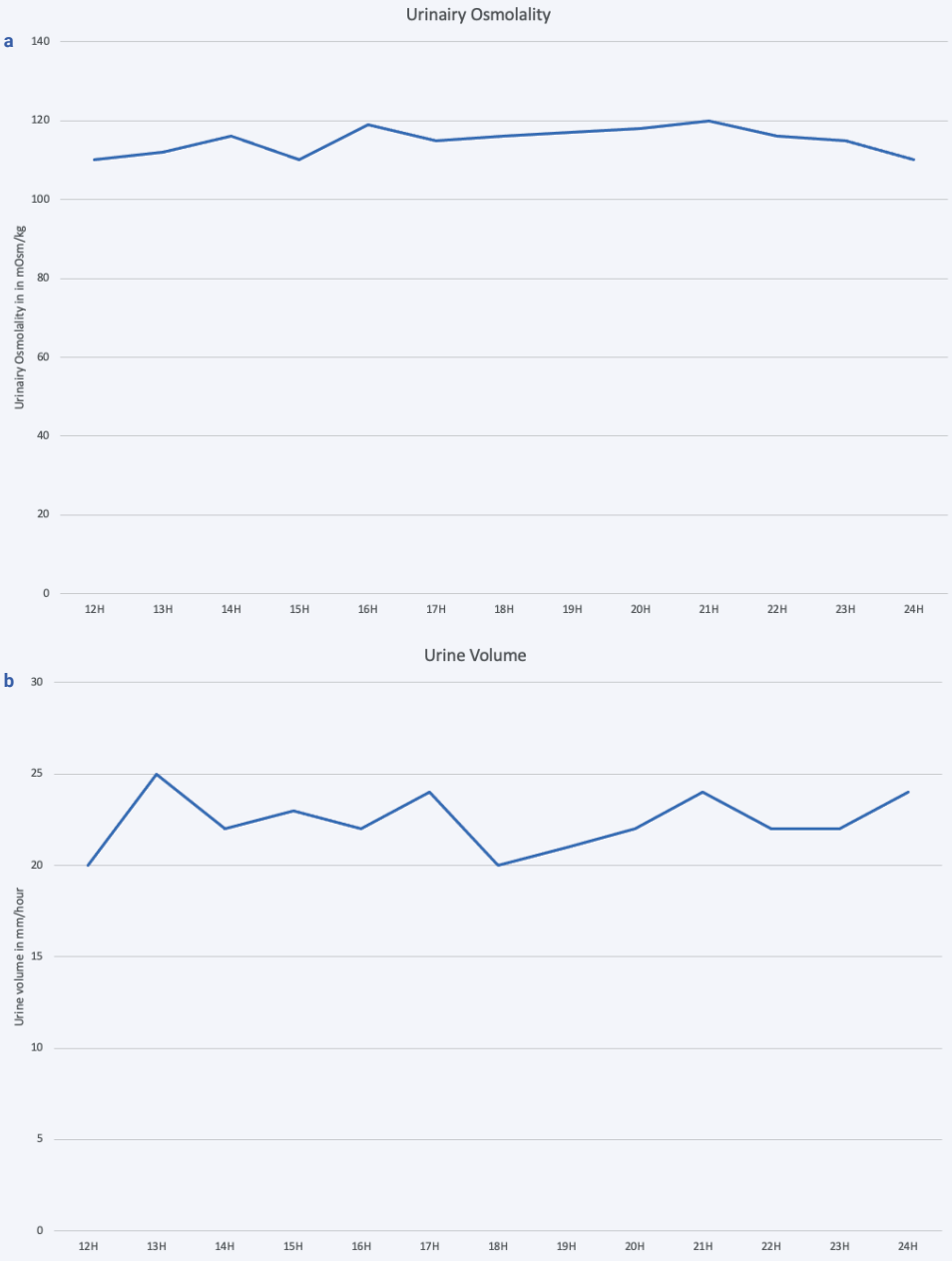
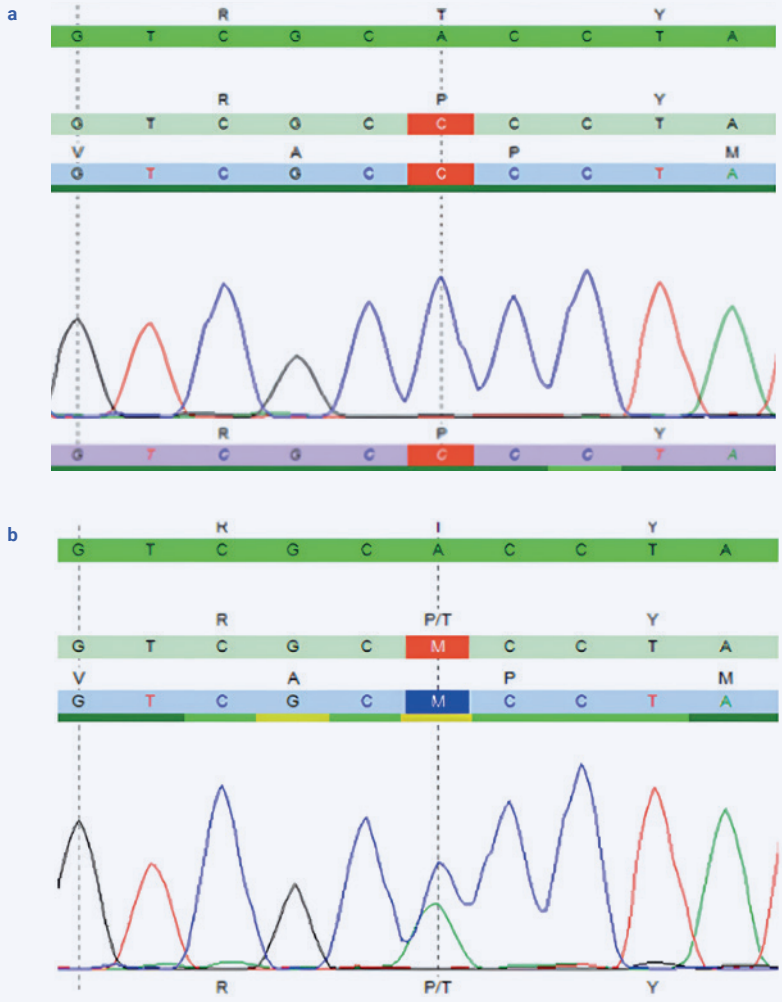


FIGURE 3 a, b: Sequencing analysis for AVPR2.

3a: Sequencing analysis shows hemizygous mutation in children (reference = A (green line), child = C). 3b: Sequencing analysis of the mother shows a heterozygous mutation (reference = A (green line), mother = M, i.e. mixture of C and A).



The patient's clinical course was marked by slow but steady improvement. He did not show dramatic catch-up growth, but progressively—though with difficulty—reached the 1st percentile for weight. Head circumference and length also increased gradually over time, following a consistent upward trend on the growth chart.

The clinical course was marked by gradual weight gain, eventually reaching the third percentile. At 7 months of age, he required hospitalization for a COVID-19 infection, which was managed without major complications. Due to persistent feeding refusal and inadequate oral intake, a nasogastric tube was placed at 16 months of age to ensure sufficient caloric and fluid intake. Hydrochlorothiazide therapy was continued and progressively adjusted according to the patient's weight gain and indomethacine was added.

Literature Review and Discussion

Pathophysiology

The kidneys play a crucial role in regulating urine concentration in response to vasopressin (antidiuretic hormone, ADH), which is produced by the hypothalamus and released by the posterior pituitary gland. Vasopressin release is primarily triggered by increased plasma osmolality or decreased blood volume. It acts by binding to V2 receptors on the basolateral membrane of cells in the distal tubules and collecting ducts. Vasopressin binding activates G-protein–coupled receptors, stimulating adenylate cyclase to convert ATP into cyclic adenosine monophosphate (cAMP). This increase in cAMP activates protein kinase A (PKA), which phosphorylates aquaporin-2 (AQP2) water channels.

Phosphorylated AQP2 is then translocated to the apical membrane of the principal cells in the collecting duct, allowing water reabsorption from the tubular lumen. This mechanism concentrates the urine and conserves body water (1,3,4,5,12).

Variants in *AVPR2* or *AQP2* impair this vasopressin-mediated signaling cascade, resulting in reduced water reabsorption and the characteristic polyuria and polydipsia observed in congenital nephrogenic diabetes insipidus (NDI) (3,12).

Clinical Manifestations

The hallmark features of congenital NDI include polyuria, polydipsia, dehydration, and electrolyte imbalances. Infants typically present with failure to thrive, irritability, and recurrent dehydration episodes. Excessive urination can lead to electrolyte disturbances such as hypernatremia, hyperchloremia, metabolic acidosis and urinary tract dilation. The correlation between genotype and phenotype is crucial to understand ow genetic variations can influence the severity of conditions related to water reabsorption and vasopressin responsiveness. In cases where there is a genetic variant affecting the aquaporin channels or vasopressin receptors, the degree of impairment in water reabsorption can lead to varying phenotypic expressions, such as different levels of polyuria or dehydration (2,3,12).

Diagnostic Challenges

Diagnosing congenital NDI is challenging due to its rarity and clinical overlap with other causes of polyuria and polydipsia. Key diagnostic tests include measurements of serum and urine electrolytes, serum and urine osmolality, and responsiveness to desmopressin or AVP, which can also be used in infants. If needed, a water deprivation test may be performed, although it carries risks and requires strict monitoring. Copeptin measurement is highly specific and can aid in the diagnosis, but it is not routinely available and should not delay clinical decision-making. Genetic testing for *AVPR2* or *AQP2* variants confirms the diagnosis of congenital NDI (5,7,12).

Identifying polyuria in neonates can be particularly difficult, especially in the context of poor weight gain. While gastroesophageal reflux disease (GERD) is a common differential diagnosis in infants with poor weight gain, it is not a cause of polyuria. Therefore, it is crucial to distinguish between poor weight gain related to feeding issues and that due to pathological water loss. Other causes of neonatal polyuria to consider include uncontrolled diabetes mellitus, central diabetes insipidus, post-obstructive diuresis, Bartter syndrome, osmotic diuresis due to hyperglycemia or hypercalcemia, and increased intake of fluids.

Management Strategies

Management aims to correct dehydration, maintain electrolyte balance, and reduce polyuria. Initial treatment involves rehydration with oral or intravenous fluids and correction of electrolyte abnormalities (6,8). The use of free water via a nasogastric tube helps balance more complex cases, as was the situation with

this patient. Thiazide diuretics, amiloride, and nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce urinary output by enhancing water reabsorption in proximal and distal tubules (6,9).

In this case, oral hydrochlorothiazide therapy combined with a low-salt diet was initiated immediately after diagnosis, leading to normalization of urine volume and laboratory parameters.

Nutritional management is essential to reduce renal osmotic load and consequently minimize urine output. Since maximal urine osmolality is impaired in NDI, urinary volume is mainly dependent on solute intake — particularly dietary salt and protein. During infancy, feeds should provide a low renal osmotic load (around 15 mOsm/kg/day) to reduce polyuria, support feed tolerance, and promote growth. A simplified formula is commonly used in clinical practice to estimate the renal osmolar load:

Renal osmolar load (mOsm) = [Protein intake (g) × 4] + [2 × (Na + K in mmol)] (12).

Beyond infancy, salt control can be gradually relaxed, moving toward a reduced-salt or "no added salt" diet by the age of 2 years. Strict salt restriction is not required and may impair growth, as sodium plays a key role in cellular proliferation, protein synthesis, and overall development. Salt tolerance varies individually and is often self-regulated by the child to avoid complications such as polyuria or nocturnal enuresis.

Protein intake should meet the recommended daily allowance to support normal growth. Excessive restriction should be avoided as it may compromise nutrition; however, in children with problematic polyuria, a moderate adjustment toward the theoretical minimum protein requirement (based on age or height-age) may be beneficial (12).

Though typically classified as diuretics, thiazides paradoxically reduce polyuria in NDI by inducing mild hypovolemia, which enhances proximal tubular reabsorption of sodium and water via aquaporin-1 (AQP1).

Amiloride is not a first-line treatment but can be added when thiazide-induced hypokalemia occurs. It enhances proximal sodium and water reabsorption similar to thiazides and helps reduce potassium loss.

Prostaglandin synthesis inhibitors—such as indomethacin—not only enhance water permeability and reabsorption in the collecting duct by reducing prostaglandin interference, but also promote proximal sodium and water reabsorption through inhibition of COX-1 and COX-2 pathways. These dual effects contribute to the overall reduction in polyuria.

In summary, both amiloride and NSAIDs can potentiate the effect of thiazides by increasing proximal sodium reabsorption and thereby reducing polyuria (1, 9, 10).

New therapies are currently under investigation, including gene therapy, pharmacological chaperones, and cell-based therapies (11). Advances in genomic sequencing and precision medicine may enable individualized treatment approaches based on the patient's specific genetic variant profile (11).

Ongoing monitoring of growth parameters, urine output, fluid intake, electrolyte levels, kidney function, and renal ultrasound to rule out urinary tract dilatation is essential to assess treatment efficacy and adjust management accordingly.

Prognosis

Compliance with treatment and regular follow-up visits are essential for managing congenital nephrogenic diabetes insipidus (NDI). This condition can lead to significant challenges, including dehydration and electrolyte imbalances, which may impair growth and neurodevelopment, particularly in early childhood.

Lifelong management is often required, as current treatments primarily aim to reduce polyuria and maintain fluid and electrolyte balance rather than correct the underlying defect in water reabsorption. However, it should be noted that pharmacological treatment—typically with thiazide diuretics, amiloride, and NSAIDs—may be tapered or discontinued over time, especially as children become better able to regulate their own fluid intake and avoid dehydration.

Close medical supervision remains important to detect and prevent potential complications, such as urinary tract dilatation due to chronic high urinary flow rates.

By adopting a proactive, age-adapted management strategy and ensuring continuous monitoring, caregivers and healthcare providers can support optimal long-term outcomes for children with congenital NDI

Conclusion

Congenital nephrogenic diabetes insipidus is a rare genetic disorder characterized by impaired renal response to vasopressin, leading to polyuria, polydipsia, and electrolyte imbalances. Early diagnosis, appropriate management, and long-term follow-up are crucial to improve outcomes and quality of life of affected individuals. This clinical case supports the pathogenic significance of a hemizygous A>C transition at nucleotide 610, resulting in a missense Thr204Pro variant in the *AVPR2* gene.

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

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Kingella kingae Bacteremia: A Case Series

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Keywords
Sepsis ; bacterial diseases ; Kingella kingae.

Abstract

Background
Up to the early 1990s, when culture techniques and molecular detection methods were developing, *Kingella kingae* was considered a rare bacterium in the human body. Meanwhile, *K. kingae* is regarded as a prime etiology of skeletal system infections in children between 6-48 months.

In this case report, we will discuss three distinct cases of *K. kingae* bacteremia in young children.

Cases
Despite their different presentations, the three cases were unified by the common finding of a respiratory tract infection along the course of their illness. The severity of the disease varied among the cases; going from a mild upper airway infection to a septic child, however, antibiotic therapy, whether administered intravenously or otherwise, was consistently selected in all three instances, yielding favorable outcomes.

Conclusion
Kingella kingae is well known to cause septic arthritis. Other types of presentation are less well known and probably under-reported, as we will demonstrate here. It is therefore important to recognize these clinical courses and respond promptly with appropriate treatment for the patient. After all, there is always a risk of secondary endocarditis and osteomyelitis. However, the bacteriological identification of *K. kingae* can be challenging. Proper interpretation of blood cultures or utilization of genetic testing is therefore critical.

Introduction

Kingella kingae is a facultative anaerobic, β-hemolytic, Gram-negative microorganism, which is challenging to identify in routine solid cultures of blood or body fluids, such as synovial fluid or bone exudate (1).

Up to the early 1990s, when culture techniques and molecular detection methods were developing, *K. kingae*, was considered a rare pathogen to the human body (2). It was only by improvement of those techniques and increasing familiarity with the bacterium that it is becoming clear that its presence may have been underestimated (1).

Meanwhile, *K. kingae* is regarded as a prime etiology of skeletal system infections in children between 6 to 48 months (3). However, due to persistent difficulties detecting the organism, there is still an underdiagnosis of the infections caused by this pathogen (4).

Most patients with skeletal infections show a good response to conservative treatment with antibiotics (5). Duration of this therapy can differ from weeks to months, according to the type of infection (6-8).

Evolving techniques and clinical recognition show that *K. kingae* infections in the pediatric population, are broader than only skeletal infections. Therefore, it is essential to be aware of the possible clinical manifestations, to consider the possibility of the causality of *K. kingae*, and order the appropriate diagnostic tests. The various diagnostic techniques can range from taking a blood culture and allowing it to grow for a sufficient period, PCR testing on joint fluid in cases of arthritis, as well as an oropharyngeal swab with PCR testing for *K. kingae*.

In this case series, we will present three cases in which *K. kingae* seemed to be the underlying cause of illness.

Case 1

An 11-month-old girl was referred to the emergency department by her general practitioner due to high spiking fever and refusal to eat and drink. Her medical history was unremarkable, and she was vaccinated according to the national vaccination schedule.

The 11-month-old patient had been unwell for the previous four days, presenting with a fever of up to 41°C, and appeared to be experiencing diffuse pain and discomfort. She also had a mild cough and rhinitis. Her mother had recently tested positive for SARS-CoV-2, but the patient tested negative on her initial respiratory swab testing.

On clinical examination, the patient was found to have severe gingivostomatitis. Blood sampling on admission showed a significantly elevated C-reactive protein (CRP) level of 133 mg/L, but no significant leukocytosis, 13000/µL, cfr Table 1. An initial blood culture was taken. The patient was admitted to the hospital with a tentative diagnosis of gingivostomatitis and was treated with rehydration and systemic analgesia. This led to a good clinical recovery.

TABLE 1: Overview of laboratory results of the three patients.

	Patient 1	Patient 2	Patient 3
Hb	11.9 g/dL	12.5 g/dL	10.1 g/dL
WBC	13 000/µL	21 600/µL	8700/µL
Neutrophils	74 %	29 %	30 %
CRP	133 mg/L	10.90 mg/L	0.9 mg/L

However, on the third day of admission, the patient again refused to eat and had a high fever. On clinical examination, lung auscultation revealed bilateral crackles. A repeat blood test was performed, but the results did not show a rise in inflammatory markers. The initial blood culture remained sterile and a second blood culture was taken. A chest X-ray showed moderate bronchopneumonia (Figure 1). Due to difficulty in obtaining intravenous access, the patient was started on oral amoxicillin. Overnight, she developed hypoxemia and was started on temporary oxygen supplementation through a nasal cannula.

The next day, the patient showed some improvement. The fever had resolved after 12 hours of antibiotic treatment, but she still looked very sick and her appetite had not returned. However, the second blood culture showed growth of *K. kingae* within 24 hours of sampling. Given the severity of the patient's illness and the potential risk of developing endocarditis, as well as the fact that the blood culture showed unusual rapid growth of *K. kingae*, intravenous antibiotic treatment with cefotaxime was considered necessary for an initial 7 days. An ultrasound of the heart did not show evidence of endocarditis. The patient responded well to treatment and was discharged from the hospital after 10 days. She was continued on oral amoxicillin for a further 7 days.

Case 2

The second case is that of a 7-month-old boy who was brought to the emergency department due to a 4-day fever accompanied by asphyxiating coughs. The parents were alarmed by his breathing difficulties during the night, which prompted them to seek medical attention. He also refused to eat and seemed to have difficulty swallowing.

On clinical examination, the boy was found to be in a generally good condition, but he had bouts of coughing that ended in vomiting. He was also breathing forcefully, and auscultation revealed the presence of crackles and very discreet wheezing. There were mild signs of an upper respiratory tract infection. His oxygen saturation fluctuated between 91 and 95%.

A blood test showed a high white blood cell count and a low C-reactive protein level, cfr Table 1. A blood culture was initiated. A chest X-ray showed mild bilateral infiltration (Figure 1).

The boy was admitted to the hospital for cardiorespiratory monitoring and nebulized bronchodilator (short acting β2 mimetic). He made a quick recovery and was discharged 2 days after admission. The blood culture grew *K. kingae* after 48 hours, and the boy was treated from that moment on with an oral course of amoxicillin for 7 days. At the start of therapy, his main symptoms were still coughing and rhinitis.

Case 3

The last case is that of an 8-month-old girl with a history of gastroesophageal reflux disease (GERD), for which she is being treated with omeprazole, and cow's milk protein allergy, based on clinical findings and with a favourable progression after starting a cow's milk protein-free diet. She was referred by her GP to the emergency department (ED) due to a varicella (VZV) infection, with refusal to eat, vomiting, and risk of dehydration. She was also suffering from a significant cough. Her general condition had deteriorated, and she had developed a fever in the previous 24 hours.

On clinical examination, the child was found to be lethargic and had abnormal chest auscultation, with the presence of rhonchi and a mild wheeze. There was no respiratory distress. She also had bilateral otitis media without effusion. The chickenpox lesions were in a crusted state, without any sign of secondary bacterial skin infection.

Bloodwork was normal, cfr Table 1. A chest X-ray did not reveal signs of pneumonia (Figure 1). A blood culture was initiated.

Due to dehydration, the child was admitted for intravenous (IV) rehydration and amoxicillin was initiated to treat the ear infection. The blood culture grew *K. kingae* after 48 hours. As the child had already made a good recovery, she was discharged home on an oral course of amoxicillin.

Discussion

In the cases described above, all three patients presented with different clinical images. Nevertheless, they all had *K. kingae* bacteremia.

K. kingae is a normal component of the oropharyngeal flora in children aged 6 to 48 months (2). Its prevalence peaks at around 10% between 12 and 24 months of age, then declines as children develop immunological maturity. In children with underlying medical conditions, *K. kingae* infections may also occur at older ages (7). Colonization by *Kingella kingae* is marked by the periodic replacement of existing strains with newly acquired ones (9).

The colonized oropharyngeal mucosa serves as the primary source of child-to-child transmission, with daycare attendance linked to higher carriage rates and an elevated risk of invasive disease (10, 11). Investigations of these outbreaks showed that isolates from symptomatic children and asymptomatic carriers in the same classrooms were genotypically identical, suggesting that the infections were caused by virulent strains that had spread widely within the facilities (7).

Nevertheless *K. kingae* infections mostly pass mildly in children, the bacteria can enter the bloodstream through damaged mucosal tissue and lead to systemic infections (6).

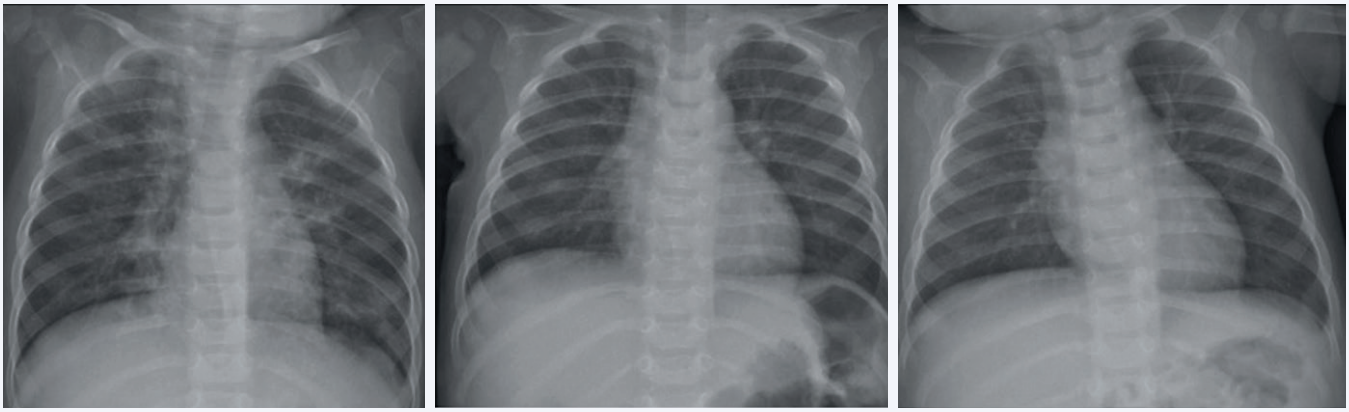
It is suspected that a viral infection, particularly a gingivostomatitis, could promote the entrance of the *K. kingae* infection in to more sterile body compartments and lead to a bacteremia(12, 13).

The second case showed an evolution from a lower respiratory tract infection to occult bacteremia. With no clinical, nor biological signs of a serious bacterial illness, and as the patient showed clinical improvement during hospitalization, no antibiotic treatment was seemed necessary. However, as the blood culture grew *K. kingae*, we decided to start antibiotic treatment because of the potential and severe complications of this infection.

Finally, in the third case, the girl presented with VZV infection. This might again suggests that *K. kingae* may have gained access from the oropharyngeal flora to the rest of the body due to the viral infection.

It is important to be aware that in most cases, we see a rather mild presentation of a K kingae infection, which highlights the need for

FIGURE 1: Overview of the X ray images of the thee patients. None of the X-rays show evidence of lobar pneumonia.



Patient 1 Patient 2 Patient 3

a high level of clinical suspicion (7). Most patients with invasive *K. kingae* disease experience moderate fever, although some remain afebrile. Constitutional symptoms are usually absent, except in cases of endocarditis. Peripheral white blood cell count, C-reactive protein levels, and erythrocyte sedimentation rate are typically mildly to moderately elevated, though they may also be normal (7, 14-16).

The difficulty in diagnosing a *K. kingae* infection lies in the fact that the organism is difficult to culture and often yields positive blood cultures only at a late stage, after 48 hours. A recent study (Yagupsky P., 2022) shows the differences in techniques used to detect *K. kingae* (8, 17). The blood culture is still used, where there is a better specificity than sensitivity. However, it should be realized that the time to positivity defers from 1 to 4 days, and therefore a sufficient observation is needed before the culture is labeled negative. There can be PCR testing on joint fluid in cases of arthritis and oropharyngeal swab tests with PCR testing for *K. kingae* (8) Sensitivity and specificity of the oropharyngeal swab PCR assay for *K. kingae* were 100% and 90.5%, respectively (2). So a negative result could be used to exclude *K. kingae* infections and to prevent more invasive diagnostic measures.

The question in all three cases was whether or not to treat with intravenous antibiotics or, in case two, even to treat at all. Before initiating any treatment, it is important to determine whether the case involves a bacteremia with still clinical wellbeing or a septic child (7). In our first case it was clear to start with intravenous antibiotics, whereas in case two and three we had a child with a bacteremia but further on was in a good clinical condition. We started nevertheless with our treatment, but following some evidence found in literature, we started on oral antibiotics. This decision was made given the risk of the severe complications caused by *K. kingae* bacteremia, such as sepsis, endocarditis or osteomyelitis (7, 18).

There is no clear consensus on the optimal treatment regime for *K. kingae* infections in the literature. Due to the absence of specific guidelines for treating *K. kingae* infections, patients have been treated with various antibiotics based on protocols designed for infections caused by more common pathogens (7).

Most *K. kingae* infections are generally susceptible to betalactam antibiotics (1). However, some invasive strains are beta-lactamase producing and consequently resistant to beta-lactam antibiotics. Therefore, it is recommended to start with a broad-spectrum second or third generation cephalosporin and switch to a more specific antibiotic based on the antibiogram (2).

In the case of bacteremia, it is recommended to start with intravenous antibiotics. However, in case of clinical wellbeing, and a good evolution after initial treatment, oral administration can be considered and should be safe, as we have also addressed in case two and three (7). In case of skeletal infections for example, current recommendations state that when there is a good clinical response and a CRP value below 20 mg/L, oral antibiotics can be administered (2, 8, 15). This is also why we chose to initiate treatment of the patients in the second and third case with oral antibiotics, on which they showed a very good response.

There is no clear consensus on the optimal duration of antibiotherapy for *K. kingae* infections (7). However, some guidelines suggest that the duration of antibiotic treatment for skeletal infections should be based on the type of infection, with osteomyelitis requiring treatment for 3-6 weeks (2, 19, 20). For bacteremia, the guidelines are less specific. Some recommend a duration of 1-3 weeks, but others state that the clinical appearance of the patient is the most important factor to consider ((7).

In our cases, we achieved clinical recovery with a duration of treatment of 14 days in the first case, and 7 days in the second and third cases. However, it is important to note that these were small case studies and further research is needed to determine the optimal duration of treatment for *K. kingae* infections.

Follow-up during and after treatment is important to ensure that the infection has been cured and to prevent the development of any complications. With our patients we did a clinical follow-up that was reassuring, but no new blood cultures were taken.

Conclusion

In the cases described, *K. kingae* infections presented with varied clinical manifestations, highlighting the challenge in diagnosis and the importance of a high index of suspicion. Although the infection often presents mildly, it can progress to invasive disease, particularly in children with underlying medical conditions8. The ability of *K. kingae* to enter the bloodstream and cause severe complications, such as sepsis, endocarditis, or osteomyelitis, underscores the need for prompt treatment and close monitoring (14, 16).

Due to the lack of specific treatment guidelines, management often follows protocols developed for more common pathogens (7). While most *K. kingae* infections are susceptible to beta-lactam antibiotics, the potential for beta-lactamase production in some strains necessitates broad-spectrum coverage initially, with adjustments based on the antibiogram. Our cases demonstrate the feasibility of starting with intravenous antibiotics, followed by oral antibiotics if clinical improvement is observed, particularly in patients with mild bacteremia and good overall condition.

The duration of treatment remains an area of uncertainty, with guidelines suggesting 1-3 weeks for bacteremia and 3-6 weeks for bone infections (7, 19, 20). It stays important to distinguish between sepsis and bacteremia. In our small cohort, a 14-day treatment regimen was sufficient for the first case, while 7 days of treatment led to recovery in the second and third cases. Clinical follow-up is crucial for ensuring complete resolution of the infection, and further research is needed to define optimal treatment durations for *K. kingae* infections.

These findings emphasize the importance of early detection, appropriate antibiotic therapy, and careful follow-up to prevent complications associated with *K. kingae* bacteremia in young children.

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▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables. DÉNOMINATION DU MÉDICAMENT Beyfortus 50 mg solution injectable en seringue préremplie. Beyfortus 100 mg solution injectable en seringue préremplie. COMPOSITION QUALITATIVE ET QUANTITATIVE Beyfortus 50 mg solution injectable en seringue préremplie : chaque seringue préremplie contient 50 mg de nirsévimab dans 0,5 ml (100 mg/ml). Beyfortus 100 mg solution injectable en seringue préremplie Chaque seringue préremplie contient 100 mg de nirsévimab dans 1 ml (100 mg/ml). Le nirsévimab est un anticorps monoclonal humain de type immunoglobuline G1 kappa (IgG1κ) produit dans des cellules d'ovaires de hamster chinois (CHO) par la technologie de l'ADN recombinant. Excipients à effet notoire : ce médicament contient 0,1 mg de polysorbate 80 (E433) pour chaque dose de 50 mg (0,5 ml) et 0,2 mg pour chaque dose de 100 mg (1 ml). FORME PHARMACEUTIQUE Solution injectable. Solution limpide à opalescente, incolore à jaune, de pH 6.0. INDICATIONS THÉRAPEUTIQUES Beyfortus est indiqué pour la prévention des infections des voies respiratoires inférieures dues au virus respiratoire syncytial (VRS) : - Chez les nouveau-nés et les nourrissons au cours de leur première saison de circulation du VRS. – Les enfants jusqu'à l'âge de 24 mois qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS (voir rubrique 5.1). Beyfortus doit être utilisé conformément aux recommandations officielles en vigueur. POSOLOGIE ET MODE D'ADMINISTRATION Posologie Nourrissons au cours de leur première saison de circulation du VRS La dose recommandée est une dose unique de 50 mg administré par voie intramusculaire pour les nourrissons dont le poids est <5 kg et une dose unique de 100 mg administré par voie intramusculaire pour les nourrissons dont le poids est ≥5 kg. Beyfortus doit être administré dès la naissance chez les nourrissons nés au cours de la saison d'épidémie à VRS. Pour les nourrissons nés en dehors de la saison, Beyfortus doit être administré idéalement avant la saison d'épidémie à VRS. La posologie chez les nourrissons dont le poids est compris entre 1,0 kg et 1,6 kg est basée sur une extrapolation, aucune donnée clinique n'est disponible. L'administration du traitement chez les nourrissons de moins de 1 kg est susceptible d'entraîner une exposition plus élevée que chez les nourrissons pesant plus de 1 kg. Par conséquent, les bénéfices et les risques de l'utilisation du nirsévimab chez les nourrissons de moins de 1 kg doivent être soigneusement évalués. Les données disponibles sont limitées chez les enfants extrêmement prématurés âgés de moins de 8 semaines (âge gestationnel [AG] < 29 semaines). Il n'y a pas de données cliniques disponibles chez les nourrissons dont l'âge post-menstruel (âge gestationnel à la naissance + âge chronologique) est inférieur à 32 semaines (voir rubrique 5.1). Enfants qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS La dose recommandée est une dose unique de 200 mg administrée en deux injections intramusculaires (2 x 100 mg). Beyfortus doit être administré idéalement avant le début de la deuxième saison d'épidémie à VRS. Chez les individus devant subir une chirurgie cardiaque avec circulation extracorporelle, une dose supplémentaire peut être administrée dès que l'individu est stable après l'intervention, afin de garantir des taux sériques de nirsévimab adaptés. Si l'intervention a lieu dans les 90 jours suivant l'administration de la première dose de Beyfortus, la dose supplémentaire au cours de la première saison d'épidémie à VRS doit être de 50 mg ou de 100 mg selon le poids, ou de 200 mg au cours de la deuxième saison d'épidémie à VRS. Au-delà de 90 jours, la dose supplémentaire peut être une dose unique de 50 mg indépendamment du poids au cours de la première saison d'épidémie à VRS, ou de 100 mg au cours de la deuxième saison d'épidémie à VRS, afin de couvrir le reste de la saison de circulation du VRS. La sécurité et l'efficacité du nirsévimab chez les enfants âgés de 2 à 18 ans n'ont pas été établies. Aucune donnée n'est disponible. Mode d'administration Beyfortus doit être administré uniquement par voie intramusculaire. Il doit être administré par voie intramusculaire, de préférence dans la partie antérolatérale de la cuisse. Le muscle fessier ne doit pas être utilisé systématiquement comme site d'injection en raison du risque de lésion du nerf sciatique. Si deux injections sont nécessaires, des sites d'injection différents doivent être utilisés. Pour les instructions concernant les précautions particulières de manipulation du médicament, voir la rubrique 6.6. CONTRE-INDICATIONS Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1. EFFETS INDÉSIRABLES Résumé du profil de tolérance L'effet indésirable le plus fréquent était les éruptions cutanées (0,7 %) survenues dans les 14 jours suivant l'administration. La majorité des cas étaient d'intensité légère à modérée. De plus, une fièvre et des réactions au site d'injection ont été rapportées à un taux respectif de 0,5 % et 0,3 % dans les 7 jours suivant l'administration. Les réactions au site d'injection étaient non graves. Liste des effets indésirables Ci-dessous sont présentés les effets indésirables rapportés chez 2 966 nourrissons nés à terme et prématurés (AG ≥29 semaines) ayant reçu du nirsévimab dans le cadre d'études cliniques et dans le cadre de la surveillance après commercialisation (vor rubrique 4.4). Les effets indésirables rapportés au cours des études cliniques contrôlées sont répertoriés par classe de systèmes d'organes (SOC) MedDRA. Au sein de chaque SOC, les termes préférentiels sont présentés par fréquence décroissante puis par gravité décroissante. La fréquence de survenue de chaque effet indésirable est définie comme suit : très fréquent (≥1/10) ; fréquent (≥1/100 à <1/10) ; peu fréquent (≥1/1 000 à <1/100) ; rare (≥1/10 000 à <1/1 000) ; très rare (<1/10 000) et fréquence indéterminée (ne peut être estimée à partir des données disponibles). Affections du système immunitaire · Indéterminé – Hypersensibilité1 1 Effet indésirable rapporté dans le cadre de notification spontanée Affections de la peau et du tissu sous-cutané · Peu fréquent - Eruptions cutanées2 2 L'éruption cutanée était définie par les termes préférentiels groupés suivants : rash, rash maculopapuleux, rash maculeux. Troubles généraux et anomalies au site d'administration · Peu fréquent - Réaction au site d'injection3 ; Fièvre 3 La réaction au site d'injection était définie par les termes préférentiels groupés suivants : réaction au site d'injection, douleur au site d'injection, induration au site d'injection, oedème au site d'injection, gonflement au site d'injection. Nourrissons avec un risque plus élevé d'infection sévère par le VRS au cours de leur première saison de circulation du VRS La sécurité d'emploi a été évaluée dans l'étude MEDLEY chez 918 nourrissons à risque plus élevé d'infection sévère par le VRS, dont 196 très grands prématurés (AG <29 semaines) et 306 nourrissons porteurs de maladie pulmonaire chronique ou d'une cardiopathie congénitale hémodynamiquement significative pendant leur première saison d'épidémie à VRS, qui ont reçu du nirsévimab (n=614) ou du palivizumab (n=304). Le profil de sécurité du nirsévimab chez les nourrissons l'ayant reçu au cours de leur première saison d'épidémie du VRS était comparable à celui du comparateur palivizumab et cohérent avec celui observé chez les nourrissons nés à terme et prématurés d'AG ≥29 semaines (études D5290C00003 et MELODY). La sécurité d'emploi a également été évaluée au cours de l'étude MUSIC, étude ouverte, non contrôlée, à dose unique, menée chez 100 nourrissons et enfants immunodéprimés d'âge ≤ 24 mois, qui ont reçu du nirsévimab lors de leur première ou deuxième saison d'épidémie à VRS. Les sujets présentaient au moins l'une des conditions suivantes : immunodéficience (combinée, en anticorps ou autre étiologie) (n = 33) ; corticothérapie systémique à forte dose (n = 29) ; greffe d'organe ou de moelle osseuse (n = 16) ; chimiothérapie immunosuppressive (n = 20) ; autre traitement immunosuppresseur (n = 15) et infection par le VIH (n = 8). Le profil de sécurité du nirsévimab était cohérent avec celui attendu pour une population d'enfants immunodéprimés et avec celui observé chez les nourrissons nés à terme et prématurés d'AG ≥ 29 semaines (études D5290C00003 et MELODY). Le profil de sécurité du nirsévimab chez les enfants pendant leur deuxième saison d'épidémie à VRS était cohérent avec celui observé pendant leur première saison d'épidémie à VRS. Nourrissons nés à terme et prématurés entrant dans leur première saison à VRS La sécurité d'emploi du nirsévimab a également été évaluée au cours de l'étude HARMONIE, étude multicentrique randomisée, ouverte, menée chez 8 034 nourrissons nés à terme et prématurés (AG ≥29 semaines) entrant dans leur première saison de VRS (non éligibles au palivizumab), qui ont reçu soit du nirsévimab (n=4 016) soit aucune intervention (n=4 018) pour la prévention des hospitalisations liées aux infections des voies respiratoires inférieures à VRS. Le profil de sécurité du nirsévimab administré lors de la première saison de VRS était cohérent avec le profil de sécurité du nirsévimab observé au cours des études contrôlées contre placebo (études D5290C00003 et MELODY). Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via : Belgique : Agence Fédérale des Médicaments et des Produits de Santé : www.afmps.be – Division Vigilance : Site internet : www.notifieruneffetindesirable.be – e-mail: adr@fagg-afmps.be Luxembourg : Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé – Site internet : www.guichet.lu/pharmacovigilance TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, France NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ EU/1/22/1689/001 50 mg, 1 seringue préremplie à usage unique EU/1/22/1689/002 50 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/003 50 mg, 5 seringues préremplies à usage unique EU/1/22/1689/004 100 mg, 1 seringue préremplie à usage unique EU/1/22/1689/005 100 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/006 100 mg, 5 seringues préremplies à usage unique DATE DE PREMIÈRE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION Date de première autorisation : 31 octobre 2022 DATE DE MISE À JOUR DU TEXTE Date d'approbation : 04/2025. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

* Beyfortus® est désormais également remboursé pour les jeunes enfants (<2 ans) qui subissent une chirurgie cardiaque avec circulation extracorporelle pendant leur première ou deuxième saison de VRS, ou les jeunes enfants (<2 ans) qui restent vulnérables à une maladie grave due au VRS pendant leur deuxième saison de VRS (comme décrit dans les recommandations du CSS (avis 9760)).

Référence:
1. Beyfortus® RCP, Avril 2025

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