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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. Pour la liste complète des excipients, voir rubrique 6.1. 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. Beyfortus doit être utilisé conformément aux recommandations officielles en vigueur. POSOLOGIE ET MODE D'ADMINISTRATION Posologie 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 avant le début de la saison d'épidémie à VRS, ou dès la naissance chez les nourrissons nés au cours de 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 nirsevimab 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). Chez les nourrissons devant subir une chirurgie cardiaque avec circulation extracorporelle, une dose supplémentaire peut être administrée dès que le nourrisson 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 doit être de 50 mg ou 100 mg selon le poids. Au-delà de 90 jours, la dose supplémentaire peut être une dose unique de 50 mg indépendamment du poids, afin de couvrir le reste de la saison de circulation du VRS. Il n'y a pas de données disponibles sur la sécurité et l'efficacité d'une administration répétée. 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. Instructions relatives à l'administration Beyfortus est disponible sous la forme d'une seringue préremplie de 50 mg et d'une seringue préremplie de 100 mg. Vérifier les étiquettes collées sur l'emballage extérieur et sur la seringue préremplie pour vous assurer d'avoir choisi la présentation correcte requise de 50 mg ou de 100 mg. Seringue préremplie de Beyfortus 50 mg (50 mg/0,5 mL) avec tige de piston violette. Seringue préremplie de Beyfortus 100 mg (100 mg/1 mL) avec tige de piston bleue clair. Étape 1 : En tenant le Luer Lock d'une main (éviter de tenir la tige du piston ou le corps de la seringue), dévisser le capuchon de protection de la seringue en le tournant dans le sens antihoraire avec l'autre main. Étape 2 : Fixer une aiguille sur la seringue préremplie en tournant délicatement l'aiguille, dans le sens horaire sur l'embout Luer Lock de la seringue préremplie, jusqu'à rencontrer une légère résistance. Étape 3 : En tenant le corps de la seringue d'une main, tirer délicatement sur le capuchon protecteur de l'aiguille avec l'autre main pour l'enlever. Ne pas tenir la tige du piston pendant le retrait du capuchon protecteur de l'aiguille, au risque de déplacer la butée en caoutchouc. Ne pas toucher l'aiguille et ne pas la mettre en contact avec une surface. Ne pas remettre le capuchon protecteur sur l'aiguille et ne pas retirer l'aiguille de la seringue. Étape 4 : Administrer tout le contenu de la seringue préremplie en injection intramusculaire, de préférence dans la face 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. 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 pyrexie 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 La liste ci-dessous présente les effets indésirables rapportés chez 2 966 nourrissons nés à terme et prématurés (AG ≥29 semaines) ayant reçu du nirsévimab dans le cadre d'essais cliniques. Les effets indésirables rapportés au cours des essais cliniques contrôlés 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 de la peau et du tissu sous-cutané • Peu fréquent - Eruptions cutanées1 1 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'injection2 ; Pyrexie 2 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 La sécurité d'emploi a également été évaluée dans l'essai 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 (614) ou du palivizumab (304). Le profil de sécurité était comparable à celui du comparateur palivizumab et cohérent avec le profil de sécurité chez les nourrissons nés à terme et prématurés d'AG ≥29 semaines (essais D5290C00003 et MELODY). Immunogénicité Comme avec toutes les protéines thérapeutiques, il existe un potentiel d'immunogénicité. 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 – 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 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 : 11/2023 Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

Référence:
1. Beyfortus RCP, nov 2023. MAT-BE-2400390-1.0-052024

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Contents

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Belangrijk: Borstvoeding is de ideale voeding voor zuigelingen. Neocate Syneo is een voeding voor medisch gebruik. Dieetvoeding bij koemelkeiwitallergie, meervoudige voedselallergieën en andere indicaties waarbij een dieet op basis van aminozuren wordt aanbevolen. Te gebruiken onder medisch toezicht. Informatie uitsluitend bestemd voor het (para) medisch korps.

Referenties: 1. De Boissieu D, et al. J Pediatr. 1997;131(5):744–7. **2.** Vanderhoof JA, et al. J Pediatr. 1997;131(5):741–4. **3.** Burks AW, et al. Pediatr Allergy Immunol. 2015;26(4):316–22. **4.** Fox AT, et al. Clin Transl Allergy. 2019;9(1):5. 5. Candy DCA, et al. Pediatr Res. 2018;83(3):677–86. 6. Sorensen K, et al. Nutrients. 2021;13:2205. 7. Sorensen K, et al. Nutrients. 2021;13:935.

V.U. : Danone Belux nv – Werkhuizenkaai 160 – 1000 Brussel – 05/2024

From butterflies to mosquitoes…

With the arrival of the summer holidays and the long-awaited return of the sun in Belgium, we are delighted to bring you this latest issue of Belgian Journal of Paediatrics, focusing on tropical paediatrics.

Human beings have always been attracted to travelling and discovering the world. This may have something to do with our original instincts as nomadic hunter-gatherers. We need to explore, to venture out, to encounter new territories, new realities. In all eras and cultures, travel has been encouraged and seen as a positive step towards personal and social development. In the 16th century, Michel de Montaigne said that *travel shapes youth*. Later, in the 19th century, Emile Zola went further, saying that *nothing develops intelligence like travel*. At the same time, the American author Mark Twain wrote that *travel is fatal to prejudice, bigotry, and narrow-mindedness*. The Danish writer Hans-Christian Andersen, author of many stories for children and also great traveler, poetically described the benefits of travelling with these words: "*To move, to breathe, to fly, to float, to gain all while you give, to roam the roads of lands remote, to travel is to live.*" At this time of year, and with this issue, we want to make travel a safe and serene experience, even for our youngest patient. A very practical article provides advice on what to anticipate and what to pay attention for travelling with children.

In the recent decades, interactions and exchanges between continents, countries and peoples have contributed to a rapid and major economic boom conceptualised by the term globalization. As our two guest editors, Daan Van Brusselen and Dimitri Van der Linden, suggest, this globalisation now goes beyond purely economic aspects and has an impact on medicine and healthcare. A minor event, a microscopic infectious agent, a benign bite with a vector in a faraway country can lead to severe consequences that are later felt on the other side of the world… Here, the famous "butterfly effect" is related to the action of mosquitoes! In children who have previously travelled, we need to be able to recognize the symptoms and to offer treatment for a potential tropical disease. It is also important to take rapid action to avoid contagion. For this purpose, a panel of paediatric experts presents consensus recommendations for the management of malaria in Belgium.

Endemic infectious agents can be transported to countries thousands of kilometers away from their region of origin, not only by patients but also by the carriage of their vectors. Each year, several cases of Plasmodium infections transmitted by African mosquitoes are reported in the vicinity of Belgian airports. In addition, climate change, which is now becoming a reality, may also favor the occurrence and the epidemic development of diseases that were previously found only in warmer and/or more humid countries. The example of Human West Nile virus infection and its risk of local transmission in Belgium is discussed by Mark Wojciechowski and colleagues.

On behalf of the Editorial Committee, we would like to thank the two guest editors and the many authors who are experts in infectious and tropical diseases for their contribution to this outstanding theme issue.

Beside the theme articles, this issue also features several case reports and original studies. The "Child Advocacy" section details the demands and prospects for the organization of care for rare diseases. In the “Made in Belgium” section, Tania Vanhee summarizes her doctoral thesis, completed jointly at ULB and VUB. She studied the fear, anxiety and phobia of the dentist and analysed a federating instrument about the different material and behavioral techniques for ideal patient management.

We hope you enjoy reading this issue and we wish you a bright and sunny summer.

Christophe Chantrain and Marc Raes, Editors-in-chief

Uw vragen of commentaar
Vos questions ou commentaires

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Si vous ne recommandez pas la vaccination contre le MenB à vos patients,

qui le fera ?

81% des parents considèrent leur médecin comme la source principale d'information concernant la vaccination de leurs enfants (n=800)[2]

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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Theme issue articles - Editorial

‘Tropical Troubles’: When falling Coconuts Aren't the Only Concern

It is with great pleasure that we introduce this special edition of the Belgian Journal of Paediatrics, dedicated to the intricate realm of tropical paediatrics. As guest editors, we reflect on our past years with Médecins Sans Frontières (MSF) and other organizations, where we witnessed firsthand the inseparable bond between tropical paediatrics and humanitarian work. While we are currently more in Belgium than in the tropics, we find fulfillment in continuing to contribute to the education of healthcare workers in the tropics and to Belgian medical staff dealing with tropical diseases.

In recent years, the number of paediatricians with experience in infectiology and travel medicine has increased slightly. However, for the majority, the field of tropical medicine remains a bit mysterious. It is precisely this gap in knowledge and awareness that motivates the publication of this special issue. Publishing an issue on tropical medicine in summer is timely, considering the surge in travel during this season.

The ‘tropics’ refer to the region of the Earth around the equator (encompassing the area between the Tropic of Cancer in the Northern Hemisphere and the Tropic of Capricorn in the Southern Hemisphere). The subtropics are the adjacent areas, also characterized by warm temperatures and high humidity. The geography of the tropics profoundly influences the health landscape of these regions. Pathogens like dengue, malaria and many parasites thrive in tropical climates with mosquitos and humid soils, but diseases like malnutrition and TB are also fueled by factors like overcrowding and poverty, that are prevalent in many Low- and Middle Income Countries (LMIC), but on the rise in Belgium as well.

Originally we also invited people to send articles on diseases like sickle cell anaemia that are more prevalent in ‘tropical regions’ and that we see more often when working in LMIC. But after some remarks and reflection, we realised that considering sickle cell disease as a tropical condition might not align with a "woke" perspective as it could perpetuate harmful stereotypes and overlooks its current global prevalence and the diverse populations affected by this genetic disorder.

As we consider the ecological impact of travel, it is imperative to keep the environmental footprint of air travel in the back of our minds. While air travel facilitates global connectivity, it also contributes to carbon emissions that impact the very environments we seek to explore and protect. Another factor to consider is the widespread use of unecological sunscreens (containing chemicals known to be harmful to marine life, such as oxybenzone and octinoxate), while mineral-based UV filters like zinc oxide and titanium dioxide are available.

Vector-borne diseases remain a significant threat in (sub)tropical regions, but also more and more in European areas (cfr. the articles on West Nile and ‘travelling with children’ in this special edition). This underscores the importance of preventive measures such as DEET and other mosquito repellents. However, it is crucial to exercise caution in their application, mindful of the potential toxic effects on child health, taking into account the precautionary principle. Balancing the benefits of protection against mosquito-borne illnesses with potential risks requires a nuanced approach, taking into account other measures like long sleeves and sleeping under an impregnated bednet.

We are delighted to present a new Belgian Paediatric Malaria protocol, developed collaboratively with leading experts in the field. This edition also features updates on travelling with children, alongside insightful articles on emerging tropical diseases such as West Nile virus, Pott's disease, Leishmania, and neurocysticercosis. Furthermore, we end with the groundbreaking research of Bieke Tack's PhD on one of the most significant causes of bacteremia in sub-Saharan Africa, Non-Typhoid Salmonella. We extend our heartfelt appreciation to all contributors who have generously shared their expertise and insights in this edition.

Warm (tropical) regards,

Daan Van Brusselen

Dimitri Van der Linden

Child AdVOCacy

"Giving children a **voice** in healthcare"

Unheard Children's Voices in Health Care

Ann De Guchtenaere [a,c], Levi Hoste [b,c], Jeroen Verlinden [d]

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Keywords

Child advocacy ; Rare diseases.

Introduction

As long as children, young people, and their parents do not have a structural voice in the organisation of federal and regional health care in Belgium, it is our duty as paediatricians (and as advocates of children's rights, especially in health care) to give them this voice.

A children's rights reflex focuses on recognising and respecting the individual rights of children, as outlined in the Convention on the Rights of the Child. This concept differs from other approaches, such as child friendliness, which are more discretionary and based on what is deemed good for children without ensuring their rights. A children's rights reflex ensures an automatic and structural attitude that approaches situations from a children's rights and participation perspective.

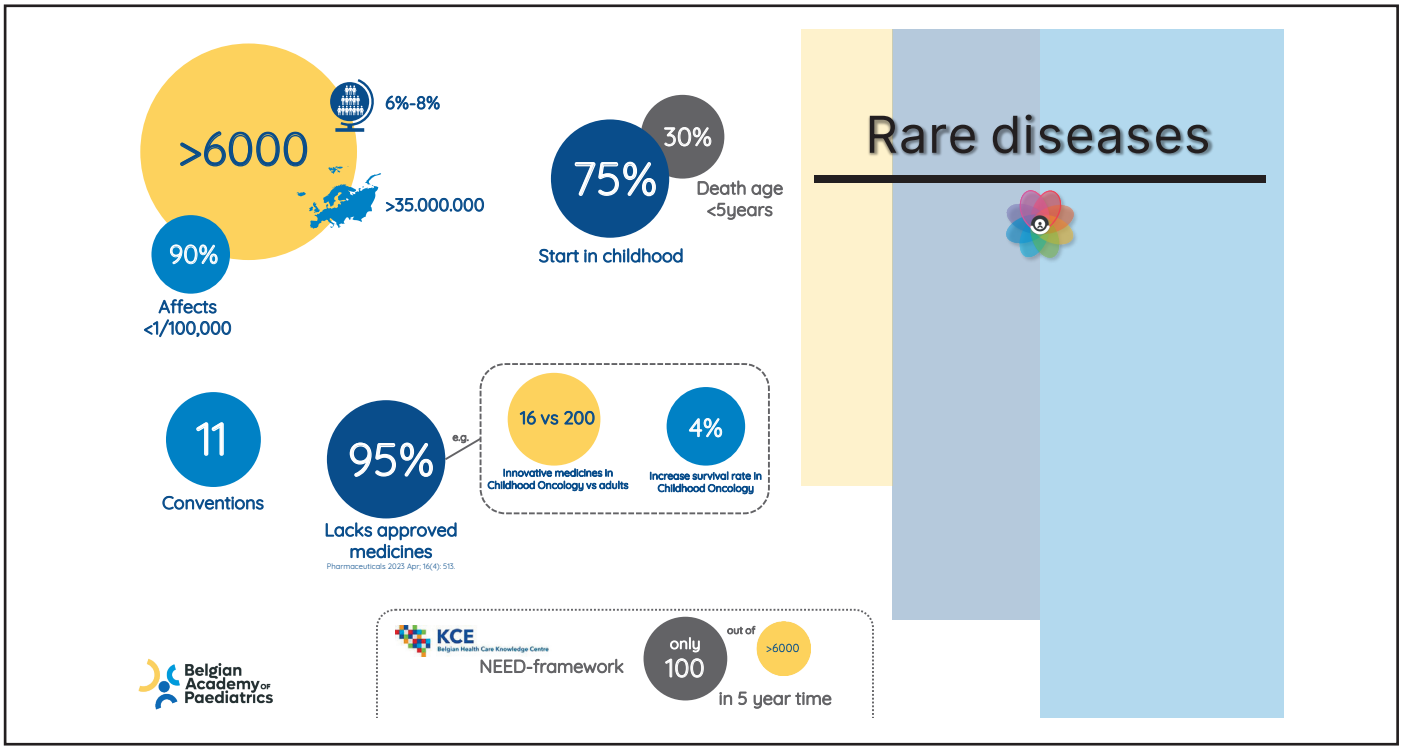
We aim to strengthen the position of children and young people by integrating a children's rights reflex into policy, research, and practice.

In this section, we provide them with that voice by backing up our figures with a statement or story that has appeared on social media or in the news in the last 3 months indicating children's health-care 'inequity' and 'inequality'.

This issue focuses on the entire journey from symptom onset to treatment for rare diseases, highlighting how the paediatric population is disproportionately affected.

The figures

To date, there are more than 6000 rare diseases affecting between 6% and 8% of the global population and more than 35 million people in the



European Union. These diseases often manifest early in life, either at birth or during childhood, have lifelong symptoms and can progressively worsen, become chronic or relapsing and lead to life-threatening conditions. Alarmingly, 75% of rare diseases have an exclusive onset in childhood, and approximately 30% of these children die before reaching the age of five.

Over 90% of rare diseases affect less than 1/100,000 patients, which contributes significantly to the limited knowledge of most rare diseases among healthcare workers (1). In order to recognise early symptoms and understand the complexity of the individual needs of patients and their families, a qualitative educational program and significant exposure is necessary for all healthcare workers involved in paediatric care. However, today the Belgian healthcare system lacks a solid quality framework and competency requirements, leading to potential delays in diagnosis and mismanagement. Only 11 (rare) diseases are supported by affordable paediatric multidisciplinary care.

Furthermore, only 5% of rare diseases have effective treatments available, meaning that 95% lack approved medicines (2). Thus, it is crucial to incentivise the development of medications for this significantly affected population. Since the European Orphan Regulation on Medicinal Products and the European Paediatric Regulation were enacted, there has been an increase in the development of paediatric appropriate medicines, but much more work remains to be done, in particular to promote development in diseases that predominantly affect children and to develop a framework that facilitates drug development based on mechanism of action studies. Currently, knowledge about rare diseases is still limited, and the lack of approved treatments has led to the harmful off-label use of medicines by physicians and pharmacists.

Exemplative, every type of childhood cancer is a rare disease. The most significant advancements in oncology have been made for adults. Since 2007, more than 200 cancer drugs for adults have been approved. In the same period, only 16 drugs have been approved for paediatric cancers. This disparity is also evident in young patients' access to innovative clinical trials: access remains an exception in paediatric cancer. As a result, the average survival rate for childhood cancer has stagnated. Since the year 2000, the survival rate has increased by only about 4% (3).

The voice

RaDiOrg (Rare Diseases Organisation Belgium) has serious concerns about the current NEED framework developed by KCE (Belgian Health Care Knowledge Centre) to address unmet needs in rare diseases. The methodology, aiming to analyse 100 diseases over five years, is inadequate given that there are over 6100 rare diseases, of which only 6% have effective treatments. The slow pace of the framework needs to be reconsidered as it relies heavily on data and spokespersons with essential information that is lacking for many rare diseases. Furthermore, while the framework focuses on disease-level analyses, it fails to reflect individual patient needs, the diverse manifestations of diseases, and cross-cutting medical needs. RaDiOrg suggests that different methodological choices could better address the vast, often invisible, unmet needs of patients, fostering greater equity in health care.

Conclusion

Industry often claims that the problem of drug development gaps goes beyond a lack of commercial potential. Factors such as the state of knowledge, access to research populations and an existing infrastructure for collaboration play a key role. Existing research infrastructure that connects physicians, patients and caregivers, such as the Belgian Paediatric Clinical Research Network (BPCRN), has shown to tackle many of these challenges 1) by the facilitation of paediatric studies and increasing Belgium's attractiveness for clinical trials, 2) by developing well-educated trial sites and promote education among all stakeholders, and 3) by identifying patients' needs and engaging patients in every phase of research. The benefits of this model have been clearly validated in an international context (e.g., within the IMI2-funded conect4children project) and the BPCRN is now seeking – together with its stakeholders – for a sustainable future. That such future is viable has been clearly demonstrated in paediatric oncology, where national connectedness is formally embedded in a European context, where academic and industry research organisations are co-developing supported by governments, patient organisations and a critical amount of structural funding. Future investments in both oncology and non-oncology research, should clearly focus on paediatrics and rare diseases, and leverage existing research infrastructure in order to provide a maximal benefit for patients and families.

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The content of this article aligns with recommendations number

in the Plan Care for the Child

May we invite all paediatricians who are active on LinkedIn, Instagram, etc., to support your feeds and posts with the following hashtags:

#unmetneeds #invisibleneeds #rarediseases #needfordata #needforvisibility #needforspokespersons #needforresearch #childrensrights

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Avec les professionnels de santé, pour la petite enfance

Belgian Paediatric Malaria Treatment Guideline 2024

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Keywords

Malaria; diagnosis; drug therapy; children; guideline

Abstract

The Belgian Paediatric Malaria Treatment Guideline 2024 addresses the need for early diagnosis and specialized care in managing paediatric malaria, a potentially life-threatening disease. It outlines the protocol developed for the treatment of malaria in children in Belgium, shaped by an extensive collaborative process among paediatric infectious disease specialists across the country. The guideline highlights the importance of early recognition of malaria symptoms and rapid initiation of treatment and the need for specialized advice early onwards.

Introduction

Malaria remains a potential life- threatening disease caused by *Plasmodium* parasites transmitted by *Anopheles* mosquitoes. In 2022, there were 249 million malaria cases globally that led to 608 000 deaths in total. Of these deaths, 76% were children under 5 years of age (1).

The five *Plasmodium* species that can infect humans are *P. falciparum, P. vivax, P. ovale, P. knowlesi and P. malariae*. Incubation can range from six days until months and rarely years depending on the species. The majority of *P. falciparum* infections (85%) becomes clinically apparent within one month after infection, with less than one percent of cases presenting after 6 months. In contrast, only 25% of non-falciparum malaria cases present within one month after infection/travel, while 60% appear within six months and 90% within a year (2).

Severe malaria is a medical emergency. Children with malaria can deteriorate extremely quickly. Early diagnosis and prompt treatment initiation is vital. Malaria should always be ruled out in a child with fever (current or recent history) returning from a malaria-endemic area up to twelve months after return, regardless of any malaria chemoprophylaxis. Advise from a paediatric infectious diseases specialist should be obtained as early as possible, and cases of severe malaria should preferably be managed in a centre with paediatric intensive care facilities.

Method

During an interdisciplinary meeting focused on paediatric malaria treatment between Citadel Hospital and CHU St. Pierre, disparities in treatment practices came to light. Motivated by a desire to align with the latest advances in the field, we aimed at creating a unified Belgian protocol, receiving approval from the Belgian Study group of Travel Medicine.

We reached out to paediatric infectious disease specialists from various Belgian hospitals, requesting their local malaria treatment protocols. Twelve hospitals from all regions of Belgium contributed their protocols, allowing a comprehensive comparison of diagnostic and treatment practices.

A series of virtual meetings were held from February to July 2022 - a period still affected by the COVID-19 pandemic - during which we compared these protocols with the most recent guideline of the World Health Organisation (WHO, February 2022) and the United Kingdom National Malaria guidelines (2016) (3, 4).

This collaborative effort among paediatric specialists in paediatric infectious diseases and travel medicine culminated in the protocol presented, aiming to enhance our collective expertise and practice in treating paediatric malaria in Belgium.

Diagnosis

1. Travel history

A detailed travel history is paramount for children presenting with fever following their return from a malaria-endemic area. The travel should include travel dates, destinations including airport transfers, activities (e.g., trips to rural areas), chemoprophylaxis (medication, dosing and adherence), and (travel) vaccinations. Keep in mind that despite chemoprophylaxis, no preventive measure offers 100% protection against malaria.

To assist in assessing the malaria risk, the Belgian Study group of Travel Medicine provides an annually updated world map of the malaria risk. For

the most recent version of this map, please scan the provided QR code (Figure 1) to visit the website. https://artsen.wanda.be/en/a-z-index/malaria-world-map.

2. Symptoms and clinical examination

Symptoms in children can manifest as non-specific 'flu-like' symptoms, ranging from fever, malaise, headache, respiratory symptoms to abdominal complaints like vomiting and diarrhoea, mimicking infectious enteritis. The clinical examination is often non-specific but signs like pallor, petechiae, jaundice, tachypnoea, splenomegaly, lethargy or abnormal neurological examination can be present.

3. Differential diagnosis

Given the wide range of potential aetiologies for fever in children returning from tropical countries, clinicians must maintain a broad differential diagnosis. This approach ensures that other conditions, such as sepsis, pneumonia, influenza, meningo-encephalitis, dengue and other arboviruses, enteric fever, rickettsiosis, leptospirosis, tick-borne relapsing fever (various *Borrelia* species in several tropical areas) or other commonly acquired viral infections are considered alongside malaria.

4. Laboratory investigations

To confirm malaria and identify the infecting species a rapid diagnostic test (RDTs), detecting *Plasmodium* antigens), AND a thin/thick blood smear are recommended.

An RDT does not exclude formally a diagnosis of malaria because of the risk of a false negative test in case of very high parasitaemia (prozone effect), low parasitaemia (below level of detection), the possibility of mutant *P. falciparum* parasites (with some antigen deletion) or the lower sensitivity in case of non-falciparum malaria. A positive RDT always needs to be completed by a thick and thin smear to allow the determination of species, diagnosis of mixed infections, the staging and quantification of parasites. If despite a negative result a high index of suspicion for malaria persists (e.g., persistent fever, exposure in sub-Saharan Africa, presence of splenomegaly, unexplained thrombocytopenia,…) a thick smear must be repeated every 12-24 hours; this is especially relevant in cases where partial chemoprophylaxis has been given. In case of three negative thick smear tests performed over a 72 hours' time- period malaria is considered to be unlikely. Nucleic acid tests (e.g., PCR) for malaria are available but only performed in reference laboratories for confirmation of the microscopic results or in case of doubts.

Clinicians should be aware that fever in a returning traveller can be caused by other infections than malaria and that co-infections can occur. So alongside diagnostic testing for malaria it remains important to perform routine baseline testing and other explorative investigations (Table 1).

Figure 1: QR code linking to world map of malaria risk (https://artsen.wanda.be/en/a-z-index/malaria-world-map).

Table 1: Laboratory investigations to perform in case of fever after a stay in the tropics (suspected malaria infection).

Baseline tests to be taken in case of a suspected malaria		
	Probable test result if malaria +	**Remarks**
Rapid malaria antigen test Thin smear Thick smear	positive	range of sensitivity % and specificity % depends on the species and the used test
C- reactive protein (CRP)	< 10	
Full blood count including Reticulocytes	anaemia thrombocytopenia reticulocytosis	anaemia can be delayed white blood cells are often normal, so consider alternative diagnosis or coinfection if abnormal
Liver function test	hyperbilirubinemia (direct) transaminitis	
Glycaemia	frequently low	
Signs of haemolysis	hyperbilirubinemia (indirect), LDH, AST : high haptoglobin : low	
Coagulation	sometimes (but certainly not always) deranged in severe malaria	
Blood gas : pH lactate	acidosis increased lactate	
Renal function Electrolytes	deranged in acute phase or severe cases	proteinuria, haematuria hyponatremia is a sign of severe malaria
Blood culture		differential diagnoses
Blood group + cross-matching		if severe anaemia (transfusion preparation)
Additional investigations to consider based on clinical features and differentials		
G6PD	expedite results if *P. vivax* / *P. ovale* is confirmed	deficiency of G6PD = contra-indication of primaquine administration
Urine: microscopy and culture		differential diagnoses
Chest X-ray	lung oedema	differential diagnoses: pneumonia
Lumbar puncture		differential diagnoses: to perform if suspicion of meningitis
Storage serum	serology and virology	differential diagnoses
ECG		long QTc
Cerebral Magnetic resonance imaging (MRI)	cerebral malaria : oedema, ischemia (rarely)	
Fundoscopy	severe malaria: malarial retinopathy (retinal whitening, vessel discoloration, retinal haemorrhages optic disc oedema)	In 25-30% of cases of cerebral malaria

Management

Criteria for severe malaria

Severe malaria occurs when the infection is complicated by severe haemolysis or end- organ failure. It is important to distinguish between uncomplicated 'non-severe' and 'severe' malaria since this will guide the management (Figure 2). The criteria for severe malaria reported in Table 2 are those of the WHO guideline for malaria except for the cut-off values for severe anaemia and parasitaemia which are adapted to the Belgian standards based on expert opinion (3).

Hospital admission versus ambulatory care

It is highly recommended to admit all children diagnosed with *P. falciparum* malaria for at least a period of 24h as the infection can rapidly evolve.

Figure 2 : Management.

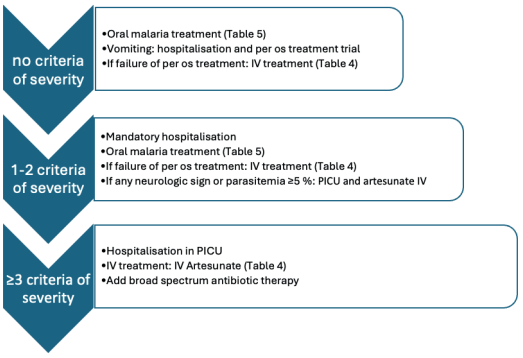


Table 2 : Overview of criteria for severe malaria.

Criteria for severe malaria	
Neurologic signs	impaired consciousness or prostration seizures
Severe anaemia	Hb < 7 g/dl
Metabolic acidosis	Ph < 7.3 or BE > 8 mEq/L or HCO3 < 15 mmol/L or lactate ≥ 5 mmol/L
Coagulation	significant bleeding (nose, gums, venipuncture site...) thrombocytopenia < 20.000/mm^3 signs of disseminated intravascular coagulopathy (DIC)
Renal failure	oligo-anuria:< 1 ml/kg/h in infants and < 0.5 ml/kg in 6 h for older children creatinine (plasma or serum) > 3 mg/dl
Hypoglycaemia	glucose < 40 mg/dl
Respiratory failure	hypoxemia SaO2 < 92 % signs of respiratory distress
Jaundice	total bilirubin > 3 mg/dl
Signs of shock	compensated or not compensated: tachycardia, altered peripheral perfusion, capillary refill > 3 sec, hypotension
Parasitaemia	> 2 % parasites in red blood cells

After discussion with a paediatric infectious diseases specialist, some children who fulfil ALL the outpatient criteria (Table 3) may be treated in an ambulatory setting after taking the first dose of treatment at the emergency unit and after supervision of minimum 4 hours. Those patients should receive at least two more treatment doses in hand before going home to complete the full 3-day treatment. They should be seen at the consultation or at the emergency service the next day to insure the tolerance of the treatment.

Table 3 : Criteria for outpatient treatment.

Criteria to be met before considering outpatient treatment
• Age ≥ 5 years
• Parasitaemia <1%
• Normal bilirubinaemia (<1.3mg/dl)
• No co-morbidity
• Possibility of close follow-up
• AND absence of any criteria of 'severe malaria'

Treatment

The choice of treatment depends on the species and the severity of the malaria. The first choice for the treatment of severe malaria is Artesunate IV. If artesunate IV is likely to be delayed/not available, IV quinine could be administered (as soon as possible) but as a second line antimalarial drug. This should be switched to IV artesunate as soon as it is available.

In case of non-severe malaria, the first choice of treatment is an artemisinin-based oral combination therapy (ACT). For an infection with *P. ovale* or *P. vivax* this should be followed by primaquine (after G6PD deficiency has been ruled out) to prevent relapse from liver hypnozoites.

In the event of vomiting, the oral medication may be re-administered within 60 minutes of ingestion or if the treatment is visible in the vomit. If persistent vomiting occurs, consider switching to IV treatment.

Tables 4 and 5 provide an overview of the treatment regimen and dosing.

Table 4 : Treatment of severe malaria.

Severe malaria	
Drug	Comment
FIRST CHOICE: **Artesunate (Malacef® IV)*:** < 20 kg: 3 mg/kg/dose IV ≥ 20 kg : 2.4 mg/kg/dose IV at t0h, t12h, t24h, then 1x/day **As soon as PO treatment possible: ALWAYS complete by a full oral ACT treatment** of 3 days	- Given by slow IV injection at a maximum rate of 3 ml/min of the 10 mg/ml solution (30 mg/min) - Administer for at least 24 h, during maximum 7 days, or until switch to oral therapy is possible. - No need for dose adaptation in case of kidney or liver failure.
SECOND CHOICE (if Artesunate not available): **Quinine hydrochloride IV** Loading dose: 20 mg/kg (max 1000 mg) slow IV over 4-6h diluted in 10 ml/kg G5% (or G10% if hypoglycaemia at the start) Then 8h after start: 10 mg/kg (max 500-600 mg) over 2-4 h in 10ml/kg G5% (max 250 ml) 3 x/d for first 48h or until switch to artesunate IV (ASAP in PICU) **As soon as PO treatment possible: ALWAYS complete by a full oral ACT treatment** of 3 days	- ECG prior administration is preferable - The infusion rate should not exceed 5 mg/kg/h. - Concentration of infusion fluid should be 2 mg/ml. - Monitor glycaemia/4h during treatment and provide continuous cardiac monitoring during administration (cave arrhythmias and hypotension). - Frequency of dosing should be reduced to 2x/day if IV quinine continues for more than 48h(maximal a total of 5-7 days). - In case of renal or liver failure: same dosing but the frequency of administration is reduced (1x/24h).
THIRD CHOICE (in case of non-availability of the 1e or 2nd choice): **any oral antimalarial treatment awaiting transfer to centre where IV treatment is possible**	- 1st choice of oral treatment: ACT - 2nd choice: Atovaquone/Proguanil (Malarone®)

*Artemisinin resistance is seen in some countries such as Cambodia, Laos, Myanmar, Thailand, Vietnam and there are signals of emerging resistance in some countries in East Africa. In travellers returning from areas with documented evidence of artemisinin resistance, contact a malaria expert to discuss treatment.

Monitoring and follow-up

Hospital admissions

There should be a very low threshold to admit patients with severe malaria to a paediatric intensive care unit. Monitoring of vital signs, Glasgow coma scales and urinary output are important. Glycaemia should be monitored at least every four hours, particularly in unconscious patients. Be careful with fluid administration and give maximum 70% of the maintenance fluid.

It is difficult to rule out sepsis in a shocked or severely ill child so a low threshold to start empirical parenteral broad-spectrum antibiotics (e.g., ceftriaxone) together with the anti-malarial treatment should be applied.

Daily monitoring of parasitaemia and laboratory parameters (full blood count) is essential for assessing treatment efficacy and identifying potential complication. The parasitaemia may increase over the first 24 hours, especially in severe malaria, and does not usually indicate treatment failure or resistance. Continue monitoring until asexual blood stage parasites are no longer seen on the blood film. Gametocytes (sexual stages) may persist or appear during or after treatment and does not indicate treatment failure. The rapid diagnostic test and Polymerase Chain Reaction (PCR) for malaria can remain positive during treatment. In case the parasites are not cleared at Day 3 after the start of the treatment (corresponding to Day 0), the possibility of (partial) resistance to artemisinin should be considered and expert advice must be sought since no clear recommendations exists in those specific cases.

Clinicians should be aware of the risk of delayed haemolysis with IV artesunate treatment, usually between day 7 and 21 and especially seen in cases of initial hyperparasitaemia. Note that this risk also exists (but much less frequently) after oral ACT (see below). Inform the patient about warning signs for haemolysis before discharge and organise a full blood count and blood film 14 to 28 days for all severe cases who had to be treated with IV artesunate. After discharge all patients with severe malaria should therefore receive a follow-up consultation (day 7 to day 14) and the patient should be informed to seek urgent medical advice in case of recrudescence of fever up until 28 days after initiation of treatment in view of potential therapy failure. During this consultation chemoprophylaxis measures for any next travel to a tropical area should be discussed with the patient.

Ambulatory care

A close follow-up is warranted and a clinical review (or at least a telephone contact) around day 2-3 is advised to ensure treatment adherence, subsidence of fever and clinical improvement. Preferably at day 3 or 4 and or the latest at day 7 a full blood count and blood film should be performed. At day 7 a follow-up consultation should be done and the patient should be informed to seek urgent medical advice in case of recrudescence of fever up until 28 days after initiation of treatment in view of potential therapy failure. During this consultation chemoprophylaxis measurements for any next travel to tropical area should be discussed with the patient.

Therapy failure

If *P. falciparum* parasitaemia persist (>3 days) or in case of evolution towards severe malaria or an increase in parasitaemia on day 2 or 3 despite adequate treatment, one should consider an early treatment failure, which could be due to partial resistance to artemisinin. Recurrence of fever and parasitaemia from 1 to 4 (6) weeks after initial treatment (with no new exposure) corresponds to late treatment failure, which could reflect resistance to any of both drug component, but also (and more likely) bad compliance or insufficient dosing or absorption of treatment (vomiting, unusual pharmacokinetics of a patient, drug interaction). Therapy failure seems on the increase in Belgium in the past few years (5).

In both scenarios (persistence or recurrence of parasitaemia), expert opinion (at least of the paediatric infectious diseases specialist) should be sought and preferably the Institute of Tropical Medicine in Antwerp (Prof. dr. Emmanuel Bottieau or the infectious disease specialist on call) should be contacted to discuss the appropriate treatment and the performance of genomic analysis of the parasite to better understand the underlying reasons for treatment failure and to properly guide management decisions.

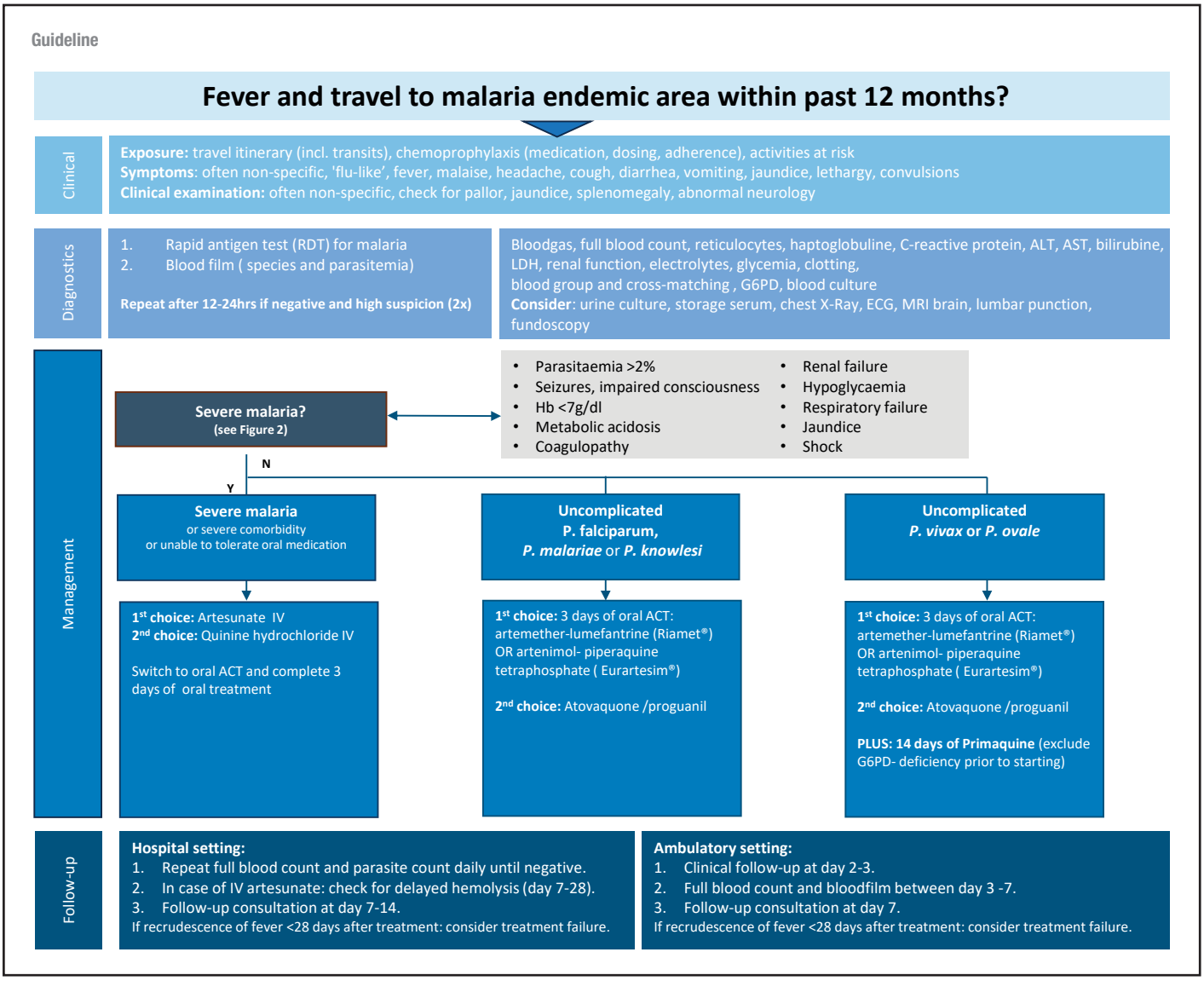
Table 5 : Treatment of uncomplicated malaria.

Uncomplicated malaria

P. falciparum, P. malariae or *P. knowlesi* malaria

Drug	Comment
FIRST CHOICE: **ACT (artemisinin-based combination therapy).** 2 options are available in Belgium: **Riamet®:** 6 doses in 3 days (t0h, t8h than t24h, t36h, t48h et t60h)	- An ECG is advised prior to administration only in patients at risk of QTc prolongation (co-medication, vomiting with subsequent hypokalaemia,...) † - If vomiting, the use of alizapride is permitted. **Riamet®: tablet of artemether 20 mg / lumefantrine 120 mg** Absorption is enhanced by fat; therefore recommended to use with milk/food. Can be crushed and mixed with food or milk.
< 5 kg (¥) — Dissolve 1 tablet 20/120 mg in 5 ml water and give 1 ml/kg body weight by mouth followed by normal feed.(WHO) 5 < 15 kg — 1 tablet 20/120 mg 15 < 25 kg — 2 tablets 20/120 mg 25 < 35 kg — 3 tablets 20/120 mg ≥ 35 KG — 4 tablets 20/120 mg	
Eurartesim®: 1x/day for 3 days	**Eurartesim®: tablet of artenimol 40mg / piperaquine tetraphosphate 320 mg** Mix tablets only with water and administer immediate after preparation. To take preferably on an empty stomach. Tablets can be cut in 2 and crushed.
< 5 kg (¥) — 2.5 mg/kg artenimol and 20 mg/kg piperaquine tetraphosphate/dose 5 < 8 kg — ½ tablet 40/320 mg 8 < 11 kg — ¾ tablet 40/320 mg 11 < 17 kg — 1 tablet 40/320 mg 17 < 25 kg — 1½ tablets 40/320 mg 25 < 36 kg — 2 tablets 40/320 mg 36 < 60 kg — 3 tablets 40/320 mg 60 < 80 kg — 4 tablet 40/320 mg ≥ 80 KG — 5 tablets 40/320 mg	
SECOND CHOICE If ACT treatment is not available or contra-indicated (e.g., long-QT)	
Malarone®: 1x/day for 3 days	**Malarone®: adult tablet atovaquone 250mg/proguanil 100mg, paediatric tablet atovaquone 62,5mg/proguanil 25mg** This treatment can only be taken if it was not used as chemoprophylaxis. Tablets can be crushed and mixed with food or milk. To be taken daily at the same hour.
5 < 9 kg — 2 tablets ped (62.5/25) 9 < 11 kg — 3 tablets ped (62.5/25) 11 < 21 kg — 1 tablets 250/100 21 < 31 kg — 2 tablets 250/100 31 < 40 kg — 3 tablets 250/100 ≥ 40 KG — 4 tablets 250/100	
ALTERNATIVE TREATMENT: **Oral Quinine** Quinine 10 mg/kg (quinine sulphate) 3x/day po for 4-5 days (max 500 mg)	Magisterial preparation Combined with - **Clindamycin** 20 mg/kg/d divided in 3x/d po for 7 days (max 600 mg/dose) **OR** - If older than 8 years: **Doxycycline** **<45 kg:** doxy 2.2mg/kg 2x/d po for 7 days (max 100 mg/dose) **>45 kg:** doxy 100 mg/d 2x/d po for 7 days
P. vivax or P. ovale malaria	
Same initial treatment as for *P. falciparum, P. malariae or P. knowlesi* malaria (see above).	
FOLLOWED BY PRIMAQUINE **after determination of G6PD activity** 0.5 mg/kg (max 30 mg/dose) 1x/day for 14 days For a total of 7 mg/kg/cure(magisterial preparation) If mild-moderate G6PD deficiency (10-50%): Primaquine 0.75 mg/kg 1x/week for 8 weeks. If severe G6PD deficiency (<10%): contra-indication of Primaquine.	To clear the residual hypnozoites. Primaquine can cause gastrointestinal upset and should be given after food. If not well tolerated, reduce daily dose and increase the duration (to obtain the same total dose).

Caution: ¥ Children < 5 kg: prefer IV treatment over oral treatment (crushed tablets).
†If QTc >500msec, both ACT are contra-indicated (see alternative regimens). If QTc 450-500msec, consider drug administration under cardiac monitoring.
Possible interactions with other QT-prolonging drugs or anti-arrhythmic drugs are e.g. fluoroquinolones, macrolides, rifadine, depression treatment, triazoles, cisapride, anti-epileptic drugs (carbamazepine et phenytoin) or drugs that alter the concentration of piperaquine (antiretroviral treatment, domperidone...).



Conclusion

The Belgian Paediatric Malaria Treatment Protocol 2024 provides a comprehensive framework for the diagnosis, treatment, and monitoring of malaria in children. This guideline is summarised in the flowchart. Early recognition, appropriate treatment, and careful monitoring are key to improving outcomes in paediatric malaria cases.

Conflict of interest

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

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Awaiting the First Locally-Acquired Human West Nile Virus Infection in Belgium

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Keywords

West Nile virus ; Humans ; Child ; Belgium.

Abstract

West Nile virus is an arthropod-borne *Flavivirus* transmitted by *Culex* mosquitoes. Birds are the primary hosts. However, the virus can be transmitted to humans through mosquito bites. Human infection is mostly asymptomatic, but 1 in 5 may develop illness: West Nile fever or severe West Nile neuroinvasive disease. Although the virus and disease are spreading in Europe, no locally acquired infections have been reported in Belgium. However, there is a real risk that West Nile virus infections will occur in Belgium in the near future. Because children can become infected and ill, pediatricians must be aware of the disease. In this manuscript, we describe the symptoms and epidemiology of West Nile virus disease.

Introduction

The West Nile virus (WNV) is a single-stranded RNA virus of the family *Flaviviridae*, genus *Flavivirus*. It is an arthropod-borne virus ("arbovirus") transmitted by mosquitoes, mainly of the genus *Culex*. Birds, both migratory and non-migratory, are the primary hosts of WNV. The virus is maintained in nature in an enzootic bird-mosquito-bird transmission cycle. The virus can be transmitted to mammalian species through mosquito bites. In particular, humans and horses can develop disease. However, they are considered dead-end hosts because they do not contribute to the transmission cycle (Figure 1) (1).

Human WNV infection was first detected in a woman in the West Nile district of Uganda in 1937 (2). WNV is the most widely distributed arbovirus in the world (3). It is widespread in Africa, the Middle East and western Asia. Serological surveys have demonstrated WNV circulation in Europe since the 1950s. Human disease affects southern, eastern and western Europe, and human cases have increased in recent decades (4, 5). The virus emerged in the Americas in 1999. After its initial detection in New York, the virus spread dramatically and rapidly across the continent. Today, WNV is the leading mosquito-borne viral infection and the most common cause of viral encephalitis in the United States (6). This rapid spread and the potential for serious health problems are reasons for careful vigilance.

Human WNV infection

Human infection can result in 3 scenarios: asymptomatic infection, febrile illness (West Nile fever (WNF)), or severe disease affecting the central nervous system (West Nile neuroinvasive disease (WNND)). Asymptomatic infection occurs in approximately 80% of infected individuals, WNF in approximately 20%, and WNND in ≤ 1% (1, 7). In terms of incidence, pediatric cases account for 4% of all WNND cases, while 96% of WNND occurs in adults (8, 9).

After an incubation period of 2 to 15 days (up to 21 days in immunocompromised individuals), WNF in children presents as a relatively mild illness with fever (sometimes high), headache, muscle weakness, muscle and joint aches, and fatigue (10). In 50-80% of cases, a maculopapular rash develops on the chest, back, and arms. Other possible symptoms include vomiting and diarrhea, eye pain, and lymphadenopathy. Acute symptoms last 3 to 10 days, but full recovery, especially from fatigue, may take up to 60 days (11, 12).

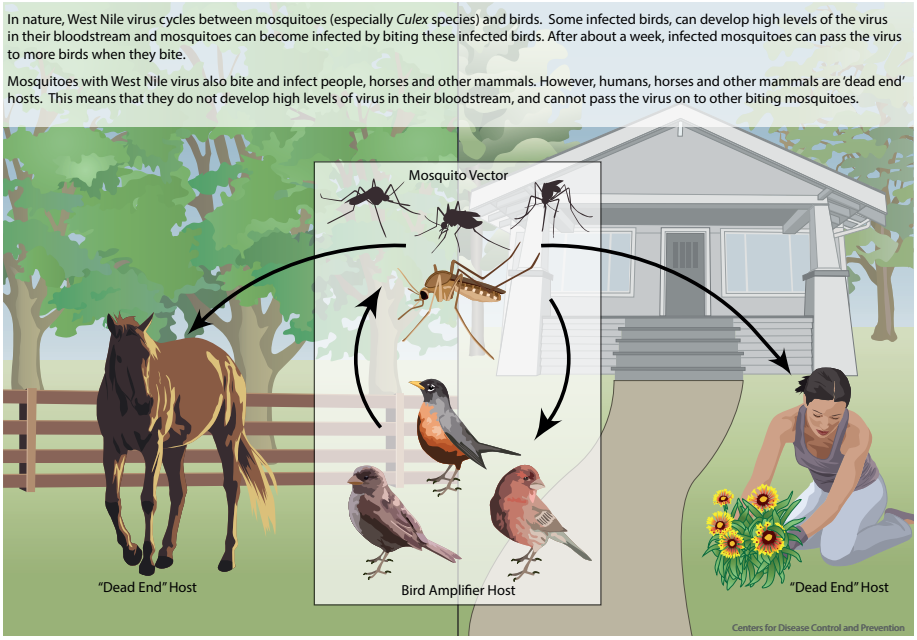
The 3 most common presentations of WNND in children are meningitis, encephalitis, and acute flaccid paralysis (AFP). In contrast to adults, meningitis is a more likely presentation in children than encephalitis. Meningitis is characterized by nuchal rigidity, headache, and other classic meningitis symptoms. Besides headache, encephalitis can present with altered consciousness, lethargy, personality changes, focal neural deficits, seizures, and other movement disorders. AFP has been reported in 1% of children with WNND and may occur with or without encephalitis. As in poliomyelitis, WNV-associated AFP is caused by invasion of the anterior horn cells, resulting in progressive asymmetric flaccid paralysis without sensory abnormalities, sometimes requiring mechanical ventilation (9, 11, 12). Brain magnetic resonance imaging often appears normal, but signal abnormalities may be observed in the basal ganglia, thalamus, and brainstem in cases of WNV encephalitis, and in the spinal cord in cases of WNV acute flaccid paralysis (10). Recovery from WNND takes weeks to months and may result in long-term sequelae, mainly fatigue and apathy, in 50% of cases. Although children with WNND have a better prognosis than older, they remain at risk for serious neurological sequelae or death, with a mortality rate of 1% compared to 14% in adults (13). WNV infections can also trigger Guillain-Barré syndrome (10). Finally, WNV infections can rarely cause cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, chorioretinitis, pancreatitis, hepatitis, and orchitis.

Transmission of the virus is primarily through a mosquito bite and occurs when mosquitoes are most active, which is from June to November in Europe (14). Therefore, WNV is primarily a seasonal disease.

Transmission by blood transfusion or organ donation has been described, but can be prevented by screening blood and organ donors in areas of WNV activity.

In 2002, a case of intrauterine transmission was first described in a child born to a mother infected with WNV at 27 weeks' gestation who developed neuroinvasive disease. The infant had severe central

Figure 1: West Nile virus transmission cycle (CDC).



nervous system abnormalities and chorioretinitis at birth, with positive markers for WNV infection in blood and cerebrospinal fluid (both anti-WNV IgM positive) and in placental and umbilical cord tissue (both WNV PCR positive) (15). Subsequently, several studies were conducted on the occurrence of intrauterine transmission (16-19). In a total of 120 pregnant women with WNV infection, there were 3 newborns with possible congenital infection: 1 infant with WNV meningitis at 10 days of age, 1 infant born with rash (and bicuspid aortic valve and aortic coarctation), and 1 infant with fatal WNV encephalitis. The problem is that congenital intrauterine infection could not be diagnosed with certainty due to the lack of umbilical cord blood and serum from the newborns. Intrauterine transmission is possible, but apparently very rare.

A first case of transmission through breastfeeding was also described in 2002. A breastfeeding mother had contracted WNV infection from a postpartum transfusion and developed WNND. WNV RNA and specific IgM antibodies were detected in the breast milk. The infant remained healthy, but at 25 days of age, serum specific IgM antibodies turned positive (20). Hinckley et al. reported on 6 infants breastfed by mothers with WNV infection. 5 of the 6 infants developed no clinical or biological signs of infection. 1 infant developed a rash 11 days after the onset of maternal infection, but was not tested (21). Analysis of a total of 46 breast milk samples from mothers with WNV infection revealed specific IgM antibodies in 15/46 (33%) (18, 21). In conclusion, mother-to-child transmission through breastfeeding is possible, but remains rare. The Centers for Disease Control and Prevention (CDC) recommends continued breastfeeding during maternal WNV infection because the risk of WNV transmission does not outweigh the benefits of breastfeeding (22).

Laboratory diagnosis is accomplished by the detection of anti-WNV IgM (and IgG) antibodies in the blood or cerebrospinal fluid (CSF) or by the detection of viral RNA by PCR in the blood or CSF (1, 7, 11). CSF pleocytosis is generally lymphocytic, but can be neutrophilic in the beginning (10).

Anti-WNV IgM antibodies typically become detectable 3 to 9 days after the onset of symptoms and can persist for 30 to 90 days, sometimes up to a year. Therefore, a positive IgM test result may not always indicate acute infection. Anti-WNV IgG can be detected as early as 8 days following illness onset (it generally appears shortly after IgM) and persists for years (10). Diagnosis based on IgG requires collection of an acute and convalescent sample (2 to 3 weeks apart) to demonstrate seroconversion or at least a 4-fold increase in titer. Diagnosis based on antibodies is complicated by significant cross-reactivity with antibodies to other viruses of the genus *Flavivirus*, e.g. after infection with tick-borne encephalitis virus or dengue virus, but also after vaccination against yellow fever or Japanese encephalitis. Positive results should be confirmed by a virus neutralization assay. IgM detection in CSF indicates central nervous system infection and is typically detectable 1 to 8 days after the onset of neurologic illness.

Diagnosis can also be confirmed by detection of viral RNA by PCR in blood or CSF. However, as in most arboviruses, viremia is low, and the viremic period is short, making the probability of detecting WNV infection by molecular testing relatively low. Viral RNA can be detected in blood from 2 to 18 days post-infection and up to 5 days post onset of symptoms. The sensitivity in a whole blood sample is 86.8%, and it is lower in CSF. WNV is excreted in the urine during acute infection and remains detectable for a longer period than in the blood. Therefore, urine may be a useful non-invasive specimen to detect WNV. According to the European Centre for Disease Control and Prevention (ECDC), whole blood is the preferred sample for testing.

To date, there is no specific treatment for WNV disease (7). Treatment is supportive. Treatment with intravenous immunoglobulin (IVIG) in 2 cases of AFP has been described, but it is unclear whether it has any effect (11). Research into specific IVIG with high anti-WNV titers, monoclonal antibodies, antivirals, and the potential benefits of corticosteroids in aiding recovery is still in its early stages (23).

Unlike in horses, there is no vaccine available for humans. However, a number of human vaccine candidates is in preclinical development (24, 25).

After recovery, immunity to WNV is thought to be lifelong (12).

Epidemiology of human WNV disease in European countries

Geographic distribution

The ECDC has reported a total of 825 human cases of West Nile Virus (WNV) infection across the European Union (EU), European Economic Area (EEA), and European Enlargement countries in 2023 (14). This is the third highest number of cases after the peak years of 2018 (1549 cases) and 2022 (1116 cases). The geographic distribution is shown in Figure 2. There were 65 deaths (0.8%).

804 cases were due to locally acquired infection. 21 cases were travel-related (13 of which were in another European country). Most cases occurred between July and September.

Figure 2: Number of cases in 2023 by country.

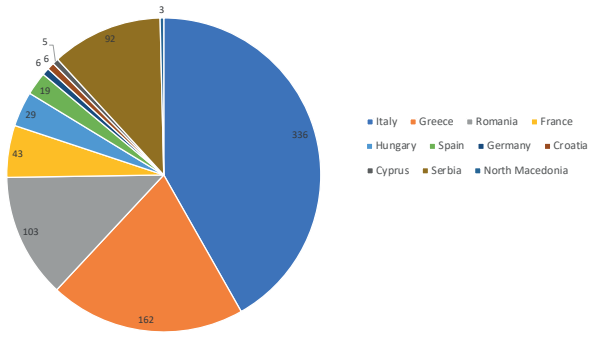
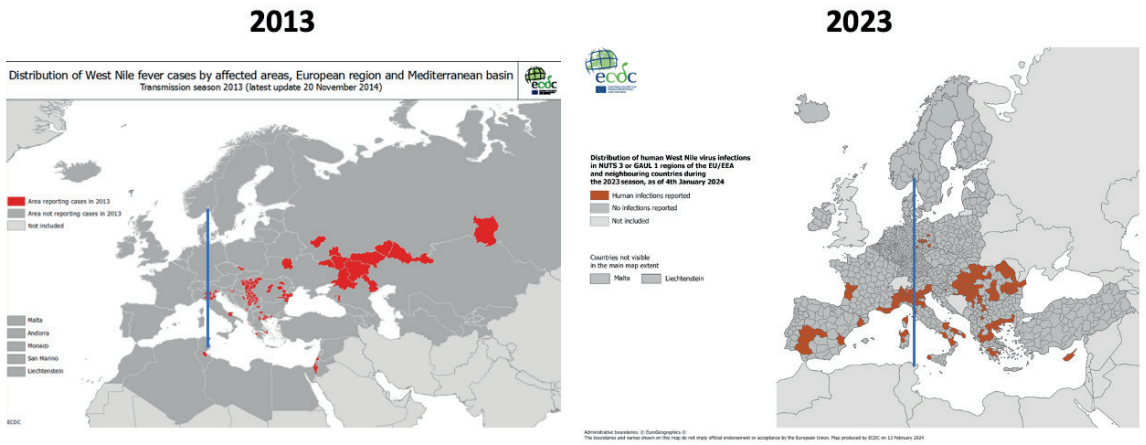


Figure 3: Distribution of WNV cases by affected areas, comparison 2013-2023.



Importantly, although there were fewer cases than in 2022, the number of affected regions increased by 31%, indicating a geographic expansion of the virus. This expansion is illustrated in Figure 3, a comparison between the years 2013 and 2023, in which a westward expansion can be observed.

In 2023, there were no cases of WNV reported in Belgium. However, between 2012 and 2022, 7 cases were recorded, all of which were travel-associated (26).

Dynamics of infection

The co-occurrence of WNV, mosquito vectors, primary avian hosts, and susceptible humans is necessary for the emergence and spread of an epidemic. In addition, there is the influence of climate and environment. All these elements influence the dynamics of infection.

In Europe, human WNV infections are mainly caused by WNV lineages 1a and 2. Historically, lineage 1a has been the most important. However, in 2004, lineage 2 emerged in Hungary and became responsible for most outbreaks between 2010 and 2020 (27). This lineage originated from South Africa and was probably introduced into Hungary by migratory birds between 1996 and 2004 (27, 28). The spread of WNV lineage 2 eventually resulted in a major outbreak in Europe in 2018, marking the highest number of human cases ever recorded in the EU/EEA. Similar to other viruses, WNV lineages undergo mutations in the genome. This genetic plasticity poses a constant risk of the emergence of genotypes with increased virulence (29). Shifts in lineage and/or virulence have been associated with regional spread of the virus. Shifts may occur locally or, more importantly, as a result of the reintroduction of variant virus clades by migratory birds. Such reintroductions are common in Europe. Genomic analyses have identified at least 13 reintroductions with multi-year persistence (27). This is illustrated by the emergence of a new, more pathogenic WNV 1a variant in northern Italy in 2021 (30).

Mosquitoes of the genus *Culex* (*Cx*) are a major vector of WNV (31). Mosquitoes become infected with WNV when they suck blood from a sick bird. After development, the virus ends up in their salivary glands and is transmitted during the next blood meal. The virus does not harm the mosquitoes, which can carry the virus for life (32). In addition, vertical transmission from infected female mosquitoes to their offspring has been described, which contributes to the survival of WNV (33, 34). In Belgium *Cx pipiens* and *Cx torrentium* are the most prevalent *Cx* species (35, 36). There are 2 biotypes of *Cx pipiens*: *Cx pipiens pipiens* and *Cx pipiens molestus*, as well as hybrid forms that combine characteristics of both biotypes. *Cx pipiens pipiens* is an ornithophilic mosquito that mainly bites birds and occasionally humans. It plays an important role in the enzootic mosquito-bird-mosquito cycle. *Cx pipiens molestus* and the hybrid forms are more anthropophilic and act as bridging vectors to humans and other mammals. *Cx torrentium* is also an ornithophilic species but also considered a bridging vector (37). Another *Culex* species, *Cx modestus*, is increasingly found in Europe, including Belgium. This species is anthropophilic and may be more competent at transmitting WNV to humans than *Cx pipiens* (38, 39).

Birds are natural hosts and reservoirs for WNV. The mosquito-bird-mosquito cycle maintains the circulation of the virus. Migratory birds are considered important introducers of WNV into new regions (5, 40). Outbreaks of WNV infection often occur in late summer and early fall, coinciding with the arrival of large numbers of migratory birds. Infection of migratory birds has been documented by virus isolation and antibody detection. Domestic birds can also become infected.

Disease in birds is characterized by loss of coordination, head tilt, tremors, weakness, and apparent loss of vision (32). The susceptibility of birds varies, with corvids (crows, jays, ravens, magpies) being most likely to die from the disease. Birds of prey (owls, falcons, hawks, etc.) are also particularly susceptible, potentially because they prey on infected animals (41).

Both humans and horses typically do not reach a level or duration of viremia adequate to transmit the virus to mosquitoes, making them dead-end hosts for WNV. As in humans, infection in horses is usually asymptomatic. 10% of infected horses show neurological signs of disease; mortality in horses with clinical signs is approximately 33% (7, 32). Presumptive diagnosis is made on the basis of specific IgM antibodies. Vaccination against WNV is available for horses.

Surveillance of mosquitoes, sick birds and horses by public health officials is essential for the detection of WNV.

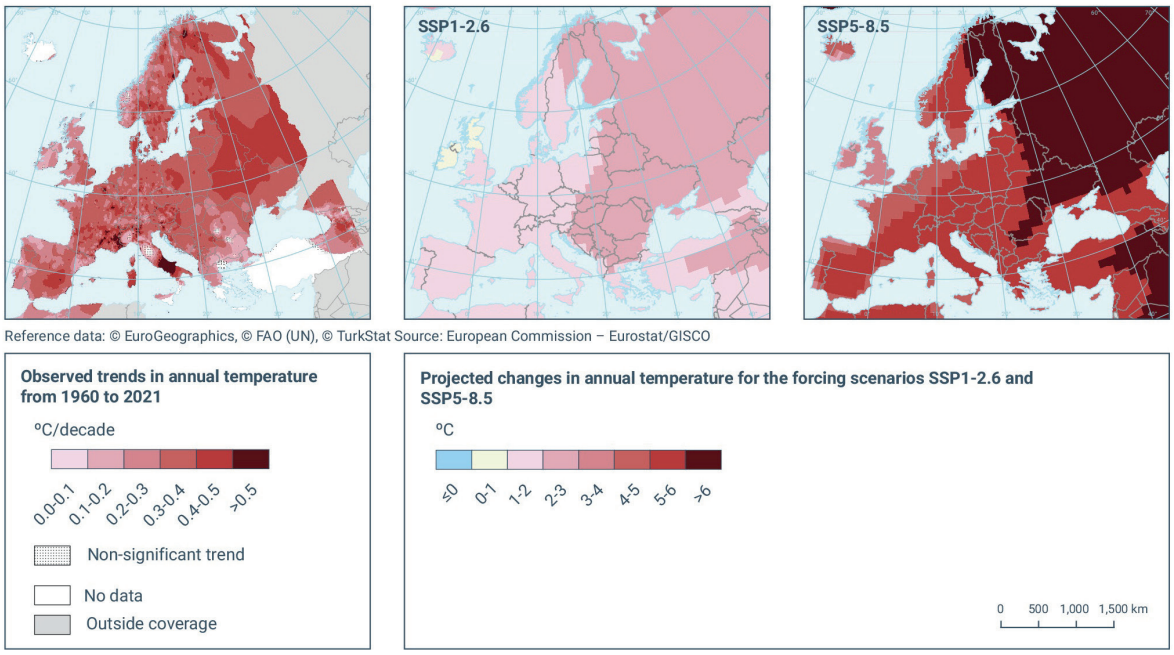
To initiate and sustain a human epidemic, there must be regular interactions between infected mosquitoes and humans. These interactions are significantly shaped by environmental factors such as temperature, rainfall, wetlands, vegetation, proximity to migratory bird routes, periurban environment, and human and mammalian density. While understanding the complexities of these relationships on a global scale can be challenging, ongoing research is revealing some clear connections (5, 42). There is a positive correlation between higher mean temperature and mosquito abundance and activity, increased circulation of WNV and transmission risk in birds and occurrence of WNV infection in humans and mammals. The temperature during the warmest quarter of the previous year appears to be the main driver of WNV outbreaks in Europe (43). Above-average spring temperatures may also be a precursor to an outbreak in the second half of the year. Warmer temperatures also influence human behavior by increasing outdoor activities and the risk of exposure to mosquitoes. *Cx.* vectors are present in both rural and urban environments, where human population density may also play a role in the risk of infection.

The presence of wetlands is positively associated with the abundance of mosquitoes and birds and the transmission of WNV to humans and mammals. Proximity to migratory bird flyways is also important.

Climate change could profoundly influence environmental factors.

Europe is getting warmer (Figure 4). Heat waves are becoming more frequent and severe, and summers are getting longer and warmer. This

Figure 4: European Environment Agency, Projected temperature changes under the best and worst greenhouse gas emission scenarios.



is anticipated to lead to the expansion of viral vectors and hosts, thereby facilitating the virus's spread to new areas, particularly in western and central Europe. It has been calculated that, depending on the CO_2 release scenario, the risk of WNV infection could increase by a factor of 2.5 to 5 (3, 44, 45). There is also an overall trend toward less precipitation in southern and western Europe. Drought conditions with stagnant pools of water increase the interaction between vectors and hosts, increasing the likelihood of virus transmission and disease. But there is also an increased risk of exceptional rainfall and flooding, which can bring more standing water for mosquito breeding.

Migratory birds play an important role in introducing the virus to new areas (40, 45). They bring the virus to Europe from southern stopovers in Africa or the Middle East. The spread of WNV to more northern parts of Europe carries the risk of the virus spreading not only from the south in the spring, but also from the north during fall migration. Climate change may also lead to changes in migratory patterns, which may also contribute to the spread of WNV to new regions (46).

What about Belgium?

Epidemiologic surveillance of WNV in Belgium is carried out by the National Reference Centre for Arboviruses at the Institute of Tropical Medicine in Antwerp. Between 2012 and 2022, 7 travel-associated human infections were identified. The travelers were all adults and came from Djibouti (2), Greece, the Democratic Republic of Congo, South Sudan, Serbia, and Kosovo. No autochthonous human infections and no infections in birds or horses were identified (26).

However, there is a clear risk of WNV infection in Belgium. The vectors *Cx. pipiens pipiens*, *Cx. pipiens molestus*, their hybrids and *Cx. torrentium* are widespread and the presence of *Cx. modestus* has been demonstrated (38, 47). There is a wide variety of native bird species, and Belgium is located on the East Atlantic Flyway for migratory birds. Numerous habitats foster mosquito-bird interactions, such as nature reserves, wetlands, vegetated areas near ponds or lakes, and human-made small bodies of stagnant fresh water in periurban regions, like buckets, bottles, gutters, and water storage tanks. Belgium has a high human population density, along with having the highest number of horses per capita among EU countries (48). Additionally, West Nile Virus transmission is ongoing in neighboring countries such as France, Germany, and the Netherlands. Considering the impact of climate change, it is highly likely that the virus will emerge in Belgium in the near future. Therefore, it is worrisome that active surveillance of birds and horses was halted in 2017 (26).

Although WNV is notifiable throughout Belgium, only cases acquired in Europe need to be reported.

Conclusion

There is a genuine risk of West Nile Virus (WNV) infections in Belgium in the near future. It is crucial for pediatricians to give serious consideration to WNV when assessing children with unexplained fever, rash, meningitis, and/or encephalitis, as well as acute flaccid paralysis during the mosquito season.

Conflict of interest disclosure

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

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Travelling with Children: an Update

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Abstract

A 'healthy' journey starts with a good preparation, especially when travelling with children. It is important that travelling parents inform themselves timely in order to have sufficient time to arrange everything before departure. In general, it is recommended to schedule a travel consultation at least six to eight weeks before departure, but for some vaccinations more time may be necessary. Travel medicine is an increasingly complex medical specialization. Therefore it might be recommended to consult a travel clinic, general practitioner with specific knowledge in travel medicine or paediatrician specialized in infectious diseases / travel medicine prior to travel, especially when going to the tropics or for more adventurous prolonged journeys. This article offers an updated overview of the current pre-travel recommendations for children, aiming to facilitate safe and healthy travel.

The role of the GP or general paediatrician

Many parents first turn to their pharmacist, general practitioner (GP) or general paediatrician for travel advice. Or they might casually mention that they are going to visit their friends or family in Africa, Asia or Latin America, often only when actively asked. Being able to provide correct information about this is essential. Not all travellers recognize the importance of medical preparation for their journeys, positioning GPs, pharmacists and paediatricians as vital in raising awareness among travelling parents. For example, during a consultation you can proactively ask about future travel plans, especially when people have their roots in the Global South. Most routine vaccinations are available at the pharmacy and can be given by any doctor. Only yellow fever vaccination must be given in an accredited yellow fever travel clinic. However, especially for tropical journeys, prolonged trips, adventurous travel or rural areas it might be advised to obtain specialized advice and refer to a travel clinic or a paediatrician with a background in travel medicine.

Belgian Travel Medicine Guidelines

The Belgian travel medicine guidelines are based on information from the World Health Organization (WHO), advice from the Superior Health Council (SHC), and guidelines written by the Belgian Study Group for Travel Medicine. To make these guidelines free of charge available for travellers and physicians, the Institute for Tropical Medicine in Antwerp has created 'Wanda', with financial aid of the Flemish Department of Health (1). This is a reference tool for travel medicine and consists of a website (www.wanda.be) and a mobile application, available for Android and iOS (Figure 1). It contains information about mandatory and recommended vaccinations per country, health risks, travel advice for specific target groups (e.g., children and pregnant women) and general topics such as the 'travel pharmacy'. There is also a separate section on the website for doctors who provide travel advice, with extensive disease sheets and detailed information in English (1).

Figure 1.
Scan the QR code to go directly to wanda.be

The travel consultation

To make a correct assessment of the traveller's risk profile, a number of factors must be taken into account: first of all, of course, the destination(s) and stopovers, then also the duration of stay and the activities that are planned (for example contact with animals, staying with locals or in remote areas), season, underlying health problems, vaccinations already received and future travel plans.

Specific advice when travelling with children

In general, children are exposed to the same health risks as adults, but the consequences can be more serious. Traveller's diarrhoea, dengue and tuberculosis are often more severe. If not treated in time malaria can rapidly be fatal in young children. In addition, some vaccines work less well or should not be administered below a certain age. Children are more sensitive to the sun, to motion sickness and to pressure changes during take-off and descent in an airplane, resulting in earaches (1).

Term infants are allowed to fly from seven days of age (1). If a child has frequent episodes of otitis or a recent ear infection, it can be considered to administer oxymetazoline nasal drops right before take-off or descent. Pressure in the middle ear can be equalized by swallowing or chewing, so allow the child to drink, suck or chew during ascent and descent (bottle, breast or pacifier).

A few points of interest:

- **Frequent breastfeeding and/or drinking** is even more important for children than for adults. This is related to the fact that the child's body consists of a larger percentage of water than adults and is more prone to dehydration.
- **Keep the threshold for medical advice low**. In case of fever or general malaise, the threshold should be lower to contact a physician, because of the possible rapid progression of diseases like malaria or dehydration in young children. This is particularly important considering the challenges of accessing timely medical assistance in unfamiliar settings.
- **Sun protection**: advise parents that babies should be kept in the shade and dressed in clothing that covers the entire body. Regularly

Table 1. Use of mosquito repellents in children.

	Minimal age	Concentration	Total duration of treatment (months)
DEET *N,N-diethyl-m-toluamide*	>6 months	20%: children and pregnant women 30-50% adults	Duration of protection varies with concentration: higher concentrations protect longer. Neurotoxicity reported in supratherapeutic dosages.
IR3535 *Ethyl butyl acetyl aminopropionate*	>6 months	20%: children and pregnant women 30%: adults	
(P)Icaridine	>2 years	20-25%	
Citrodiol *p-menthane 3.8 diol or PMD*	>6months	20-25%	

Table 2. Atovaquone-proguanil prophylactic dosage.

Weight of child in kg	Number of tablets per day
<5	Not recommended
5 - 7	½ junior tablet
8 - 10	¾ junior tablet
11 - 20	1 junior tablet or ¼ adult tablet
21 - 30	2 junior tablets or ½ adult tablet
31 - 40	3 junior tablets or ¾ adult tablet
From 40	1 adult tablet

apply a sunscreen with a high sun protection factor (SPF 50+). DEET-containing insect repellents reduce the effectiveness of sunscreen, so apply sunscreen more frequently when you use DEET (2). For babies the carriage can be covered to create shade, but it should not be completely enclosed in order to prevent overheating.

- **Keep the child far away from animals**: do not let them stroke, feed or touch them even if the animal looks cute and healthy or if the animal is dead. Children can be scratched while playing and therefore become infected (e.g. with rabies) without somebody knowing this. Discuss rabies pre-exposure vaccination when staying in a country where rabies occurs. Do not let a child play barefoot outside, not even on the beach or in the sea (1).
- **Altitude disease**. Children are not more susceptible to altitude sickness, but it is more difficult to recognize. Irritability, restlessness, muscle tension, loss of appetite, less playing, sleep disorders or vomiting can indicate altitude sickness. Therefore, descend immediately with young children who are unwell above an altitude of 2500 meters. It is better not to spend the night above 2000 meters with children under the age of two and above 3000 meters with children under the age of ten. If a rapid climb is unavoidable, acetazolamide (2.5 mg/kg every 12 hours, maximum 125 mg per dose) can be used although experience is limited in children.
- **Diarrhoea while travelling: prevention and treatment**. Foodborne infections occur worldwide, but the risk is higher in countries in Asia, the Middle East, Africa and Latin America with lower hygiene standards. Although travellers are often advised to 'boil it, cook it, peel it, or forget it' this has never been proven to be effective. Poor hygiene practices in local restaurants and deficiencies in hygiene and sanitation infrastructure are likely the largest contributors. In tropical countries it is generally recommended to avoid (semi-)raw food like salads, uncooked/unbaked food, fruits that you have not peeled yourself or washed thoroughly in clean water, uncooked or unpasteurized milk products, dishes based on raw eggs, raw or undercooked fish and seafood, dishes that have been left at room temperature for hours, ice cream from street vendors, tap water and ice cubes, street stalls (unless the food has been thoroughly cooked and is eaten immediately on the spot). Traveller's diarrhoea is the most common travel-related infectious disease and is usually caused by eating or drinking food or water contaminated with bacteria (e.g. *Escherichia coli* (ETEC), *Campylobacter jejuni*, *Shigella* spp., *Salmonella* spp.) Children who take acid suppression or recently received antibiotics are even more prone to it.

Sometimes traveller's diarrhoea is caused by a virus or parasites such as giardia or amoebae. Oral Rehydration Solution is the most important treatment, especially in children who are prone to dehydration, and should be in the traveller's pharmacy. In case of severe diarrhoea (blood or mucus in the stools, high fever, severe abdominal cramps, liquid stools more than six times per 24 hours), medical attention is required. *Preventive antibiotics (such as azithromycin) should not be prescribed routinely to travellers, but can be considered for patients* who are immunocompromised or have an underlying condition making them more prone to complications (e.g. Crohn's disease, insulin dependent diabetes mellitus, severe heart failure, small therapeutic window of medication,…) (1).

Malaria prophylaxis

Children with malaria can rapidly develop high levels of parasitaemia and are at increased risk for severe complications. When travelling to malaria endemic areas mosquito preventive measurements are important and in certain high risk areas additional malaria chemoprophylaxis is advised. The recommendation for malaria preventive measures per country can be found on 'wanda.be'. Malaria chemoprophylaxis is available for children from 5 kg onwards.

Always protect a child against mosquito bites and let them sleep under an impregnated mosquito net. Long sleeves are recommended (esp. in the evening for the malaria-vector *Anopheles*, but also during the day against *Aedes* mosquitos in dengue, chikungunya and yellow fever areas).

Data on the use and safety of mosquito repellents in travelling children are sparse and there are often contradictory international

recommendations. Therefore, it's advised for young children and pregnant women to use repellents *only if the other mosquito repellent measures cannot be applied* sufficiently and to *wash it off when it is no longer needed*. Never apply it on the hands, near eyes or the mouth of young children. The label instructions for product application and re-application should be followed but bear in mind that the duration of protection is often shorter than the manufacturer suggests on the bottle. The mosquito repellents that can be used on children are listed in table 1.

Prophylactic Malaria medication:

Atovaquone-proguanil, doxycycline and mefloquine are used as malaria chemoprophylaxis. In practice atovaquone-proguanil is most often prescribed for children. For optimal absorption atovaquone-proguanil should be taken with a fatty meal. Unfortunately no syrup is available, but the tablets can be cut using a pill cutter. It is advisable to bring a pill cutter when travelling and cut the tablets as needed, rather than pre-cutting all doses at home. Preferably the tablets should be swallowed but if this is not possible, they can be crushed, however this will result in a bitter taste which makes adherences more challenging. Junior tablets are almost as expensive as adult tablets, so adult tablets are preferably used. A full junior pill tastes less bitter compared to a partial adult dose so this might still be considered in case of difficult adherence if there are no financial constraints. Alternatives are doxycycline, but this can only be used from the age of 8 years onwards (and can cause significant phototoxicity): it should be taken from one day before entering a malaria risk area until 28days after leaving. Mefloquine can be used from 5 kg, it is only taken once a week and needs to be started 2-3 weeks before entering a malaria risk zone until 28 days after leaving. Mefloquine can potentially have serious side effects (e.g. anxiety, insomnia, depression, suicidal mood,…): if this occurs, the use should be discontinued immediately and it should be switched to another malaria prophylaxis. If mefloquine has never been taken, it's advised to start at least 3 weeks before travel to monitor side-effects. Since 2014, it is mandatory to inform patients about potential side effects of mefloquine and a patient warning leaflet needs to be signed and kept by the traveller during use (1).

Vaccinations

In addition to discussing measures against mosquitos and preventive malaria medication, vaccinations are an important part of the travel advice. A trip is always a good time to check whether the basic vaccination schedule for the patient is still up to date and to supplement the schedule with the available travel vaccinations. We hereby give an update on important vaccines. Which vaccines are currently advised for a specific country can be found on wanda.be (1). For the Flemish regions registering all vaccines in Vaccinnet is essential in order to avoid misunderstandings or double vaccinations (3).

Tetanus-diphtheria-pertussis, hepatitis B, influenza, COVID19 and pneumococcal vaccination must always be checked in the basic vaccination schedule and updated if necessary. The status of measles-mumps-rubella and poliomyelitis vaccination should also be verified.

Measles, Mumps, Rubella (MMR)

Travellers are considered fully vaccinated for measles if they have received two vaccinations with a minimum interval of four weeks after the age of twelve months or have already had measles. Travellers born after 1970 who have not had measles and have not been vaccinated twice are eligible for free vaccination. Based on seroprevalence data, it is known that travellers born before 1970 usually have had measles.

Measles is on the rise worldwide and can be dangerous for young children. Measles is one of the most contagious infections in the world and the virus remains active and contagious in the air or on infected surfaces for up to two hours after contact (4). When travelling to a country with a measles outbreak (see Wanda: measles- countries with an outbreak) an earlier measles vaccination can be recommended (1). It is possible to administer the MMR vaccine *from 6 months onwards. If the child is between 6 and <12 months of age and travelling to a country with a measles outbreak a MMR vaccine should be administered*. This will only provide temporary protection and should therefore not be counted: one should administer it again after the age of 12 months (routine schedule) with a minimal interval of 28 days between the two MMR vaccines. For children who already received the first dose at the age of 12 months the second dose should be brought forward and given prior to travelling to a country with an outbreak: this second dose may be counted in the schedule as long as they were given after the age of 12 months and with at least one month interval. Ideally an interval of 28 days should be taken into account between the MMR and yellow fever vaccine, but if this is not feasible it's preferably to give the MMR vaccination and the yellow fever vaccination simultaneously (1).

Poliomyelitis

Global vaccination programs have almost eradicated poliomyelitis. The disease only occurs in a few countries in Asia and Africa. Polio vaccination is recommended for all travellers who have not had a full basic vaccination schedule. In addition, a one-time booster after the age of 16 is also recommended for all travellers to Asia or Africa. For countries where there is circulation of wild polio virus 1 (WPV1), circulating vaccine derived polio virus 1 or 3 (cVDPV1 or cVDPV3), with a risk of international spread, evidence of recent (<12 months) polio vaccination is required when leaving the country after a stay of four weeks or more. A list of these countries can be found on wanda.be.

Travel related vaccinations

Yellow fever

Yellow fever is a life-threatening arboviral infection transmitted by *Aedes* mosquitoes.

It occurs in Sub-Saharan Africa and Latin America. The yellow fever vaccine (Stamaril®) is a live attenuated vaccine. Vaccination is recommended in countries where there is a risk of yellow fever transmission. In accordance with the International Health Regulations (2005) some countries demand a proof of vaccination on entry. The vaccine is recommended *from the age of 9 months onwards* and can exceptionally be administered from 6-8 months (relative contra-indication). It is never given before the age of 6 months because of the risk of 'yellow fever vaccine-associated neurologic disease (YEL-AND)' occurring in babies under 6 months. It should be given at least ten days before arrival and a one-time booster is recommended for a subsequent trip to a yellow fever area. Twenty percent of patients have a slight flu-like syndrome after a few days. A very rare side effect is yellow fever vaccine-associated neurologic disease (YEL-AND) or yellow fever vaccine-associated viscerotropic disease (YEL-AVD). In Belgium the *yellow fever vaccine is the only vaccine that has to be administered in accredited travel medicine clinics*.

Hepatitis A

Hepatitis A is transmitted faeco-orally by ingestion of contaminated food or water and causes acute viral hepatitis. In recent decades there has been a decline in the incidence due to better food hygiene and improved sanitary facilities. There is still a high prevalence of hepatitis A in sub-Saharan Africa and some parts of South Asia, but outbreaks also occur in other countries in Latin America, North Africa, the Middle East, and other parts of Asia. Vaccination is recommended for all travellers to areas where hepatitis A occurs. The schedule consists of two vaccines, given with an interval of 6 to 12 months, after which lifelong protection occurs. In case the interval would be longer than 12 months, the schedule does not need to be restarted, but the second dose can just be administered and will still count as a second dose. In young children hepatitis A is mostly mild, but transmission to adolescents or adults is one of the reasons why vaccination is still recommended. The vaccine can be given from the age of 1 year. In case of an outbreak it is sometimes given at an earlier age (from 6 months onwards), but a dose administered prior to 12 months of age might result in suboptimal immune response and is therefore not considered a valid dose: the whole schedule should be repeated after the age of 12 months. The junior dosage is used until the age of 16 years; afterwards the adult dosage can be used.

Typhoid fever

Typhoid fever is caused by *Salmonella typhi* and is transmitted through contaminated food or water. As it only lives in humans, they are the sole vector. Symptoms include high fever, headache, nausea, abdominal pain, constipation or diarrhoea. Severe cases may lead to serious complications (e.g. intestinal perforation) or even death. But improved living conditions and antibiotic therapy have reduced mortality and morbidity in industrialized countries. The best protection consists of meticulous application of the 'safe food and drink advice' (see above). Typhoid fever currently primarily occurs in the Indian subcontinent. The risk in countries in Asia, Central / South America and Africa is lower. There is a typhoid vaccine available (Typhim Vi®) that provides 60-70% protection from 14 days after administration. This can be given *from the age of two years* and the duration of protection is a maximum of three years. The vaccine is recommended for travellers who will be in India, Nepal, Pakistan, or Bangladesh for more than three weeks, those visiting friends and relatives (VFR) for extended periods (>3weeks), or travellers staying in poor hygienic conditions in any country with a risk of typhoid fever.

Rabies

Rabies is a viral infection that can be contracted by inoculation of saliva from an infected mammal (including dogs, cats, monkeys, bats) through a bite or scratch or by a lick on mucous membranes or a wound. It can have a very long incubation period and is always fatal. A pre-exposure (PrEP) vaccination schedule consists of *two vaccines (Rabipur®) with at least a week's* interval. In principle PrEP vaccination is advised starting from the age of 1 year (since most children don't walk before and have therefore less risk on bites). There is however no real age limit for rabies vaccination. Until 2 years of age Rabipur 1ml is always given intramuscularly. In older individuals some centres give Rabipur 2 x 0,1 ml intradermally, in practice as soon as intradermal vaccination is practically possible, often from 8 years of age ore older. For each risk contact, the schedule must always be supplemented by washing the wound thoroughly with soap and then the post-exposure policy (PEP) with two booster vaccines (with an interval of 3 days). In people without rabies PrEP, this consists of a series of four or five vaccinations and sometimes additional administration of anti-rabies immunoglobulins (RIG or MARIG), which should be started as soon as possible after a bite or scratch after (remote) advice from a (paediatric) infectiologist. Other schedules are available for immunocompromised patients.

Meningococci ACWY

Meningococci can cause sepsis and meningitis. Clusters and outbreaks can occur anywhere in the world, but the highest frequency of disease is seen in the meningitis belt in Sub-Saharan Africa during the dry season from December to June. Travellers who have close contact with the local population ('visiting friends and relatives', medical staff, etc.) or who are traveling for more than 4 weeks or who have a spleen disorder, or certain immune disorders are advised to be vaccinated before departure with a conjugated meningococcal ACWY vaccine (Nimenrix® or Menveo®). Outbreaks have also been linked to pilgrimages to Mecca such as Hajj or Umrah. Vaccination with a meningococcal ACWY vaccine is mandatory for everyone from the age of two who goes on pilgrimage to Mecca; the certificate for this specific indication remains valid for five years after vaccination with a conjugate vaccine. It should be noted that since the second half of 2023, all children in Belgium are offered Nimenrix® at the age of *15 months* in the child welfare centres. For younger at risk travellers, a vaccine can be administered starting from 6 weeks old, following an adapted schedule. If given between 6 weeks and 6 months: it is recommended to administer two doses with a two-month interval, followed by a booster dose after the age of 12 months. If the vaccine is given between 6 months and 1 year, one dose is required, with a booster dose after the age of 12 months (with a minimum interval of 2 months). A booster is recommended by the Superior Health Council at 15 years of age (even when not travelling) as part of the routine vaccination schedule although not yet reimbursed and might be advised before travelling depending on the age of the child and the timing of the previous vaccination.

Tick-borne encephalitis

Tick-borne encephalitis (TBE) is a viral infection transmitted by ticks and exceptionally by the ingestion of unpasteurized dairy products. The disease is usually mild, but sometimes neurological symptoms occur that can lead to permanent residual damage or even death. TBE mainly occurs in certain forested areas in Europe (central Europe but also Scandinavia) and Eastern Europe. A vaccine is available (FSME-IMMUN®). A *lower junior dose is used for children aged one to sixteen years*. It consists of three doses with the second vaccine given 1 to 3 months after the first, and the third 5 to 12 months after the second dose. A first booster is necessary after 3 years and a second revaccination after 5 to 10 years (or for people >60 years old: after 3 years).

Japanese encephalitis

Japanese encephalitis is a viral infection spread by Culex mosquitoes. In most people the disease is mild and the symptoms resolve within a few days. In a minority, neurological symptoms will develop (meningitis/ encephalitis), with a high risk of permanent residual damage or even death. The disease only occurs in South / Southeast Asia and Eastern Australia. The risk is generally low for travellers, but it increases with long-term or frequent stays or a stay in the countryside. The Japanese encephalitis vaccine (Ixiaro®) consists of *2 doses given with an interval of 4 weeks*. A booster should be given after 12 to 24 months, after which the duration of protection is at least 10 years. No junior vaccine is available but children from *2 months to 3 years should receive half a dose of the vaccine*. In case of stock disruptions in Belgium or insufficient time to complete the schedule before departure, the patients can obtain the vaccines sometimes at their travel destination. A list of locations where it can be acquired is provided by the International Society of Travel Medicine (https://www.istm.org/clinic-directory/).

Dengue

Dengue is an arboviral infection transmitted by *Aedes* mosquitoes. This can cause fever, vomiting, headache, muscle and joint pain. In exceptional cases (but more often in infants), severe dengue can occur with bleeding, shock and multi-organ failure; this risk is greatest with a second dengue infection. A dengue vaccine (Qdenga®) has been available on the Belgian market since 2023. The vaccine reduces the risk of a serious dengue infection. It is *only recommended for travellers if they have already had a first dengue episode* and travel to a high-risk area for a prolonged period of time (>4 weeks or frequent stays) and can receive two doses before departure. The duration of protection has not yet been determined. It is a live attenuated vaccine and should not be used in certain immune disorders, during pregnancy or while breastfeeding. It can be administered from the age of 6 years onwards and consists of 2 vaccines with an interval of 3 months.

Immunosuppression

When children have to begin immunosuppressive therapy for any reason, it is crucial to vaccinate them beforehand, particularly against yellow fever. This important step is often overlooked because there may not be immediate travel plans. However, since the therapy could extend over several years, failing to vaccinate before starting treatment could restrict the child's travel opportunities in the future. Additionally an immunosuppressed child who is planning to travel to the tropics should seek expert travel medicine advise prior to travelling.

'Visiting Friends and Relatives' and risk of tuberculosis

'Visiting friends and relatives' (VFR) are a specific group of people with their roots in the 'Global South' who frequently travel to their countries of origin to visit friends, (grand)parents and other family members. They sometimes stay in (often crowded and less ideal) family residences in more rural areas and are therefore more exposed to vector-borne and diarrheal pathogens. Focusing on the importance of malaria preventive measures including the necessity of malaria chemoprophylaxis is

especially important in this subgroup. Adequate vaccination and discussing prevention and treatment of diarrhoea is essential.

A recent study also suggested that VFR trips to high-tuberculosis-incidence countries play a significant role in the epidemiological dynamics of tuberculosis (TB) in regions with low TB incidence. In Spanish VFR children with a negative tuberculin skin test (TST) at baseline, 2.6% turned out to have latent TB when retested (with TST or interferon gamma release assay (IGRA)) 8 to 12 weeks after return. It has therefore been suggested to target paediatric VFR travellers – as a high risk group – for prevention (by performing TST or IGRA) 8-12 weeks after returning (5). BCG (bacillus Calmette-Guérin) vaccination is not routinely available on the Belgium market but can be imported from abroad in certain Belgian clinics (https://www.wanda.be/en/a-z-index/travel-clinics-in-belgium). For children younger than five years who are repeatedly visiting or spending more than six months in a high-risk country BCG vaccination is recommended. If it's not possible to obtain it in Belgium beforehand they should be advised to get it locally upon arrival (1).

Conclusion

Whether a trip nearby or far away is planned, it is important to get appropriate medical travel advice. The website and application www.wanda.be can be used as a guidance but should always be supplemented with a travel consultation: either in a travel clinic, or with a general practitioner or paediatrician with expertise in travel medicine. When checking vaccinations, it is important to first check the basic vaccinations (with special attention for measles when travelling to regions where measles outbreaks occur) and then consider which additional travel vaccinations are useful based on the travel destination and the risk factors.

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Pott's Disease in Children: a Case Report and Review of Current Practices

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Abstract

Spinal tuberculosis, also called Pott's disease, is a prevalent disease in low- and middle-income countries but can also be seen in Europe. Back pain is the main presenting complaint, and the majority of patients do not experience systemic symptoms. Complications include spinal deformation and medullar compression with associated neurological symptoms. In many cases there is a significant delay between the appearance of symptoms and diagnosis, which may make the outcome worse and underlines the importance of a good understanding of this pathology. Treatment includes tuberculostatic therapy as well as surgery in selected cases. We describe the case of a 15 year old girl presenting with respiratory complaints and spinal tuberculosis, and we review and discuss available knowledge about this important disease.

Introduction

First described by Sir Percival Pott in 1779, spinal tuberculosis, also called Pott's disease, represents half of musculoskeletal tuberculosis, which represents 10% of extrapulmonary tuberculosis, and 1% of all tuberculosis cases (1, 2). Around 1300 children were affected by tuberculosis in 30 countries of the European Union and European Economic Area countries in 2022 according to the last Surveillance Report of the World Health Organization (3).

Pott's disease most frequently involves the thoracic vertebrae and is multi-focal in 51% of cases (of which 8% involving adjacent vertebrae) (1, 4, 5). In 90-95% of cases, spinal tuberculosis involves the anterior part of the vertebral body (2).

The management of spinal tuberculosis in children is subject to debate. This report describes a 15-year old girl who was admitted to the hospital with chest pain and dyspnoea. She was diagnosed with pneumonia, pleural effusion and thoracic Pott's disease. We aim to discuss current knowledge and review available guidelines for this important disease.

Clinical case

A previously well 15 year old girl of Congolese origin and living in Mayotte for 2 years presented with a 4 month history of lateral thoracic pain and exertional dyspnoea. There was no fever and her general condition was good. Her vaccination status was unknown. There were no known tuberculosis (TB) contacts. On clinical examination, she had a dry cough and decreased breath sounds at the right lung base.

The blood tests performed showed mild inflammation (CRP 30 mg/L [N < 5.0 mg/L], with normal leucocyte count) and a microcytic anaemia (Hb 11.6 g/dl [N 12-16 g/dL], mean corpuscular volume 76.8 fL [N 78-100 fL]). HIV serology was negative. The chest X-ray showed a right basal pneumonia with pleural effusion. There was no adenopathy on examination or chest X-ray. Pleural fluid examination showed inflammation with a lymphocytic predominance. Direct examination, culture and PCR for *Mycobacterium tuberculosis* were negative. The 3 gastric aspirates performed were also negative. Her tuberculin skin test showed an induration of 15 mm and the interferon-gamma release assay was also positive. A CT scan of the chest, abdomen and pelvis was performed, which showed a middle lobe consolidation and a significant right pleural effusion, as well as a small lytic lesion of the antero-superior corner of the T10 vertebral body, with an anterior abscess measuring 10 mm in antero-posterior diameter at the T9-T10 level. MRI confirmed a spondylodiscitis at T9-T10 level and a prevertebral abscess, and showed damage to the right sacroiliac joint, presumably from TB. There was no spinal cord compression (see Figure 1).

She was referred to a tertiary hospital, where an ultrasound-guided vertebral biopsy was performed, which revealed acid-fast bacilli on microscopy. The diagnosis of tuberculosis was confirmed by GeneXpert, with a strain susceptible to rifampicin. She was started on a standard four-drug oral regimen of isoniazid 5 mg/kg, rifampicin 12 mg/kg, pyrazinamide 30 mg/kg and ethambutol 20 mg/kg, plus pyridoxine. Gene sequencing confirmed a fully sensitive strain. The index case was not identified.

Despite good compliance, her condition worsened, with persistent back pain and an increase in abscess size and vertebral signal on T2 sequences on a subsequent MRI. A second biopsy was performed after 5 weeks of treatment, which showed the persistence of *M.tuberculosis*, which was still sensitive to rifampicin by GeneXpert. It was thought that her evolution could be explained by reduced diffusion of the drugs to the lesion. Immune reconstitution, which occurs during the first weeks of TB therapy, could also explain this paradoxical reaction and is a likely cause in the context of good adherence.

The pleuropulmonary disease resolved with treatment. An immunologic work-up showed no abnormality. The prevertebral abscess was drained by minimally invasive surgery. MRI after surgical drainage showed an almost complete drainage of the abscess, and a stability of the signal in vertebrae T9-T10 and of the anterior part of T11. The presacral collection was stable. The 4 drug combination therapy was continued for 7 months, followed by isoniazid and rifampicin for 1 month (total duration of 8 months). This long duration of 4 drug therapy was justified by concerns about initial treatment failure. She was asked to wear a rigid brace. The further evolution was satisfactory. 15 months after initiation of treatment, she occasionally complains of back pain due to discopathy, but her life has returned to normal.

Discussion

Pathology of Pott's disease

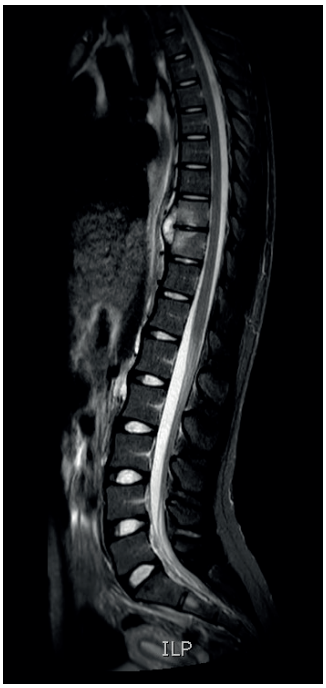
M.tuberculosis affecting the spine typically spreads by haematogenous route, facilitated by vertebral vascularisation. The primary focus is pulmonary in the majority of cases (4, 6). In the retrospective paediatric study performed by Benzagmout et al, a concomitant pulmonary infection was found in half of the cases (4). Other routes of dissemination include direct inoculation after a trauma or surgery and contiguous dissemination from adjacent tissues, but these are not commonly seen in children (6).

M.tuberculosis is deposited by terminal arterioles on the anterior part of the vertebral body, which is the usual initial site of infection (7). The common blood supply of adjacent vertebral bodies by segmental arteries explains multifocal disease (1). Infection then spreads to the central part and to the cortex of the vertebral body. Eventually it can disseminate below the anterior or posterior longitudinal ligaments, as well as through the periosteum, causing bulging of the vertebral surface and devascularisation of the periosteum (1, 4, 8). The formation of a cold abscess around the lesion is a characteristic feature of spinal tuberculosis (1).

Infection tends to disseminate subligamentary, but can also spread to the adjacent soft tissues and cause paravertebral or epidural abscesses, which can compress the spinal cord and cause neurological complications. Motor deficit is the first manifestation, as motor fibres are more sensitive to compression than sensory fibres, which are more sensitive to ischaemia (2). Collateral circulation prevents ischaemia of neural fibres (2).

Intervertebral disc lesions can occur in children, whose discs are still vascularised (1, 4, 7). Destruction of the disc and adjacent vertebrae leads to spinal deformity in the form of gibbus (hump-shaped deformity involving 2-3 vertebrae) and kyphosis (convex curvature of the spine when many vertebrae are involved) (9). A flat vertebra may be seen in cases of severe compression (1).

Figure 1: Initial MRI, T2 sequence. Hypersignal of the vertebral bodies T9-T10 and pre-vertebral abscess.



Clinical findings

The clinical picture includes back pain, systemic symptoms and symptoms due to complications. Some features are specific to certain localisations.

Back pain is the most common symptom and is present in 90-100% of the cases (8). Back pain at rest at the level of the lesion is characteristic (9). Its intensity varies with the level of bone destruction and spinal instability and is higher in thoracic lesions (9). Aggravating factors include movement, coughing and weight bearing. Axial pain is due to bone destruction, mass effect from abscesses, and spinal instability, whereas radicular pain is due to mass effect or vertebral collapse (7, 9). Back rigidity and muscle spasm may contribute to the pain (1).

Systemic symptoms occur in only 20-30% of cases and are more common in cases associated with pulmonary tuberculosis (1, 8, 9). They include asthenia, fatigue, fever (most often in the evening), sweating, loss of appetite and weight loss (4). They start insidiously, which explains the usually long diagnostic delay. In adults, Batirel et al found a median diagnostic delay of 78 days, while Khanna et al. found a median delay of 3 to 6 months (5, 7).

Complications include abscess in 69% of cases, neurological deficit in 40% of cases, and spinal deformity in 16% of cases (5).

Abscesses are cold, painless and grow slowly. Their subligamentous spread causes a mass effect with specific characteristics depending on their location.

Neurological deficit is caused by spinal cord compression and gives the related symptoms: radicular pain, motor deficits ranging from paresia to paraplegia (or even tetraplegia in the case of cervical spine lesion), sensory loss and continence disorders. Paraplegia may occur at any time and at any stage of the vertebral disease (1). The prognosis of early paraplegia is better than that of late paraplegia (1). Kumar et al. proposed a classification of paraplegia in spinal tuberculosis, reflecting spinal cord compression. Other classifications also exist (2).

Spinal deformity is particularly pronounced in children as their spine is very flexible, ossification is still in progress, and vertebral lesions cause impairment of anterior growth. Risk factors for spinal deformity include age less than 10 years, lesion of more than 3 vertebrae, and a thoracic location (4). Furthermore, a spinal deformity is less well tolerated when it affects the thoracic region (4, 9). Khanna et al. classify kyphosis reconstruction into three types according to severity (7). Rajasekaran et al. define 4 "spine at risk" signs, namely subluxation, retropulsion of the vertebral body, lateral translation and toppling, which have a prognostic value (9). According to the authors, the presence of more than 2 signs is an indication for surgery, while more than 3 signs indicate a risk of progression to severe kyphosis (7, 10). Childhood Pott's disease presents the particularity of ongoing deformity even after healing of the disease due to the growing nature of the spine (9).

Diagnostic features

Isolation of *Mycobacterium tuberculosis* by culture or molecular assays is required to make a definitive aetiological diagnosis. CT-guided biopsy is the gold standard to collect the sample. If there is a surgical indication, it can also be obtained surgically (1, 7).

Radiological findings

Plain radiographs are abnormal in 99% of cases and may show a volume loss of the vertebral plate and disc, anterior osteopenia and lytic lesions, osteosynthesis, the presence of an abscess, and spinal deformity in late disease (1, 7). Of note, osteolysis is visible on plain radiographs when half of the bone density has already been lost, which implies late diagnosis (1, 4, 7). Concomitant pulmonary lesions are present in 50-70% of the cases (4, 6).

CT scan detects bone lesions earlier and more accurately than plain radiographs. The exact bony extent of lesions, the condition of the posterior column and joints, and the stability of the spine can all be assessed. As stated by Khanna et al., it may detect smaller lesions, the presence of calcifications in abscesses and epidural lesions with bony fragments, and show the aetiology of spinal cord compression. Most of all, it is used to perform CT scan-guided biopsy (7).

Full-spine and gadolinium-enhanced MRI is the examination of choice and allows early detection of lesions (4). Its sensitivity is 93% and its specificity is 96% (1). MRI is useful to evaluate the spinal cord, abscesses, soft tissues, vertebral anomalies and collapse, intervertebral discs, the presence of a tuberculoma or other lesions, and spinal deformity (1, 4, 7). It may also be used for follow-up. Lesions appear hypointense on T1 sequences and hyperintense on T2 sequences. Lesions of concern in spinal TB include multifocal disease with respect to the intervertebral disc, enhancement of the adjacent soft tissues, and abscesses or collections of granulation tissue in the peri-vertebral area. Subligamentary abscesses with thin and smooth walls have 90% specificity for TB (4, 8).

FDG-PET scan is not very specific, causes irradiation and is expensive. It can help identify a hypermetabolic abscess in order to perform a biopsy, but is generally not used to diagnose spinal TB (2, 9).

Scintigraphy has good sensitivity but low specificity. Tc99m scintigraphy, used for bone, has 35% false negatives, while gallium scintigraphy, used for inflammatory processes, has 70% false negatives. It can detect disease before MRI, but as there is no pathognomonic image for spinal TB, scintigraphy is of limited use for the work-up (1, 2, 8).

In terms of neuroimaging guidance for biopsy, ultrasound has been proven to be safe and effective and has several advantages, including the absence of ionising radiation, fast acquisition time, and good structural and vascular characterisation (11).

Laboratory testing

Detection of acid-fast bacilli by Ziehl-Neelsen staining has low sensitivity. Culture on Lowenstein's medium also has poor sensitivity (around 75%) in spinal TB due to paucibacillary disease, with the risk of false negatives, and has a long turnaround time of 6 to 8 weeks (12).

Due to the limitations of culture, histopathology is of value in the diagnosis of spinal TB. Characteristic findings include epithelioid cell granuloma, granular necrosis, lymphocytic infiltration and Langerhans cells (7).

Molecular assays are increasingly being used for diagnostic purposes. Their advantages include rapid turnaround time, detection of paucibacillary disease, and testing for resistance. A recent Cochrane review reported a sensitivity range of 96-100% and specificity of 53-100% for Xpert MTB-RIF (Cepheid) in bone aspirate, and sensitivity of 88-96% and specificity of 97% for the newer Xpert MTB-RIF Ultra (Cepheid) (13).

The erythrocyte sedimentation rate (ESR) is elevated above 20 mm/h in 60-83% of the cases and normalises with treatment (14). A full blood count may show inflammatory anaemia; the leucocyte count is normal in more than half of the cases (8).

Tuberculin skin test (TST) and Interferon-Gamma Release Assay (IGRA) may be helpful, but do not differentiate between latent and active tuberculosis. The TST is positive in 63-90% of cases of spinal TB (8).

Treatment

A. Medical

Drug-sensitive spinal TB is treated with standard anti-tuberculosis drugs, the intensive phase consisting of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) and the continuation phase consisting of isoniazid (H) and rifampicin (R) (15-18). These drugs have a good bone penetration (except in lesions with sclerotic wall). Drug-resistant spinal TB is less common and its management is more complex and beyond the scope of this review (19). The duration of treatment for drug-sensitive spinal TB is controversial, as there is no clear biological or radiological marker of cure. Shorter regimens, as long as they are effective, reduce unnecessary drug exposure. The main risk is recurrence of disease if treatment is incomplete.

The main guidelines (listed in Table 1) vary in their recommendations for the duration of treatment, with total durations ranging from 6 to 12 months. Longer durations are justified by the risk of severe complications if spinal TB is insufficiently treated, and by the difficulty of assessing treatment response. However, a recent systematic review and meta-analysis including only randomised controlled trials in adults and children, comparing short course of 6 months with a longer course of at least 9 months, with a follow-up period of at least 12 months after completion of chemotherapy, found that the healed status of spinal TB was equivalent in both groups, suggesting that shorter course of treatment may be considered in spinal tuberculosis, although more homogeneous and specific paediatric studies are needed (20). Studies with longer follow-up periods are reassuring regarding the efficacy of 6-month regimens (21-23).

B. Surgical

The aim of surgical treatment is to drain the abscess if present, decompress and remove dead tissue from infected areas, improve spinal stability and prevent or correct spinal deformity (9). Surgical indications suggested by most studies include worsening neurological deficit, significant abscesses (especially with psoas involvement), severe kyphosis, absence of response to conservative treatment, and lesions with a sclerotic rim (1, 4). The choice of the surgical approach depends on factors such as age, comorbidities, location and number of lesions, severity of kyphosis, and surgeon expertise (9). The details of surgical management are a controversial topic and are beyond of the scope of this review.

C. Supportive

Traditionally, bed rest and back bracing were advocated in all cases. These measures are no longer recommended in the absence of surgical treatment, with the exception of cranio-occipital and in some cases cervical disease (1, 2, 7). Back bracing is considered unnecessary, as it has not been shown to be effective in preventing the progression of kyphosis and spinal stability is rarely compromised. There is no guideline on back bracing for surgery and the decision is left to the surgical team.

Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS)

TB-IRIS, as stated by Lanzafame et al., is an excessive immune response against *M. tuberculosis* that may occur in both HIV-infected and uninfected patients, during or after completion of anti-TB therapy (24). Three forms have been described. Paradoxical IRIS is defined as recurrent, new or worsening symptoms in a treated case after initiation of anti-TB drugs. Unmasking IRIS is an antiretroviral therapy (ART)-associated form of tuberculosis in which subclinical infection becomes apparent after ART initiation, usually in the first 3 months after ART initiation (25). IRIS of the central nervous system has been individualised from previous categories due to its specific features (25).

Lanzafame et al. propose 4 criteria to define TB-IRIS: initial clinical and radiological improvement with the start of TB treatment, secondary worsening during or after TB treatment, no condition reducing the efficacy of anti-TB drugs, and no alternative explanation for the clinical worsening (24). The localisation of TB-IRIS is independent of the primary localisation and most commonly involves the lymph nodes and the lungs (24).

Table 1: Summary of guidelines concerning treatment of paediatric spinal TB.

	Target population	Duration of quadritherapy (months)	Duration of bitherapy (months)	Total duration of treatment (months)
American Thoracic Society / Centre for Disease Control and Prevention / Infectious Diseases Society of America 2016 (15)	Children	2	7-10	9-12
British Infection Society 2009 (16)	Children and adults	2	10 if CNS involvement	12 if CNS involvement
WHO 2022 (17)	Children	2	10	12
NICE 2016 updated 2024 (18)	Children and adults	2	4 10 if CNS involvement	6 12 if CNS involvement

CNS=Central nervous system.

No specific diagnostic test has yet been found to differentiate IRIS from other causes of clinical worsening. Clinicians should be aware of this and not assume that exacerbation of symptoms and signs is due to wrong diagnosis, poor adherence, malabsorption of medication, treatment failure, resistance, adverse effect of drugs or immunodeficiency.

Anti-TB drugs should be continued in most cases. Steroids are beneficial, as shown in an RCT performed by Meintjes et al. (26). Other anti-inflammatory or immunomodulatory agents have been used anecdotally, and surgical intervention may be necessary (25, 27-29).

Conclusion

Spinal tuberculosis is a disease with insidious onset, with back pain often being the only sign. Delayed diagnosis increases the risk of complications, which can be severe. The duration of medical treatment and surgical management is still subject under debate, with shorter drug regimens showing promise. Reserving surgery for complicated cases and adapting the duration of chemotherapy to the clinical, biological and radiological response may be the best approach, but more studies are needed, notably large RCTs including children, as paediatric evidence is still scarce. This case review highlights the need to include Pott's disease in the differential diagnosis of a child presenting with thoracic or back pain.

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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.

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Mediterranean Sun, Sea, Sand and … Leishmaniasis

Two Case Reports

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Keywords

Leishmaniasis ; pancytopenia ; sandfly.

Abstract

We present two recent cases of visceral leishmaniasis diagnosed in Belgian children, presenting with typical clinical signs of high fever, splenomegaly and pancytopenia.

Although the differential diagnosis of this clinical presentation is extensive, the diagnosis of visceral leishmaniasis should be considered in the event of a travel history to endemic countries in tropical and subtropical regions, as well as in the south of Europe.

Introduction

Leishmaniasis is a vector-borne disease caused by the *Leishmania* parasite.

The disease is transmitted by the bite of an infected female sandfly, a tiny (2-3mm) and silent insect vector. These sandflies thrive in moist climates and are found in tropical and temperate regions of the world.

While this disease was once a standard textbook "tropical" disease, it can also be acquired in subtropical and other warm climates. In Europe, leishmaniasis is endemic in all southern countries bordering the Mediterranean Sea and the Black Sea.

Infection can range from asymptomatic to severe. Most people who become infected with the parasite, do not develop any symptoms. The ratio of asymptomatic individuals to active disease varies depending on the virulence of the parasite species, host characteristics and study design (1).

Asymptomatic infections can become symptomatic years to decades after exposure in people who have become immunocompromised.

Cutaneous (CL), mucosal (ML) and visceral (VL) leishmaniasis are the 3 clinical syndromes caused by an infection with the *Leishmania* parasite.

CL is the most common form and typically presents with painless, ulcerative lesions on exposed skin, leaving scars. ML is a rare and aggressive form of CL affecting the mucosal areas of nose or mouth. CL and ML can cause substantial morbidity, whereas VL can be life threatening and fatal without treatment (2-5).

Leishmaniasis is endemic in almost all continents, except for Australia and Antarctica. CL is endemic primarily in North Africa, the Middle East and South America. VL is found mainly in East Africa, the Indian subcontinent, Central and Southwest Asia, the Middle East, as well as in Brazil and Latin America. It is also endemic in southern Europe.

Climate change seems to be influencing the spread of the disease through changes in the incidence and geographic distribution of sandflies (5, 6).

We describe two cases of VL in children diagnosed after traveling in Europe.

It is important to raise awareness of this disease and to actively search for the parasite in case of a relevant travel history, especially in the presence of typical signs such as pancytopenia, fever, and splenomegaly.

Case reports

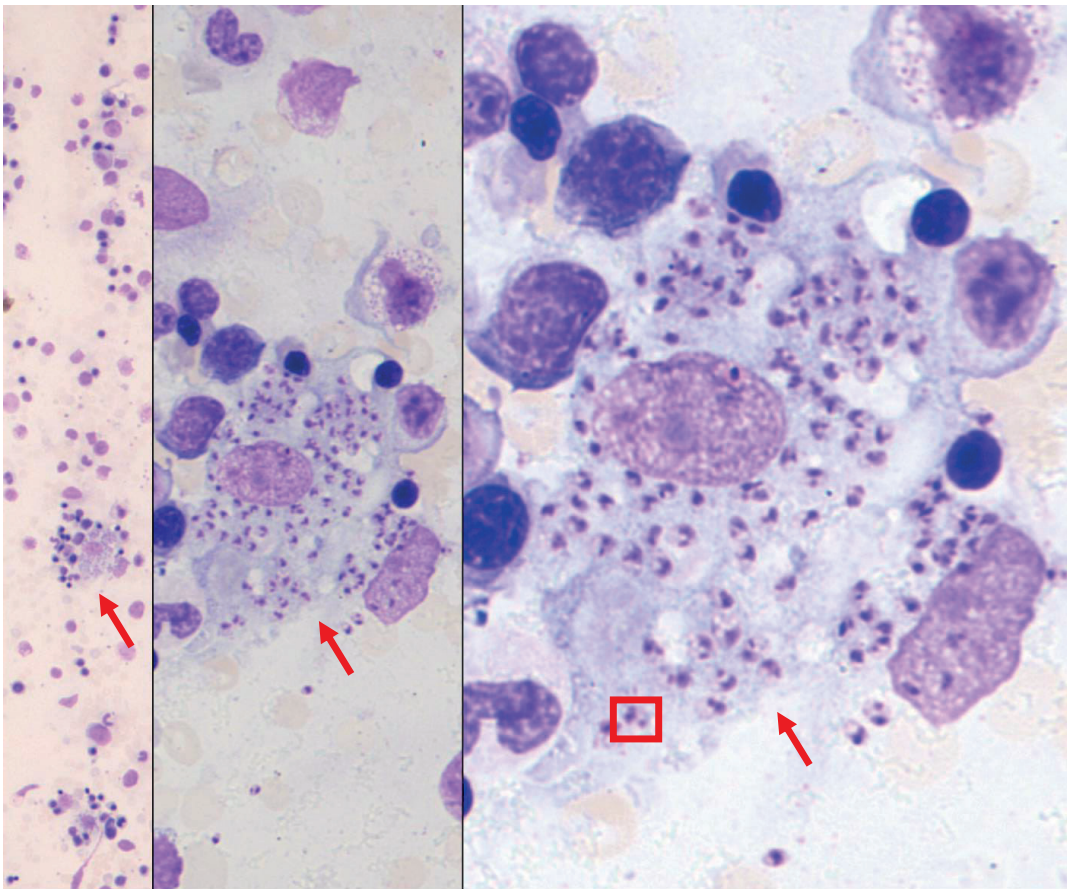
Case 1

A 20-month-old girl is referred to the pediatrician because of a 3-week history of fever and non-bloody diarrhea. Initially she also had a productive cough that resolved after 1 week. Between episodes of fever she is well. The parents noted that she probably lost weight, about 1 kg. Her medical history is uneventful. She was born and lived in Spain until 1 year of age and is vaccinated according to the Spanish schedule. At the time of presentation, she lives with her mother in Belgium, with regular visits to her father in Spain. The parents did not report any contact with domestic or farm animals; no insect or tick bites were noted.

On clinical examination, she is in good general health but appears pale. The clinical and neurological examination is normal except for a splenomegaly of 10 cm below the costal margin.

Initial blood tests show pancytopenia (hemoglobin 6.5 g/dl [N 11.5-13.5], white blood cell count 5430/µl [N 6000-17500] with neutropenia 870/µl [N 1500-8500] and 86000 thrombocytes/µl [N 150000-450000]) and mildly elevated CRP (46,3 mg/l [N <5]), AST (61 U/l [N < 37]) and LDH (548 U/l [N 157-272]). Ferritin is elevated to 1208 µg/l [N 7-140]. Coagulation and renal function tests are normal. Multiple blood cultures were negative, as was a stool bacterial culture. Abdominal echography confirms splenomegaly, without hepatomegaly nor enlarged intra-abdominal lymph nodes. Chest x-ray is unremarkable.

Because of primary suspicion of a hematologic malignancy, the patient is referred to the Pediatric Hematology Department of the Ghent University Hospital for bone marrow examination. This reveals no infiltration by malignant cells, but multiple parasites compatible



Microscopic picture of a May-Grunwald-Giemsa-stained bone marrow aspirate (patient 1). A macrophage (red arrow) with amastigotes is shown at different magnifications (left 10x; middle 50x; right 100x). Amastigotes consist of small, spherical, intracellular inclusions with a prominent nucleus and kinetoplast (red square).

with *Leishmania* amastigotes are seen on direct examination (Figure). Prompt treatment with liposomal amphotericin B is started and given in 7 doses (total dose 21 mg/kg). The girl also receives a red blood cell transfusion for worsening anemia, as the Hb dropped to 5.5 g/dl. The patient defervesces within 24 hours of the first dose of amphotericin B. The diagnosis is later confirmed by PCR performed by the Institute of Tropical Medicine Antwerp (ITM), which reveals the *Leishmania infantum* species.

The blood count and splenomegaly gradually recovered, with normal WBC, Hb and thrombocytes and no splenomegaly at consultation 2 months after hospitalization. She remains without signs of relapse during the 3 year follow-up period.

Case 2

A 9-month-old Caucasian girl presents with a 4-week history of daily fevers, initially associated with a mild cough. She had received antibiotic treatment with amoxicillin 1,5 weeks before, following a presumptive diagnosis of post-viral bacterial bronchitis, after which she defervesced for two days. There is no history of rash, articular complaints or B symptoms. She has an incomplete vaccination status (polio vaccine only) due to parental vaccine hesitancy. She has traveled to Spain (Valencia region) twice in the past year.

On clinical examination, she is pale and has a marked splenomegaly (6 cm below the costal margin).

The blood sample shows marked anemia (Hb 6.3 g/dl), thrombocytopenia (41000/µl) and leukopenia 3180/µl with neutropenia of 394/µl. Inflammatory markers are elevated with a CRP of 92 mg/l and a high IgG level of 16 g/l [N 3.02-10.37]. Serology is negative for EBV, parvovirus, *Toxoplasma*, rubella, CMV, HIV, hepatitis B and C, mumps, measles, and varicella. Blood and urine cultures are negative. A nasal swab PCR reveals the presence of adenovirus and rhinovirus. The tuberculin skin test and IGRA test are negative.

Chest x-ray shows mild peribronchial attenuation without mediastinal enlargement. Ultrasound confirms splenomegaly of 10 cm without hepatomegaly or enlarged lymph nodes.

After case discussion with the pediatric hemato-oncologists, she is referred to the Pediatric Hematology Department of the Ghent University Hospital for bone marrow aspiration to rule out hematologic malignancy, which is negative, after which she is transferred to the regional hospital for further treatment and follow-up.

However, despite broad-spectrum antibiotics, she continues to have high fever. She appears clinically well, with only persistent splenomegaly. Because of the suspicion of hemophagocytic lymphohistiocytosis (HLH) with worsening cytopenia (Hb 6,9 g/dl, WBC 1560/µl, thrombocytes 31000/µl), increasing ferritin to a maximum of 1624 µg/L and a high triglyceride level of 704 mg/dl [NL ≤ 150], she is again referred to the tertiary center.

With the persistent cytopenia and clinical clue of HLH, the initial bone marrow is reexamined thoroughly and a sparse *Leishmania* amastigote is detected on direct examination, corroborating the diagnosis of VL.

Treatment with liposomal amphotericin B IV is started and continued with a total dose of 21 mg/kg, given in 7 doses. She becomes afebrile within 24 hours. The diagnosis is confirmed by a positive *Leishmania* PCR at the ITM (Antwerp), revealing the *Leishmania infantum* species.

At consultation 6 weeks after the start of treatment, she shows no more splenomegaly and all cell lines have recovered, and she remains well after a 3 months of follow-up.

Discussion

Visceral leishmaniasis results from the dissemination of *Leishmania* parasites throughout the reticuloendothelial system and is usually caused by the species *L. donovani* and *L. infantum*. It has an incubation period ranging from weeks to 6 months. As shown in both cases, the disease typically presents insidiously, which explains the latency of diagnosis in many cases. Clinical manifestations include fever, weight loss, hepatosplenomegaly (usually a more prominent splenomegaly), and pancytopenia due to bone marrow suppression, hemolysis, and splenic sequestration. Blood tests also show a high total protein and low albumin levels, with hypergammaglobulinemia. VL is almost always fatal if untreated and requires prompt evaluation and treatment. The

term kala-azar, which means black fever in Hindi, is often reserved for severe cases of VL, although the terms kala-azar and VL are sometimes used interchangeably. VL is an opportunistic infection in persons with HIV or cell-mediated immunosuppression. HIV infection increases the risk of VL infection, and VL progression of HIV disease, with a high disease burden in parts of Eastern Africa. HIV co-infected patients may present with atypical clinical manifestations (2).

Some cases of VL are associated with hemophagocytic lymphohistiocytosis (HLH), as in case 2. HLH is a life-threatening systemic inflammatory disorder caused by excess immune activation triggered by certain infections. The clinical syndrome includes pancytopenia, fever, splenomegaly, hypertriglyceridemia, and elevated ferritin with bone marrow evidence of hemophagocytosis. Most patients with HLH secondary to VL respond to antileishmanial therapy alone, adjunctive therapy being needed sometimes in case of delayed diagnosis (7).

The diagnosis of VL should be suspected in any patient presenting with compatible signs and symptoms (fever and splenomegaly), blood results (pancytopenia), especially with a travel history to an endemic region.

Diagnosis can be made by microscopic visualization of the characteristic amastigotes in smears or tissues, molecular detection of parasite DNA, parasite isolation by in vitro culture and serologic testing. For optimal guidance in the laboratory diagnostic approach, early consultation with expert advisors and reference laboratories is recommended.

Parasite detection and identification remains the gold standard.

Bone marrow aspiration is the preferred specimen for diagnosis of VL by microscopy, with a high specificity and 50-80% sensitivity. The sensitivity of microscopy on spleen tissue is higher (>90%) but spleen aspiration for diagnosis is discouraged because of the high procedural risk of life-threatening bleeding. PCR on bone marrow smears or tissue samples is the method of choice as it has high sensitivity and specificity and allows for species identification, which is important for treatment guidance. Parasite culture can take weeks to become positive and is used only for specific indications such as drug resistance evaluation and for research purposes.

Serologic testing can provide supportive evidence for the diagnosis and is recommended in persons suspected of having VL in whom bone marrow biopsy or aspiration cannot be performed, or when microscopy and PCR are negative. The sensitivity and specificity of serologic tests depend on the assay and antigens used, as well as host factors. Antibody levels can be lower or even undetectable in persons with HIV or other cellular immunodeficiencies (2, 8-10).

Treatment of VL varies by region and species identification due to variable drug susceptibility and can be challenging. Prompt treatment of VL with liposomal amphotericin B is now recommended as the first-line treatment due to the widespread high-level resistance to previously used antimonial drugs. Total dose and dosing schedule vary according to the clinical presentation, the *Leishmania* species and host factors (immunocompromised or not) (10).

Control of leishmaniasis is based on vector control (reduction of sandfly bites), and prompt diagnosis and treatment of the disease to reduce the infection reservoir. Sandflies are nocturnal and can be found both indoors and outdoors. Bites may go unnoticed because of the small and silent vector. These small sandflies can even pass through the holes of an ordinary mosquito net, so fine-mesh or insecticide-impregnated nets are useful. Travelers can protect themselves from bites by avoiding outdoor activities from dusk to dawn, by minimizing uncovered skin and applying DEET (diethyl-m-toluamide) containing insect repellent to exposed skin (11, 12).

Conclusion

Leishmaniasis is endemic in large parts of the world and can be imported even from a nearby travel destination such as Spain, southern France, Greece, or Italy. Consider the diagnosis of visceral leishmaniasis in patients with a clinical syndrome of fever, splenomegaly, pancytopenia and a relevant travel history (even in the distant past). The gold standard for diagnosis is the detection of the parasite in affected tissue, with bone marrow being the preferred diagnostic sample. In case of suspicion expert advice should be sought for guidance on diagnosis and therapy.

Sandfly bites may go unnoticed because they are very small. The risk of infection can be reduced by vector control, insecticide-treated bed nets, covering the skin (especially from dusk until dawn) and DEET.

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

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An Unusual Cause of Paediatric Epilepsy in Europe: a Case of Neurocysticercosis

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Keywords

Neurocysticercosis ; seizures ; Taenia solium ; child : case report.

Abstract

We describe a case of symptomatic epilepsy in an 8-year-old child of Burundian origin who was admitted to an emergency department in Belgium. Neurocysticercosis is a rare cause of epilepsy outside areas endemic for *Taenia solium*. The 'pig tapeworm' is responsible for neurocysticercosis by larval invasion of the central nervous system. The clinical presentation and therapeutic options are reviewed, with a focus on the severity, stage, and location of the infection.

Introduction

We describe a case of symptomatic epilepsy in an 8-year-old child of Burundian origin who was admitted to an emergency department in Belgium. Neurocysticercosis is a rare cause of epilepsy outside areas endemic for *Taenia solium*. The 'pig tapeworm' is responsible for neurocysticercosis by larval invasion of the central nervous system. The clinical presentation and therapeutic options are reviewed, with a focus on the severity, stage, and location of the infection.

An 8-year-old boy of Burundian origin was admitted to the paediatric emergency department of Wallonie Picarde Hospital Centre (CHWAPI) in January 2023. While at home, the child exhibited oral automatisms and decreased responsiveness, followed by loss of consciousness and a tonic seizure with urinary incontinence. The emergency team administered benzodiazepines rectally at home, after which the child gradually regained consciousness during his transfer to the hospital.

On admission, the boy was in good general condition, alert, and breathing normally. He had amnesia of the events. General examination was normal except for nasal congestion and a tongue bite. The neurological examination was normal.

The boy had a similar episode one year earlier at school, where he experienced non-specific malaise, loss of responsiveness, and confusion. The local medical team found him to be conscious, oriented, and with normal neurological status. The boy complained of transient occipital headache prior to the loss of responsiveness. He did not exhibit abnormal movements or involuntary urinary incontinence. After a few hours of observation, he was discharged with follow-up in general paediatrics.

There was no contributing medical, surgical or family history. The patient was born and raised in Burundi until the age of 6 years, when he arrived in Belgium in November 2020. He received the recommended vaccination schedule in Burundi, including the BCG vaccine, and then continued with the standard vaccination schedule in Belgium. There was no ongoing chronic treatment.

Blood tests on admission were normal. The electroencephalogram (EEG) performed on the same day revealed slow brain activity for his age, but no ongoing epileptic activity. A 24-hour EEG performed 2 days later was normal.

The diagnostic workup included cerebral imaging with computed tomography scan (CT) and magnetic resonance imaging (MRI), which

Figure 1: Cerebral MRI (A, B and C) and CT-scan (D and E). The solid arrow indicates the calcified cysticercus. The hollow arrow indicates a sequela ring of demyelination.

A: Axial T2WI shows an hypointense granulomatous punctiform lesion in the left parietal lobe surrounded by a slight vasogenic oedema. **B**: Axial T1 post-contrast reveals peripheral enhancement. **C**: Axial DWI image shows the absence of restricted diffusion, demonstrating the absence of a viable scolex. **D** et **E**: Axial CT slices in bone (D) and parenchymal (E) reconstruction confirming the calcified nature of the lesion.

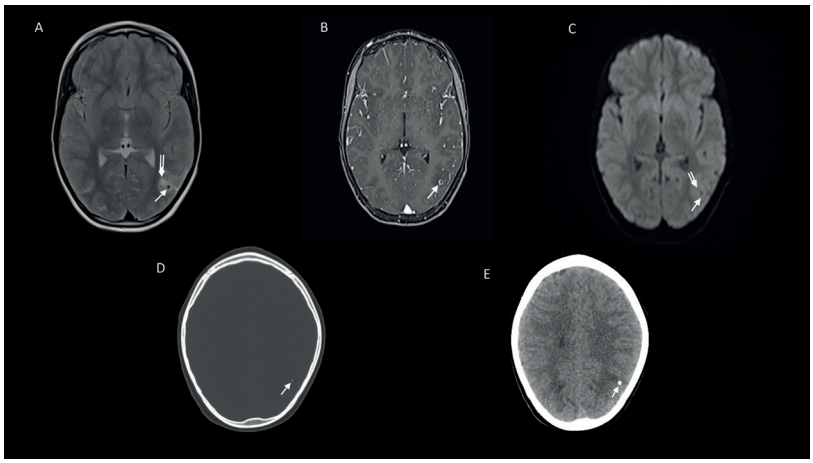

Table 2: Laboratory data on admission.

CEREBROSPINAL FLUID ANALYSIS				
Cytology, chemistry				
Analysis	**Unit**	**Index**	**Normal values**	**RESULT**
Red blood cells	/µL		< 10	0
White blood cells	/µL	++	< 10	**13**
Lymphocytes	%		40 - 80	few
Monocytes/macroph.	%		15 - 45	rare
Chloride	mEq/L	+	120 - 130	**132**
Lactate	mg/dL		9 - 26	12.9
Proteins	mg/L		150 - 450	279.1
Glucose	mg/dL	-	50 - 80	*46.5*
Parasite serology				
Analysis	**Unit**	**Index**	**Normal values**	**RESULT**
Taenia solium IgG (ELISA)	Ratio		<1.00	**3.58**
Taenia solum antigen			Negative	**26**
Molecular diagnosis				
Analysis	**Unit**	**Index**	**Normal values**	**RESULT**
PCR multi			Negative	Negative
E. coli K1, H. influenzae, L. monocytogenes, M. pneumoniae, N. meningitidis, S. agalactiae, S. pneumoniae.				
Cytomegalovirus, Enterovirus, H. simplex 1, H. simplex 2, Human herpesvirus 4 (EBV), Human herpesvirus 6, Human parechovirus, Varicella zoster virus, Cryptococcus neoformans/gattii				
Bacteriology				
Analysis	**Unit**	**Index**	**Normal values**	**RESULT**
Direct examination				Negative
Culture				Negative

revealed small calcifications in the left parietal region, right frontal region and lentiform nucleus bilaterally, and in the quadrigeminal cistern (Figure 1). A subsequent MRI of the spinal cord showed no lesions and an ophthalmological examination was normal. Cerebrospinal fluid (CSF) analysis was positive for intrathecal *Taenia solium* antibodies (ELISA) and antigen (Table 1).

These findings suggested epilepsy secondary to neurocysticercosis (NCC). The diagnosis of NCC was made definitively based on the Del Brutto criteria: parenchymal brain calcifications on neuroimaging (major neuroimaging criterion), detection of specific anticysticercal antibodies or cysticercal antigens by immunodiagnostic tests, clinical manifestations suggestive of NCC and an individual coming from an area with endemic cysticercosis (three major clinical/exposure criteria) (1). The standard therapeutic management of neurocysticercosis with positive antigen testing includes antiparasitic treatment. However, in this case, since the calcifications found by cerebral imaging indicate old cysts without viable parasites and due to the long seizure-free interval, no antiparasitic treatment nor long-term anti-epileptic treatment was initiated.

No stool sample was analysed as the work-up indicated a calcified, late form of NCC, probably acquired before the patient left Burundi. Other family members never presented with symptoms suggestive of cysticercosis or NCC, and no work-up was initiated for them at this time.

Taenia solium: two clinical presentations

Taenia solium is a segmented flatworm that infects pigs and humans. In humans, the adult tapeworm resides in the small intestine and attaches itself to the intestinal wall. The tapeworm's body is made up of proglottids, i.e. segments containing eggs, which are shed in the faeces. Pigs become intermediate hosts when they ingest the eggs found in human faeces. These eggs release larvae that penetrate pig's the intestinal wall and form cysticerci in different tissues, particularly muscles. When humans consume undercooked pork meat, they ingest cysticerci, which will mature and develop into adult worms in the intestine, leading to taeniasis (2). Infected individuals may have mild or no symptoms, but they excrete *Taenia solium* eggs in their faeces. Diagnosis is made by identifying eggs or proglottids in the stool, although the sensitivity of the test is low (around 40%) (3).

Humans are the final hosts of *Taenia solium* and thus the only transmitters of the eggs: human cysticercosis occurs when humans ingest eggs, in areas with suboptimal faecal hygiene, either in the environment or via tapeworm carrier, sometimes themselves (autoinoculation). Food or water is contaminated by the ingested eggs or faecal-oral transmission occurs, and the larvae hatch and migrate to the tissues. Symptoms vary depending on the location of the cysts. Cysts of the brain and eye can cause severe disorders (NCC), while cysts in muscles or skin usually cause mild symptoms (cysticercosis). The diagnosis of cysticercosis involves antibody- or antigen-based serological blood tests, and radiological identification of cysticerci.

Cysticercosis is a common disease in several regions of the world, including Latin America, sub-Saharan Africa, South-East Asia, and parts of India. Assessing taeniasis prevalence is challenging due to the mild symptoms of taeniasis and limited the access to diagnostics in endemic areas. Areas endemic for cysticercosis are defined by the WHO as areas with porcine cysticercosis (4).

Neurocysticercosis

The term neurocysticercosis refers to the infection of the central nervous system by the larvae of *Taenia solium*, which encyst themselves and form cysticerci. The clinical manifestations vary depending on the host's immune response, as well as the location, number, stage and size of the cysticerci (5).

Cysticerci undergo distinct stages of evolution, which are associated with specific symptoms and imaging characteristics. During the vesicular stage, the cysts are initially small and filled with fluid, in which a scolex can sometimes be identified. These cysts are viable and often asymptomatic, although they can cause headaches or visual disturbances. On neuroimaging, they appear as rounded or oval cysts with a thin wall and an eccentric scolex. During the colloidal stage, cysts become gelatinous and undergo inflammatory transformation. This results in a thickening of the cyst wall and surrounding vasogenic edema. The scolex is often no longer visible. This stage is associated with the onset of more pronounced neurological symptoms, including seizures, and severe attacks of headaches. Finally, the cysts reach the granular-nodular and then calcified stages, during which time the perilesional vasogenic edema resolves and calcium deposits develop. Fully calcified cysts are generally asymptomatic, although they may also cause epileptic seizures. They ca be identified on cerebral CT as hyperdense lesions.

Parenchymal cysts primarily manifest as epilepsy and motor disorders, sometimes accompanied by headaches. The clinical intensity correlates with the stage of cysticerci evolution and their quantity.

Ventricular or subarachnoid cysts often asymptomatic at the initial stage, but may subsequently present with sudden clinical manifestations, including headaches, dizziness, and vomiting when mobile ventricular cysts obstruct cerebrospinal fluid circulation. Racemose NCC is a form of extraparenchymal NCC, that is characterised by the presence of numerous neurocysticerci, which are clustered in appearance. This form of NCC s associated with a poorer prognosis.

Overall, epilepsy is the most common manifestation of NCC, which is the leading cause of late-onset epilepsy in endemic areas.

Diagnosis

The diagnosis of NCC is complex due to the varying diagnostic criteria according to the disease stage (6). The del Brutto criteria have become nowadays the reference for establishing a diagnosis of NCC (1). A definitive diagnosis is made when the parasite is demonstrated in histological samples or when brain imaging reveals a cystic lesion with a scolex, or on a set of epidemiological, clinical, serological, and imaging criteria, as all elements have variable sensitivity and specificity.

Antibody-based serological tests are poorly sensitive when the parasitic load is low and cannot distinguish active infection from past exposure. Antigen-based assays lack sensitivity but usually reflect the presence of viable cysts for which anthelminthic treatment may be beneficial. These tests performed on the serum sample are unable to differentiate between cysticercosis and NCC. The same tests can be performed on CSF but the correlation between serum and CSF test results is partially dependent on the localisation of the cysticerci and the severity of NCC (7).

Although our patient displayed positive antigen testing on CSF, the low value and the radiological findings being more suggestive of a calcified form of NCC meant that no anthelminthic treatment was considered. Furthermore, as CSF analysis results were obtained early during the work-up, no blood serology was performed.

The sensitivity of brain CT is not optimal for vesicular lesions, which are better identified by MRI. However, CT is superior in the detection of calcifications, which are not common in young patients. The MRI can better predict the stage of the NCC based on the presence of the scolex or surrounding vasogenic edema. The imaging workup will specify the form of the infection based on the location of the lesions.

Treatment options

A multidisciplinary management approach must be tailored for each patient with NCC, involving neurologists, neurosurgeons and infectious disease specialists (8). Therapeutic options include anthelminthic drugs (albendazole and/or praziquantel), systematically combined with corticosteroids to prevent or treat cerebral inflammation in symptomatic patients. Surgery may be considered for unique, large, critical, or intracranial pressure-inducing cysts. Symptomatic treatment addresses specific symptoms with antiepileptic drugs although no specific epilepsy treatment modality exists for NCC.

With regard to parenchymal forms, the most appropriate treatment varies according to the development stage of the cysticerci (anthelminthic treatment in vesicular stage, combined with corticosteroids) and clinical presentation (with or without antiepileptics). In the case of extra-parenchymal NCC, a more complex case-by-case adaptation is required, frequently involving neurosurgery and a longer course of anthelminthic treatment (9).

Preventive measures include maintaining proper hygiene and treating taeniasis to prevent proglottids release in the environment and ensuring thorough cooking of pork to prevent taeniasis.

The prognosis for NCC is dependent upon a number of factors, including the location, number, severity of symptoms, response to treatment, and the presence of complications. In countries with greater resources, early diagnosis and appropriate treatment have been shown to yield favourable outcomes. Mortality is relatively low, with rates of 0.3% to 3%. However, severe complications such as hydrocephalus and meningitis can result in higher mortality rates.

Neurocysticercosis in children

NCC occurs mainly in older children because of its mostly asymptomatic latency period. Epilepsy is the most common symptom, raising suspicion especially in endemic areas. Acute headache or atypical neurological symptoms in children may also be suggestive. Occasionally, developmental delay may be the only clinical clue. Due to the reactivity of the child's immune system, inflammatory reactions around cysticerci can be sudden and severe. Ventricular cysticerci are more common in children. Therapeutic approaches are similar to those in adults (10).

Although NCC is a leading cause of acquired epilepsy in endemic areas, the differential diagnoses should not be overlooked. Regardless of the cause, the management of paediatric seizures has the same goals as adult management: crisis management to prevent complications, identification of reversible or immediately life-threatening causes, and prevention of short- and long-term complications.

Conclusion

The diagnosis of neurocysticercosis is uncommon outside endemic areas for porcine cysticercosis and requires a multidisciplinary evaluation and management. In the emergency room, the occurrence of a first epileptic seizure or the presence of suggestive symptoms in a patient with features consistent with neurocysticercosis should prompt investigation for this diagnosis. Indeed, certain forms or stages of NCC may require specific treatments.

Conflict of interest

The authors declare that they have no conflict of interest.

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How to clean and care for baby's skin

The power of Pampers® wipes

Nothing is as plump and perfect as a baby's skin, but, not all is as perfect as it seems. From the moment a baby is born, this soft and squishy barrier is hard at work, protecting them from infection, irritants and much more.[1,2] All whilst still being delicate and vulnerable!

Did you know that at birth, the stratum corneum is up to 30% thinner than adult skin? And that baby's skin continues to develop even beyond the first 3 years of life![3,4,5,6]

That's not all; for roughly the first two and half years of their life, babies' bottoms are covered 24 hours a day by a diaper, where the skin is exposed to humidity and irritants like pee and poo... **This is why it's up to all of us to protect babies' delicate skin from day one!**

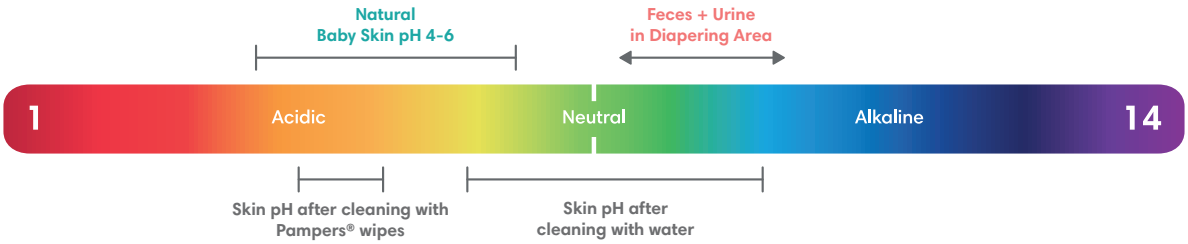
Understanding pH Balance for Healthy Baby Skin

Balanced skin pH (between 4-6)

- Healthy baby skin surface is naturally acidic
- During the first days of life, baby's skin develops a protective layer - an acid mantle - which helps healthy development of stratum corneum and protects against infection[7]

Elevated skin pH (above 6.0)

- Increases the activity of fecal enzymes that break down the skin barrier
- Damages the stratum corneum barrier, changes the microbial flora and increases the risk of infection[8]



Why water and cotton might not be enough?

Cleaning method is important in helping to restore natural skin pH

Pampers® baby wipes are made of a soft, cloth-like substrate, with **a unique blend of fibre shapes and sizes** which keep them **absorbent, and flexible to pick up mess from every crease and curve** of the skin while staying gentle. Intentionally designed wipe lotion - such as Pampers® baby wipes - has a number of ingredients that help to **clean skin, and help restore healthy skin pH.**[8,12] While water is a foundational component of baby wipes, water alone is not optimal to support baby's skin.

Ingredients in Pampers® Wipes

	Include citric acid based buffering system that helps restore skin's natural acidic pH and help inactivate fecal enzymes	Water has a poor pH-buffering power and neutral pH. It cannot restore skin's natural pH and decrease fecal enzyme activity[3,9,10]
pH Buffering System Helps restore natural skin pH		
Emulsifiers Efficiently remove urine and stool	Contain water and emulsifiers to remove both water-soluble and oily mess	Poor cleaner, especially of oily substance found in stool and on skin[3,9,11]
Conditioners Help restore skin appearance and improves feel	Soft with conditioners to gently glide across skin	Washing with water alone can have a drying effect on infant skin[3,10]
Preservatives Inhibit the growth of germs	Inclusion of a mild preservative to help prevent the growth of germs	Cannot stop germs from growing

Pampers® Wipes - everyday safe and high performing products

Over the past decades at Pampers®, we have been innovating to provide everyday safe & high performing products that can be used confidently.

We not only intentionally design products to protect your little ones skin, all of Pampers® baby wipes and their ingredients undergo rigorous testing to ensure they are safe, effective and gentle for babies' delicate skin. Every product we make must live up to the most demanding standards of all – yours.

What is NOT in Pampers® Harmonie Aqua

- Parabens
- Dye
- Ethanol/Rubbing Alcohol
- Natural Rubber Latex
- Methylisothiazolinone
- Sulfates
- Fragrances
- Phenoxyethanol

Gentle Skin Protection

Helps restore natural skin pH, made with 99% water

Dermatologically tested

100% Plant-Based Fibres

Recommended by SHA dermatologists

Suitable from **Day One**

We are accelerating our journey towards plastic free wipes

Our Harmonie wipes **are now fully plastic-free**

And we will not stop there!

We remain committed to **correct disposal**

With clear "Do not flush logo" across our portfolio, and SUP logo on plastic SKU, in compliance with the EU regulation

Why do we believe biodegradability for wipes can be misleading?

Regardless of their composition...

A used wipe is typically wrapped inside a used diaper and then disposed of in normal household waste, which is usually incinerated or landfilled where biodegradability makes no sense

Many authorities don't accept human waste in the organic bin in Europe

Baby wipes are used to clean baby's bottom, meaning that they contain human waste (pee and poo), and therefore pathogens, creating a biohazard in home composting

Biodegradability claims can be perceived as a 'license to litter' plastic into the environment for consumers[13]

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Non-Typhoidal *Salmonella* Infections Unmask the Challenges in Pediatric Febrile Illness Care in DR Congo

PhD Thesis Presented on December 20, 2023, at KU Leuven, Leuven, Belgium

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Keywords

Non-typhoidal *Salmonella* ; bloodstream infection ; antimicrobial resistance.

Severe febrile illness resulting from malaria or bacterial infections, such as pneumonia or invasive *Salmonella* infections, account for more than a third of global under-five mortality cases (1). Particularly in children in sub-Saharan Africa, non-typhi *Salmonella* (NTS) frequently cause bloodstream infections that are ten times more fatal than severe malaria infections (2–4). The high NTS burden in children in sub-Saharan Africa is attributed to highly invasive sub-Saharan African NTS strains and to frequent comorbidities that compromise the immune response such as Plasmodium falciparum malaria, anemia, malnutrition and HIV (5). The diagnostic uncertainty and barriers to treatment of invasive NTS infections further increase mortality (5).

I was fortunate to conduct my PhD research in DR Congo in collaboration with Belgian (Institute of Tropical Medicine Antwerp, KU Leuven), national (Institute of National Biomedical Research Kinshasa, Hôpital St. Luc Kisantu, DR Congo) and international (International Vaccine Institute) partners. I investigated the challenges to manage invasive NTS infections in children under-five and evaluated potential solutions, many of which can be generalized to other causes of severe febrile illness.

Prevention is better than cure: how to contain NTS infections?

Based on sentinel blood culture surveillance data from 2007 onwards, I revealed the increasing occurrence of NTS bloodstream infections in DR Congo (6). Three quarters of bloodstream infections in children under-five admitted to a district hospital in Kisantu were caused by NTS (6). Most NTS were extensively drug resistant due to concurrent ampicillin, cotrimoxazole, chloramphenicol, third generation cephalosporin and fluoroquinolone or azithromycin resistance (6 and unpublished data). Vaccines are being developed to prevent these invasive, highly resistant NTS infections, but must target multiple serotypes to be effective. I demonstrated that, although most NTS were serotype Typhimurium and Enteritidis, a Typhimurium serovariant which lost the vaccine-targeted O5-antigen had emerged (variant Copenhagen) (6).

Interestingly, NTS bloodstream infections mainly occurred during the rainy season. Based on longitudinal analysis of the surveillance data, satellite-based estimates of rainfall data and malaria statistics, I demonstrated that both the seasonal increase in *P. falciparum* malaria and rainfall by itself account for the seasonal NTS dynamics (7). This stresses the importance of malaria control to reduce the NTS burden, but also suggests water borne NTS transmission and thus the importance of clean water and sanitation measures.

The need for speed: how to improve prehospital care?

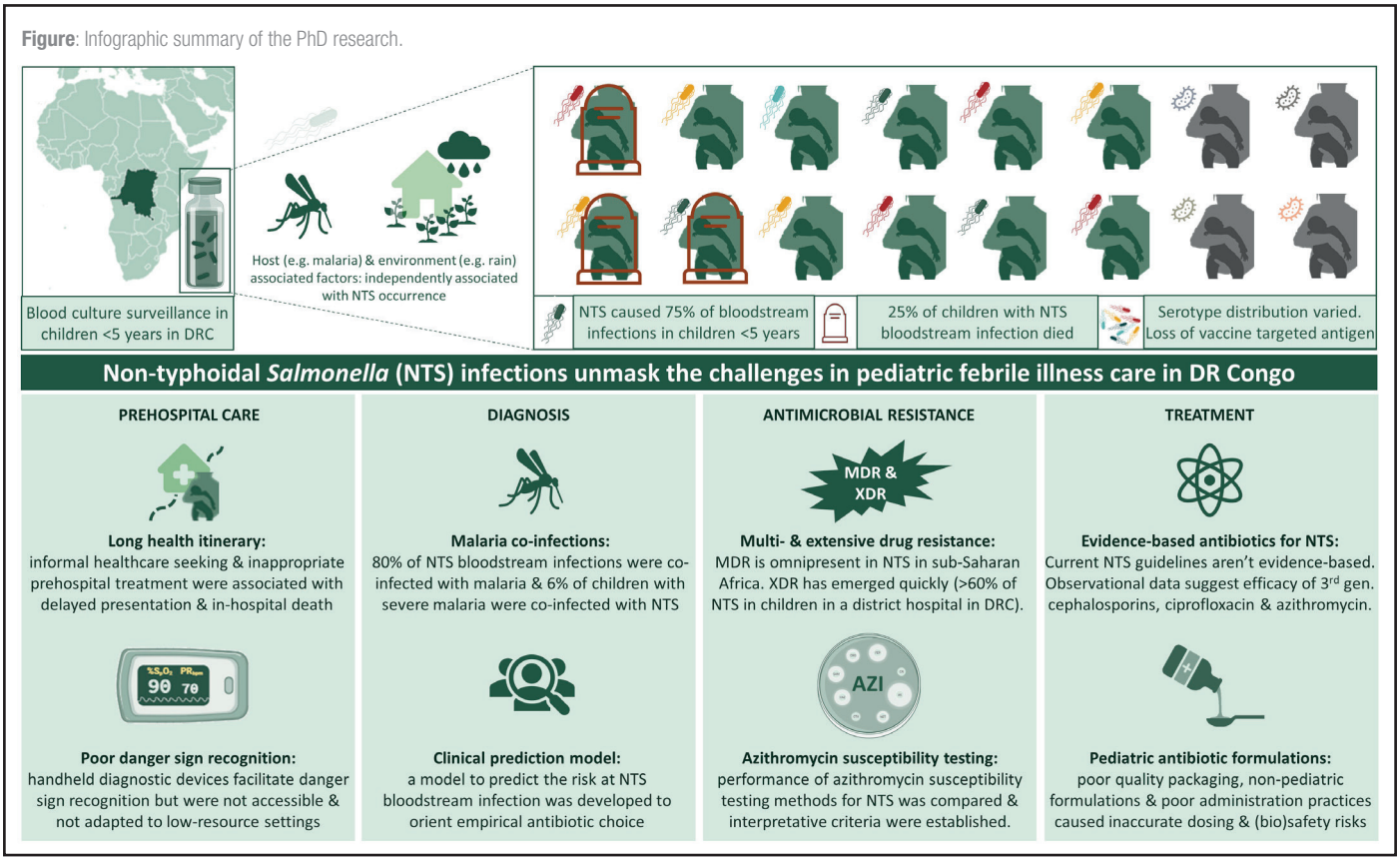
Over an 18-month period, 2682 children admitted to Kisantu hospital with severe febrile illness were enrolled in prospective observational cohort studies (unpublished data). Sadly, 7% (185/2682) of them died (unpublished data). From the subset of children with NTS bloodstream infection, 24% (80/333) died, which is very high, particularly when compared to a case fatality of 3% (37/1277) in children with severe P. falciparum malaria (8 and unpublished data). Irrespective of severe febrile illness etiology, death mostly occurred during the first 2 days of hospital admission and was associated with delayed presentation (8). Both death and delayed presentation were associated with informal prehospital health care seeking and inappropriate prehospital management (8).

Recognition of clinical danger signs is essential for timely hospital referral, but frontline healthcare workers often have limited clinical training and expertise in low-resource settings. Handheld diagnostic devices can help them to recognize danger signs, such as high fever, rapid breathing, severe anemia or hypoglycemia. However, we observed difficulties with device selection, procurement and shipment, adoption and maintenance of a tympanic thermometer, a multimodal oximeter with automated respiratory rate measurement, a hemoglobinometer and a glucometer. We therefore described the end-users' needs that must be considered to improve access to affordable, well performing, robust and user-friendly devices adapted to low-resource settings (9,10).

Finding a way out of the maze: how to improve hospital care?

Early diagnosis and prompt appropriate treatment are essential to improve survival. Unfortunately, NTS bloodstream infection have a high diagnostic uncertainty. Eighty percent (265/333) of children with NTS bloodstream infection were co-infected with *P. falciparum* malaria and no pathognomonic clinical signs and symptoms could be identified in my research (unpublished data). Vice versa, As a result, blood cultures are required for diagnostic confirmation, but access to blood cultures in sub-Saharan Africa is limited and the time from sampling to final results

Figure: Infographic summary of the PhD research.



(identification & antibiotic susceptibility testing) is 3-5 days. Two-thirds (189/313) of NTS isolated during the prospective studies in Kisantu had extensive drug resistance due to concurrent non-susceptibility to ampicillin, cotrimoxazole, chloramphenicol, third generation cephalosporins and fluoroquinolones (unpublished data). Due to the combination of diagnostic uncertainty and high antibiotic resistance, NTS are often not covered by empirical antibiotics (mostly intravenous third generation cephalosporins). Therefore, I developed a clinical prediction model for settings where NTS are often resistant to standard-of-care empirical antibiotics. which can be used to modify empirical antibiotic choices based on the predicted NTS risk (unpublished data). Clinicians can use this model to decide to modify a child's empirical antibiotic treatment based on the predicted NTS risk.

In a systematic review and meta-analysis, I revealed that, despite the rapidly increasing antibiotic resistance in NTS, antibiotic treatment recommendations for invasive NTS infections are merely extrapolated from typhoid fever or based on expert consensus, as good-quality data on the efficacy of antibiotics to treat invasive NTS infections are missing (11). The review also revealed that, while azithromycin is often recommended to treat NTS, azithromycin susceptibility testing is not done because there are no recommendations on how to test and interpret it. In a multi-laboratory study with bio-banked NTS isolates from five surveillance collections I established that disk diffusion performed well to test azithromycin susceptibility in field settings and determined the epidemiological cut-off to interpret azithromycin susceptibility in invasive NTS infections (12).

Finally, I compared the survival of children with NTS bloodstream infection enrolled in one of the prospective observational studies in Kisantu based on the administered antibiotic treatment. Children with NTS bloodstream infection who received susceptibility-matched third generation cephalosporins, ciprofloxacin or azithromycin (n = 142) had a significantly better survival than children who only received susceptibility-mismatched antibiotics (n = 77, hazard ratio = 0.16 [0.30-0.09]) (unpublished data). These observational data provide the first evidence on the efficacy of third generation cephalosporins, fluoroquinolones and azithromycin to treat NTS bloodstream infections in children under-five in sub-Saharan Africa. Last but not least, I described how poor quality and non-pediatric antibiotic formulations and poor prescription and administration practices cause inaccurate antibiotic dosing and (bio) safety risks and require local, national and supranational action (13).

The insights on azithromycin susceptibility testing and antibiotic treatment of NTS generated as part of this PhD research were integrated in the European antibiotic susceptibility testing guidance and antibiotic treatment guidelines from the World Health Organization, respectively (14, 15). The observations regarding poor access to and quality of pediatric formulations, have triggered national regulatory action in DR Congo.

In conclusion, this PhD thesis reports the high burden of NTS bloodstream infections in children under-five in DR Congo. The control, diagnosis and treatment of NTS bloodstream infections is very challenging. To prevent NTS infections, future research should focus on a better understanding of environmental transmission, NTS vaccine development and the potential impact of the new malaria vaccines (RTS,S/AS01 and R21/Matrix-M). Formalizing, training and monitoring the primary healthcare sector, improved detection of clinical danger signs with "tropicalized" handheld diagnostic devices, and increasing access to blood culture diagnostics can accelerate NTS diagnosis. Finally, promptness and appropriateness of NTS treatment must be improved by strengthening the evidence on antibiotic treatment (drug, duration, oral switch) with clinical trial data and integrating these data in user-friendly treatment algorithms, by facilitating adoption of antibiotic susceptibility testing in field settings and reference laboratories, by improving access to good quality and age-appropriate antibiotic formulations and administration devices (including infusion devices), and by improving early supportive management.

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ERRATUM: We are republishing the article "Feasibility and safety of early mobilization in critically ill children: a prospective experimental study" by Damien Moerman et al (Belg J Paediatrics 2024;1:11-15). There were some errors in the text due to an error on our part at the time of publication.

Research articles

Feasibility and Safety of Early Mobilization in Critically Ill Children: A Prospective Experimental Study

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Keywords

Early mobilization ; feasibility ; pediatric intensive care unit ; pediatrics ; critically ill children ; safety.

Abstract

Objectives:

The study aims to evaluate the feasibility and the safety of early mobilization in critically ill children under 2 years old and its impact on comfort scores.

Methods:

Children were recruited in our tertiary care pediatric intensive care unit. One session of upper and lower limb mobilization was performed within 48 hours after admission. The heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressures (SBP and DBP, respectively) and pulse oximetry oxygen saturation (SpO_2) were recorded before (T0) and at the end of the mobilization (T1). Parameters were also noted at 10 min (T2), 30 min (T3) and 1 hour after the end of the mobilization (T4). The EDIN score and the Comfort-B score were used to assess comfort.

Results:

Twenty patients were included and mobilized. HR, SBP and DPB showed no change at the end of the mobilization compared to baseline (138 bpm ± 20 vs 133 bpm ± 15; 101 mmHg ± 18 vs 94 mmHg ± 12; 54 mmHg ± 11 vs 49 mmHg ± 7, respectively). RR and SpO2 did not statistically change during the study. Four sessions of mobilization were interrupted because of discomfort associated with increased EDIN and Comfort-B scores. No technical adverse events were recorded.

Interpretation:

Early mobilization is feasible and safe in most stable critically ill children under 2 years old as long as the height and type of surgery allow for mobilization of the patient. Discomfort was observed in 20% of the children.

Introduction

Children admitted to the pediatric intensive care unit (PICU) can experience cognitive, psychologic, and functional sequelae as a consequence of critical illness. Immobility is associated with complications including muscle weakness, pressure ulcers, and venous thromboembolism that may impact the length of stay in the PICU (1). As a result, there is a great interest in early mobilization. The perceived benefits of early mobilization in critically ill children are a shorter duration of mechanical ventilation, improved wake – sleep rhythm and a shorter length of stay in the PICU (1). Nevertheless, the efficacy of early mobilization in the pediatric population remains unclear due to the low level of evidence (2). Moreover, the feasibility and safety remain poorly described in this population: the main barriers reported were hemodynamic instability, the risk of vascular catheters and endotracheal tubes dislocation, and the sedation level (1,3).

Early mobilization is defined as non-mobility interventions (passive range of motion) to prevent muscle atrophy and maintain range of motion (ROM) and mobility interventions (active ROM, in bed cycling, transfers) to enhance endurance, strength, and balance (3). Early mobilization should be started within 48 hours of PICU admission (4). In a Canadian survey, only 10% of children admitted to the PICUs were mobilized within 48 hours of admission (3). The chest physiotherapy sessions were favored over mobilization (4). Despite different working practices, the physical therapists are infrequently consulted for early mobilization in European PICUs (5). This low frequency of prescription could be explained by the lack of expertise of the medical team to recognize a patient who would require early rehabilitation and the absence of dedicated physiotherapists to the PICU (6). Nevertheless, the numbers of children who received physical therapy increased when a mobilization protocol was implemented in the PICU (7,8).

In addition, the feasibility and safety of early mobilization has been demonstrated in critically ill children older than 3 years (9,10). Younger age has been identified as a barrier to physical rehabilitation, despite reassuring studies on the safety of early mobilization in children younger than 3 years old (4,8,11,12). An inpatient rehabilitation program based on standardized care pathways was shown to be safe for infants (median age: 1.1 years) after extracorporeal ventricular assist device placement (12). Early mobilization after liver transplantation in children (median age: 1.1 years) was also well tolerated (8). No adverse events associated with early mobilization were observed (8,12).

Based on these statements, we hypothesized that an adapted early mobilization program can be performed safely without major changes in parameters. The aim of this study was to evaluate the feasibility and the safety of early mobilization in critically ill children under the age of 2 years by investigating the impact on cardiorespiratory parameters and comfort scores.

Materials and methods

Setting

A prospective experimental study was conducted in the PICU at Cliniques universitaires Saint-Luc from September 2016 to February 2017 following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE statement). The PICU is a polyvalent tertiary unit caring for various pathologies, including pediatric cardiac surgery and liver transplantation. This study was performed in line with the principles of the Declaration of Helsinki. The protocol study was approved by our institutional research ethics board (2016/11JUI/316). The clinical trial was recorded in the National Library of Medicine registry (NCT02958124).

Written informed consent was obtained from parents or legal guardians for all patients included in the study.

Participants

All children younger than 2 years of age admitted for 24 to 48 hours in our PICU were eligible for inclusion. Children with cardiorespiratory instability were excluded. Cardiorespiratory stability was defined as no sweating, no signs of respiratory distress (nasal flaring, increased work of breathing, paradoxical breathing, stridor, grunting), adequate oxygenation [pulse oximetry within the target values of the child, oxygen index (OI) ≤ 20 (OI is a marker of the severity of hypoxic respiratory failure, combining FiO_2, PaO_2 and mean airway pressure (MAP): $OI = FiO_2 \times MAP \times PaO_2\text{-}1$. The higher the value, the more severe the oxygenation disorder), Positive End Expiratory Pressure (PEEP) between 4 and 8 cmH_2O], inspiratory pressure ≤ 30 cmH_2O, adequate respiration (respiratory rate or RR twice maximum the target values), adequate heart rate (HR) and systolic arterial blood pressure (increased by maximum of 20% compared to basal state), arterial or venous pH ≥ 7.25, no inotrope/vasoactive drugs (except for dobutamine ≤ 5 µg/kg/min or milrinone ≤ 0.8 µg/kg/min, corresponding to a low severity of hemodynamic impairment allowing safe mobilization), lactic acid ≤ 2.5 mmol/L. The cardiorespiratory parameters were collected 30 min before the start of the mobilization session.

Children receiving high frequency oscillatory ventilation or extracorporeal membrane oxygenation or with delayed chest or abdomen closure were also excluded.

Protocol study

Monitoring data and scores were documented at the first mobilization session between 24 and 48 hours after admission. Only one mobilization session per patient was included in the study; further sessions were not recorded. Passive mobilization of the upper and lower limbs was performed by the same trained physiotherapist. Shoulder circumductions, elbow flexions and extensions, wrist and fingers flexions and extensions, pelvis movements, triple bilateral flexions (like pedaling) and feet flexions and extensions were performed bilaterally. All these movements were performed in all patients and each movement was repeated for 10 times. The range of motion was maximal. Mobilization was carried out 30 min after morning care. During one hour after the session, no procedure or manipulation was carried out to ensure the validity of measurements. Each child received continuous or discontinuous enteral feeding. At the time of the study, there were no institutional guidelines for early mobilization.

Use of sedative and analgesic medications were based on local protocols according to international recommendations. The specific choice of drug and its administration interval depended on the personal evaluation of the physician in charge of the child, with the help of the bedside nurses and comfort scales. Continuous or discontinuous sedation or analgesia are administered to ensure safety and to control discomfort while keeping children awake. In case of minor agitation or crying during the session, some non-pharmacological facilitators such as pacifier, glucose, cuddly toys, music or massage were used to comfort the child. No additional sedation was given during the mobilization.

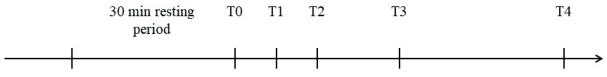
The mobilization was interrupted in case of important agitation, defined by reaching the discomfort threshold (Echelle Douleur Inconfort Nouveau-né (EDIN) and Comfort-Behavior (Comfort-B) scales) accompanied by one of the following criteria: increased work of breathing (nasal flaring, paradoxical breathing, stridor, grunting), increase in HR > 20% compared to basal state, increase in systolic or diastolic blood pressure (SBP or DBP) > 20% compared to basal state, occurrence of hypotension, increase in RR > 2 times the normal values, decrease in oxygen saturation (SpO_2) of > 4% below the target values of the child for > 60 sec, or accidental catheter removal (arterial, central venous, peripheral or urinary catheter).

Outcome measures

The primary outcome was the feasibility and safety of early mobilization in children aged 0 - 2 years old admitted in the PICU. The feasibility was defined as the ability to perform one full mobilization session of all upper and lower limbs through their full range of motion in critically ill children. The safety was assessed by the stability defined by change of respiratory and hemodynamic parameters. All the variables (HR, RR, SBP, DBP and SpO_2) were measured using a bedside monitor (Philips, Amsterdam, the Netherlands). These parameters were recorded continuously and noted before (T0), at the end (T1), 10 min (T2), 30 min (T3) and 1 hour after the mobilization (T4) (Figure 1). Adverse events such as endotracheal tube removal or catheter loss (arterial, central venous, peripheral or urinary catheter) were also recorded.

Figure 1: Experiment timeline.

T0, before the mobilization; T1, at the end of the mobilization; T2, 10 min after; T3, 30 min after and T4, 1 hour after the end of the mobilization.



The secondary outcome was to evaluate the impact of early mobilization on comfort assessed by the EDIN score for extubated children and the Comfort-B score for intubated children. The EDIN score is a score used to quantify the pain and discomfort in preterm and neonatal children (13). Nevertheless, this scale was chosen because it was already used in daily standard care to assess the comfort of children up to 9 months in our PICU. Five criteria (face, body, sleep, relational and reassurance necessity) are rated from 0 to 3 points. The higher the score, the worse the comfort: a cutoff score above 5 suggests discomfort. The Comfort-B score was developed and validated to measure pain and discomfort in mechanically ventilated children from birth to adolescence in PICU (14). When using the Comfort-B score, no other pain or sedation scale is necessary. We used the new version of Comfort-B score, without the physiological items: the arterial blood pressure and HR are difficult to assess. Each item (alertness, calmness or agitation, respiratory response, movements, muscle tone and facial tension) is rated from 1 to 5. The total score is calculated by adding up all individual scores: a score below 10 indicates excessive sedation, between 11 to 17 is the child comfortable, from 17 to 22 (potentially painful or discomfort) and a score > 23 indicates a clearly uncomfortable, painful child. We defined our discomfort threshold as a score greater than 5 on the EDIN score and above 17 on the Comfort-B score (13-14). Comfort assessments were performed before (T0) and at the end of the mobilization (T1), and 10 min after the session (T2).

During the mobilization, four patterns of behaviors were also recorded (calm, grimace, crying and agitation).

Statistical methods

The sample size was estimated on HR variation. Preliminary data from 10 subjects were used. Considering a standard deviation (SD) value of 14 bpm, adopting a significance level of .05, a power of 80%, the sample size was estimated to be 19 participants. This change of 14 bpm is also described as a reference from a pediatric study (15). Statistical analyses were performed using SPSS Statistics 25.0 (IBM Company, Armonk, New York, USA). The analysis of all outcomes followed the intention-to-treat principle. All values were expressed as mean ± standard deviation,

when data were normally distributed, otherwise by median, minimum and maximum values. Parametric and nonparametric analyses were used in accordance with the results of the Kolmogorov-Smirnov test. Repeated measures analysis of variance were used to evaluate the effect of mobilization on hemodynamic and respiratory parameters (within factors: time). Mauchly's sphericity was verified. Friedman test was used in the absence of the distribution normality. This nonparametric test was also used to measure the comfort of the child. All these statistical tests used a significance level of 5%.

Wilcoxon rank-sum tests were applied for post hoc comparisons using the Bonferroni correction, comparing each time point to another to find the significant change. Significance level was therefore set at $p < .01$.

Results

A total of 135 infants were eligible for inclusion. Ninety-three patients were excluded, of whom 72 due to cardiorespiratory instability, 18 due to absence of parental consent and 3 due to delayed chest or abdomen closure. Forty-two children were recruited. Among them, 14 children discontinued the study for inapplicable protocol due to their height: their height did not allow triple bilateral flexion of the lower limbs (pedaling). Eight post-surgical patients had contraindications to the mobilization because the surgical site involved the spine or the esophagus (esophageal anastomosis). A total of 20 infants were included (Figure 2). The baseline characteristics of the patients are described in Table 1.

Primary outcomes

Feasibility and safety

Twenty patients were included and mobilized: 15 spontaneously breathing without respiratory support and 5 invasively mechanically ventilated children. Sixteen sessions were completed and 4 sessions (3 cardiac patients and 1 patient with head trauma) were discontinued because of important agitation.

Table 2 shows physiologic and safety outcomes. The HR varied during the study period ($p = .03$) and changed significantly between T1 and T3 ($p < .01$). The SBP and DBP were also influenced by mobilization during the study period ($p = .02$ and $p = .04$, respectively). The SBP significantly decreased between T1 and T3 and, T1 and T4 ($p = .009$ and $p = .005$, respectively). The DBP also significantly decreased between T1 and T2 ($p = .006$). HR, SBP and DBP showed no change at T1 compared to baseline. RR and SpO_2 did not statistically change during the study.

Four mobilization periods were early discontinued because of a 20% increase in HR (n=2), a 20% increase in SBP and DBP (n=3) or a 4% decrease in SpO_2 (n=3). All the parameters returned to baseline 10 minutes after early discontinuation.

Table 1: Clinical characteristics of the patients at baseline.

Variables	Total (n = 20)
Age (days)	162 [1; 434]
Weight (kg)	6 [3; 10]
Female gender	12 (60)
Reasons for admission	
Congenital heart disease	14 (70)
Neurologic disease	3 (15)
Lung disease	2 (10)
Digestive disease	1 (5)
Ventilation	
Spontaneous breathing without NIV	15 (75)
Invasive ventilation	5 (25)

NIV, non-invasive ventilation.

Values are expressed as median with min-max values in square brackets, or numbers with percentage in round brackets.

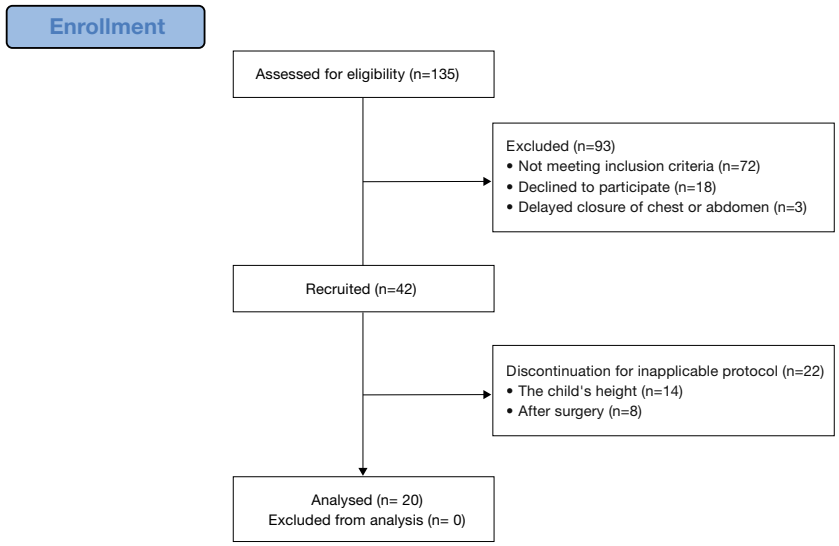
No adverse events were observed.

Secondary outcomes

EDIN scores changed over time ($p = .02$). EDIN scores showed no significant difference between T0 and T1. However, EDIN scores changed significantly between T1 and T2 ($p < .01$). Before mobilization, all the 15 spontaneously breathing patients were non-painful with EDIN scores ranging from 0 to 5. After mobilization, 3 of these 15 children had a score above 5. Mobilization was discontinued in 2 of them due to an increase in EDIN score from 2 to 7 and from 5 to 14. In the 5 ventilated patients, mobilization was discontinued in 2 patients due to an increase in Comfort-B score from 8 to 22 and from 10 to 19 (Figure 3).

Four types of reactions were noticed during the mobilization session: calm (n=8), agitation (n=6), tears (n=4) and grimaces (n=2). Half of the children needed facilitators such as glucose, cuddly toys or massage to calm down.

Figure 2: STROBE flow diagram.



Discussion

The aim of this study was to examine the feasibility and safety of early mobilization for children from 0 to 2 years in the PICU. Practical recommendations for early mobilization in critically ill children are lacking (4,16).

The feasibility and safety of early mobilization were evaluated in 20 children aged 1 day to 14 months admitted to the PICU. HR, SBP and DBP showed no change at the end of the mobilization (T1) when compared to baseline. RR and SpO_2 did not change significantly during the study period. In some children some parameters changed after the mobilization session without clinical importance. No technical adverse events were recorded. Our results are similar to other pediatric studies. Choong et al. showed no difference in cardio-respiratory and hemodynamic parameters after

Table 2: Change in parameters at different times.

	T0	T1	T2	T3	T4	p-value
HR (bpm)	133 ± 15	138 ± 20	129 ± 15	128 ± 14	131 ± 14	.03 [a,*]
RR (cycles/min)	31 ± 13	33 ± 12	32 ± 12	30 ± 10	32 ± 13	.64 [a]
SBP (mmHg)	94 ± 12	101 ± 18	96 ± 14	93 ± 13	93 ± 13	.02 [a,*]
DBP (mmHg)	49 ± 7.0	54 ± 11	49 ± 8.0	48 ± 8.0	49 ± 7.0	.04 [a,*]
SpO_2 (%)	99 [87; 100]	98 [81; 100]	98 [88; 100]	99 [89; 100]	98 [89; 100]	.44 [b]
EDIN scale (point)	2 [0.0; 5.0]	2 [0.0; 14.0]	2 [0.0; 6.0]			.02 [b,*]

HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, peripheral oxygen saturation.

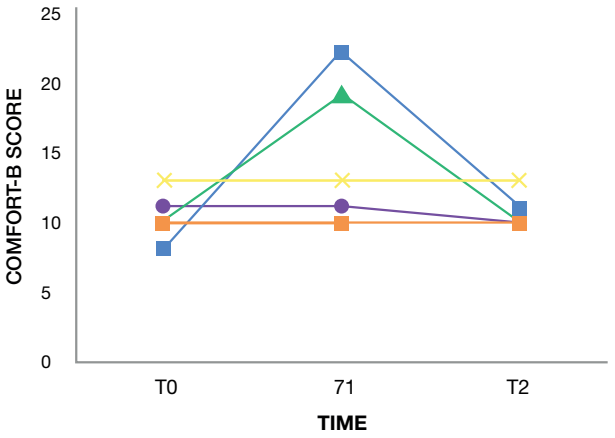
T0, before the mobilization; T1, at the end of the mobilization; T2, 10 min after; T3, 30 min after and T4, 1 hour after the end of the mobilization.

Values expressed as mean ± *SD* or median with min–max values in square brackets.

[a] *p*-value (Within Subjects – Factor = Time); [b] *p*-value (Friedman test); * $p < .05$.

Figure 3: Evolution of Comfort-B scores.

T0, before the mobilization; T1, at the end of the mobilization, T2, 10 min after the end of the mobilization.



passive mobilization with a cyclo-ergometer or active mobilization with a video-game in children aged 3 to 17 years (17). Abdulsatar et al. also reported feasibility of a 25 minutes Wii™ session for 8 children aged 3 to 18 years without changes in HR, RR, blood pressure and SpO_2, compared baseline (18). Additionally, these studies, like ours, showed no accidental tube displacements or extubations.

Sessions were feasible in 16 cases (80%) and discontinued in 4 cases (20%). All the children were calm and stable before treatment but they wiggled and turned during the mobilization.

Discomfort in these children was shown by changes in EDIN and Comfort-B scores, as well as hemodynamic and respiratory parameters. They all calmed down without need for sedative drug administration. Few studies focus on discomfort expressed by agitation as an adverse event (19). In the pediatric population, study data suggest that rates of potential safety events range from 1% to 6% (5,11,19). The European PARK-PICU study reported 6% potential adverse events: the most frequently reported events were a decrease in SpO_2, a change in HR and blood pressure (5). Adverse events are also described in critically ill adults. Schweickert et al. encountered one severe adverse event in 498 mobilization sessions in ventilated patients (desaturation less than 80%) (20). Hickmann et al. reported that adverse events, such as hypotension, hypertension and tachycardia, occurred in 10 activities (0.8% of total sessions) (21). The incidence of early mobilization adverse events in critically ill adults ranges from 1% to 6% including parameters changes, tube removals, skin injuries and falls (22–25).

We used facilitators such as a pacifier, glucose, cuddly toys, music or massage to relax the child during the mobilization. These facilitators can be considered as bias for evaluation of the child's behavior in the face of early mobilization. However, our nursing staff regularly uses these non-pharmacological techniques during treatments to avoid increasing sedation and analgesics. We therefore considered this technique to be common during the physiotherapy session with infants.

Several limitations to our study should be noted. First, our cohort was small due to strict inclusion criteria and surgical contraindications, the main limiting factor regarding external validity. Second, we did not include sedative and analgesic drug doses which could have had an impact on our results. Nevertheless, our unit has a strong culture of optimizing analgesia and minimizing sedation while maintaining infant safety and comfort. In addition, the comfort scales do not allow good discrimination of agitation and pain. Finally, our study did not assess the benefits of early mobilization. Muscle strength in young children is difficult to evaluate in clinical settings due to lack of non-invasive and reliable assessment tools. Peripheral muscle ultrasound could be a promising tool for bedside muscle assessment in children, as demonstrated in adults (26–29).

Conclusion

Early mobilization is feasible and safe in most stable critically ill children under 2 years old as long as the height and type of surgery allow for mobilization of the patient. Discomfort expressed by agitation is described as an adverse event. Future large-scale studies are still needed to assess the effect of early mobilization in children under 2 years old.

Acknowledgments

Professeur William D'Hoore (Institut de recherche santé et société, Université catholique de Louvain) is gratefully acknowledged for his assistance during statistical analysis.

Conflict of interest

GR has received research support from the Institut de Recherche Expérimentale et Clinique (Université catholique de Louvain, Brussels, Belgium).

Ethical considerations

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the regional Ethic Committee in Cliniques universitaires Saint-Luc and Université catholique de Louvain in Brussels (2016/11JUI/316).

Written informed consent was obtained from parents or legal guardians for all patients included in the study.

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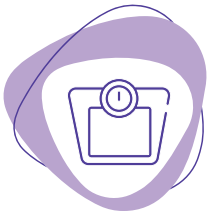
Cow's milk protein allergy: supporting growth

Management of cow's milk protein allergy (CMPA) requires an eliminiation diet. However, such a diet has consequences for micronutrient intake. To cover the needs of children over the age of one, and to support the growth of the CMPA child in particular, intakes must be perfectly adapted to their situation.

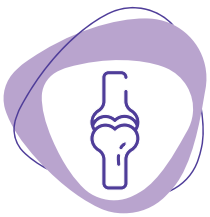
In all nutritional guidelines, recommended intakes are based on the child's growth needs. At the age of one, Belgium's Superior Health Council (HGR-CSS)[1] estimates energy requirements at 80 kcal/kg/d for both sexes. During the second year, they range from 57 kcal/kg/d to 84 kcal/kg/d depending on the child's advancing age (months), level of activity and gender[1]. Growth requires increased protein intake. The development and consolidation of the skeleton calls for increasing calcium levels[2].



The disadvantages of the elimination diet

The elimination diet is the cornerstone of the management of cow's milk protein allergy (CMPA). As breast-feeding is best for the child[3], mothers should be advised to avoid cow's milk protein in their own diet[4]. If breast-feeding is not possible, in addition the elimination of cow's milk from their diet is necessary and the replacement of the milk will be an extensively hydrolysed formula for the rest of their first year. In cases of severe allergy, or if there is no improvement compared with the previous formula, an amino acid-based formula is recommended[5]. Given the contribution of cow's milk to the intake of micronutrients such as calcium, zinc, riboflavin, magnesium, phosphorus, pantothenic acid, vitamin B12 and vitamin D, the elimination diet without compensatory intake of these micronutrients may be harmful to the growth in height and weight of children allergic to cow's milk proteins[6].

de Almeida[7] has shown that children with this allergy (IgE-mediated form) who do not receive a suitable infant formula or a vegetable alternative to milk have lower intakes of proteins and branched-chain amino acids than those who do. Rodrigues *et al*[8] studied a group of children aged 1 to 5 suffering from cow's milk protein allergy and put on an elimination diet. More than one child in four in this group (26.3%) had feeding difficulties. The authors found an association between these difficulties and low weight for age. By comparing the bone status of children with CMPA for more than four years with that of healthy children, Jensen *et al*[9] showed that the weight and height of children with CMPA were lower than those of healthy children. They were able to calculate that calcium intake in allergic children was only around 25% of the recommended intake. They concluded their study by recommending calcium supplementation for children allergic to cow's milk protein. These findings were subsequently confirmed, in particular by Boaventura *et al*[10] who also noted a significantly lower fat intake. In the children they examined who were on a milk-free diet, they also recorded lower serum concentrations of retinol (25.9% of children), beta-carotene (59.3% of children), lycopene (48.1%) and 25(OH) vitamin D (70.3%) than in healthy children with comparable characteristics.



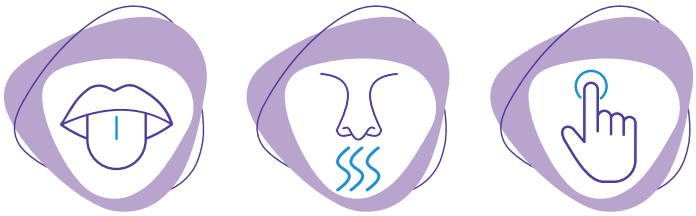
The need for a suitable formula

Maintaining a CMPA child on an elimination diet beyond the age of one year must therefore be managed using a formula specially adapted to this type of child. It is not only a question of meeting the growth needs of a child of this age. Care must also be taken to prevent potential nutritional deficiencies[11]. In addition, the infant formula offered must be acceptable to the child, both in terms of texture and flavour.

Sorensen *et al*[12] enrolled around thirty CMPA patients (mean age 2 years and 7 months) in a study. Due to various pathologies (food allergy for the most part, but also food intolerance or eosinophilic oesophagitis), these children were fed an amino acid-based formula or substitute milk. For 4 weeks, they were given an amino acid-based formula specially designed for children over one year of age (Neocate® junior). This formula was designed not only to meet the micronutrient requirements of children of this age, but also to appeal to them in terms of texture and flavour. At the end of the four weeks, protein and energy intakes had remained stable. Intakes of most micronutrients had improved. The increase was significant for zinc, copper and vitamin B2. After 4 weeks, more patients than at the start of the study reached the recommended intake levels for several micronutrients: zinc (77% vs. 53%), copper (97% vs. 73%), vitamin B6 (90% vs. 67%) and B2 (97% vs. 67%). In four weeks, the children's weight had improved significantly (+0.41 kg), as had their head circumference (+1.11 cm).

A major factor: sensory perception

In Sorensen's study[12], a large proportion of parents reported that their child liked the taste (68% of children) and texture of the amino acid formula (73%). It should be remembered that the formula is specially designed in terms of taste and texture to produce a food that appeals to children. These sensory aspects are very important for three reasons. Firstly, if they are perceived positively, they encourage children to consume food with these characteristics. Secondly, in the specific case of children of this age, they help to broaden the range of foods enjoyed by the child. Lastly, they are important for ensuring the child's compliance and thus guaranteeing appropriate nutritional intake. In a test carried out on children who were given infant formulas before diversification, Menella *et al*[13] showed that the perception of flavours has an impact on food preferences. Moreover, this effect of aroma-based experiences, which children have through breastfeeding but also through infant formulas and the first foods in the diversification process, is long-lasting. A factor that is important for later health[14].



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Outcome of Febrile Infants ≤3 Months of Age Admitted to the Emergency Department of a Belgian Tertiary Pediatric Hospital

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Keywords

Febrile infant ; fever without source ; serious bacterial infection ; viral infection ; emergency department.

Abstract

Background: Fever in infants under 3 months of age is a frequent cause for visits to the pediatric emergency department. Most children present with fever without a source and undergo multiple medical examinations to rule out serious bacterial infection (SBI), which often results in hospitalization. This study aimed to document fever outcomes in newborns and infants under 3 months old based on hospitalization data. The goal was to find a prediction rule that would enable healthcare professionals to identify febrile infants at risk for SBI.

Methods: A single-center retrospective study was conducted, covering the period from January 2016 to December 2022. In total, 150 infants aged up to 3 months old were admitted for fever without a source at the emergency department of Cliniques Universitaires Saint-Luc in Brussels, Belgium. The patient's medical history, clinical presentation, and complementary test results were analyzed to identify predictors of SBI.

Results: The results showed a significant increase in C-reactive protein levels (CRP=12.8mg/L in SBI cases; 5.5mg/L in viral infection cases, p-value=0.04) and neutrophil numbers in BI cases in children under 4 weeks old. No anamnestic or clinical factors were found to effectively differentiate febrile children aged less than 3 months at risk of developing SBI.

Conclusion: Further investigations are necessary to identify infants at risk for SBI using new biological parameters, including procalcitonin levels. The management protocol for these children must be re-evaluated to determine which complementary tests should be performed, whether hospitalization is necessary, and which patients are eligible for admission.

Introduction

Fever in infants, defined as a rectal temperature ≥38°C, is a common reason for Emergency Department (ED) visits in infants under 3 months old (1–3). These patients often present with fever without a clear diagnosis despite medical history, physical exams, and blood tests, resulting in a diagnosis of fever without a source (FWS). Infants in this age group are at a higher risk of serious bacterial infection (SBI), due to perinatal exposure and limited immunity compared to older children (4–7).

Differentiating simple viral infections (VI) from SBI based solely on medical history and clinical criteria is challenging. The main cause of SBI is urinary tract infections (UTI), while instances of meningitis and bacteremia have markedly declined over the past three decades due to herd immunity from vaccination (6). However, it is important to keep in mind that these conditions can be life-threatening (8,9). This challenge often results in additional tests, empirical antibiotics, and preventive hospitalizations. Therefore, it is critical to strike a balance between minimizing risks for patients and managing the time and costs of testing (10).

Although algorithms exist to differentiate between low- and high-risk infants, their inconsistent use in practice leads to unnecessary hospitalizations and procedures (3,11–15). Many febrile infants under three months are hospitalized to rule out SBI, resulting in discharges without a definite diagnosis (i.e., probable viral infections (VI)). Invasive investigations and antibiotics are frequently initiated in all infants, even those without SBI, potentially increasing the risk of adverse effects, complications, and antibiotic resistance(16,17).

Therefore, it is crucial to evaluate the usefulness of a panel of complementary tests in febrile infants and establish an optimal management strategy. This descriptive retrospective study aims to document the outcomes of infants under 3 months who were admitted for fever without a source (FWS) at the emergency department (ED) of Cliniques Universitaires Saint-Luc in Brussels. The objective is to identify clinical or biological markers that can predict SBI in order to reduce unnecessary tests, antibiotic use, and hospitalizations for low-risk infants. Management and diagnostic procedures in infants under 3 months were assessed, and their characteristics and clinical presentations at ED admission were compared to enhance care quality and cost-effectiveness.

Methods

Study design and settings

This is a retrospective, descriptive, single-center study that utilized historical data collected from the medical records of pediatric patients aged 0 to 3 months who presented with a rectal temperature of ≥38°C, as reported by their caregiver, at the pediatric ED of Cliniques Universitaires Saint-Luc clinics, a Belgian tertiary hospital, from January 2016 to December 2022. The exclusion criteria for this study included a known diagnosis at admission that could account for the presence of fever, prior hospitalization in neonatal or pediatric intensive care units, and comorbidities predisposing to increased infection risks, such as cancer, primary or secondary immunosuppression, extreme prematurity (i.e., less than 28 weeks of gestation), congenital heart disease, or asplenia (18). Only children who had been hospitalized were considered for this study. The hospital's ethics committee (ethics committee of Cliniques Universitaires Saint-Luc, N° 2023/02MARS/11) approved the study. Informed consent was not required due to the study's retrospective design.

For assessment purposes, patients were categorized into subgroups based on age and infection type. The subgroups included newborns under

4 weeks old, young infants aged 1 to 3 months old, and infections caused by either viruses or bacteria (19). According to our in-house guidelines, the management of fever in infants under 4 weeks old should include a full septic work-up, including systematic blood analysis such as a full blood count and CRP. For patients under 1 month old, physicians perform a series of tests including blood cultures, urinalysis (clean-catch, urinary catheterization or suprapubic puncture), and lumbar punctures (LP). For patients between 1 and 3 months old, physicians only perform a LP based on biological criteria (WBC >15 000/mm^3, WBC <500/mm^3 and/or CRP >40mg/L), as well as the infant's clinical assessment and general condition (i.e., sepsis or clinical signs suggestive of meningitis such as irritability or bulging anterior fontanel) (20). The threshold for determining positivity in urine culture varies depending on the method employed. For bags or clean-catch, the threshold is greater than 100,000 CFU. For urinary catheterization, the threshold is greater than 50,000 CFU. For suprapubic punctures, the detection of more than one germ is necessary.

All data were collected in a secure Excel document restricted to authorized personnel only. The data collected included obstetrical and neonatal history, such as intrapartum infection, premature rupture of membranes, vaginal smear results for group B *Streptococcus*, delivery route, birth weight and height, and prenatal jaundice. Patient characteristics, such as gender, age, and comorbidity, were also recorded, along with presenting symptoms at admission, duration and degree of fever, diagnostic test results, and antimicrobial treatments administered, including antibiotic or antiviral therapy. Hospitalization and rehospitalization within 30 days were also noted.

Table 1: Description of the total population.

	N=150
Age (mean [SD]), w	4.9 [2.5]
Fever duration (median [IQR]), h	8.00 [2.00; 24.00]
Peak fever (median [IQR]), °C	38.50 [38.20; 39.00]
Comorbidities, n/N (%)	14/150 (9,3)
Heart disease	2/150 (1,3)
Endocrinological problem	1/150 (0,67)
Uro-nephrologic pathology	4/150 (2,66)
Digestive disorder	3/150 (2)
Hematological pathology	3/150 (2)
ENT disorder	1/150 (0,67)
No comorbidities, n/N (%)	136/150 (90,7)
Symptoms beyond fever, n/N (%)	
Rhinitis	46/150 (30,7)
Cough	38/150 (25,3)
Skin rash	23/150 (15,3)
Diarrhea	27/150 (18)
Vomiting	18/150 (12)
Abdominal pain	25/150 (16,7)
Decreased appetite	52/150 (34,7)
No other symptoms, n/N (%)	23/150 (15.3)
Good general condition, n/N (%)	87/150 (58)
Notion of contagion, n/N (%)	92/150 (61,3)
Blood biology (CRP, WBC, neutrophil), n/N (%)	148/150 (98.7)
Urine analysis, n/N (%)	138/150 (92)
Nasal swab, n/N (%)	124/150 (82.7)
LP, n/N (%)	62/150 (41.3)
Antibiotic administration, n/N (%)	85/150 (56.7)

Numbers of individuals within the overall population exhibiting diverse study parameters, encompassing epidemiological characteristics, complementary tests, and initial therapeutic management

(w=weeks; h=hours; CRP=C-reactive protein; WBC=white blood cells; SD=standard deviation).

Statistical analysis

The study presented demographic and clinical data using standard statistical measures. Continuous variables were expressed as mean ± standard deviation, non-continuous variables as median followed by interquartile range, and categorical variables as numbers and proportions. Linear regression was used for continuous variables. Normality was tested using the Shapiro-Wilk test, and depending on the distribution of the variables, either a Student's t-test or Wilcoxon test was performed for continuous or categorical variables, respectively. The Pearson's chi-squared test was used to analyze the associations between categorical variables. Our research team conducted all statistical analyses using R software (R. Coreteam 2021). A significance level of 5% was set for all analyses.

Results

Analysis of the whole cohort

A total of 150 individual ED attendances were recorded during the study period. Table 1 summarizes the epidemiological characteristics, complementary tests, and initial therapeutic management. The mean age of the children was 4.9 weeks, and all presented with FWS for less than 24 hours. Blood testing was performed in 98.7% of cases, while urinalysis and nasal swab were performed in 92% and 82.7% of cases, respectively, regardless of the children's age. In the study, 41.3% of infants underwent LP, and 56.7% received intravenous antibiotics.

The study population was divided into two subgroups based on infection type: viral or bacterial. Of the total population, 17 cases of SBI were identified (11.3%), with eight cases in infants under four weeks old and nine cases in infants between one and three months old. The remaining 133 infants had VI (see Figure 1).

Of the infants diagnosed with SBI, 47% were male and 53% were female. In our cohort, UTI was the primary cause of SBI, accounting for 50% of infected cases in children under four weeks old, compared to 77% in the older subgroup. The most frequently identified pathogens were: *Klebsiella pneumoniae* (33%), *Pseudomonas aeruginosa* (16,7%), *Escherichia coli* (16,7%), *Citrobacter koseri* (16,7%), and *Enterococcus faecalis* (16,7%).

Regarding the complementary laboratory tests performed, the median CRP level (7.00mg/l [1.50; 12.60]) and the urine white blood cell count (WBC) (26.00 x10^3/µL [8.00; 116.00]) were higher in bacterial than viral diseases (1.20mg/l [0.80; 5.00] and 4.00 x10^3/µL [1.50; 14.00], respectively), with statistically significant between-group differences (Table 2).

Our analysis revealed that rehospitalizations were more common within 30 days in SBI cases than in VI cases. Overall, the clinical presentation upon ED admission was quite similar between both groups, without any real between-group differences noted. In terms of contagion, 53% of patients were in the SBI group and 62.4% were in the VI group (p-value 0.26). In summary, no statistically significant clinical or anamnestic criteria were found to predict patients at high risk of developing SBI.

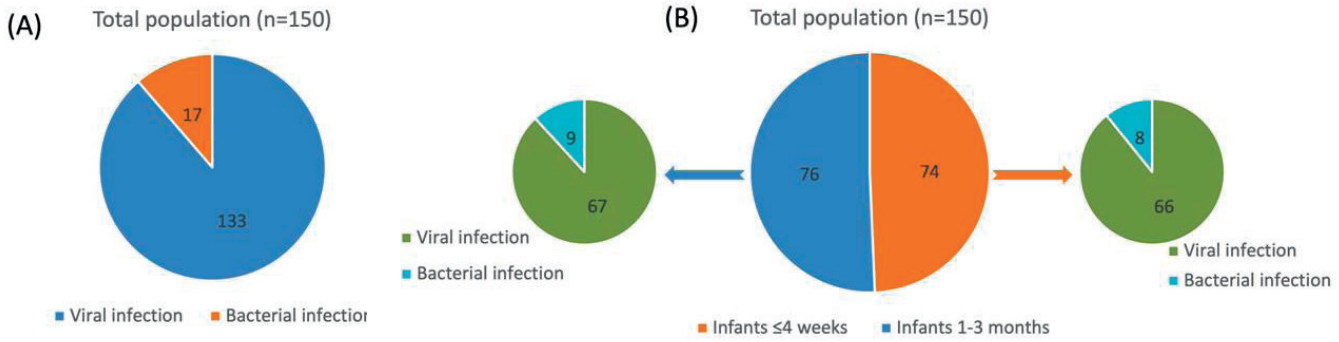
Subgroups of infants less than four weeks old based on infection type

In the second step, the study population was divided into two subgroups based on age: 74 infants under four weeks old and 76 between 1 and 3 months old (see to Figure 1 and Table 3). Children less than 4 weeks old accounted for 49% of our sample, of which 10.8% were diagnosed with SBI. In over half of the cases, no clinical symptoms other than fever were present upon ED admission. However, infants with SBI had a higher CRP level (10.45mg/L in SBI vs. 1.00mg/L in VI, p-value=0.004) and a higher neutrophil count (47.75 x10^3/µL in SBI vs. 31.90 x10^3/µL in VI, p-value=0.02) upon ED admission (Table 3).

Figure 1: Distribution of study population groups

(A) Pie chart depicting the distribution of diagnosed infections among patients admitted at ED for FWS within the study population.

(B) Nested diagram representing the distribution of the study population according to age, then according to the diagnosis made following their emergency admissions for FWS.



As LP is a standard part of the management protocol for febrile infants under 4 weeks old, it was routinely performed in these cases (21). Yet, no difference were noted in the results from LP in terms of neutrophil numbers, protein levels, and glucose levels between VI versus SBI.

Subgroups of infants between one and three months old based on infection type

Children aged from one to three months represented 51% of our sample, including 11.8% diagnosed with SBI. Compared to younger children, no statistically significant differences in CRP levels (3.60mg/L in SBI vs. 1.60mg/L in VI, p-value=0.36), WBC counts (10.77 x103/µL in SBI vs. 9.26 x103/µL, p-value=0.25), and neutrophil numbers (37.00 $x10^3$/µL in SBI vs. 31.20 $x10^3$/µL, p-value=0.62) were observed (Table 3). When LP was performed, a higher protein level was found in VI cases (45.50mg/dL in VI vs. 25.00mg/dL in SBI, p-value=0.03). However, none of the studied parameters were able to predict SBI.

Discussion

This retrospective study evaluated the management and outcome of infants less than three months old admitted for FWS at the ED of a Belgian tertiary care pediatric hospital. Overall, 11.3% of the children exhibited a SBI, which is consistent with published data reporting SBI rates reported ranging from 5 to 15% (6,22,23). This number is rather relevant and helps to understand the practice of conducting routine complementary tests in young febrile infants . As previously mentioned, UTI was the primary cause of SBI. However, urine was mostly collected using an Urinocol collection bag or via the midstream technique. Sample contamination resulting in a false diagnosis cannot be excluded. Therefore it is important to search for UTI in a sterile manner, using urinary catheterization or suprapubic puncture.

Our study aimed to identify biomarkers that can predict low-risk SBI patients. We analyzed thoroughly anamnestic, clinical, and biological criteria, as currently applied at Cliniques Universitaires Saint-Luc. However, we were unable to reliably identify children at low-risk of SBI who could be discharged without close monitoring and empirical antibiotics, thereby saving time and costs. The clinical presentations of the two groups, SBI and VI, on ED admission were similar. Children with SBI did not exhibit altered general conditions or states of shock more commonly than those with VI. Accurate diagnosis was complicated as those with simple VI could also be irritable upon febrile peaks. It is worth noting that febrile children under 3 months old tended to visit the emergency department more frequently within the first 24 hours of fever onset, allowing for better follow-up regarding disease progression. Surprisingly, lumbar puncture was only performed in 55% of infants under 4 weeks old. This figure is unexpected, as most international guidelines recommend lumbar puncture in febrile infants under four weeks old (21). This may be due to the clinical presentation and the decision to monitor with hospitalization. In literature reports, cerebrospinal fluid

Table 2: Baseline characteristics of patients, stratified by the type of infection.

	VI (N=133)	BI (N=17)	p-value
Terms, weeks of pregnancy	39.00 [38.00; 40.00]	39.00 [38.00; 40.00]	0.75[b]
BH, cm	49.89 ± 2.26	48.92 ± 0.79	0.0036[a]
BW, kg	3.3 ± 0.47	3.14 ± 0.43	0.2 [a]
BMI	14.55 ± 1.7	14.42 ± 1.27	0.82 [a]
HC, cm	34.66 ± 1.56	34.5 ± 1.14	0.64 [a]
Age, w	5.0 [3.0; 7.0]	5.00 [3.00; 8.00]	0.4 [b]
CW, kg	4.36 [3.85; 4.70]	4.08 [3.70; 5.10]	0.97 [b]
CH, cm	54.49 ± 3.23	53.83 ± 3.42	0.60 [a]
CHC, cm	37.13 ± 1.82	37.45 ± 1.67	0.63 [a]
Fever duration, h	8.00 [2.00; 24.00]	9.00 [3.50; 24.00]	0.60 [b]
Fever peak, C°	38.50 [38.20; 38.90]	38.50 [38.20; 39.00]	0.66 [b]
CRP level, mg/L	1.20 [0.80; 5.00]	7.00 [1.50; 12.60]	0.0057 [b]
WBC, $x10^3$/µL	8.94 [6.63; 12.90]	9.98 [5.81; 10.83]	0.95 [b]
Neutrophils, $x10^3$/µL	31.50 [25.20; 42.80]	41.30 [30.60; 49.70]	0.036 [b]
Lymphocytes, $x10^3$/µL	45.24 ± 17.19	41.52 ± 14.85	0.35 [a]
Urine WBC, $x10^3$/µL	4.00 [1.50; 14.00]	26.00 [8.00; 116.00]	0.0020 [b]
LP WBC, $x10^3$/µL	6.00 [4.00; 14.00] (N=54)	4.50 [4.00; 12.20] (N=8)	0.57 [b]
LP neutrophils, %	0 [0; 27] (N=54)	16.50 [0.00; 33.75] (N=8)	0.75 [b]
LP proteins, mg/dl	54.50 [43.50; 72.75] (N=54)	44.70 [34.75; 51.75] (N=8)	0.076 [b]
LP glucose, mg/dl	57.30 ± 7.9 (N=54)	58.88 ± 12.37 (N=8)	0.74 [a]
Hospitalization duration, d	2.00 [2.00; 3.00]	2.00 [2.00; 3.00]	0.76 [b]
Antibiotic therapy duration, h	48.00 [48.00; 48.00] (N=71)	42.00 [24.00; 66.00] (N=14)	0.18 [b]
Rehospitalization within 30 days, %	8.3 (N=11)	29.4 (N=5)	0.007[c]

BH=Body height at birth; BW=Body weight at birth; BMI=Body mass index; HC=Head circumference; CW=Current weight; CH=Current height; CHC=Current head circumference; CRP= C-reactive protein; LP=Lumbar puncture; WBC=White blood cells; SD=Standard deviation; d=Days; h=Hours; w=Weeks

[a] Student's t-test, [b] Wilcoxon test, and [c] Pearson's chi-squared test were performed.

Table 3: Characteristics of patients and statistical analysis stratified by both age groups and the type of infection within the study population

	INFANTS ≤ 4 WEEKS			INFANTS AGED 1-3 MONTHS		
	VI (N=66)	BI (N=8)	p-value	VI (N=67)	BI (N=9)	p-value
Terms, weeks of pregnancy	39.00 [38.00; 40.00]	38.50 [38.00; 39.00]	0.14 [b]	39.00 [38.00; 40.00]	40.00 [39.00; 40.00]	0.06 [b]
BH, cm	50.09 ± 2.01	48.40 ± 0.54	0.0002 [a]	49.81 ± 2.54	49.29 ± 0.75	0.27 [a]
BW, kg	3.35 ± 0 .48	3.08 ± 0.26	0.04 [b]	3.25 ± 0.46	3.20 ± 0.54	0.82 [a]
BMI	14.41 ± 1.74	14.19 ± 1.37	0.79 [a]	14.70 ± 1.67	14.74 ± 1.33	0.96 [a]
HC, cm	35.00 [34.00; 36.00]	34.50 [34.00; 35.00]	0.36 [b]	34.34 [33.00; 36.00]	34.50 [34.00; 35.75]	0.72 [a]
Age, w	3.00 [3.62; 4.45]	3.00 [2.00; 4.00]	0.80 [b]	7.00 [5.50; 8.00]	8.00 [6.00; 10.00]	0.11 [b]
CW, kg	4.04 ± 0.56	3.53 ± 0.51	0.03 [a]	4.69 ± 0.744	5.07 ± 0.58	0.08 [b]
CH, cm	53.26 ± 2.79	49.75 ± 0.35	0.000009 [a]	55.89 ± 3.15	55.0 ± 2.9	0.49 [a]
CHC, cm	36.32 ± 1.34	35.67 ± 0.29	0.03 [a]	38.47 ± 1.73	38.52 ± 1.01	0.94 [a]
Fever duration, h	4.50 [2.25; 24.00]	14.00 [5.00; 21.00]	0.63 [b]	12.00 [2.00; 24.00]	7.50 [3.25; 36.00]	0.84 [b]
Fever peak, C°	38.40 [38.10; 38.70]	38.45 [38.35; 38.77]	0.28 [b]	38.60 [38.20; 39.00]	38.70 [38.00; 39.00]	0.77 [b]
CRP level, mg/L	1.00 [0.50; 4.67]	10.45 [6.35; 19.32]	0.004 [b]	1.60 [0.95; 5.00]	3.60 [1.00; 7.00]	0.36 [b]
WBC, x10^3/µL	8.67 [6.95; 12.92]	8.62 [4.75; 10.43]	0.28 [b]	9.26 [5.51; 11.88]	10.77 [7.32; 17.95]	0.25 [b]
Neutrophils, x10^3/µL	31.90 [24.93; 40.77]	47.75 [40.35; 66.12]	0.02 [b]	31.20 [25.50; 42.80]	37.00 [30.00; 41.30]	0.62 [a]
Lymphocytes, x10^3/µL	43.24 ± 17.92	34.21 ± 14.11	0.13 [a]	47.21 ± 16.33	48.01 ± 12.88	0.87 [a]
Urine WBC, x10^3/µL	3.00 [1.75; 11.00]	26.00 [6.50; 112.50]	0.03 [b]	7.00 [1.50; 14.50]	21.00 [12.00; 100.50]	0.03 [b]
LP WBC, x10^3/µL	6.00 [3.50; 21.00] (N=36)	4.00 [4.00; 12.00] (N=5)	0.63 [b]	5.00 [4.25; 7.50] (N=18)	5.0 [4.00; 13.50] (N=3)	0.58 [a]
LP neutrophils, %	1.00 [0.00; 44.00] (N=36)	0.00 [0.00; 30.50] (N=5)	0.81 [b]	0.00 [0.00; 17.00] (N=18)	33.00 [16.50; 33.50] (N=3)	0.37 [b]
LP proteins, mg/dl	58.00 [46.50; 84.25] (N=36)	49.00 [46.00; 60.00] (N=5)	0.42 [b]	45.50 [39.00; 67.25] (N=18)	25.00 [23.00; 31.50] (N=3)	0.03 [b]
LP glucose, mg/dl	55.91 ± 8.16 (N=36)	53.80 ± 8.04 (N=5)	0.60 [a]	59.65 ± 7.01 (N=18)	67.33 ± 15.31 (N=3)	0.48 [a]
Hospitalization duration, d	2.00 [2.00; 3.00]	3.00 [2.00; 3.50]	0.20 [b]	2.00 [1.00; 3.00]	2.00 [1.00; 2.00]	0.60 [b]
Antibiotic therapy duration, h	48.00 [48.00; 48.00] (N=49)	48.00 [36.00; 84.00] (N=8)	0.94 [b]	48.00 [48.00; 48.00] (N=22)	24.00 [24.00; 42.00] (N=6)	0.06 [b]

BH=Body height at birth; BW= Body weight at birth; BMI=Body Mass Index; HC=Head circumference; CW=Current weight; CH=Current height; CHC=Current head circumference; CRP= C-reactive protein; LP= Lumbar puncture; WBC=White blood cells; SD=Standard deviation; d=Days; h=Hours; w=Weeks

[a] Student's t-test and [b] Wilcoxon test were performed.

protein levels are typically higher in cases of suspected SBI than in cases of viral infection (24,25). However, in our study, when LP was performed on children between one and three months old, the protein level was surprisingly higher in VI than SBI. One possible explanation for this inconsistency could be attributed to the limited sample size of the SBI group.

This limited understanding of fever etiology also applies to the biological field. The C-reactive protein (CRP), an inflammatory marker measured during the initial biological work-up, is often normal or only slightly increased, which can lead to false reassurance. Although CRP levels were higher in cases of SBI in children under four weeks old, we also observed that fever duration was longer in this subgroup, suggesting a potential bias. The addition of a procalcitonin assay to the management protocol would have been appropriate. This biomarker has been shown to display more rapid kinetics than CRP levels, making it more suitable for clinicians (7,26). Additionally, it is worth noting that the procalcitonin assay is included in the 'Step-by-Step' algorithm developed by a European group of pediatric emergency physicians (14). The goal was to accurately identify febrile infants at low-risk of SBI, who could thus be discharged without any LP or empirical antibiotic therapy. The initial results are promising (7,26). However, during the COVID-19 pandemic, the step-by-step approach was effective in identifying SBI but misclassified most children as high-risk, leading to unnecessary care (27).

Other biological parameters are currently being investigated to help physicians better identify children at low risk of SBI. These include polymerase chain reaction (PCR)-tested viremia or using a host-protein (BV) score based on circulating immune protein levels (18,19). Therefore, a more comprehensive approach, including the use of procalcitonin, is required.

Strengths and weaknesses

To our knowledge, this study is the first of its kind to analyze the clinical course of children under 3 months old who were admitted to the ED and subsequently hospitalized for FWS at a tertiary Belgian hospital. We consider this to be a strength of the study. The retrospective single-center design employed in this study is subject to limitations inherent to this type of study design. One such limitation is that presumed VI or SBI etiologies were only retrospectively applied. Although our study's SBI rate aligns reasonably well with published data, its relevance may be limited. Therefore, it may be challenging to draw conclusions applicable to routine practice. Additionally, we focused solely on febrile infants under 3 months old who were assessed at ED admission and subsequently hospitalized, excluding those who were discharged. We did not assess procalcitonin levels, despite its proven sensitivity in detecting bacteremia and bacterial meningitis in young febrile infants (7,26). Additionally, we identified two significant weaknesses in the supplementary tests conducted: the use

of non-sterile urine collection, primarily through the bag method, and a significant omission of lumbar puncture in almost half of febrile children under 4 weeks of age, despite guideline recommendations. It is important to note that the diagnosis of urinary tract infection was based on the recorded concluding diagnosis in patients' medical records. However, since the urinary collection method was not mentioned and threshold values differ for each type of collection method, the number of urinary tract infections in this study may have been over or underestimated.

Conclusion

The management of febrile children under 3 months of age admitted to the ED and the need to hospitalize these children for further monitoring remain a subject of debate. The implementation of new guidelines in our institution, including procalcitonin dosage, would likely be beneficial to improve the selection of children at low-risk for SBI, thereby reducing unnecessary diagnostic tests, antibiotic treatments, and hospitalizations, eventually resulting in time and cost savings. Further studies are required to assess the specific impact of algorithms such as 'Step-by-Step' or the 'Pediatric Emergency Care Applied Research Network (PECARN) rule' after their implementation (28).

Conflicts of Interest

The authors have no conflicts of interest relevant to this article to disclose.

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Maintenance Intravenous Fluids in Pediatrics: Survey in Belgium about Daily Practice

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Keywords

Children; fluids ; maintenance ; intravenous.

Abstract

Objective

Prescribing intravenous maintenance fluids is daily practice for many pediatricians. In 2018, the American Association of Pediatrics published the first evidence-based clinical practice guideline on this topic, but many pediatricians have not incorporated it into their clinical practice. To pursue safety in prescribing intravenous maintenance fluids, a standardization of care is wise. We aim to describe the current practice in Belgium to evaluate the need for further local guidelines.

Methods

We conducted a cross-sectional electronic survey of pediatricians currently working in a Belgian pediatric ward. The survey consisted of general questions about prescribing habits and questions about two specific cases.

Results

122 respondents completed the survey. There is a wide variation in baseline checks before starting fluids, and electrolyte monitoring during maintenance intravenous fluid administrations is not regularly performed in 43%. The Holiday and Segar formula, used by 102 respondents, remains the most popular method of calculating the rate, although many respondents use different methods depending on the case. The type of solution used is also very variable with 18 different fluids mentioned, much depending on the case.

Conclusion

A great variety in type and rate exists in the prescription of intravenous fluids as well as differences in monitoring. Our results show that pediatricians tailor IV fluids to each case and deviate from their own protocol in many cases. While a strict protocol may prove difficult, a guidance through the important considerations and current literature may well be a valuable addition to promote safety in prescribing intravenous maintenance fluids.

Introduction

Background and relevance of the study

A large amount of intravenous (IV) fluids is prescribed daily for hospitalized children for various reasons. Although guidelines for fluid resuscitation and rehydration have become increasingly available, literature and guidelines on the type and the best way to prescribe IV maintenance fluid (IV-MF) remain scarce. The European Society of Pediatric and Neonatal Intensive Care (ESPNIC) defines IV-MF as "*the water and electrolyte prescription designed to replace anticipated physiologic water and electrolyte losses over the ensuing 24-h period*" (1). However, there are numerous interpretations of what constitutes IV-MF, evident from the various definitions found in literature. These definitions sometimes encompass rehydration or aim at correcting electrolyte imbalances. Such diversity makes it challenging to conduct high-quality trials or reviews.

The optimal tonicity of IV-MF has also been a subject of debate. Tonicity affects extracellular fluid osmolality: hypertonic solutions cause cells to shrink, hypotonic solutions cause swelling, and isotonic solutions maintain cell size. Historically, hypotonic solutions were used as IV-MF. Since the late 1990s, an increased number of reports were published questioning the use of hypotonic solutions due to the risk of iatrogenic hyponatremia, hyponatremic encephalopathy or even death (2, 3). Multiple RCT's and meta-analyses have described higher incidences of hyponatremia in hypotonic IV-MF compared to isotonic IV-MF (4-6).

In 2018, the American Academy of Pediatrics (AAP) published a guideline on IV-MF recommending that "*patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia*" (7). While this statement is generally accepted, many pediatricians have yet to incorporate it into their clinical practice (8, 9).

There has been even more discussion about the need for balanced solutions (with electrolyte content approaching that of plasma). In adults NaCl 0.9%, an unbalanced solution, can cause hyperchloremic acidosis, hyperkalemia and acute kidney injury (AKI). Literature in children is sparse, but the use of balanced solutions in resuscitation results in less acidosis, shorter length of stay (LOS), and faster normalization of pH in diabetic ketoacidosis (10-12). When used for maintenance, some studies support balanced fluids, while others could not show significant clinical differences (13-15). However, given that NaCl 0.9% could lead to hyperchloremic acidosis, AKI, hyperkalemia, hypertension, inflammation, and coagulopathy, it is advisable to use alternative products (4). Similar discussions surround the optimal potassium content, but confirmatory evidence on this topic remains scarce (16).

The Holliday and Segar (H/S) formula, published in 1957, has been widely used to calculate the rate of IV-MF (17). Although alternative methods were developed later, none have surpassed its popularity (18). However, because the H/S formula is based on caloric expenditure in healthy

children, it often overestimates actual fluid needs (19). This limitation was noted in studies of children admitted to pediatric intensive care units (PICU's), where recommendations to restrict the rate to, for example, 50-80% have been made (1).

Aim

Aiming to create national guidance for the prescription of IV-MF, the Be-PIV research group developed a survey to assess current daily practices in various hospitals across the country. This survey covers both the description of the most used fluid compositions and the methods used for calculating the rate of administration.

Methods

Study design and methods

We conducted a cross-sectional electronic survey among pediatricians and pediatric residents currently working in Belgian pediatric wards. Our aim was to target pediatricians working with non-critically ill children aged 1 month to 16 years. Clinical practices in neonatal (intensive care) units (NICU's), and PICU's were excluded.

According to the National Institute for Health and Disability Insurance (RIZIV/INAMI), there were 508 pediatric residents and 2154 licensed pediatricians registered as of March 2023. However, not all of them are actively working in hospitals. Therefore, we compiled a list of pediatric wards obtained from the Federal Public Service of Health and researched each pediatric team online. This yielded a total of 997 pediatricians working in pediatric wards, with 350 in the Flemish region, 256 in Brussels, and 391 in the Walloon region.

Survey development

The survey was crafted following extensive review of current literature and modeled after the recently published survey of ESPNIC (8). To mitigate responder bias and confirm demographic diversity, the first part of the survey included questions about the respondent's hospital type and personal function. The second part comprised general queries on fluid prescriptions and two specific cases (Box 1 and Box 2). These cases provided a broad description of common pediatric ward pathologies and served to confirm the general approach indicated in the earlier section.

Box 1: Case description.

Holliday-Segar's *formula* *Based on weight*	1-10 kg = 100 mL/kg/day 11-20 kg = 1000 mL + 50 mL/kg>10kg/day >20 kg = 1500 mL + 25 mL/kg>20kg/day
Oh's *formula* *Based on weight*	1-10 kg = 4 mL/kg/hour 11-20 kg = 40 mL + 2 mL/kg>10kg/hour >20 kg = 60 mL + 1 mL/kg>20kg/hour
Adelman-Solhaug *formula* *Based on body surface area*	1500 mL/m^2/day
Neonate/infant *Different variations* *Based on weight and/or months of age*	*Example* <6 kg = 150 mL/kg/day 6-8 kg = 125 mL/kg/day 8-10 kg = 100 mL/kg/day

Box 2: Common formula's for calculating infusion rate.

Case 1	14-year-old boy (50 kg, 180 cm) admitted for elective thoracic surgery for a pectus excavatum (NUSS-bar). Postoperative nausea despite medication. Does not tolerate nasogastric tube feeding.
Case 2	8-week-old infant (4.5 kg). Admitted to general ward with bronchiolitis and 1L/min O2. Parents refuse nasogastric tube.

Questions were presented in both multiple-choice and free-text formats to facilitate descriptive analysis and gather free-form suggestions.

Accompanying the survey was an informative text explaining the survey's objective. Completion of the survey was considered implicit consent to participate in the study. The survey was drafted in English to encourage a higher response rate across all regions of Belgium.

Full access to the survey is available upon request.

Data collection

The electronic survey was conducted online using Jotform software from March to May 2023. It was first introduced at the Congress of the BVK-SBP (Belgische Vereniging voor Kindergeneeskunde – Société Belge de Pédiatrie) in March 2023. Subsequently, several follow-up emails were sent to the entire network of the VVK (Vlaamse Vereniging voor Kindergeneeskunde), SFP (Société Française de Pédiatrie), and the BAoP (Belgian Academy of Paediatrics). A final reminder was sent by contacting the secretaries of all pediatric wards in Belgium. Only fully completed surveys were considered eligible for analysis.

Data analysis

The data were imported into Excel for further descriptive analysis. Multiple-choice answers are presented as percentages. Characteristics of respondents (position, type of hospital employment, etc.) were only utilized for descriptive analysis.

Results

Participants

One hundred and twenty-two respondents completed the survey resulting in a response rate of 12%. While our numbers may be low, the structure of our survey allows for responses to be entered from a hospital unit rather than an individual. One-third of respondents report working primarily in a university hospital while the remainder work in regional hospitals. Of these, 79% indicate report working with residents, with the remaining 21% working without residents (Figure 1).

Respondents' roles were evenly distributed among pediatric residents, general pediatricians, and pediatric subspecialists, with 39%, 33%, and 26%, respectively. In addition, 2% of respondents are currently completing a pediatric fellowship (Figure 2). Years of experience in pediatrics ranged from 3 to 30 years.

Protocols and check ups

Of all respondents, 65% claim that some form of guideline, protocol, or agreement is available in their hospital for the prescription of IV-MF.

Before starting IV-MF, 82% check baseline electrolytes, glycemia, and/or kidney function, while 18% do not. Follow-up check-ups are not regularly done in 43% of cases. The remaining respondents have a variable method of follow-up, ranging from once a week to daily, depending on baseline values or underlying conditions.

More than half of the respondents report that patients on IV-MF are weighed daily, while 9% do not monitor the patients' weight. In 38% of responses, some form of fluid balance is monitored. However, what is used to calculate the fluid balance varies significantly. Some respondents only consider enteral intake, continuous IV fluids, diuresis, and stools, while others also include the volume of medication, flushes and sometimes an estimation of the insensible losses.

Volume and rate

The most used formulas to calculate the rate of infusion of MF are described in Box 1. The preferences for these formulas are illustrated in Figure 3. H/S formula is the most frequently used method for prescribing the rate of infusion (102 out of 122 respondents). Among these, 37 respondents use only the H/S formula, while 7 use only Oh's formula and 3 use

Figure 1: Type of hospital in which the respondent mainly works.

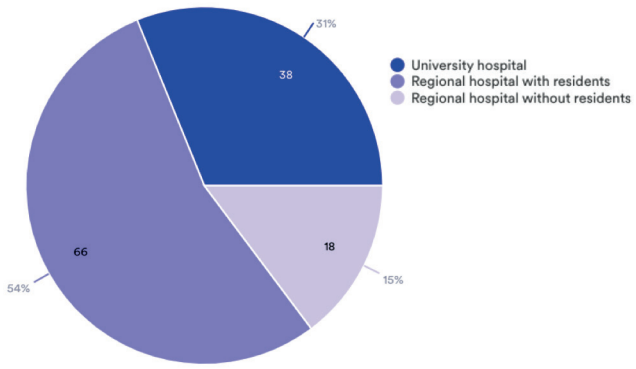


Figure 2: Respondents' level of training

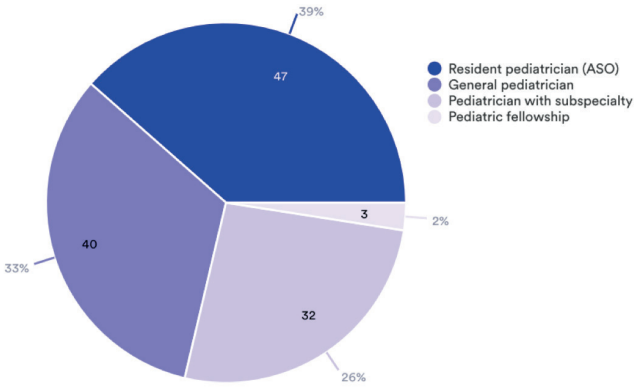
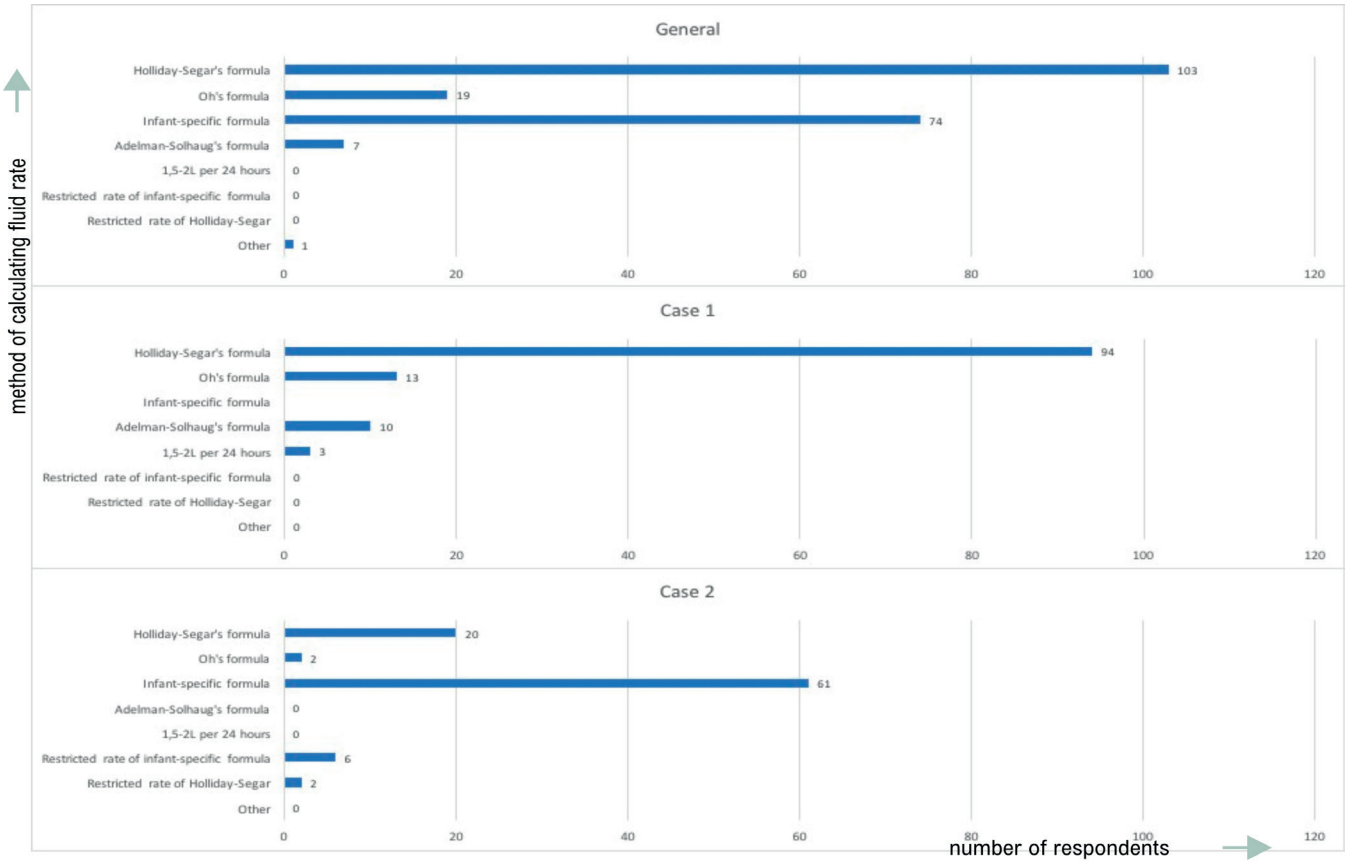


Figure 3: Number of respondents' answers to 'What method of calculating the rate of IV-MF do you use in general (top), in case 1 (middle), and in case 2 (bottom).' The x-axis displays the absolute number, while the y-axis represents the different possibilities.



only Adelman-Solhaug's (A/S) formula. Additionally, 69 respondents use a combination of methods depending on the age of the patient, with a variation of the method described in Box 1 being the most common alternative. Few other calculation methods outside of the ones described earlier are used.

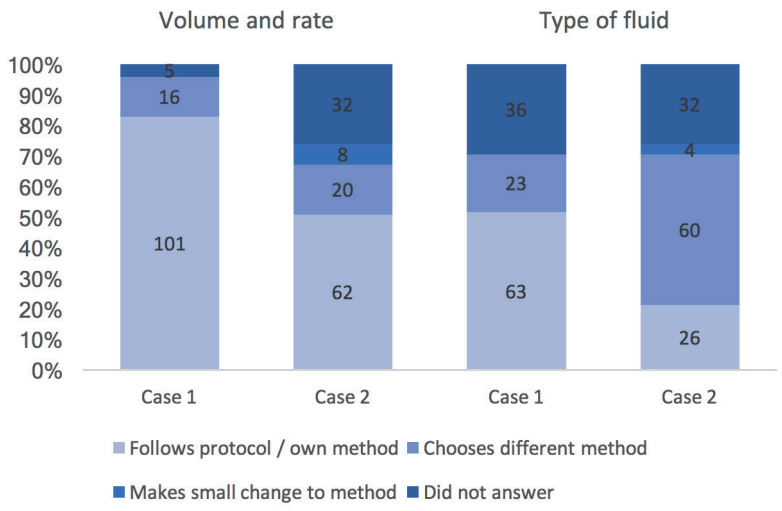
When presented with a specific case (Box 2), multiple respondents deviated from their original answers regarding the prescription of MF (Figure 4).

In Case 1, concerning a teenager after elective surgery, only four respondents would not start IV-MF in the first place. The H/S formula remains the most widely used, with 93 out of 118 responses. Out of seven respondents that claim to use A/S method, only five would use it in this case. Additionally, six respondents who initially stated they only use the H/S formula switch to A/S formula in this case. Three respondents would consider the case as that of an adult patient and would prescribe 1.5-2L per 24 hours. Among the four respondents not starting IV-MF, one would immediately start total parenteral nutrition, while the other three would attempt a combination of anti-emetics and oral rehydration salts.

In case 2, the answer of 90 respondents showed a broad variation in rate calculation.

Among the 56 respondents who initially stated the use of infant-specific formula in infants in the general part, eight used H/S formula in this case. Additionally, 19 respondents who claimed in the general question that they do not use a specific infant-based formula switched to this option when given this specific case. In total, only seven respondents restricted fluid in this case due to the risk of increased ADH secretion.

Figure 4: Deviations from general protocol per case in terms of calculation of rate and volume (left) and type of solution.



Type of fluid

A wide variety of solutions is used as IV-MF, with the content and characteristics described in Table 1. Generally, more than half of the fluids (52%) frequently used as IV-MF are hypotonic. The choice of fluid differs considerably when asked in general compared to when asked in the context of a specific case. In case 1 and case 2, 49% and 42% of respondents respectively claim to use some type of hypotonic solution. As evidenced by the differences in answers between the general question and the cases, respondents deviate from their own protocol in 19% and 52% respectively in case 1 and case 2. Figures 4 and 5 illustrate these differences.

More than half of the respondents say they don't calculate sodium or potassium requirements in both cases. Only 16% and 30% calculate the glucose requirement in case 1 and 2 respectively.

In specific cases, such as the follow-up question in case 2 where the infant presents with hyponatremia, 80% of respondents will deviate from their usual IV fluid prescription protocol.

Discussion

The survey highlights the inherent complexity involved in prescribing IV-MF for the pediatric population. Pediatricians must consider various factors such as the patient's age, weight, underlying pathology, and baseline evaluations.

The implementation of existing guidelines in specific clinical cases, as revealed in this survey, was rather low: in 72% of the cases hypotonic fluids were still used. Almost 97% of the respondents used the correct rate in older children, but only 24% in neonates. Only a fraction of the respondents correctly decreased the rate when there were signs of increased ADH secretion.

The reasons for this were not always clear. Perhaps it is a lack of awareness due to insufficient dissemination of guidelines, or a lack of understanding of the rationale behind the guidelines and how to apply them in specific contexts. In addition, respondents' personal preferences may have conflicted with the guidelines, or deviations from the guidelines may have been based on clinical assessments of the child. While it was beyond the scope of this survey to explore the motivations for adopting a different approach, it led us to question the feasibility of strict national guidelines.

A crucial aspect of safely prescribing IV-MF, given its nature as a drug, is establishing a correct definition, correct target group and correct indications. Our literature review revealed a lack of consensus on the definition of MF, making it challenging to compare different protocols and assess adherence to guidelines. The definition of IV-MF used in this study focused on temporarily substituting fluids and electrolytes to maintain homeostasis when the child was unable to receive maintenance fluids enterally (which remains the

Figure 5: Number of respondents' answers to 'What type of solution do you use as MF in general (top), in case 1 (middle), and in case 2 (bottom).' The y-axis displays the absolute numbers, while the x-axis represents the different possibilities.

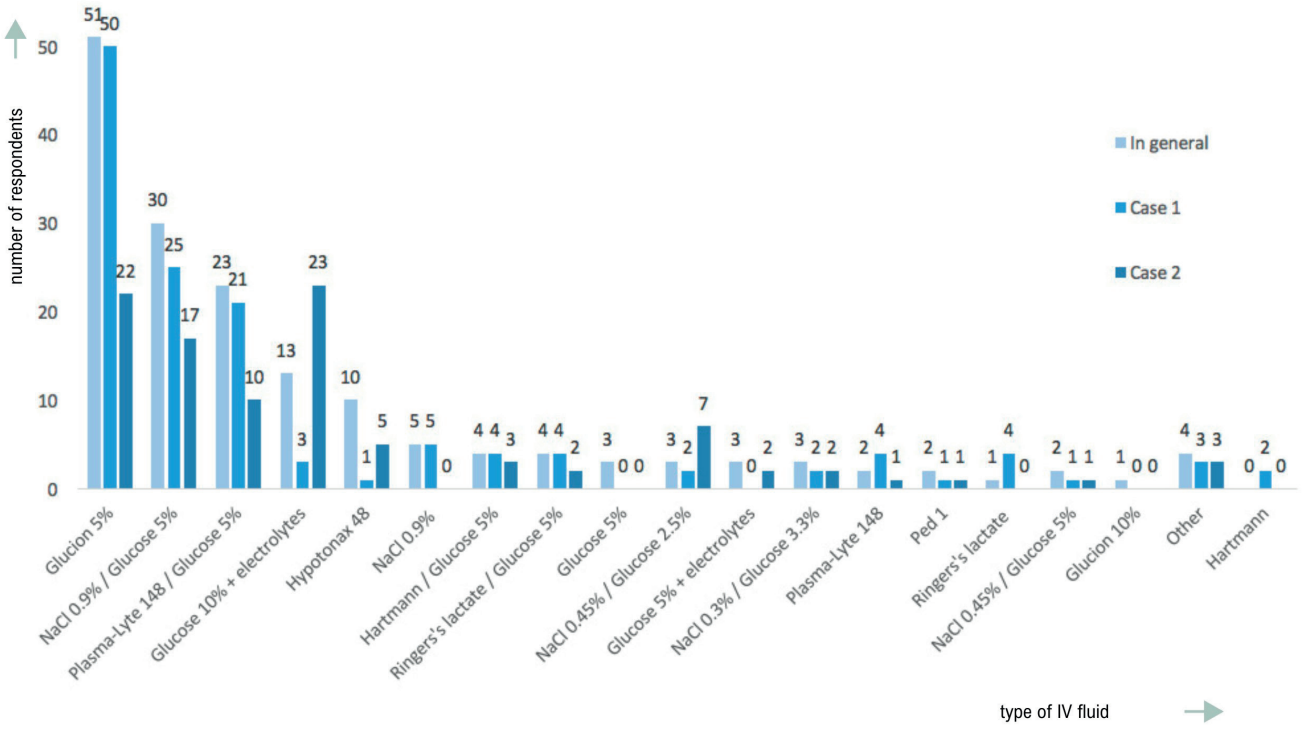


Table 1: Content and characteristics of different types of fluids. (*) depending on electrolytes.

TRADE NAME OF FLUID	TONICITY	BALANCED	OSMOLARITY (MOSM/L)	NA+ (MMOL/L)	K+ (MMOL/L)	GLUCOSE
Glucion 10%	Hypotonic	No	725	54	26	Yes
Glucion 5%	Hypotonic	No	447	54	26	Yes
Glucose 10% + electrolytes	*	No	*	*	*	Yes
Glucose 5%	Hypotonic	No	278	0	0	Yes
Glucose 5% + electrolytes	*	No	*	*	*	Yes
Hartmann	Isotonic	Yes	278	131	5	No
Hartmann / Glucose 5%	Isotonic	Yes	555	131	5	Yes
Hypotonax 48	Hypotonic	Yes	372	25	5	Yes
NaCl 0.3% / Glucose 3.3%	Hypotonic	No	285	51	0	Yes
NaCl 0.45% / Glucose 2.5%	Isotonic	No	293	77	0	Yes
NaCl 0.45% / Glucose 5%	Hypotonic	No	432	77	0	Yes
NaCl 0.9%	Isotonic	No	308	0	0	No
NaCl 0.9% / Glucose 5%	Isotonic	No	585	154	0	Yes
Ped 1	Isotonic	Yes	420	41	30	Yes
Plasma-Lyte 148	Isotonic	Yes	296	140	5	No
Plasma-Lyte 148 / Glucose 5%	Isotonic	Yes	572	140	5	Yes
Ringer's Lactate	Isotonic	Yes	278	131	5	No

preferred method). In case 2, the indication for IV-MF was questioned, given the consensus and recommendation to prioritize enteral feeding whenever feasible (20). Although choosing not to initiate IV-MF was an option provided to respondents, deviations from their own protocols may partly stem from this uncertainty regarding the indication. An IV-MF is also not intended to correct fluid or electrolyte imbalances. In cases where correction is needed, a patient-tailored approach will be needed.

As mentioned earlier, hospitalized children often have different caloric expenditure and therefore different volume needs compared to healthy children. Several factors contribute to this variability. For instance, increased water loss may occur due to conditions such as burns, fever, gastrointestinal losses, excessive sweating, and polyuria. Conversely, patients with kidney failure may exhibit decreased urinary output. Moreover, there are numerous instances where the body's normal regulatory mechanisms for maintaining homeostasis are compromised. This is particularly relevant for children admitted to hospitals, as various non-osmotic factors can influence ADH-secretion, including nausea, pain, stress, central nervous system disturbances, or pulmonary disease. In such cases, it may be necessary to implement a relative fluid restriction compared to what is calculated by the H/S formula.

There are some limitations to our study. Our response rate was not high, but it is very difficult in Belgium to obtain exact data on the number of pediatricians actively working in hospitals. Relying on hospital websites might have both overestimated or underestimated our numbers. Due to the voluntary nature of this survey, it is also more likely that pediatricians with a greater interest in this topic would have responded, which makes it impossible to avoid respondent bias. Consequently, we were unable to reliably determine if our sample was truly representative of Belgian pediatricians working in a hospital setting.

We did not ask respondents to indicate their region of activity, so we were unable to distinguish between Flemish- or Walloon-trained pediatricians, which might have provided means of identifying regional variations in practice.

Furthermore, one might argue that due to the frequency with which pediatricians prescribe IV-MF, guidelines may not always be consulted. It remains unclear whether factors such as tonicity or anions in IV-MF are consistently considered by all pediatricians. Given the diversity of literature on these topics, keeping up to date is a challenge.

Conclusion

In this survey on the use of IV-MF, we investigated the availability of protocols and local practices among Belgian pediatricians. We found a wide variety in the choice of fluid types and observed a low adherence to existing guidelines.

The lack of high-quality studies and reviews on the type and rate of IV-MF indicates that there is probably no simple solution for a ‘one size fits all’ approach. Pediatricians customize their method of prescribing IV-MF based on factors such as the patient's weight, age, and current health status.

Setting up a high-quality clinical trial in which pediatricians would have to adhere to a strict protocol of IV-MF to confirm or disprove certain differences in rate and content is no easy task. However, it's crucial to recognize that IV fluids are medications and should be treated as such. This entails clear consideration of the indication, baseline assessment at the outset, monitoring of effects, and regular reassessment of the need for continued treatment.

In this regard, a consensus recommendation that guides Belgian pediatricians through important considerations could be highly valuable. By providing an easy-to-follow approach and summarizing key findings from recent high-quality literature, both young and experienced pediatricians can make evidence-based decisions.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

None of the authors has a conflict of interest to declare.

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Pneumococcal Meningoencephalitis as Rare Complication of Ear Infection in a 4-Month-old Girl: A Case Report

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Abstract

Streptococcus pneumoniae is a common cause of bacterial meningitis. It rarely causes more serious infections such as brain abscess, encephalitis, encephalomyelitis, or meningoencephalitis. We report a 4-month-old girl with a severe course of meningoencephalitis caused by *Streptococcus pneumoniae* as a complication of bilateral otitis media. She was treated with ceftriaxone, dexamethasone, multiple antiepileptic drugs, and neurosurgical drainage of subdural empyema. Gradual neurological improvement was observed. However, follow-up MRI revealed extensive cortical and subcortical damage with profound cerebral volume loss. This case illustrates that early recognition and timely appropriate treatment are crucial for a positive outcome.

Keywords

Case report ; children ; *Streptococcus pneumoniae* ; meningo-encephalitis ; complication of ear infection.

Introduction

Streptococcus pneumoniae is commonly found in the respiratory tract of healthy people, especially children. It is transmitted by respiratory droplets. When disease does occur, it is usually mild and the most common symptoms are acute otitis media and sinusitis. However, more severe clinical presentations such as pneumonia, bacteraemia and meningitis are not uncommon. They are associated with high mortality and morbidity. It is estimated that *Streptococcus pneumoniae* causes more than one million deaths in children worldwide each year. The development of meningoencephalitis is rare (1-7).

Case report

A 4-month-old girl with no relevant medical history and fully vaccinated up to the current age presents to the emergency department of a secondary hospital with a fever of 39°C for the past 2 days. Inspection of the left ear reveals a highly purulent otorrhoea with no possibility of inspection of the tympanic membrane. At this time, the clinical examination by the emergency physician shows a normal neurological examination. Amoxicillin is started and reassessment by the paediatrician is recommended in the next few days.

The next day, the child returns to the emergency department with post-feeding vomiting, drowsiness and sleepiness. In the emergency department, the child begins to convulse, with twitching of the left arm and leg, and gaze deviation to the left. The emergency physician administers midazolam (0.5mg/kg) intranasally as there is no intravenous access. Vital signs are stable, except for a brief desaturation to 88%, for which 5 L/min oxygen is administered by mask.

When the paediatrician arrives, the child is pale, unresponsive to stimuli and still has slight twitching of the left arm. Intravenous access is obtained and midazolam IV (0.1 mg/kg) is administered. After administration, the convulsions stop and a post-ictal state is observed.

On further examination, a clearly bombed anterior fontanel is noted, there is obvious hepatomegaly (3 cm below the rib, midclavicular diameter of 8.5 cm on ultrasound), purulent otorrhoea on the left side, but no clinical signs of mastoiditis. Prior to lumbar puncture, a CT scan of the brain is performed, showing no midline shift, two wide open fontanelles, no ischaemic areas, but signs of otitis/mastoiditis on the left side. The results of the examination of the cerebrospinal fluid (CSF), blood and urine are shown in Table 1. After taking cultures, dexamethasone, ceftriaxone and acyclovir are given intravenously and a maintenance infusion is started.

The child is admitted to the paediatric ward, but after a few hours the seizures recur, initially bilateral, then lateralised to the right with subtle twitching of the arms and legs, and now gaze deviation to the right. A new dose of IV midazolam does not stop the convulsions. Brief bradycardia (85/min) occurs once. There is also obstructive breathing which requires a jaw thrust. In consultation with a tertiary centre, a loading dose of phenobarbital is administered, which leads to resolution of the seizures. The patient is transferred to the paediatric intensive care unit (PICU) of the tertiary centre.

During her stay in the PICU, increasing seizures are observed. A new CT scan of the brain shows a left frontal empyema for which neurosurgical drainage with irrigation is performed. Despite surgery, the seizures persist, requiring a wide range of antiepileptic drugs: midazolam, valproic acid, phenobarbital, levetiracetam and finally propofol. The patient was intubated and mechanically ventilated for a total of 12 days. An interictal electroencephalogram (EEG) showed baseline activity that was unstructured for the age, notable bilateral frontocentral low-voltage, and no epileptiform changes. A brain magnetic resonance imaging (MRI) scan was performed and showed diffuse areas of oedema and diffusion restriction in the cortex of both cerebral hemispheres, most prominent in the high biparietal, right frontotemporal and left parietotemporal regions, confirming the diagnosis of pneumococcal meningoencephalitis with a severe encephalitis component (Figure 1). Ceftriaxone was administered intravenously for a total of 10 days, then changed to high-dose amoxicillin intravenously for a further 14 days (total duration of intravenous antibiotics 24 days). Oral amoxicillin was continued for 21 days (total duration of antibiotics 35 days). Dexamethasone was given for 4 days.

During the PICU stay, sedation is systematically reduced and a progressive improvement in neurological outcome is observed. After a total stay in the PICU of 15 days, the patient is able to leave the PICU and is transferred to the regular ward. She still has severe axial hypotonia and asymmetry with a right-sided disadvantage, for which intensive rehabilitation is initiated. After a further 3 weeks on the regular ward, the patient is able to leave the hospital.

On discharge from the tertiary centre, the patient was treated with levetiracetam and valproic acid. Valproic acid was discontinued because of impaired liver tests, which recovered rapidly after discontinuation of the drug.

An examination after 2.5 months of multidisciplinary rehabilitation revealed still evident but already improving hypotonia, asymmetry to the right in the upper limbs, difficulty organising postural changes, limited grasping, short attention span and difficulty with visual tracking.

A check-up one month later with the paediatric neurologist showed a very favourable evolution. The clinical neurological examination is within normal limits for the age and no significant developmental difference with peers

Table 2: Laboratory data on admission.

Laboratory test (SI units)	Result	Normal range	Antibiogram
CEREBROSPINAL FLUID			
Leukocytes (/µL)	150	< 5	
Glucose (mg/dL)	5	60 – 80	
Protein (mg/dL)	223	8 – 32	
Lactate (mmol/L)	13.8	1.1 – 2.8	
Culture	*Streptococcus pneumoniae*, serotype 19A		S: - Gentamycin high level - Cefepime - Penicillin - Amoxicillin - Linezolid - Moxifloxacin - Cefuroxime - Cefotaxime - Tetracycline - Erythromycin - Clindamycin - Meropenem - Vancomycin - Teicoplanin - Chloramphenicol - Trimethoprim/ Sulfamethoxazole I: - Levofloxacin
BLOOD			
Leukocytes (/µL)	5600	6000 – 13 200	
CRP (mg/L)	156	< 10	
Glucose (mg/dL)	129	50 – 80	
AST (U/L)	126	< 90	
ALT (U/L)	71	< 49	
Culture	Negative		
URINE			
Leukocytes (/µL)	6.16	0 – 10	
Glucose (mg/dL)	2029	0 – 33	
Culture	Negative		
CEREBROSPINAL FLUID/BLOOD			
Glucose ratio	0.03	> 0.5	

CRP, C-reactive protein; AST, aspartate-aminotransferase; ALT, alanine-transaminase; S: susceptible standard dose; I: susceptible increased exposure.

has been observed. An EEG shows no epileptiform activity. Brainstem evoked response audiometry (BERA) shows normal hearing on the right and limited hearing loss on the left, but at the time of testing the patient has otitis media with effusion on the left. A control MRI shows extensive cerebral tissue loss, a greatly dilated supratentorial ventricular system and still severe meningeal thickening (Figure 2). Treatment with levetiracetam and physiotherapy are continued.

As the patient was infected with pneumococcal serotype 19A, which is part of the Prevenar 13 vaccine, of which she has already received 2 doses, an immunity check was carried out. There is no asplenia, complement and immunoglobulins A, M and G are normal. There is a mannose-binding lectin (MBL) deficiency, but this does not seem to fully explain the severe clinical picture. Additional blood samples should be taken for further diagnosis.

Discussion

Definition and pathogenesis

Acute meningoencephalitis is a common cause of death and neurodevelopmental problems in children. The infection can be caused by a variety of agents, including viruses, bacteria, mycobacteria and protozoa, or it can be parainfectious and immune-mediated. Meningoencephalitis typically starts with symptoms such as fever, headache, stiff neck and sensitivity to light. However, as the infection progresses, additional symptoms may occur, including nausea, vomiting, altered mental status and even seizures.

Figure 1: Brain MRI (T2, axial) on admission to PICU showing diffuse oedema and diffusion restriction in the cortex of both hemispheres.

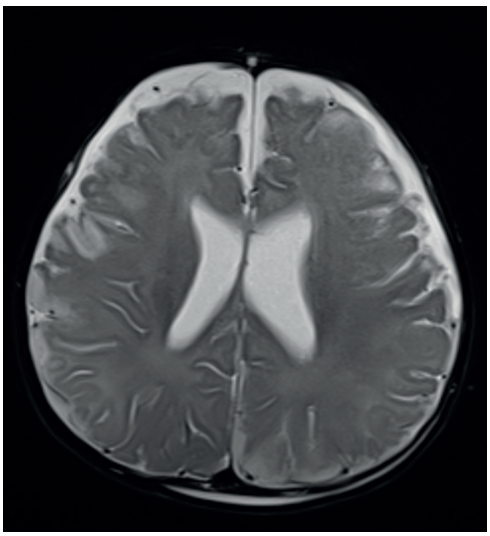
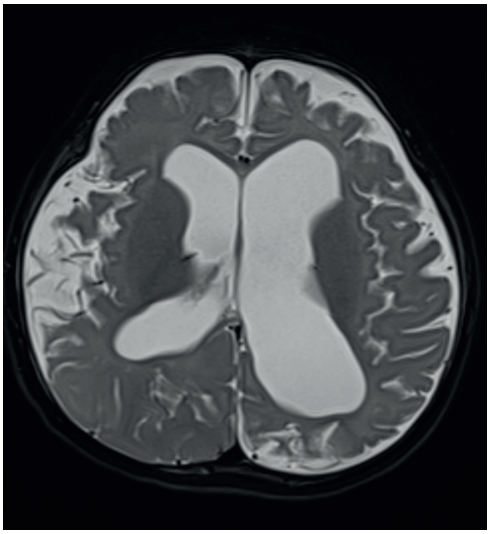


Figure 2: Control brain MRI (T2, axial) 3 months after admission to PICU showing extensive brain tissue loss, dilated supratentorial ventricular system and severe meningeal thickening.



In severe cases, individuals may develop coma or other neurological deficits (3, 6, 8). In infants, headache and photophobia are usually overlooked and neck stiffness with fontanelle bulging is often absent, making early diagnosis more challenging.

Streptococcus pneumoniae is a common inhabitant of the respiratory tract and can spread to the bloodstream and cross the blood-brain barrier, or the bacteria can reach the brain through an abnormally formed connection between the nasopharynx and the subarachnoid space, for example in mastoiditis, where the bacteria spread through the bone into the brain causing meningitis. Certain risk factors may increase the likelihood of developing pneumococcal meningoencephalitis, including young age, advanced age, a weakened immune system, chronic diseases, alcohol abuse, or recent head trauma (1-3, 6).

Clinical and biochemical findings

Diagnosis of pneumococcal meningoencephalitis involves a thorough physical examination and analysis of cerebrospinal fluid and blood cultures to identify the causative bacteria. Imaging studies such as CT or MRI of the brain may also be used to assess the extent of brain involvement. An EEG may provide additional information, typically showing a non-specific slowing of background activity. An EEG is particularly important in patients with persistent unexplained altered mental status to exclude status epilepticus (2, 3, 8).

Treatment

Prompt and appropriate treatment of pneumococcal meningoencephalitis is essential. First, the patient's airway, breathing and circulation should be assessed and stabilised if necessary. Meningoencephalitis is a life-threatening emergency that requires prompt empiric therapy. Antibiotics such as penicillin or cephalosporins are commonly used to target the bacteria. In our region, surveillance reports (data to 2022) show that *Streptococcus pneumoniae* is resistant to penicillin in 14.3% of strains that were tested and caused invasive disease. Resistance to cefotaxime is reported at 3.5% (9). Acyclovir should be started in all patients at risk of herpes simplex encephalitis. Antiepileptic drugs should be given if the patient presents with seizures, as well as in patients with a Glasgow Coma Scale (GCS) < 8 and in patients with signs of increased intracranial pressure. A few studies report the controversial role of corticosteroids, which should be considered in patients with cerebral oedema or increased intracranial pressure to reduce inflammation and improve outcomes (6, 8, 10). The timing of corticosteroid administration is important, with studies showing that it should be given early in the disease process, preferably before or with the start of antibiotics. The duration of treatment is best limited to 48 hours (11).

Prognosis

Despite advances in medical care, pneumococcal meningoencephalitis can be associated with serious complications. These can include brain damage, hearing loss, vision loss, cognitive impairment and, in severe cases, death (20%). Therefore, early recognition, prompt diagnosis and aggressive treatment are critical in the management of this condition (3). A recent study shows that children with pneumococcal meningoencephalitis are at high risk of sensorineural hearing loss. In the population studied, 30% of children had unilateral or bilateral sensorineural hearing loss (12). A few studies have shown a protective effect of corticosteroids on the outcome of sensorineural hearing loss, with one placebo-controlled, double-blind study showing a reduction from 38% (group without corticosteroids) to 14% (group with corticosteroids). However, the data are highly variable and often outdated (13, 14).

Pneumococcal meningoencephalitis can be prevented by vaccination. Vaccines against Streptococcus pneumoniae, such as pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPSV), are available and recommended for infants, children, older adults and people with certain medical conditions that increase their risk of infection. Studies examining the incidence of pneumococcal meningoencephalitis before and after the introduction of PCV vaccination in the United States show a dramatic decrease in incidence. In children under 2 years of age, the incidence fell from 10.16 cases per 100 000 children in 1998-1999 to 3.66 cases per 100 000 children in 2004-2005, a decrease of 64% (1, 15).

However, infection may occur despite vaccination, in which case underlying immunological disorders should be investigated. Primary immunodeficiencies (PID) known to underlie clinical disease caused by encapsulated bacteria such as *Streptococcus pneumoniae* include congenital asplenia, complement deficiency and antibody deficiency. In the study, 10% of children with invasive pneumococcal disease were found to have PID, and this rate increased to 26% in children over 2 years of age (16).

Conclusion

We report the case of a 4-month-old girl with meningoencephalitis caused by *Streptococcus pneumoniae* serotype 19A as a complication of an ear infection. Although this complication is rare, it is important to be aware of it because of the serious consequences it can have. Early recognition and appropriate treatment are crucial for a positive outcome. Further research is needed to determine the incidence of the complication, the role of corticosteroids, the prognosis of the infection and the possible pathways and underlying conditions leading to the infection. It is recommended that children who develop the complication undergo immunological screening to identify an underlying immunodeficiency.

Conflicts of interest:

All authors declare no conflicts of interest.

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The Diagnostic Process of an Ultra-rare Disease: Free Sialic Acid Storage Disorder (Salla Disease) in a 11-Month-old Infant, a Case Report

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Keywords

Neurodevelopmental impairment ; lysosomal storage disease ; neurometabolic disorder ; free sialic acid storage disease ; Salla disease ; pediatric global developmental delay.

Introduction

Imagine the challenge: recognizing deviation from the norm. In pediatric medicine, we often encounter impaired cognitive and motor development. Although rare, metabolic disorders remain an important cause, accounting for 1-5% of patients with neurodevelopmental disorders (1). Successful diagnosis of developmental delay acknowledges the balance of allowing for borderline natural cognitive and motor progression while simultaneously identifying a potential aberrant course of pediatric development (2). The entire process of neurodevelopmental evaluation, aside from diagnostic testing, is time consuming. This case report illustrates the diagnostic process, the importance of considering metabolic disorders in the differential diagnosis, and the contributory potential of comprehensive genetic investigation in a patient with neurodevelopmental disorder caused by Salla disease, a rare free sialic acid storage disorder (FSASD).

Case description

An 11-month-old male infant presented to a secondary care center with severe cognitive and motor developmental delay. Concerns had been reported by the mother since 6 months of age, as he remained unable to sit unsupported. Despite the initiation of physiotherapy, there was no developmental progress. At the age of 11 months, the neuropsychological assessment corresponded to a 4-month-old infant in cognitive and motor development. In the absence of paternal information, the family history was negative. The mother reported substance abuse (tobacco, cannabis, amphetamine) during pregnancy. Fetal growth assessments were performed only in the third trimester and showed no abnormalities. He was born at a gestational age of 39 weeks and 2 days, APGAR was 9 and 9, with a birth weight of 3295 grams. Newborn screening showed no abnormalities. On examination, the blond-haired, blue-eyed boy smiled interactively and produced high-pitched sounds. Clinical examination revealed only mild facial dysmorphism, including bilaterally protruding ears with low insertion and a high palatal arch without evidence of organomegaly. Biometric data of weight, height, and head circumference were within the normal standard deviation. He preferred the supine position and was able to lift his head from his chest in the prone position. Although he could track objects within his field of vision, he was unable to reach purposefully, sit unsupported, or roll over. Neurologic examination, including ophthalmologic examination, revealed horizontal nystagmus, truncal hypotonia, clenched fists, hyperkinetic movements of the arms, increased muscle tone in the legs, and ataxia of the upper and lower limbs. Audiologic evaluations were normal.

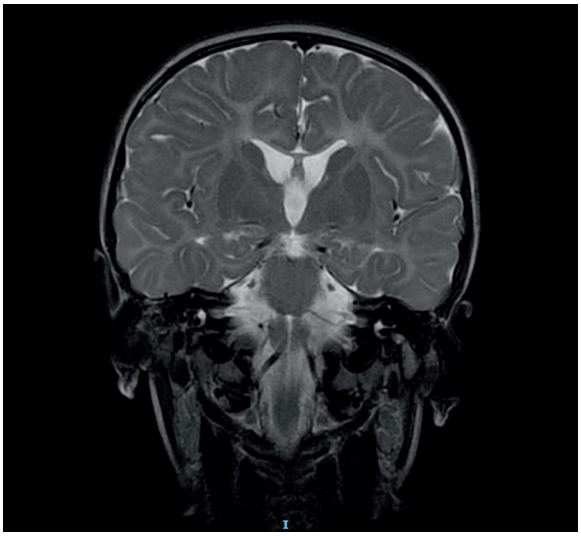
Biochemical analysis

Blood tests were negative for congenital infections, endocrine, renal, hepatic and metabolic disorders including amino acids, acylcarnitines, ceruloplasmin, copper, glycosylation defects, homocysteine. Urine toxicology was negative, but metabolic analysis including organic acids, purines, pyramidines, creatines, oligosaccharides, mucopolysaccharides, α-amino-adipic semialdehyde, and sialic acid was abnormal. Since the detection of elevated free sialic acid and markers of (galacto-)sialidosis were not in the range of (galacto-)sialidosis patients, it was initially considered abnormal due to young age and nutrition. However, repeated urine analysis, in addition to the genetics, showed a threefold increase in sialic acid levels.

Radiological imaging

Skeletal radiography was not performed. Cerebral MRI revealed hypomyelination of the basal ganglia and hypoplasia of the corpus callosum (Figure 1).

Figure 1: Cerebral MRI showing hypomyelination of the cortex and basal ganglia as well as a thin or hypoplastic corpus callosum



Genetic analysis

Following the recommendations of the Dutch guideline on diagnostic investigation in pediatric neurodevelopmental disorders, we performed a SNP array and a Fragile X panel, which showed no abnormalities. The patient was referred to a clinical geneticist at Erasmus University Medical Center. Considering the clinical presentation, the lack of paternal information and the uncertainty regarding the interpretation of the initial metabolic urine analysis, a comprehensive genetic evaluation for genetic and metabolic disorders by whole exome sequencing (WES) of the index patient and the mother was recommended. In January 2022, a homozygous mutation of the *SLC17A5* gene responsible for FSASD was identified, confirming the diagnosis of Salla disease.

Patient follow up

In parallel with the diagnostic process, rehabilitation efforts, including physical therapy, were initiated to stimulate motor development and to assess the need for specific outpatient developmental support. The patient was referred to a pediatric neurologist and metabolic pediatrician at the Center for Lysosomal and Metabolic Diseases, along with a pediatric gastroenterologist, pediatric cardiologist, and orthopedic surgeon. Cardiac ultrasound showed no cardiomegaly and electroencephalogram showed no evidence of epilepsy. In addition, multidisciplinary care included regular follow-up with a general pediatrician, ophthalmologist, rehabilitation physician, dietitian, speech therapist and social worker. Therapeutic options within the spectrum of FSASD include primarily supportive care, as curative treatments are not available. Prognosis includes regression of cognitive and motor skills after puberty, with severity related to genotype, and reduced life expectancy.

Discussion

In general, the identification of neuropsychological abnormalities in children begins primarily with parental and/or primary care concerns about cognitive and motor development. Although less common, we emphasize the need to consider metabolic disorders as a potential diagnosis in the group of neurodevelopmental disorders (2). Investigation of all medical etiologies (Table 1) could prolong the duration of the diagnostic phase. Thus, the question arises as to how ONE systematically aproaches the diagnostic process of a child with a neurodevelopmental disorder in order to minimize diagnostic delay. While there are national guidelines for the diagnostic approach to pediatric neurodevelopmental disorders (e.g., the Netherlands), there is still a need for an international guideline with widely accepted recommendations (2).

We strongly recommend the early involvement of pediatric experts in metabolic disease, neurology, and genetics to assist in the selection and sequencing of complementary investigations, in addition to history, physical examination, and neuropsychological assessment. In addition, evaluation for possible multi-organ involvement (e.g., visual, auditory, cardiac, hepatic, orthopedic) is necessary and should be systematically repeated to monitor progression over time (2, 3). Salla disease is an autosomal recessive neurodegenerative lysosomal storage disorder. Mutations of the *SLC17A* gene on chromosome 6q13 account for the spectrum of FSASD (3, 4). The global prevalence of Salla disease is less than 1 in 1,000,000. However, in Finland it is estimated to be 0.1%, with an incidence of 1 in 42,000 (5, 6). The *SLC17A5* gene encodes for sialin, which facilitates the transfer of intra- and intercellular metabolites, including free sialic acid. Dysfunctional sialin contributes to the accumulation of free sialic acid and N-acetyl-neuraminic acid (NANA), which is predominantly localized in the lysosome (4, 5).

The pathogenic mutation correlates with the severity of the FSADS phenotype (Table 2) (3, 7, 8). Clinical features of FSADS include dysmorphism (e.g., blue eyes, hypertelorism), growth retardation, recurrent respiratory infections, cardiomegaly, renal disease, inguinal hernia, skeletal dysostosis, ophthalmopathy (e.g., optic atrophy, strabismus, corneal clouding), intellectual disability, and neurological symptoms such as nystagmus, muscular hyper- and hypotonia, athetosis, and ataxia. Forty percent of individuals with infantile sialic acid storage disease develop epilepsy (3, 8, 9).

Table 1: List of potential etiologic medical conditions in neurodevelopmental disorder.

Renal disease
Liver disease
Neurological disease
Endocrine disorders
Metabolic disease (including mitochondrial disorders)
Genetic disorders
Teratogenic factors (e.g. maternal medication/intoxication)
Congenital factors (e.g. perinatal infection, neonatal complications)

Table 2: Genotype-Phenotype correlation.

Genetic mutation		
Phenotype	Mild (Salla)	Homozygote missense p.Arg39Cys
	Intermediate	Heterozygote p.Arg39Cys and *SLC17A5* variant
		Heterozygote p.Arfg39Cys and homozygote p.Lys136Glu
	Severe (ISSD)*	Heterozygote non-p.Arg39Cys *SLC175A5*

*ISSD: infantile sialic acid storage disease

Cerebral MRI often shows cortical atrophy, hypomyelination, and hypoplasia of the corpus callosum, resulting in motor and cognitive disability. One third of patients will be unable to walk. Although the mean IQ of 40 severely limits the ability to learn, receptive comprehension exceeds speech production ($p = 0.003$), facilitating the ability to communicate (8). Impaired language production was significantly associated with phenotype ($p = 0.003$) (8). Overall, the prospects for independent living without assistance are negligible (8, 9).

Although the gold standard for FSASD remains unknown, the urinary or cellular detection of lysosomal free sialic acid is considered pathognomonic for FSASD (3). Prior to the introduction of WES, a cohort study of 116 patients showed that 70% were diagnosed by urine biochemical analysis alone (10). However, the absence of biochemical detection of free sialic acid does not exclude the diagnosis of FSASD, as interfering urinary substances could potentially lead to false negatives (3, 10, 11).

In accordance with current recommendations, we advocate the use of genetic diagnostics as clinical presentation and biochemical results may be inconclusive (3). To determine whether to pursue targeted gene panel testing when a specific disorder is suspected or broad WES, we recommend a multidisciplinary review of individual features by experts in pediatric neurology, metabolic disease, and clinical genetics.

All FSASD cases report a delay in diagnosis, estimated at 2.5 years and a median age at diagnosis of 3 years (10) . However, in our case, the diagnosis was made in 13 months and the patient was 25 months old. Collaborative efforts among medical professionals from multiple centers to centralize patient care and diagnosis in a single institution may have reduced the diagnostic delay.

There are no curative or preventive treatments for FSASD. Supportive care with appropriate diagnostic testing focuses on neurologic, ophthalmologic, and cardiac morbidity, nutritional support, family support, and prenatal counseling of parents (3, 8, 9). Despite the degenerative nature of the disease, motor development continues into the twenties and cognitive development into the thirties (8, 9). Neurocognitive impairment at the time of diagnosis significantly affects future developmental potential. Life expectancy at birth is significantly reduced in all phenotypes of FSASD, with a average survival of 57 years for female patients and 59 years for male patients (9). Survival may be correlated with the level of urinary sialic acid excretion at diagnosis, with significantly improved survival when the level is <6 times elevated (10).

Conclusion

The consideration of metabolic disorders remains essential in the differential diagnosis of children with neurodevelopmental disorders. This case contributed to the understanding of the diagnosis of the ultra-rare spectrum of FSASD. We anticipate the development of an international guideline for the diagnosis of pediatric neurodevelopmental disorders in the near future.

Competing interests

The authors state no conflict of interest.

Informed consent

Informed consent was obtained from the patient.

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Congenital Naevus Sebaceous of Jadassohn in a Neonate: an Early Presentation of a Rare Lesion

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Keywords

Naevus sebaceous ; Jadassohn ; naevus sebaceous syndrome ; Schimmelpenning-Feuerstein-Mims syndrome.

Abstract

Naevus sebaceous of Jadassohn is a congenital hamartoma of the skin which, when associated with multisystemic complications, may manifest as linear naevus sebaceous syndrome or Schimmelpenning-Feuerstein-Mims syndrome. Naevus sebaceous is associated with postzygotic mutations, which may increase the risk of secondary tumour development within the lesion. Notably, secondary tumour transformation appears to be predominantly observed in adults, leading to controversy regarding the optimal timing for surgical excision. In this report, we describe a unique case of a neonate with a naevus sebaceous of Jadassohn, shedding light on the early onset of this rare lesion.

Case presentation

This case report describes the birth and clinical course of a male neonate born at term with a birth weight of 4200 grams (>90th percentile), a birth length of 55 centimetres (>90th percentile) and a head circumference of 35 centimetres (25-50th percentile).

He was born after an uneventful vaginal delivery with Apgar scores of 9/10/9 at 1, 5 and 10 minutes respectively. Pregnancy and antenatal ultrasound showed no abnormalities.

Initial clinical examination revealed a parietal erythematous, papillomatous and irregularly defined mass 3-4 cm in diameter and 2 cm thick. There was a small necrotic zone in the centre. The mass wasn't covered by skin (see Figures 1 and 2). An underlying skull defect could not be assessed.

There were no other clinical abnormalities, the patient was asymptomatic and well.

Because of this mass, he was transferred to a level 3 neonatal intensive care unit for further evaluation.

Magnetic resonance imaging (MRI) of the head revealed a soft tissue mass in the cutis and subcutis in the midline above the vertex. There was no evidence of intracranial extension or damage to the skull, nor were there any intracranial abnormalities. As computed tomography (CT) is considered to be a more sensitive examination for skull involvement, a head CT was performed, which showed a polylobular vascular tissue structure centred in the cutis/subcutis high parietal on the midline. There was no communication with the underlying skull.

Based on clinical examination and additional imaging, the differential diagnosis included fibroepithelial polyp, infantile myofibroma, or slow-flow vascular malformation.

Surgical removal, performed within the first 24 hours, was uneventful.

Histopathological examination of the parietal mass revealed a lesion consistent with naevus sebaceous (NS) of Jadassohn, which was completely excised. Sections through the various fragments showed skin with underlying adipose tissue. The epithelium, which was locally slightly verrucous, showed no signs of atypia. There were several hair follicles in the dermis and direct outflow of sebaceous glands onto the epithelium. Elsewhere in the fragment a proliferation of blood vessels was seen. The endothelial cells were not atypical. The blood vessels were dilated and congested with red blood cells. Extravasation of erythrocytes and areas of haemorrhage were seen at several sites. There were no atypical features. This benign haemangiomatous lesion was morphologically consistent with a cavernous haemangioma or vascular malformation, which appeared to have been incompletely removed.

Genetic studies could not be performed because the resection material was not preserved.

Further investigations ruled out nevus sebaceous syndrome, with ophthalmological examination, cardiac ultrasound and abdominal ultrasound showing no abnormalities. Head MRI showed no evidence of intracranial abnormalities and there was no clear evidence of skeletal abnormalities.

A medical genetics consultation was arranged for follow-up. The patient was also re-evaluated by a neurosurgeon approximately 5 months after surgery, which showed a favourable evolution, there was no recurrence of any lesions.

Follow-up was performed by the local paediatrician. No developmental problems or other associated symptoms were noted up to the present age of 2 years.

Discussion

NS of Jadassohn, first characterised by the dermatologist Josef Jadassohn in 1895, is a congenital hamartoma of the skin with hyperplasia of the epidermis, hair follicles and sebaceous and apocrine glands (1).

Clinical manifestations include linear or oval lesions with a smooth or verrucous texture, generally alopecic and in a range of colours. The scalp is the most commonly affected area, followed by the cephalic region. Involvement of the trunk and neck is less common. NS can vary in size from a few millimetres to 10cm, and giant nevi are extremely rare (2).

The association of multisystemic complications in NS leads to its classification as linear naevus sebaceous syndrome (NSS) or Schimmelpenning-Feuerstein-Mims syndrome (2, 3).

The estimated incidence of NS in newborns ranges from 0.1% to 0.3%, with no apparent gender or ethnic predilection. NSS is rare and the exact prevalence and incidence in the general population is unknown (2).

The differential diagnosis encompasses different syndromes, including cutaneous-skeletal hypophosphatemia syndrome, naevus comedonicus syndrome, Becker naevus syndrome, phakomatosis pigmentokeratotica, congenital hemidysplasia with ichthyosiform erythroderma and limb defects, and segmental outgrowth-lipomatosis-arteriovenous malformation-epidermal naevus syndrome (4).

NS is characterised histologically by immature and abnormally formed pilosebaceous units. Epidermal changes may show some acanthosis and mild papillomatosis. With age, the lesion may increase in size, with a more prominent location of the sebaceous glands high in the dermis and an increase in the number of sebaceous lobules and malformed ducts.

Despite its prevalence as a common cutaneous lesion, the phenotype described in our case can be considered a rare and atypical case, with histological changes consistent with naevus sebaceous or naevus-sebaceous-like, in addition to a vascular malformation. Few case reports document phenotypes comparable to this case and are described as papillomatous pedunculated NS (5).

NS can be caused by various genetic factors, as demonstrated by Groesser et al. who studied 65 sebaceous naevi. Their study showed that 95% of these lesions had mutations in the Harvey rat sarcoma virus (*HRAS*) gene, while 5% had mutations in the Kirsten rat sarcoma virus (*KRAS*) gene. Nonlesional tissue from 18 individuals had a wild-type sequence, confirming genetic mosaicism. Their results suggest that NS and NSS are caused by postzygotic *HRAS* and *KRAS* mutations (6).

During puberty, hormonal fluctuations can cause proliferation and hyperplasia of the lesion, resulting in enlargement and a more verrucous appearance (7).

In addition to aesthetic concerns, NS carries the risk of secondary benign or malignant neoplasms (2). Various mutations may predispose individuals to the development of secondary tumours in NS (6). Specific *HRAS* mutations identified by Groesser et al. were also present in all associated secondary tumours studied, suggesting a common genetic basis. In particular, NS and basal cell carcinoma (BCC) also share deletions in the Patched Tumour Suppressor (*PTCH*) gene, which may account for the possibility of BCC arising within NS. Other possible risk factors for BCC in NS include Fitzpatrick phototypes I and II, family history, prolonged sun exposure, use of sunbeds or radiotherapy (8).

Studies suggest that secondary neoplasms occur in approximately 10% to 20% of cases of NS, the majority of which are benign. Only about 3% of cases show some degree of malignancy, which is a rare occurrence (2). Secondary tumour transformation appears to occur almost exclusively in adults, as a retrospective analysis found that 96% of all NS-derived malignancies occurred in patients over 18 years of age, with the remaining 4% in the 11-17 year age group. Common benign tumours include trichoblastoma and syringocystadenoma papilliferum, while the most common malignant tumour is BCC (9).

A conservative estimate suggests that the lifetime risk of malignant transformation in NS is less than 2%. However, determining the true lifetime risk is complicated by divergent numbers in children versus adults from studies on NS specimens, given that the majority are excised in childhood and adolescence (1).

As secondary tumour transformation appears to be almost exclusively seen in adults, the timing of surgical intervention remains controversial. Although smaller lesions may be technically easier to remove, it is important to consider the risks of general anaesthesia in younger patients.

Figure 1: Parietal erythematous, papillomatous and irregularly defined mass with a diameter of 3-4 centimetres and thickness of 2 centimetres.

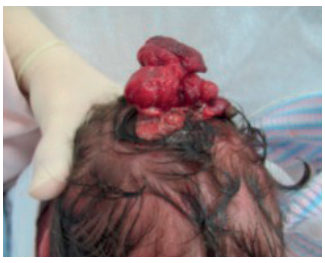
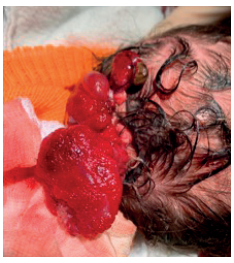


Figure 2: Close-up of the lesion, showing small necrotic zones.



Therefore, it has been suggested that excision should be performed prior to pubertal enlargement, provided that local and general anaesthesia are well tolerated, rather than waiting until malignant features develop (3).

Due to the size of the lesion in our patient, early excision appeared to be justified.

Other methods are frequently used to treat and improve Jadassohn lesions, including curettage, cauterization, cryotherapy, photodynamic therapy, topical salicylic acid, topical and systemic retinoid, topical application of vitamin D analogue, laser treatment, and dermabrasion (2).

The Schimmelpenning-Feuerstein-Mims syndrome was originally described as a triad of symptoms, including neurological impairment, seizures, and intellectual disability, associated with the presence of a NS. However, this syndrome has evolved to encompass multisystemic, extracutaneous complications involving a variety of organs including the nervous, ocular, cardiovascular, muscular, genitourinary and bone systems. The most frequently reported complications in the literature are hypophosphatemic rickets, intellectual disability, cognitive impairment, coloboma, and strabismus (2).

Due to the rarity of NSS and the extensive assessment that should follow, not all patients with NS require these examinations unless there are associated symptoms. However, if there are other associated symptoms, such as developmental delay, it is crucial to conduct assessments, including prenatal, developmental, and family histories, alongside neurological, ophthalmological, and cutaneous examinations. Any child with NS on the head or neck and developmental delay should undergo brain imaging. To evaluate for kyphoscoliosis, gait, and limb length, skeletal examinations should be conducted. Additionally, skin biopsies and relevant laboratory studies, such as serum/urine calcium and phosphate, liver and renal function tests, are critical (4).

In our patient, no resection material was retained for genetic testing. Given the lack of associated features and the low likelihood of detecting a genetic abnormality outside the lesion, it was decided not to pursue further genetic research at this time. Histopathological examination revealed findings consistent with a benign haemangiomatous lesion in addition to the sebaceous naevus. An extensive literature search did not reveal any association between haemangiomatous lesions and NS. There are few studies that have focused on assessing the prevalence of vascular malformations in NSS. Greene et al reviewed the medical records of 9 patients with NSS and concluded that 3 of these patients had various forms of vascular malformation including aortic aneurysm, carotid stenosis and lymphatic malformation (10). It remains unclear whether the vascular lesion described in our case should be considered as a separate entity.

Conclusion

This case report describes a rare and extensive phenotype of NS associated with an additional vascular malformation. The nature of this vascular malformation, whether it is associated with NS or a distinct entity, remains unknown.

NS is a common lesion in neonates. It is important to be aware of this pathology and its possible occurrence in Schimmelpenning-Feuerstein-Mims syndrome, which can affect multiple organ systems. Long-term follow-up is mandatory for the evaluation of associated symptoms and requires a comprehensive assessment.

While there is ongoing debate about the ideal management of NS, it is important to make decisions on a case-by-case basis and to recognise that there is a window of observation in affected children, given the gradual nature of secondary tumour transformation.

Conflict of interest

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

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A Paediatric Case of Unilateral Ptosis Caused by Palpebral Angiofibroma Associated with Tuberous Sclerosis Complex

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Keywords

Tuberous sclerosis ; angiofibroma ; orbit ; conjunctiva ; magnetic resonance imaging ; child.

Abstract

We present an eight-year-old patient, followed since birth for unilateral ptosis of unknown aetiology, who was diagnosed with tuberous sclerosis complex (TSC) following epileptic seizures. Earlier recognition of the palpebral angiofibroma with associated ptosis might have accelerated this diagnosis. The wide phenotypic variability makes TSC a challenging diagnosis.

Introduction

Tuberous sclerosis complex (TSC) is a rare multisystem autosomal dominant genetic disorder characterized by benign and non-invasive tumours in different organs. We present the case of an eight-year-old patient who had been followed since birth for unilateral mild ptosis and swelling of the underlying temporal bulbar conjunctiva. Despite investigation by computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and orbit, aetiology remained unknown. Over time, the patient developed ipsilateral discrete telangiectatic vessels of the superior bulbar conjunctiva. At the age of eight, the patient suffered 3 epileptic insults concurrent with a COVID-19 infection. Newly performed imaging studies unravelled the diagnosis of TSC and suggested the presence of a palpebral angiofibroma next to the presumed conjunctival swelling. Only very mild other clinical signs were present. Genetic analysis revealed the presence of mutated *TSC1* (c.1257del;p.(Arg420Glyfs*20)). Earlier recognition of the palpebral angiofibroma with associated ptosis and chemosis could have accelerated the diagnosis of TSC. The wide range of clinical manifestations from mild to severe makes TSC a challenging diagnosis. Our case adds to this variable clinical picture and will hopefully aid in earlier recognition of future patients.

Case description

A 2-month-old girl presented to the Department of Ophthalmology of UZ Leuven with mild ptosis of the right eye. The girl was the second child of healthy nonconsanguineous parents. Both pregnancy and delivery went uneventful. Ophthalmological examination showed unilateral mild ptosis with swelling of the temporal bulbar conjunctiva and normal anterior and posterior eye segment appearances. Transfontanellar ultrasonography could not demonstrate any abnormalities. Preventive occlusion therapy was initiated at this time.

At 10 months of age, the conjunctival chemosis seemed clinically suggestive of a lipodermoid, for which an orbit CT scan was requested to assess for orbital involvement. The CT scan did not show a lipodermoid, but instead revealed a blurry delineated, soft tissue swelling of the upper right eyelid with infiltration of the periorbital fat without intraorbital extension, suggesting chronic periorbital cellulitis.

An MRI of the orbit was performed at one year of age to exclude lymphangioma. MRI showed a stable lesion, but the aetiology remained unknown.

The patient was examined every six months. The girl developed a minimal asymmetrical vision for which occlusion remained recommended. At the age of four years, we clinically observed a conjunctival swelling over 180 degrees, both bulbar and at the level of the plica semilunaris. Figure 1 shows photographic documentation of the clinical findings in chronological order.

At 8 years of age, the patient was admitted for a diagnostic workup of bifrontal headache and nausea. The patient tested positive for SARS-CoV-2. During hospitalization, the patient suffered 3 tonic-clonic epileptic seizures. Intravenous levetiracetam was administered and no new epileptic insults occurred. Differential diagnosis include both secondary insults due to the COVID-19 infection and primary epileptic disease. Because of persisting lateralization, an urgent MRI of the brain was performed.

The MRI findings were compatible with TSC, with additional leptomeningeal and dural contrast enhancement. Some of the cortical tubers could already be distinguished very subtly on the first MRI of the orbit performed several years earlier, which, however, did not lead to this diagnosis considering the disparate protocol regarding MRI of the orbit versus brain as well as the different focal point of the examination (eye abnormality versus neurological symptoms) (Figure 2). In addition, some subependymal nodules were also evident, another finding described in TSC.

In the following days, the patient showed a favourable evolution with recovery of lateralization and improved overall condition. She was able to leave the hospital on oral levetiracetam.

Figure 1: The first row shows clinical pictures of the patient at the age of 1 (A), 4 (B) and 6 (C) years old. The unilateral ptosis and subsequently asymmetry is evident. The second row (A'), (B'), (C') shows the conjunctival swelling most prominent temporally, at respective ages.

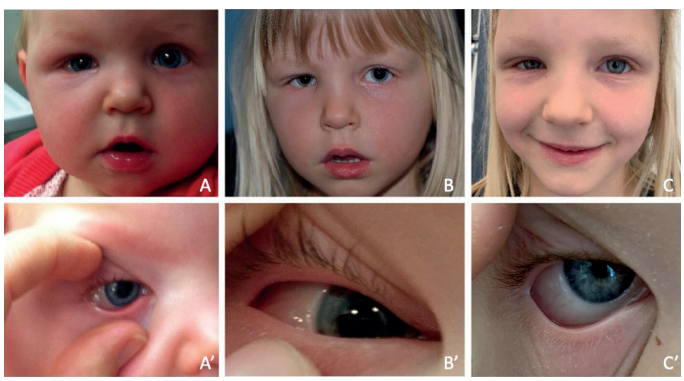


Figure 2: (A) and (B) show cerebral imaging performed by T2-weighted MRI in 2014. (A') and (B') show FLAIR images on the same levels in 2021. Some cortical tubers (arrows), intensely hyperintense in 2021, could already be distinguished very subtly in 2014 (arrows). These signs of TSC were the major clue leading to the diagnosis of a palpebral angiofibroma. (C) and (C') show respectively axial and sagittal planes of the MRI (T1-weighted with contrast) performed in 2021. The angiofibroma appears as a well-demarcated lesion in the right upper lid subcutaneous tissue with contrast enhancement due to its rich vascularization (arrows).

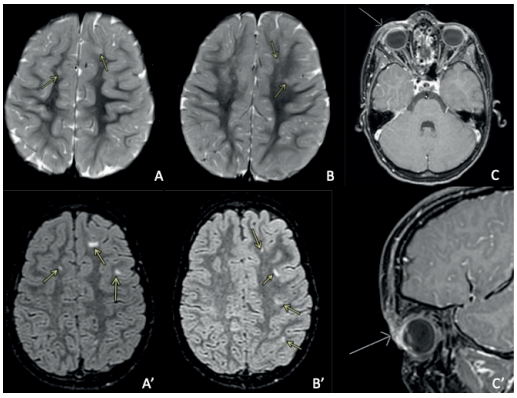
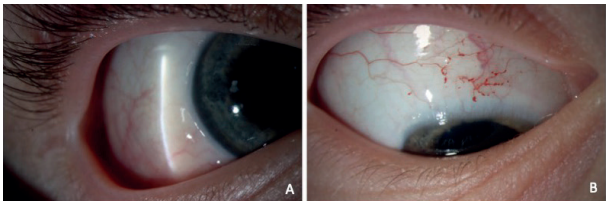


Figure 3: Clinical details through slit-lamp photography. (A) shows the angiofibroma with most prominent temporal bulbar conjunctival swelling. (B) Ipsilateral superiorly, small telangiectatic vessels of bulbar conjunctiva were observed.



Two months after admission, the patient returned for a routine ophthalmologic examination. Except for the known conjunctival swelling, we observed ipsilateral discrete telangiectatic vessels of bulbar conjunctiva, superiorly, as shown in Figure 3. A revisit of the old orbital MRI images confirmed the diagnosis of a palpebral angiofibroma next to the presumed conjunctival swelling. Dilated fundoscopic examination showed no abnormalities.

As mentioned above, TSC has a wide phenotypic diversity. This patient was on the mild end of the spectrum. Apart from a mild mathematical delay, the general development was good. Dermatologically, a low lumbar hypomelanotic patch and a shagreen patch were seen. A discrete angiofibroma was suspected on the left cheek. A limited angiomyolipoma was suspected on renal ultrasound.

Genetic analysis confirmed the presence of mutated *TSC1* (c.1257del;p.(Arg420Glyfs*20)).

Conclusion

TSC is a rare multisystem autosomal dominant genetic disorder occurring in approximately 1 in 6,000–10,000 patients. The incidence may actually be higher due to the variable penetrance and subtle clinical presentations (1). TSC is caused by inactivating mutations in the tuberous sclerosis-1 (*TSC1*) or tuberous sclerosis-2 (*TSC2*) tumour suppressor genes, resulting in hyperactivation of the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway regulates neural progenitor cell proliferation and differentiation throughout development. This causes the formation of non-cancerous tumours affecting different vital organs such as the brain, kidneys, heart, skin and eyes. TSC exhibits an extensive phenotypic diversity and clinical symptoms depend on the organs involved. The classic triad, although present only in a minority of patients, consists of seizures, mental disability and angiofibromas (1, 2). Seizures or dermatological manifestations are often the first overt clinical symptoms (1). Cerebral involvement is almost always present and represents the principal cause of morbidity and mortality (1, 3).

Retinal findings associated with TSC are hamartomas and hypopigmented macules (4). Hamartomas are present in 30 to 50 percent of the patients and are typically bilateral and multiple. These lesions do not usually cause visual impairment.

Non-retinal ophthalmological findings associated with TSC include hypopigmented sectoral lesions of the iris and ciliary body, colobomas of the iris and choroid, hamartomas of the iris and ciliary epithelium, angiofibromas of the eyelids and strabismus (2, 5). Rarely, patients may present with papilledema in the context of obstructive hydrocephalus secondary to giant cell astrocytoma (2).

With regard to neurological manifestations, a distinction was noted between *TSC1* and *TSC2*. *TSC2* mutations cause a more severe phenotype with both earlier onset and more refractory and difficult to treat seizures (1, 2). In addition, *TSC2* variants are associated with a higher incidence rate of retinal hamartomas which is the most common ocular finding (2). Patients with retinal abnormalities are more prone to develop cognitive impairment, epilepsy, renal angiomyolipoma and giant cell astrocytomas.(6)

Angiofibroma of the eyelid are the most common non-retinal finding in TSC (5). However, an ophthalmological presentation with a palpebral angiofibroma as the sole presenting sign, such as in our case, is very rare (7). Furthermore, these lesions are typically not accompanied by ptosis or conjunctival swelling. We hypothesise that the conjunctival swelling is caused by i) mechanical pressure with increased leakage from both venous and lymphatic drainage as well as ii) leakage from the highly vascularised angiofibroma.

We present a patient with a diagnosis of TSC following epileptic seizures concurrent with COVID-19 infection. Earlier recognition of the palpebral angiofibroma with associated ptosis could have accelerated the diagnosis of TSC. The extensive phenotypic variability may cause an important diagnostic delay and makes this disease a challenging diagnosis.

We aim to raise awareness among ophthalmologists, paediatricians and radiologists to consider the diagnosis of palpebral angiofibroma in patients with unilateral ptosis and undetermined conjunctival swelling.

Conflict of Interest

The authors received no financial support for the research, authorship, and/or publication of this article.

We hereby confirm that the authors have no conflict of interest to declare.

Ethics and Patient Consent

We confirm that Ethical Committee approval was obtained by the Ethics Committee Research UZ/KU Leuven (S67637).

We hereby confirm that the child's mother has read the case report in its entirety and approves of its publication, a written informed consent was obtained.

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▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt 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. 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. Beyfortus dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering 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 vóór het begin van het RSV seizoen, of vanaf de geboorte voor zuigelingen die tijdens het RSV seizoen zijn geboren. 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). Voor zuigelingen die een hartoperatie ondergaan met cardiopulmonale bypass, kan zodra de zuigeling 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 50 mg of 100 mg te zijn, afhankelijk van het lichaamsgewicht. 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, om de rest van het RSV seizoen te dekken. Er zijn geen veiligheids- en werkzaamheidsgegevens beschikbaar over herhaalde dosering. 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. Instructies voor toediening Beyfortus is verkrijgbaar in een voorgevulde spuit van 50 mg en 100 mg. Controleer de etiketten op de doos en de voorgevulde spuit om er zeker van te zijn dat u de juiste dosis heeft (50 mg of 100 mg). Beyfortus 50 mg (50 mg/0,5 ml) voorgevulde spuit met een paarse zuigerstang. Beyfortus 100 mg (100 mg/1 ml) voorgevulde spuit met een lichtblauwe zuigerstang. Stap 1: Terwijl u de Luer-lock met één hand vasthoudt (vermijd het vasthouden van de zuigerstang of de cilinder), draait u het naaldkapje van de spuit los door deze met de andere hand tegen de klok in te draaien. Stap 2: Bevestig een Luer-lock-naald aan de voorgevulde spuit door de naald voorzichtig met de klok mee op de voorgevulde spuit te draaien totdat u lichte weerstand voelt. Stap 3: Houd de cilinder met één hand vast en trek met de andere hand voorzichtig de naaldbeschermer met een rechte beweging van de naald af. Houd de zuigerstang niet vast terwijl u de naaldbeschermer verwijdert, anders kan de rubberen stop bewegen. Raak de naald niet aan en laat deze niet met in contact komen met een oppervlak. Plaats de naaldbeschermer niet terug op de naald en haal de naald niet los van de spuit. Stap 4: Dien de volledige inhoud van de voorgevulde spuit toe als een intramusculaire injectie, 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. 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 bijwerking 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. 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). Huid- en onderhuidaandoeningen • Soms - Rasha a Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen • Soms – Injectieplaatsreactieb ; Pyrexie b Injectieplaatsreactie is gedefinieerd door de volgende gegroepeerde voorkeurstermen: injectieplaatsreactie, injectieplaatspijn, injectieplaatsverharding, injectieplaatsoedeem, zwelling van injectieplaats Zuigelingen met een verhoogd risico op ernstige RSV-ziekte De veiligheid is ook 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 (614) of palivizumab (304) kregen. Het veiligheidsprofiel was vergelijkbaar met het vergelijkende geneesmiddel palivizumab en consistent met het veiligheidsprofiel bij voldragen en premature zuigelingen GA ≥ 29 weken (D5290C00003 en MELODY). Immunogeniciteit Zoals met alle therapeutische eiwitten, is er potentieel voor immunogeniciteit. 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: België: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – Afdeling Vigilantie – Postbus 97 – 1000 Brussel Madou – Website: www.eenbijwerkingmelden.be – e-mail: adr@fagg.be HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, Frankrijk NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN EU/1/22/1689/001 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/002 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/003 - 50 mg, 5 voorgevulde spuiten voor eenmalig gebruik EU/1/22/1689/004 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/005 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/006 - 100 mg, 5 voorgevulde spuiten voor eenmalig gebruik DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/ VERLENGING VAN DE VERGUNNING Datum van eerste verlening van de vergunning: 31 oktober 2022 DATUM VAN HERZIENING VAN DE TEKST Goedkeuringsdatum: 11/2023 Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau http://www.ema.europa.eu

Referentie:
1. Beyfortus SKP, nov 2023. MAT-BE-2400390-1.0-052024

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