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LA SBP REMERCIE SES PARTENAIRES POUR LEUR SOUTIEN

LA ROCHE-POSAY
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VOOR KINDERGENEESKUNDE

SOCIETE BELGE DE PEDIATRIE

Editorial

To you little Mia…

The theme of this March 2022 issue of the Belgian Journal of Paediatrics is devoted to neonatology. It was coordinated by Luc Cornette on behalf of the Belgian Association of Neonatalogists (BVN/GBN). Neonatalogists from all the 19 Belgian NICU provide an update on several topics of interest to the entire paediatric community. We thank our guest editor and all the authors for their very dedicated commitment. This issue is also the occasion to present the new logo of the BVN/GBN group. Our cartoonist Serge Ernst has put it into perspective on the journal cover and illustrated the "family-centered care" philosophy through his famous comic book character.

Exceptionally, we would like to dedicate this neonatal issue to a tiny baby girl...

To you, little Mia, who was born in the night of February 25, 2022, in the Kyiv underground metro as your mother was taking shelter from the bombing. Your birth in such dramatic circumstances is a shock for the whole of Europe. It reminds us of the stories of our parents or grandparents who described the births and deliveries in the cellars of Belgium during the bombings of the Second World War. This is not what we, paediatricians and neonatologists, expect for babies and parents !

Since 1945 and even more since the end of the cold war, our socio-economic model has led us to believe that peace, health, education or well-being for all, are values that emerge spontaneously, unquestionably, in response to sustained and continuous growth. Today, events such as the pandemic, the climate changes and the war in Ukraine, show us that the "happy globalization" does not bring, in itself, all the solutions. Whether we like it or not, other natural, political, and economic logics are also at work. As the Dutch historian and philosopher Luuk van Middelaar describes, we are currently experiencing a confrontation between the force of principles and the principles of force. History has already shown us that violence does not solve anything. Our principles and moral values progress when we become aware of their importance and their fragility… when we live them with coherence and cohesion. This is what we wish for you, little Mia… for you and for the newborns all over the world !

Beside the theme articles, we are pleased to publish research and review articles. K. Keiren and colleagues analyze the current practices on vitamin K prophylaxis in term neonates. F. De Vleeschauwer and G. Naulaers review the neuroprotective strategies of neonatal encephalopathy in low-resource settings. The "*Made in Belgium*" section summarizes the PhD thesis of Mariska de Lausnay from University of Antwerp about lower airway pathology in children with Down syndrome. She provides a systematic overview of the different pulmonary and airway problems in this specific population and provide a more patient-tailored clinical approach. At the Cochrane corner, we discuss whether the use of bottles interferes with breastfeeding success in preterm infants whose mothers want to breastfeed.

This issue also gives us the opportunity to introduce our new online submission tool. As previously announced, for several months, a working group from the editorial board has been optimizing our submission and review processes. This has led to the development of a new website (http://www.belgjpaediatrics.be) and to an update of our editorial policy. Manuscripts can now be submitted online. The instructions for authors and editorial policy are detailed at the end of this issue and on the journal website. We would like to thank Levi Hoste and Marek Wojciechowski and the "online submission tool" group for carrying out this work. It will definitely increase the visibility of our journal on a national and international level.

On behalf of the entire editorial board, we wish you a peaceful reading and a glorious springtime !

Christophe Chantrain and Marc Raes

Paediatric Clinical Research: Where Future Therapies Originate

Saturday 11 June 2022 UZ Leuven

Programme

8:45 **Registration & welcome coffee**

9:15 – 11:15 **Session 1: Socio-economic and ethical aspects of paediatric drug development**

- Welcome – prof. dr. Gunnar Buyse, chair of paediatrics, UZ Leuven
- Paediatric drug development in Europe: challenges now and ahead – prof. dr. Koen Norga, EMA & UZA
- Innovative medicine in University Hospitals Leuven – prof. dr. Frank Weekers, operational director, UZ Leuven
- European collaboration in paediatric clinical trials – prof. dr. Johan Vande Walle, UZ Gent
- Will our healthcare system become unaffordable? – prof. Yvonne Denier, KU Leuven

11:15 – 11:35 **Coffee break**

11:35 – 13:00 **Session 2: Future therapies for children in the pipeline**

Gene, cell and enzyme replacement therapy

- Gene therapy in neuromuscular disorders: successes and challenges – prof. dr. Liesbeth De Waele
- Neonatal kidney stem cells to improve quality of kidney grafts – prof. dr. Noel Knops
- Enzyme replacement therapies in metabolic disorders – prof. dr. Peter Witters

New immune therapies

- New biotherapies in paediatric rheumatic diseases – prof. dr. Lien De Somer
- Biologicals in inflammatory bowel disease – prof. dr. Ilse Hoffman
- New therapeutic options in relapsed or refractory acute lymphatic leukaemia – prof. dr. Heidi Segers
- A remedy for vitamin D resistant rickets – prof. dr. Elena Levtchenko

New pharmacological therapies and drug repurposing

- Promising results of new anti-obesity drugs: will it be a game changer for obese children? – prof. dr. Kristina Casteels
- Repurposing drugs in childhood epilepsy – prof. dr. Lieven Lagae

New devices

- New devices at the horizon for pulmonary valve replacement – dr. Bjorn Cools

Paediatric Clinical Research Unit (Petit CRU) in UZ Leuven

- Petit CRU: paediatric patient-centered golden-standard clinical research – prof. dr. Elena Levtchenko

13:00 – 14:00 **Networking lunch**

Practical information

Date and time: Saturday 11 June, 8:45 am – 2 pm

Location: MC-SQUARE Leuven, Philipssite 5 box 1, 3000 Leuven
(Parking is possible in the underground parking of the Philipssite)

Registration: please register before 27 May 2022 via this link: https://bit.ly/3o2yunm

Fee: €30 - free for students and trainees - networking lunch €20

Payment: IBAN: BE43 4320 0172 2101 (BIC: KREDBEBB),
please include the following structured message: +++ 972/2900/27025 +++

More information: Kim Rowan, e-mail: kim.rowan@uzleuven.be, tel. 016 34 38 22

Application for economy & ethics accreditation is ongoing

UZ LEUVEN

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OPROEP TOT PROJECTEN 2022

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zaterdag/Samedi 4 juni 2022

Belgian Down syndrome policlinics and Parents' Associations

"Vivre, c'est bouger"

"Leef! Beweeg!"

UZ Gasthuisberg, Leuven

Organisation

Catering : Cap Event

Stands :

Inclusie Vlaanderen, Inclusion Down, Down Syndroom Vlaanderen

Mondzorg atelier, Vigo, Elmex

Handisport et G-sport, Special Olympics

Services d'aide précoce

Kinderopvang 1-15 jaar onder voorbehoud/ Garderie 1-15 ans sous réserve

Languages

Français - Nederlands interprétation simultanée - simultane vertaling

Organising Committee

Myriam Besson, Inclusion Down asbl

Allard Claessens, Downsyndroom Vlaanderen & Down Syndrome Foundation Belgium

Anne Eeckels, Downsyndroom Vlaanderen

Sandrine Greiner, Inclusion Down asbl

Alain Mahieu, Down Syndrome Foundation Belgium

Michael Teutsch, European Commission Disability Support Group, Brussels

Marta Villar, European Commission Disability Support Group, Brussels

Scientific Committee

CProf. Dr. Griet Van Buggenhout, Centrum Menselijke Erfelijkheid, Downpoli, UZ Gasthuisberg, Leuven

Dr . Lieve Sevenants, pediater, Downpoli, UZ Gasthuisberg, Leuven

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Prof. Dr. emer. Mark Wojciechowski, pediater, oprichter Downpoli, Universitair Ziekenhuis Antwerpen

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Dr. Jelena Hubrechts, cardiopédiatre, responsable de la consultation multidisciplinaire trisomie 21, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain

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Mme. Céline Baurain, docteur en psychologie du développement, consultation multidisciplinaire trisomie 21, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain

Dr. Sophie Ghariani, neuropédiatre, consultation multidisciplinaire trisomie 21, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain

Dr. Anne Monier, neuropédiatrie, Hôpital Universitaire des Enfants Reine Fabiola HUDERF, Université Libre de Bruxelles

Dr. Tine Boiy, pediater, verantwoordelijke Downpoli, Universitair Ziekenhuis Antwerpen

Programme

08:30	Welkom - Accueil
09:00	Intro Prof. Dr. Griet Van Buggenhout, UZ Gasthuisberg Leuven, Centrum Menselijke Erfelijkheid & Downpoli
09:10	Dieetboek (stippenboek) & Preventie van obesitas – Carnet diététique & prévention de l'obésité . Tessa Bosmans, diëtist, UZ Gasthuisberg Leuven
09:40	Mond vol gezondheid - La santé plein la bouche-. Prof. Dr. Dent. Dominique Declerck, UZ Gasthuisberg Leuven
10:10	Onschuldig snurken of toch iets meer? – Ronflements innocents ou pas tout à fait? (OSAS). Prof. Dr. Mieke Boon, pneumoloog, UZ Gasthuisberg Leuven
10:40	Pauze : workshop en stands – Pause : atelier et stands

Workshop Mondzorg – Atelier Soins Dentaires . Prof. Dr. Dent. Dominique Declerck en mevrouw Marianne Vermeulen, lector UCLL, Professionele bachelor Mondzorg

11:15	Trisomie 21 en fysieke activiteit: begrippen en uitdagingen - Trisomie 21 et activité physique: concepts et défis. Prof. Dr. Marek Wojciechowski, downpoli UZA & Prof. Dr. J. Lebeer, handicapstudies, Universiteit Antwerpen
11:45	Atlanto-Axiale Instabiliteit - Instabilité atlanto-axiale. Dr. Renaud Rossillon, orthopédiste (St Pierre Ottignies)
12:15	Heupdysplasie - Dysplasie des hanches. Prof. Dr. Frank Plasschaert, orthopedist (UZ Gent)
12:45	Sportmogelijkheden in België - Possibilités de faire du sport en Belgique. Sébastien Xhrouet (G-sport Handisport)
13:00	Lunchpauze – pause déjeuner

- Tentoonstelling - Exposition: Maud Ysebaert fotografe

- Workshop Mondzorg (stand UZ Gasthuisberg Tandheelhunde) Prof. Dr. Dent. Dominique Declerck en mevrouw Marianne Vermeulen, lector UCLL, Professionele bachelor Mondzorg

14 :15	Spectacle danse, Creahm,
14:30	Getuigenis - témoignage : Charlotte De Bakker
14:50	Hoe de motivatie voor bewegen aanwakkeren - Comment motiver pour bouger? Juan Pablo Abarca De La Fuente, Directeur Sportif du Padel à l'AFT et Coach de l'équipe nationale de Belgique de Padel, Ancien Directeur de l'Académie de tennis de Justine Henin
15:10	Special Olympics : hoe beperkend kunnen onze voeten zijn? – A quel point nos pieds peuvent-ils nous limiter? Carine Haemels (Healthy Athletes Programme – Special Olympics Medical Team)
15:40	Voorstelling Europees Project "IDEAL" rond aangepaste sportmogelijkheden – Projet Européen 'IDEAL' concernant activités sportives adaptés. Debbie Van Biesen, Faculteit Bewegings- en Revalidatiewetenschappen, KU Leuven
16:05	Uitreiking van de Prijs- remise du prix "Downsyndroomoloog"
16:30	Conclusie en dankwoord – Conclusions et remerciements Allard Claessens

Inschrijvingen vanaf 15 maart 2022 - Inscriptions dès le 15 mars 2022
via https://www.downsyndrome.be/

Fondation Mustela

APPEL à PROJETS 2022

PRIX DE PÉDIATRIE SOCIALE

Groupement Belge des Pédiatres de Langue Française - ASBL - gbpf

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HAPPY 5TH BIRTHDAY BEXSERO

LE SEUL VACCIN CONTRE LE MENB
AVEC DES DONNÉES REAL-WORLD[1-4]

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.[5]

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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) **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] **Age lors de la première dose : Nourrissons de 2 à 5 mois [a] 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 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 doit 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 **Mises en garde spéciales et précautions d'emploi** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vasovagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique «Effets indésirables » . Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contreindication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles postvaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Les personnes ayant des déficits hétréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à **Neisseria meningitidis** du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. Ce médicament contient moins de 1 mmol de sodium (23 mg) par dose, c'est-à-dire qu'il est essentiellement « sans sodium ». Traçabilité Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **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 **méninge**s (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 B-1000 Bruxelles Madou Site internet: www.notifieruneffetindesirable.be e-mail: adr@afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy - Hôpitaux de Brabois Rue du Morvan 54 511 Vandoeuvre Les Nancy Cedex Tél. : (+33) 3 83 65 60 85 / 87 e-mail **:** crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments 20, rue de Bitbourg L-1273 Luxembourg-Hamm Tél.: (+352) 2478 5592 e-mail: pharmacovigilance@ms.etat.lu Link pour le formulaire : https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **10. DATE D'APPROBATION DU TEXTE** 07/10/2021 (v12). **MODE DE DELIVRANCE** Sur prescription médicale. **RÉFÉRENCES : 1.** Ladhani SN, et al. N Engl J Med. 2020;382(4):309-317. **2.** Deceuninck G, et al. Vaccine. 2019;37(31):4243-4245. **3.** Azzari C, Moriondo M, Nieddu F, et al. 2020;8[469] **4.** Rodrigues FMP, Marlow R, Simões MJ, Danon L, Ladhani S, Finn A. 2020;324(21):2187-2194. **5.** SmPC Bexsero

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Editorial

It is with great pleasure that we present a "neonatal issue" to the readership of the Belgian Journal of Paediatrics. In this volume, neonatologists from all 19 Belgian NICUs bring you an update on a variety of topics within neonatology which we considered to be of relevance to paediatricians in general: hypoxic-ischemic encephalopathy, cytomegalovirus infections, care of the extremely low birth weight infants after NICU discharge, unexpected neurologic events on the maternity ward, pathologies and prognosis in the late preterm infant, recent neonatal life support guidelines, early onset infection, developmental care policies & parental participation in the overall care, non-invasive ventilatory support.

Each manuscript has been written by a team of neonatologists from different centres, allowing for a stimulating interaction. Our explicit request was to emphasize those messages that are of interest to the general paediatrician who cares for infants on a maternity and/or N star ward. I would like to commend all authors for being so generous with their time and knowledge. I would also like to thank the members of the Bureau of the Belgian Association of Neonatologists (BVN/GBN) for their efforts during the review process. All manuscripts have been thoroughly read and corrected by Dr Filip Cools, Dr Kris De Coen, Dr Chantal Lecart, Dr Pierre Maton, Dr Vincent Rigo, Dr Liesbeth Thewissen, Dr Inge Van Herreweghe and myself.

The importance of a close collaboration between neonatologists and paediatricians is also embedded in our new logo. This logo emphasizes our philosophy of family-centred care: parents and infant are "supported" by the strong hands of doctors and nurses, not only within a NICU environment, but also on N star and maternity wards. Family-centred care always relies on a good network and on efficient communication between NICUs and maternity wards, i.e. between neonatologists and paediatricians. Family engagement in inpatient care of small or sick newborns undoubtedly leads to better developmental outcomes, enhanced clinician and staff satisfaction, and a wiser allocation of resources. As this "neonatal issue" is aimed at the adoption of "current best practises into routine clinical care", we therefore hope that our issue can be experienced as part of a national, collaborative quality improvement initiative within the care of newborn infants (and their parents), across all NICUs and maternity wards in Belgium.

Enjoy reading !

Dr Luc Cornette, Guest Editor
President of the BVN/GBN

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Newborn Life Support 2021: changes in neonatal guidelines

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Keywords

Newborn Life Support, Algorithm, Resuscitation, Airway management, Guidelines

Abstract

A review of neonatal resuscitation guidelines is conducted every 5 years. Due to the SARS-CoV-2 pandemic, the publication of these recommendations by the European Resuscitation Council has been postponed for 1 year. The purpose of this paper is to present the changes since 2015 and the new algorithm for a clinical use. Ten changes have been approved regarding umbilical cord management, meconium-stained liquor, laryngeal mask, initial inflation pressure, air/oxygen, vascular access, adrenalin, and ethics. The guidelines retain the so-called ABC approach for Airway, Breathing and Circulation. In this ABC approach, the focus is on controlling airway opening and lung ventilation while preserving the thermal balance.

Introduction

Every 5 years the European Resuscitation Council (ERC) guidelines for neonatal resuscitation are reviewed. For this purpose, the International Liaison Committee on Resuscitation (ILCoR) 2020 Consensus on Science and Treatment Recommendations for Neonatal Life Support (NLS) recommendations were supplemented by focused literature reviews undertaken by the ERC NLS guidelines group for topics not reviewed by ILCoR (1-2). Due to the SARS-CoV-2 pandemic, the publication of these recommendations has been postponed by 1 year and have been presented at the ERC congress and at our Belgian Resuscitation Council congress in March 2021.

These recommendations concern the newly born who needs assistance in the transition from intrauterine to extrauterine life. Notably, oxygenation and ventilation of the foetus move from dependence of the placental interface to independent lung ventilation ensuing specific hemodynamic modification (3). Around 5-10% of newborns experience difficulties in this transition phase and require assistance at birth. This assistance consists of stimulation, securing open airway and use of positive pressure ventilation to establish spontaneous breathing, 0.1% will need chest compressions and only 0.05% requires adrenalin treatment in combination with chest compressions and ventilation (1). These events affect only a small number of newborns, therefore, knowledge and correct application of neonatal resuscitation guidelines require a continuous training (4).

The ERC has also provided guidelines on neonatal resuscitation in the context of SARS-CoV-2 disease. Knowledge and understanding of the risks to neonates potentially exposed to this virus and the risk of transmission and infection of the virus to health care workers providing care is constantly evolving. For this reason, it is necessary to consult the ERC, national and institutional guidelines for the latest guidance and local policies regarding precautions for both treatment and caregiving (1).

In this paper we present the changes made in 2021 and the algorithm for the management of the newborn in need of support in the transition to extra-uterine life.

Changes in the 2021 guidelines

Ten topics were reviewed for the 2021 recommendations (1). A summary of these reviewed topics is shown in Table 1. The ERC guidelines were

Table 1 : Summary of the changes since 2015

Clinical Situation	Status from 2015 to 2021	Recommendation/ evidence
Management of the umbilical cord	Confirmation: Delay clamping for at least 60 sec, ideally after lung aeration New: If not possible, consider careful **cord milking (> 28 weeks)**	Moderate to high quality of evidence Low to moderate quality of evidence
Infants born through meconium-stained liquor	Routine airway **suctioning with or without laryngoscopy not recommended even in depressed infants** Priority given to lung ventilation	Weak recommendation, low certainty evidence
Use of laryngeal mask	Confirmation: Consider laryngeal mask for ineffective mask ventilation **only if > 34 weeks, >2000g**	Low- to moderate-certainty evidence
Inflation pressure	Initial inflation pressure of **30 cm H20 (term infants) and 25 cm H20 (preterm ≤ 32 weeks)**	Limited data
Air/oxygen for preterm resuscitation	Start with **0.21- 0.3 FiO_2 for preterm 28 to 32 weeks of gestation** and with **0.3 below 28 weeks of gestation**	Weak recommendation, low certainty evidence)
Chest compressions	Confirmation: If required, **FiO_2 is increased to 1** **Secure the airway**	No evidence
Vascular access	**Umbilical vein** **Intraosseous access** is a possible alternative	Weak recommendation, very low certainty of evidence
Adrenaline	**10-30 micrograms/kg** recommended if heart rate not increased despite optimal ventilation and chest compression	Weak recommendation, very low certainty evidence
Glucose during resuscitation	**250 mg/kg intravenous** in a prolonged resuscitation (reversible cause of cardiac arrest)	Expert opinion
Prognosis	Consider stopping resuscitation **20 minutes** after birth if there is no response	Low certainty of evidence

developed with the recommendations of ILCoR using the same level of evidence and strength of recommendations. Some recommendations were based on expert consensus and focused literature reviews.

Algorithm of new guidelines for clinical practice

The NLS 2021 guidelines retain the so-called ABC approach for Airway, Breathing and Circulation. The algorithm is shown in Figure 1.

Team and equipment:

Team briefing is regarded as a tool for improved communication. It serves to define the clinical context, to assign roles and responsibilities to each team member and to prepare the equipment. Prenatal counselling can help to define treatment options with the parents, including the extent of resuscitation, in order to propose an accepted care plan at the moment of birth. For each birth, attending staff trained in NLS should be present. A protocol must exist in each facility where deliveries take place to rapidly activate an expert resuscitation team for each birth (5).

The equipment and environment should be checked regularly and ideally before each birth and ready for use. Essential equipment should include a neonatal resuscitation table with radiant heating, an equipment for thermal care, a patient monitoring device (electrocardiogram, pulse oximetry (SpO_2), temperature probe), ventilation equipment (mask and T-piece resuscitator or bag) and oxygenation (air-oxygen blender). Material for airway suction, for advanced airway management (endotracheal tube, laryngeal mask), vascular access and thoracocentesis should be easily available. The same applies to essential drugs (adrenalin, glucose) and fluids (isotonic crystalloid or group O Rh-negative blood).

Birth and initial assessment of the newborn:

The assessment of the newborn may occur during the umbilical cord management. This involves assessing:

- The muscle tone
- Adequacy of breathing
- The heart rate (HR) by stethoscope or ECG electrodes for later continuous assessment

This assessment identifies neonates adapting well to the transition and who can benefit from skin-to-skin contact with the mother or partner from others newborns in need of support or resuscitation (6). During this assessment, tactile stimulation and thermal care are initiated and continued throughout assessment and treatment. Depending on the assessment, the newborn is classified into one of 3 categories :

1. Satisfactory transition: good tone, vigorous breathing or crying, HR > 100/min
2. Incomplete transition: reduced tone, breathing inadequately or apneic, HR < 100/min
3. Failed transition: floppy, breathing inadequately or apneic, HR < 60/min or undetectable.

Newborns with a satisfactory transition may benefit skin-to-skin care. The last 2 categories require support or resuscitation as detailed below. For these infants, the actions to be taken thereafter will depend on the assessment, every 30 seconds of the following:

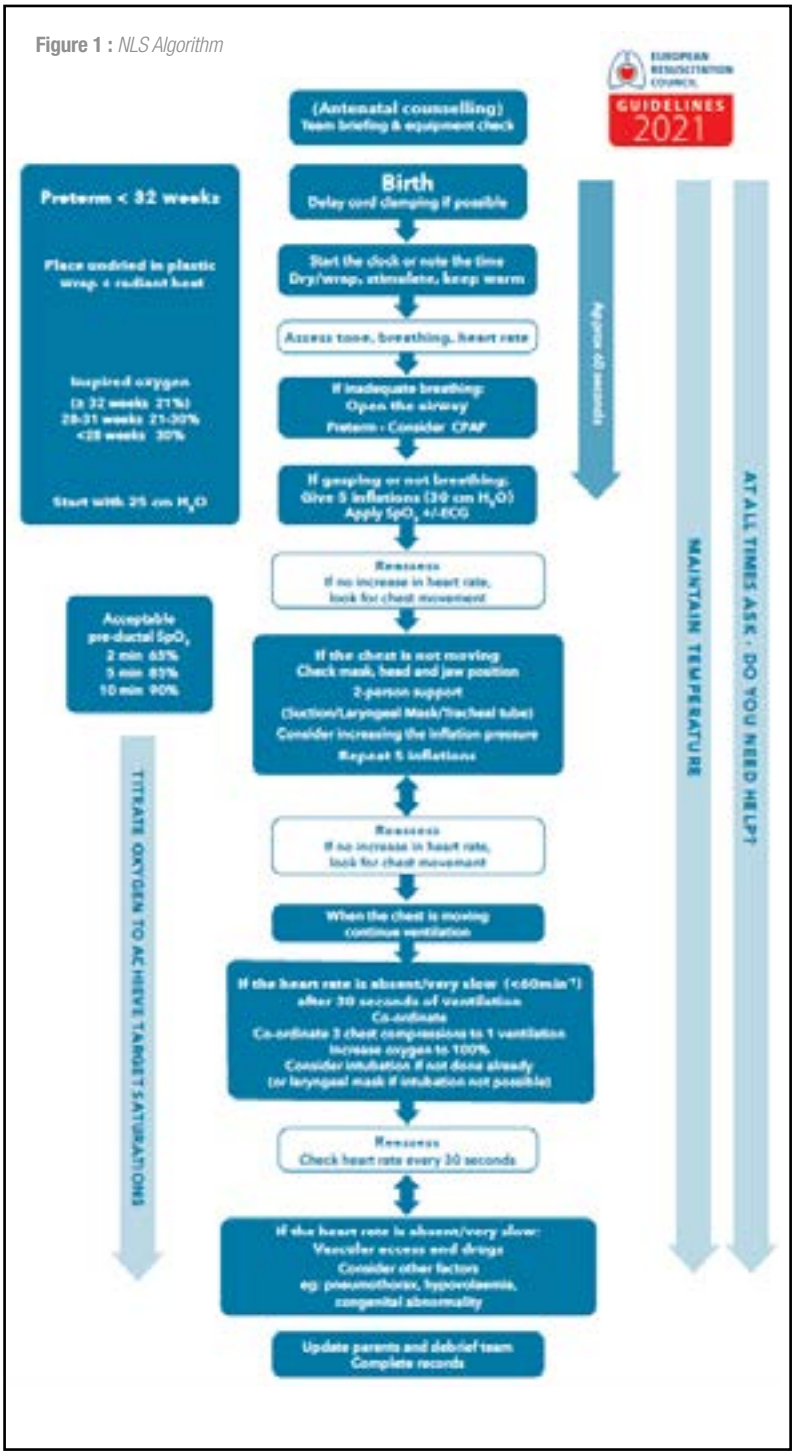
- HR
- Breathing
- SpO_2

Thermal care:

Newborns with a satisfactory transition may benefit from skin-to-skin care. For newborns requiring transition assistance, in addition to resuscitative support, maintenance of normothermia is critical. Hypo- and hyperthermia are associated with a poor prognosis and the temperature of the newborn should be monitored to avoid this (1). A combination of actions will be taken to maintain a body temperature of 36.5-37.5°C. This combination of care includes (7,8):

- Room temperature of 23-25 degrees Celsius and at least 25 degrees Celsius for preterm newborns < 28 weeks of gestation
- Avoid draughts by closing the doors and windows and programming the air conditioning appropriately
- Use of preheated radiant warmer, warm dry towel, covering hat
- Use of polyethylene bag (without drying the baby) and warmed humidified gas for babies < 32 weeks of gestation
- Use of a temperature probe to monitor the temperature
- For unplanned, outborn, infants, use of a polyethylene bag after drying the newborn. Well newborns over 30 weeks gestation can be carried skin-to-skin to preserve thermal balance during transport.

Figure 1 : *NLS Algorithm*



The admission temperature of newborn serves as a prognostic factor and can be used as a benchmark quality indicator.

Umbilical cord management to improve the transition to extra-uterine life: The ERC 2021 guidelines recommend delaying cord clamping for at least 60 seconds, ideally until after lung aeration, in a satisfactory transition. Delayed cord clamping allows the transfer of a blood volume of approximately 30 ml/kg from the placental circulation towards the foetus. It improves cardiorespiratory transition to extrauterine life by avoiding bradycardia due to the sudden drop in ventricular preload during immediate clamping. An ILCoR meta-analysis published in 2020 found no increase in hyperbilirubinemia requiring phototherapy or more severe complications related to prematurity such as intraventricular haemorrhage, retinopathy of prematurity, necrotizing enterocolitis or chronic lung disease (10).

Intact cord resuscitation cannot yet be universally recommended. When delayed clamping cannot be performed, cord milking may be considered for newborn over 28 weeks of gestation (11).

Airway and breathing:

Life support begins if the initial assessment indicates an incomplete or failed transition despite tactile stimulation. The first important step is to open and maintain the airway to allow lung ventilation (spontaneous or assisted) and to ensure the success of other resuscitative actions.

Opening the airway:

The airway is opened by placing the infant on its back with the head supported in a neutral position.

For very hypotonic neonates, jaw lift will be required to maintain an open airway. Airway obstruction is often due to incorrect positioning (12). An oropharyngeal airway may be helpful for term newborns when it is difficult to perform jaw lift and mask ventilation or for newborns with facial anomalies such as micrognathia. (13)

Airway suctioning is required only if there are secretions (such as blood, vernix, mucus, meconium) obstructing the airway and interfering with ventilation. In this situation, suction will be done under direct vision using a wide bore suction catheter (14).

Initial inflations and assisted ventilation:

Initial inflations are indicated in apnoea and gasps or if ineffective breathing is observed. They are performed without delay, using an appropriated sized face mask. The aim is to establish an adequate functional residual capacity which is an important step in the transition process. It contributes to changes in pulmonary blood flow through improved oxygenation.

Suggested inflation pressures have been increased from previous guidelines, to 25 and 30 cm H_20 for preterm neonates less than 32 weeks of gestation and neonates over 32 weeks of gestation respectively (1). The first 5 inflations are sustained and last 2 to 3 seconds. Assisted ventilation can be achieved with a self-inflating bag, a flow inflating bag or a T-piece resuscitator. The last one allows to obtain more reproducible insufflation pressures and PEEP (positive end-expiratory pressure), a more consistent inspiratory time and can support spontaneous breathing. The ventilation rate recommended by the ERC, after the five first inflations, is 30 inflations/minute (1,15).

At the same time, neonatal monitoring devices (ECG electrodes, pulse oximeter) are placed if not already done. The assessment of ventilation is based on the evaluation of HR and chest movements and is performed every 30 seconds. An increase in HR or a stable HR (if > 100/min) indicates an appropriate ventilation and oxygenation. Persistent bradycardia is a sign of hypoxia which is usually due to ineffective ventilation. Lack of chest movement may reflect airway obstruction, insufficient insufflation pressures or inappropriate sealing of the mask. If a HR response is present, ventilation should be continued until the newborn begins to breathe efficiently with a HR above 100/min.

The initial FiO_2 (fraction of inspired oxygen) according to the gestational age of the newborn is still a matter of debate. Recommendations are starting in room air at 32 weeks of gestation or more, FiO_2 0,21-0,3 at 28-31 weeks of gestation and 0,3 at < 28 weeks of gestation. The target saturations have been simplified 65% - 85% - 90% at 2 - 5 - 10 minutes of life respectively. The FiO_2 is adapted to the targeted preductal saturation, summarized in table 2, every 30 seconds to prevent both hypoxia and hyperoxia (16).

Table 2 : Initial inflation pressure, inspired fraction of oxygen (FiO2) and pulse oximetry (SpO2) target according to the gestational age

Term	Inflation Pressure	FiO_2	Minimal SpO_2 targets
Full term	30 cm H_20	0.21	65 % (2 min) 85 % (5 min) 90 % (10 min)
≥ 32 weeks			
28-31 weeks	25 cm H_20	0.21-0.3	
< 28 weeks		0.3	

Failure to respond:

If mask ventilation fails, actions should be undertaken to control the opening and integrity of the airway. These actions are as follows:

- Recheck head position, consider (or check) jaw thrust
- Recheck equipment, mask size, position, and seal
- Consider alternative open airway actions:
  - 2 persons mask ventilation
  - Inspection of the pharynx and suction of obstructive secretion if present
  - Use of an oropharyngeal/nasopharyngeal airway if unable to assure a secure airway.
  - Securing the airway through endotracheal intubation or laryngeal mask placement. It must be performed by competent caregivers with appropriate equipment.
- Gradual increase in inflation pressure until chest movement is observed
- Call for help by experts without delay

Repeat the five first inflations and check continuously the HR, chest movements and SpO_2. The actions required to control a complicated airway opening are presented in Table 3.

Table 3 : opening and maintenance of the airway

Action to be taken when mask ventilation fails
1. Recheck head position, consider or check jaw lift
2. Recheck equipment, mask size, position and seal
3. Other airway actions: - 2 persons mask support - inspection of the pharynx and suction to remove obstructing foreign matter if present - use of an oropharyngeal/nasopharyngeal airway (if unable to secure the airway) - securing the airway via tracheal intubation or laryngeal mask
4. Gradual increase in inflation pressure (until the chest is moved)
5. Call for help by expert without delay
6. Repeat inflations and check continuously heart rate, chest movement (and SpO_2)

The indications for intubation in the delivery room have not changed: ineffective face mask ventilation with no increase in HR and no chest movement despite all preventive actions (see above), prolonged face mask ventilation, chest compressions, special circumstance (suction the lower airway, congenital diaphragmatic hernia…). Tracheal tube insertion is done by trained staff with the appropriate equipment. If intubation is not possible or unsafe due to a congenital anomaly, lack of equipment or skills, the initial respiratory management with a laryngeal mask is possible and is considered a safe alternative. It should be remembered that the laryngeal mask has not been

evaluated in situations such as meconium-stained liquor, chest compressions or emergency drug administration (17). It requires a brief training on a manikin, the Belgian working group is working on an implementation of this guideline in the local NLS courses in Belgium.

Continuous Positive Airway Pressure:

In spontaneously breathing preterm infants consider CPAP to support respiration after delivery (18). Use mask or nasal prongs of an appropriate size. A T-piece resuscitator can deliver either CPAP and positive pressure ventilation with PEEP. Self-inflating bags cannot be used to provide CPAP during spontaneous respiration.

Circulation:

Chest compressions:

Chest compressions are indicated if HR is very slow (< 60/min) or absent despite 30 seconds of successful ventilation (only if chest movements is observed). Call for experienced help without delay. When starting this action, FiO_2 is increased to 1. It should be noted that this recommendation is not based on human studies and animal studies do not support it (19). The circulatory support provided by chest compressions can only be effective if lung ventilation is adequate to deliver oxygen to the myocardium. The technique of compressing with both thumbs on the lower third of the sternum, encircling the thorax, remains unchanged. The same applies to the compression to ventilation ratio, which remains 3:1. This means that the chest compression is done alternately with ventilation, corresponding to 15 cycles per 30 seconds (19). Re-assess every 30 seconds.

Adrenaline:

Exceptionally, the administration of drugs is required during the resuscitation of the newborn. Asystolia and severe bradycardia are due to severe hypoxia. Therefore, ventilation and adequate oxygenation are the critical steps to restore spontaneous circulation. Adrenaline is indicated if the HR remains very slow or absent despite 30 seconds of alternating chest compressions and ventilation. It is administered intravenously through an umbilical venous catheter at a dose of 10 to 30 mcg/kg every 3 to 5 minutes if necessary (1). When umbilical catheterization is not possible, an intraosseous access should be provided. If no venous or intraosseous access is available a dose of adrenaline of 50 to 100 mcg/kg should be administered endotracheally. However, this should not delay the insertion of the venous access.

Volume replacement:

Volume replacement is indicated in the situation of suspected blood loss or shock unresponsive to other resuscitative measures. Ten mL/kg of isotonic crystalloid or group O Rh-negative blood should be administered intravenously or intra-osseously.

Failed resuscitation: think of other factors

If there is no response to properly initiated resuscitative measures, other causes that may interfere with successful resuscitation such as pneumothorax, hypovolemia, intoxication (examples maternal medications: opiates, sedatives, beta-blockers), or congenital anomalies should be considered (1).

Preterm infants:

The algorithm applies equally to preterm newborns. In most situations, the preterm neonate needs transition support rather than resuscitation. This assistance is based on 3 main cornerstones:

1. Thermal protection with the use of heated and humidified gases and a polyethylene bag (bag designed for this purpose or feeding bag) in infants below 32 weeks of gestation and/or below 1500 g
2. Gentle ventilatory support with early application of CPAP for spontaneously breathing preterm infants with FiO_2 according to gestational age
3. Early glucose supplementation to prevent hypoglycaemia due to low glycogen stores.

Post-resuscitation care:

Newborns in need of transition support or resuscitation at birth will require specific further management. This includes, but is not limited to:

- Constant monitoring of vital parameters
- Monitoring of blood glucose levels and treatment of possible hyper- or hypoglycaemia
- Respiratory and circulatory support
- Therapeutic hypothermia for asphyxiated neonates with signs of hypoxic ischemic encephalopathy
- Updating parents

Prognosis: withdrawing or withholding resuscitation:

It seems reasonable to discontinue resuscitation 20 minutes after birth if there is a failure to restore spontaneous circulation despite well conducted intensive resuscitation due to the high risk of severe neurological impairment and of death. The recommendation of the ERC is to perform intensive treatment when there is more than 50% survival and acceptable morbidity, tailored to the regional or national outcomes. In Belgium, this generally includes most infants with congenital anomalies or newborns over 24 weeks of age in the absence of aggravating factors (hypoxia-ischaemia, intrauterine infection) (1). For overt situations with a high risk of mortality and severe morbidity such as extreme prematurity (< 22 weeks of gestational age), anencephaly or bilateral renal agenesis, it seems reasonable to withhold resuscitation (20).

When withdrawing or withholding resuscitation, the aim of care should be focused on the comfort of and respect towards the newborn and family. Decisions involving withholding or withdrawing resuscitation should be made after team discussion and informing parents by an experienced paediatrician or neonatologist.

Discussion

Several issues presented in these new guidelines deserve to be discussed:

Evidence informing the guidelines:

Most of the recommendations proposed in the guidelines have moderate to low levels of evidence. Other recommendations are based on expert opinion in support of local clinical practice (1,2,21). More well-designed studies are needed to increase the level of evidence of neonatal resuscitation guidelines. They are differences between the neonatal resuscitation guidelines proposed by the American Heart Association (AHA) and the ERC (21). We will discuss some of these differences.

Umbilical cord management:

Like the AHA, the ERC recommends delayed cord clamping when resuscitation is not required. Only the ERC suggests, in situation of incomplete transition, to delay cord clamping while providing appropriate thermal care and initial steps of resuscitation. This recommendation is based on a pilot study. Further studies are underway to support this management strategy. Umbilical cord milking is an alternative, for newborns over 28 weeks of gestation, when delayed umbilical cord clamping is not possible. This strategy is avoided before 28 weeks of gestation because a high rate of severe intraventricular haemorrhage in extreme preterm infants after cord milking is described in a single multicentre randomized controlled trial (11).

Assisted ventilation:

In the ERC recommendations, HR is not included in the criteria for initiating positive pressure ventilation, unlike in the American Heart Association (AHA) guidelines. However, a neonate with absent HR or below 100 bpm will not have spontaneous or effective breathing, so HR assessment does not appear to be essential for the initiation of insufflations.

ERC recommends a ventilation rate of 30 ventilations/minute after 5 initial inflations of 2-3 seconds. The rate is in the range proposed by ILCoR (30-60/minute) and below the range of the AHA (40-60/minute) (21). This is supported by an observational study using expired CO2 as a predictor of good ventilation, who argues that a lower respiratory rate (30/minute) allows a higher tidal volume to be administered and therefore allowed better

ventilation (15). The 5 initial inflations of 2-3 seconds are only proposed by the ERC and is based on expert opinion.

As the ILCoR, initial inflation pressures are increased to 25 and 30 cm H_20 for preterm neonates less than 32 weeks of gestation and neonates over 32 weeks of gestation respectively. This is supported in part by an observational study describing that in neonates over 36 weeks of gestation lower lung compliance required higher insufflation pressures (on average 36 cm H2O) to achieve adequate functional residual capacity (1,21,22)

Oxygen:

Concerning the FiO2 initially used, the stratification proposed by the ERC is based on expert opinion. The target saturations have been simplified 65% - 85% - 90% at 2 - 5 - 10 minutes of life respectively. Based on a meta-analysis of 8 randomized controlled trial, it was recommended that in preterm infants before 32 weeks of gestation, an oxygen saturation below 80% and/or HR below 100/min at 5 minutes of age should be avoided due to the high risk of death and severe intraventricular haemorrhage (23).

Opening and maintenance of the airway:

The algorithm suggests possibilities to manage an extremely difficult airway opening. This detailed approach to airway management is only present in the ERC algorithm. The recommendation for 2-person ventilation technique when chest is not moving is based on two studies in newborn paediatric anaesthesia (12,24).

Extreme prematurity:

Although we don't have official data, the intensive management of extreme prematurity at 22 and 23 weeks of gestation does not seem to be a common practice in Belgium. A systematic review shows that there is a wide variability in recommendations (more particularly between 23 and 24 weeks of gestational age) (25). In most neonatal intensive care units, there is general agreement for comfort care at 22 weeks of gestation and intensive resuscitation at 25 weeks of gestation.

Conclusion

The ERC neonatal resuscitation guidelines focus on thermal control, securing airway opening and guide us how to make adequate ventilation. The laryngeal mask is part of the resuscitation algorithm as an alternative to intubation. The target saturation values have been simplified. Other actions, such as increasing FiO_2 to 1 during chest compressions, are consistent with paediatric and adult resuscitation algorithms, while respecting the physiology of transition to extra-uterine life. As a result, the management of the neonate in emergency situations is clarified for less experienced caregivers in neonatal resuscitation. Most of the recommendations proposed in the guidelines haves moderate to low level of evidence. Other recommendations are based on expert opinions in support of local clinical practice. More well-designed studies are needed to increase the level of evidence of neonatal resuscitation guideline. Resuscitation at birth affects only a small number of newborns. Therefore, knowledge and correct application of neonatal resuscitation guidelines require a continuous training.

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

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Unexpected neurologic events in the maternity ward

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Abstract

Unexpected neurologic events in the maternity ward are highly suggestive of seizure activity in the newborn infant. Acute provoked symptomatic seizures associated with an early ischaemic or haemorrhagic brain insult account for more than 70% of neonatal seizures. Neonatal onset of infantile epilepsy occurs much less often. These two pathologic entities represent different types of seizures, different semiology, and different response to anti-epileptic drugs. Recognising clinical seizures in a newborn infant can be challenging and must be confirmed with video EEG monitoring. Seizures in a healthy term neonate necessitate admission to a neonatal intensive care unit. Investigating the aetiology and providing a prognosis to the parents require special expertise, including specific laboratory testing, magnetic resonance imaging of the brain and neurophysiological analysis. The purpose of this review is to highlight the aetiology and the clinical presentation of seizures in the apparently healthy term neonate and to propose a network management algorithm between paediatricians, neonatologists, and neuro-paediatricians.

Introduction

Neonatal seizures are not uncommon; the overall incidence is reported as 1-3.5/1000 of all live births (1,2). More than 70% of neonatal seizures consist of acute provoked seizures and are symptomatic of an acute brain insult such as perinatal asphyxia, stroke, or intra-cranial haemorrhage (2). In contrast, only 10% of neonatal seizures consist of early onset infantile epilepsy due to a genetic, metabolic or malformative origin (2,3).

Acute provoked symptomatic seizures and neonatal onset infantile epilepsy are two different pathologic entities. They represent different types of crises, different EEG traces, respond to different anti-epileptic drugs and need different explorations. Therefore, they must be differentiated early during the neonatal course (4).

Upon a severe perinatal asphyxiating insult, neurological depression is mostly obvious, and neonates must be admitted to a neonatal intensive care unit (NICU) to facilitate close monitoring. In contrast, arterial ischaemic stroke, cerebral sinovenous thrombosis (CSVT) and intra-cranial haemorrhage typically occur during the first hours or days of life in initially healthy term neonates at the maternity ward (5). Moreover, acute provoked symptomatic seizures in the context of these pathologies may be less obvious, as the seizures are numerous but short lasting, subtle, and even sometimes electrographic-only. Such subtle seizures can thus be missed or misinterpreted (6,7). Missing the occurrence of neonatal seizures can result in a lack of diagnosis, delayed treatment, remote neurologic sequelae, and remote epilepsy (8). This is more important as the length of stay in our Belgian maternity hospitals has recently been reduced to 48 hours.

On the other hand, rapidly controlling an epileptic crisis with an unspecific drug and without any EEG documentation or trained observation compromises a correct diagnosis and treatment (4). Seizures in a well-doing term neonate are thus a neurologic emergency and need an admission to a NICU.

In this review, we emphasize the importance of an early recognition of the seizures, the importance of an appropriate treatment, and we highlight the mandatory diagnostic pathways. We propose a care algorithm involving paediatricians, neonatologists, and neuro-paediatricians.

Clinical manifestations of neonatal seizures

Neonatal seizures (NS) are defined as a paroxysmal electro-clinical phenomenon characterized by the transient occurrence of signs and symptoms that are caused by an excessive or synchronous neuronal activity within the brain (9).

The clinical diagnosis of NS may be very challenging. Indeed, non-epileptic paroxysmal manifestations such as tremor, jitteriness, clonus, non-seizure sucking and repetitive movements during sleep are frequent in the neonatal period and can be misdiagnosed as seizure-related manifestations (6,10,11). Benign neonatal sleep myoclonus is another frequent condition characterized by myoclonus during sleep in a healthy newborn, resolving while awake and disappearing within the first months of life (3).

In 2017, the International League Against Epilepsy introduced a revised classification of seizure types including specific guidelines for NS (12). This new classification is based on clinical symptoms as well as EEG, depending on the predominant seizure type: electrographic-only seizures (i.e., clinically silent seizures) and electro-clinical seizures (including motor, non-motor, or sequential presentation) (9). Clinical events without an EEG correlate are not included in this new neonatal classification.

Clinically silent seizures represent most of the neonatal seizures: they are subclinical or electrographic only. Unless the seizure originates in or migrates to the motor cortex, the newborn will not present abnormal movements. As the newborn cannot express sensory phenomena, a seizure that is limited in a non-motor area will resume in subtle clinical manifestations, for instance recurrent apnoea (3,6,13).

Electro-clinical motor seizures include focal clonic seizures, focal tonic seizures, epileptic spasms, myoclonic seizures, and automatisms. Electro-clinical non-motor seizures include autonomic and behavioural arrest seizures. (Table 1).

Clonic seizures are the most frequent motor seizures and consist of rhythmic and repeated contractions of limbs, face, or trunk muscles. They can be focal, migrant, or multifocal. Tonic seizures are characterized by a progressive and asymmetrical stiffening of the trunk or limb. Epileptic spasms manifest as

a flexion or extension of the muscles of the trunk or extremities, they are usually associated with neonatal-onset epilepsy. Myoclonic seizures are brief contractions of muscles groups in the limb, trunk, or face. A differential diagnosis with benign sleep myoclonus is required. Apart from these typical seizure manifestations, more subtle and non-specific clinical signs should also lead to consider the possibility of an underlying seizure activity. Oro-lingual and orbito-ocular movements are suggestive of subtle seizures and unusual repetitive movements such as cycling, and boxing are suggestive of automatisms. Clinical signs of autonomic seizures include changes in heart rate or breathing pattern (e.g., apnoea), pupillary dilatation, or cutaneous flushing. Behavioural arrest seizures manifest as a sudden decrease or interruption of ongoing motor activity. Although frequent in neonates, subtle, autonomic, and behavioural arrest seizures usually present with other accompanying seizure symptoms (3).

Table 1 : 2017 ILAE classification of neonatal seizures (based on Shellhaas 2019 and Pressler 2021)

Type	Features	Aetiology	Comments
Clonic	Repetitive, rhythmic contraction, involving the same muscle group, either symmetric or asymmetric. Unifocal, multifocal or migratory presentations are described.	Typical seizure type in neonatal stroke or cerebral haemorrhage; may also be seen in HIE and in neonatal onset epilepsies.	Most reliably recognized clinical seizure type.
Tonic	Sustained increase in muscle contraction, lasting a few seconds to minutes, with asymmetric limb posture.	Often seen in genetic neonatal onset epilepsies.	
Epileptic spasms	Sudden flexion, extension, or mixed extension-flexion of predominantly proximal and truncal muscles.	May be seen in inborn errors of metabolism or neonatal onset epilepsies.	Rare and brief in neonates. Limited forms may occur: Grimacing, head nodding, or subtle eye movements.
Myoclonic	Sudden and brief involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).	Typical seizure type in errors of metabolism and preterm infant; may also be seen in neonatal onset epilepsies such early myoclonic epilepsy of infancy.	Benign sleep myoclonus is a non-seizure condition that needs to be differentiated from myoclonic seizures.
Automatisms	More or less coordinated motor activity with impaired cognition: eye deviation, sucking, chewing, boxing/cycling movements or purposeless complex movements.	Seen in HIE and preterm infant; often part of sequential seizures.	Very common but rarely isolated without other associated motor manifestation; typically oral in neonates.
Sequential	Sequence of signs, symptoms, and EEG changes at different times. No predominant feature determined.	Often seen in genetic neonatal onset epilepsies.	Often with changing lateralization
Autonomic	Distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, or thermoregulatory functions.	Seen in intraventricular haemorrhage as well as with temporal or occipital lobe lesions.	Rarely truly isolated but typically concomitant motor manifestations.
Behavioural arrest	Arrest of activities, freezing, immobilization, as in behaviour arrest seizure		Rarely isolated.
Electrographic only	Subclinical, without clinical manifestation. Electro-clinical dissociation is frequent in neonates.	Seen in HIE and preterm infant.	Facilitated by AEDs and in case of severe encephalopathy.
Unclassified	Due to inadequate information or unusual clinical features		

Aetiology of neonatal seizures

It is important to identify as soon as possible the origin of the seizures in a newborn infant. Indeed, the investigations, the molecule chosen for the treatment and the duration of the treatment will essentially depend on the aetiology of the seizures.

A. *Acute provoked symptomatic seizures*

Acute provoked symptomatic seizures are clinical seizures occurring at the time of, or in close temporal relationship with a documented central nervous system (CNS) or systemic insult, which may be metabolic, toxic, structural, infectious, or inflammatory in origin.

1. *Perinatal asphyxia* is the most common cause of neonatal symptomatic seizures (2). This paper focusses on the pathologies affecting the apparently healthy newborn in the maternity ward; asphyxiated newborns suffering from hypoxic-ischaemic encephalopathy should be referred to a NICU. Whilst some newborns with signs of mild to moderate asphyxia are admitted to the maternity ward, they may exceptionally present with seizures.

2. *Perinatal arterial ischaemic stroke (PAIS)* is the second most common cause of symptomatic seizures (2,14). PAIS occurs in about 1 in 2,300-5,000 live births. There is no specific pathology related to PAIS, and as such, PAIS is more likely to result from multifactorial conditions. In most cases, there is no particular maternal history, and the pregnancy was normal. Nevertheless, certain circumstances surrounding the birth of newborns with PAIS are found: a history of infertility, primiparity, pre-eclampsia, gestational diabetes, chorioamnionitis, signs of foetal distress, emergency caesarean section, male sex, neonatal polycythaemia, neonatal hypoglycaemia, and neonatal infection. Its pathophysiology is currently better understood, and it incriminates in most cases the occlusion of a cerebral arterial blood vessel by a clot originating from the placenta. The transitional circulation during the early hours of life with high pressures in the right chambers of the heart favours the opening of the foramen oval. This situation allows the formation of clots that can migrate directly from the placental interface into the arterial circulation. The blood flow dynamics preferentially direct the clots to the left middle cerebral artery. The other hypothesis is traumatic, i.e., an arterial lesion can occur within the context of extraction forces onto the head during the birth process (5).

The initial clinical manifestations of PAIS are most frequently motor (90%): lateralized focal or hemi-corporeal clonic seizures can occur during the second and/or third day of life. In addition, many newborns with PAIS present with apnoeic spells or cyanotic attacks. Less frequently, seizures are vegetative in nature, such as bradycardia, skin flush, hiccup or dysregulation of blood pressure or temperature. For instance, an alarming event may be acute pallor of a limb due to an arterial embolism or spasm (14). Other clinical signs include hypotonia and poor feeding.

3. *Cerebral sino-venous thrombosis (CSVT)* is less common than PAIS, its incidence ranging between 2.6 to 12 per 100,000 neonates. Such thrombosis in full term neonates usually involves the superior sagittal or transverse sinuses and less frequently the medullary veins (15). Risk factors are similar as in PAIS. Neonates with CSVT usually do not require resuscitation. They may be initially considered healthy and sent to the maternity ward prior to present with non-specific symptoms such as apnoea, hypotonia, irritability, dehydration, or poor feeding. However, seizures are the most common sign, as approximately 50% of neonates with CSVT present with seizures within 48 hours of delivery (16).

Its pathophysiology is well understood in the context of Virchow's triad, i.e., stasis of blood flow, injury of the vessel wall and perturbation of the components of blood affecting clot formation and lysis. If a thrombosis in the cerebral venous system occurs, it impedes venous outflow, resulting in increased central venous pressure. As a result, intracranial hypertension can lead to cerebral ischaemia, which may lead to infarction, often haemorrhagic in nature. Imaging of the thrombus in the sino-venous system can be difficult (16). MRI and MR venography offer the most detailed and sensitive means to assess the clot. Management of neonatal CSVT is supportive with hydration, treatment of any underlying condition and anti-epileptic drugs (AEDs). For term neonates with CSVT and without significant intra-cranial haemorrhage, anticoagulation is the appropriate treatment (15).

4. *Intra-cranial haemorrhage* in term newborn infants may be spontaneous in nature, without identifiable risk factors such as birth trauma, vascular malformation, or coagulopathy. Rarely, intracranial haemorrhages are related to mutations in *COL-4a*, bleeding diathesis due to vitamin K deficiency, inherited thrombophilia, or infection. Often, a newborn will have more than one type or location of intra-cranial haemorrhage. Term neonates with intraventricular haemorrhage should be evaluated for co-existing CSVT (16). Isolated intraventricular haemorrhage is rarely associated with seizures unless it is large or associated with parenchymal haemorrhage (2). Parenchymal haemorrhage involving cortical or subcortical grey matter may cause seizure activity and reduced consciousness levels. Large haemorrhages can be detected with cerebral ultrasound, but MRI is the most reliable technique. Acute intra-cranial haemorrhage needs prompt neurosurgical consultation, but one should be aware that acute intervention might not always be indicated. On the other hand, many healthy neonates can have small subarachnoid or subdural haemorrhages due to delivery, without seizures or other clinical signs. When faced with seizure activity in a term infant, the presence of such small haemorrhages may explain the clinical seizures, but other potential causes must always be looked for (3).

5. *CNS infection* is an uncommon cause of symptomatic neonatal seizures (i.e. 5% of newborn seizures) (2). Usually, seizures from CNS infection also present with fever as well as multi-systemic disease. Lumbar puncture is recommended in all neonates with seizures and suspected infection (6). Bacterial infections are classically due to group B *Streptococcus* and *Escherichia coli.* Viral infections can be caused by herpes simplex virus, cytomegalovirus, enterovirus, parvovirus and even rotavirus. Seizures may present at any time during the neonatal period, occurring as late as at several weeks of age, e.g., late group B *streptococcal* or herpes simplex infection. Because of the ongoing inflammation, seizures resulting from CNS infections can persist longer than in ischaemic or brain injury. Consequently, these neonates should be monitored (EEG) for a longer period. Duration of therapy (AEDs) will depend on the result of the cultures of cerebrospinal fluid.

1. *Disturbances of electrolyte or glucose homeostasis* may cause acute seizures in the newborn infant as it likewise does in older children or adults. Treatment should be directed at determining and correcting the underlying aetiology of such abnormality. Conventional AEDs are usually ineffective and unnecessary as seizures promptly cease with correction of the underlying abnormality (7). It is important to stress that any metabolic disturbance (hyponatraemia, hypocalcaemia, and hypoglycaemia) that causes seizures deserves a thorough investigation to find the underlying pathology (e.g. profound hypocalcaemia can point towards a 22q11 mutation, hypoglycaemia can be caused by nesidioblastosis). Severe and long-lasting hypoglycaemia can cause occipital located cerebral damage as seen on the MRI (17). All newborns with suspected seizures should have a bedside glucose measurement, as well as laboratory testing for electrolyte disturbances.

6. *Neonatal abstinence syndrome* can occur in newborns who are chronically exposed to opioids in utero. During the acute phase, manifestations include poor feeding, gastro-intestinal disorders, abnormal sleep patterns and neurological signs such as jitteriness, irritability, crying, tremor, hypertonia and even seizures. Finnegan scores should be obtained during observation. Some non-epileptic manifestations, such as jerking movements during benign neonatal sleep myoclonus, may be mistaken for seizures. Of neonates with neonatal abstinence syndrome, only 7.5% manifest with seizures (18). EEG is thus mandatory for confirmation prior treatment.

B. *Early onset epilepsy*

About one in eight newborns with seizures has a neonatal-onset epilepsy. These syndromes may be associated with a brain malformation or a genetic abnormality. It is important to rapidly differentiate between neonatal epilepsy and symptomatic seizures, as these two entities require different investigations and treatment (3).

1. *The benign familial neonatal epilepsy* is the most common form and is linked with a *KCNQ2/KCNQ3* variant. Neonates have focal tonic sei-

zures but look healthy and have a normal inter-ictal EEG. There often is a family history of neonatal seizures.

2. *The benign idiopathic neonatal seizures* or fifth-day fits: newborns present convulsions around the fifth day of life; these seizures resolve within the first few weeks of life. There is no family history of epilepsy; an association with rotavirus has been suggested.

3. *Epilepsies associated with brain malformations* (cortical dysplasia, lissencephaly, megalencephaly) have a poor prognosis and encompass many syndromes. The newborn often presents with an abnormal neurological examination and feeding difficulties. The EEG shows significant background rhythm abnormalities in addition to seizures. Clinical seizures are often generalized and tonic; spasms can be associated.

4. *Neonatal epileptic encephalopathies* present during the first week of life in an encephalopathic child with crises that are refractory to AEDs. *KCNQ2* mutations are often involved. MRI is usually normal. Seizures are mainly tonic, and EEG is abnormal. The prognosis is poor.

5. *Epilepsy associated with inborn errors of metabolism* often presents with multifocal myoclonus, hypotonia and an abnormal EEG between seizures. This group is also called "early myoclonic epilepsy". Aetiologies include pyridoxine-dependent epilepsies, sulphite oxidase deficiency, nonketotic hyperglycinaemia, Menkes disease, Zellweger syndrome, etc.

Confirmation of seizure activity

Seventy percent of neonatal seizures are sub-clinical or subtle (10). They may be of short duration or very focal, making their diagnosis challenging. They may not be detected clinically unless the newborn is under direct observation by a trained caregiver at the time of the seizure (10). EEG monitoring as well as video recording in NS constitute essential tools to the clinician, to prevent underdiagnoses of real seizures or overtreatment of non-epileptic events (10). Indeed, as under- and overtreatment are both harmful, accurate diagnosis is imperative and any suspicion of a seizure activity in a neonate must be confirmed with an EEG (19,20). EEG recording before initiation of treatment is essential to confirm whether paroxysmal events are real seizures as well as to document their electrical characteristics. In case of NS, precise determination of the predominant seizure type(s) can point to a diagnosis (4). All seizure activity present within the newborn EEG must therefore be described in detail by a neurophysiologist (12).

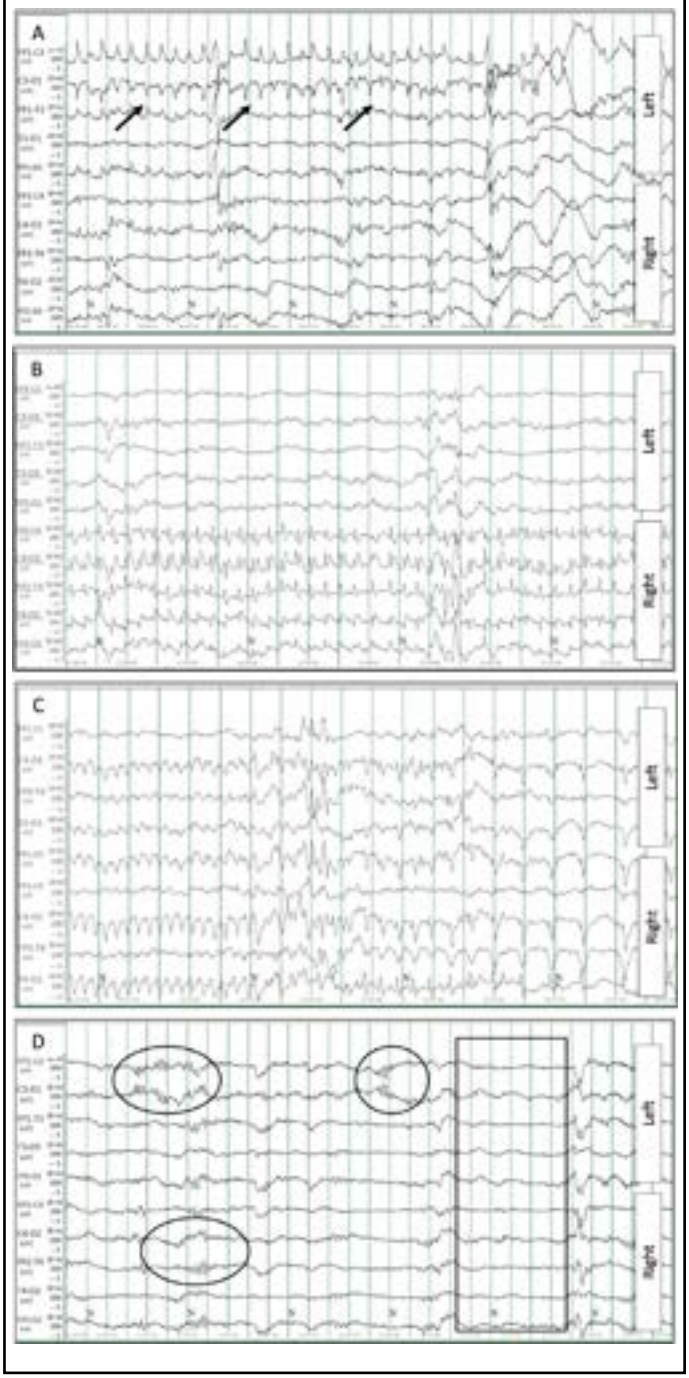
Technological advances have made EEG possible at the bedside within the incubator (21). Continuous video EEG with a conventional 10-20 montage modified for the newborn infant is considered as the gold standard (20,22). Full row EEG is a state-of-the-art technique, but its access might be difficult outside working hours. Amplitude-EEG (aEEG) can be a good alternative as it is easier to install and interpret. Nevertheless, as neonatal seizures are often of short duration (<1-2 min) and highly focal, they are often not detected by aEEG (7).

The EEG of neonates with symptomatic seizures presents in a wide variety of ways. Seizures are usually described as slow (1-3 Hz) discharges of rhythmic spikes or slow waves. The discharges are commonly localized, focal in nature, but they spread to the whole hemisphere or brain in 40% of cases (23). Change of morphology and frequency is common throughout the seizure, especially if the seizure propagates (23). Electrical crises are commonly of short duration (1 to 2 minutes) but they can be numerous, and their cumulative duration can evolve into a status epilepticus (24).

Distinctive EEG patterns according to the aetiology of the seizure activity have not been clearly described. Seizures arising from the midline vertex region are highly suggestive of CSVT (3). For PAIS, a set of non-specific observations has been noticed. Firstly, unilateral seizures are often observed on the hemisphere contra-lateral to the clinical manifestation. Secondly, the seizures are and remain focal in phase opposition on at the central region. Finally, the background rhythm between seizure activity in the affected hemisphere can be depressed, sometimes discontinuous and too rich with a rapid rhythm. (24). (Fig1)

When seizures are treated, conventional EEG monitoring should be continued up to 24 hours after resolution of the acute phase (20). Upon starting the treatment, continuous video EEG monitoring becomes even more relevant since some AEDs increase the proportion of electrical-only seizures (25). The use of AEDs may cause electro-clinical dissociation, a condition in which clinical symptoms cease to manifest, but electric seizures are still present (3). The contemporary association of aEEG gives an overview of the last hours of recording and can provide information on the crisis burden. Continuous video EEG and aEEG thus constitute unavoidable diagnostic and therapeutic tools for the acute neurologic neonatal patient.

Figure 1 : *raw EEG from patients with arterial ischaemic stroke.*
A: focal ictal discharge on the left central lead (arrow); B: right unilateral ictal discharge; C: diffused ictal discharge evolving in frequency and morphology; D: discontinuous background pattern (rectangle) with excess of theta sharp waves (circles).



Neuroradiographic investigations

Imaging findings are highly specific to differentiate focal infarction from haemorrhage, from asphyxia and from lesions due to hypoglycaemia or infection. Both cranial ultrasound and MRI are necessary for a full description of the patterns of injury. Examples of imaging findings are here summarized for focal brain injury, as the gradual improvement of imaging in the detection of stroke and other focal lesions stands as an example for neonatal brain imaging in general.

Ultrasound in arterial ischaemic stroke

PAIS can nearly always be visualized with ultrasound, except for small cortical infarcts far away from the transducer. It may however take several days before hyperechoic change is apparent beyond doubt. Even in cases of temporal or occipital infarction, targeted ultrasound from the temporal or posterior fontanelle can detect the lesion. A perforator stroke in the thalamus and striatum is particularly sensitive to detection with ultrasound. Experience with cranial ultrasound increases the detection rate of arterial stroke.

Ultrasound can help in staging the lesion (14):

· Day 1: decreased pulsatility of the affected vessel and mild hyper echogenicity.

· Over the next few days: increase of echogenicity due to the increasing presence of cell nuclei from neutrophils and macrophages; associated haemorrhage can increase the inhomogeneity; the hyperechoic stage persists for 3 to 4 weeks; cavitation follows an intermediate checkerboard pattern.

· A cavity is fully developed after 6-10 weeks; compensatory neuropil growth around the infarct may create the impression that the defect shrinks over the ensuing months; some have interpreted this as compensatory growth of the area adjacent to the infarct.

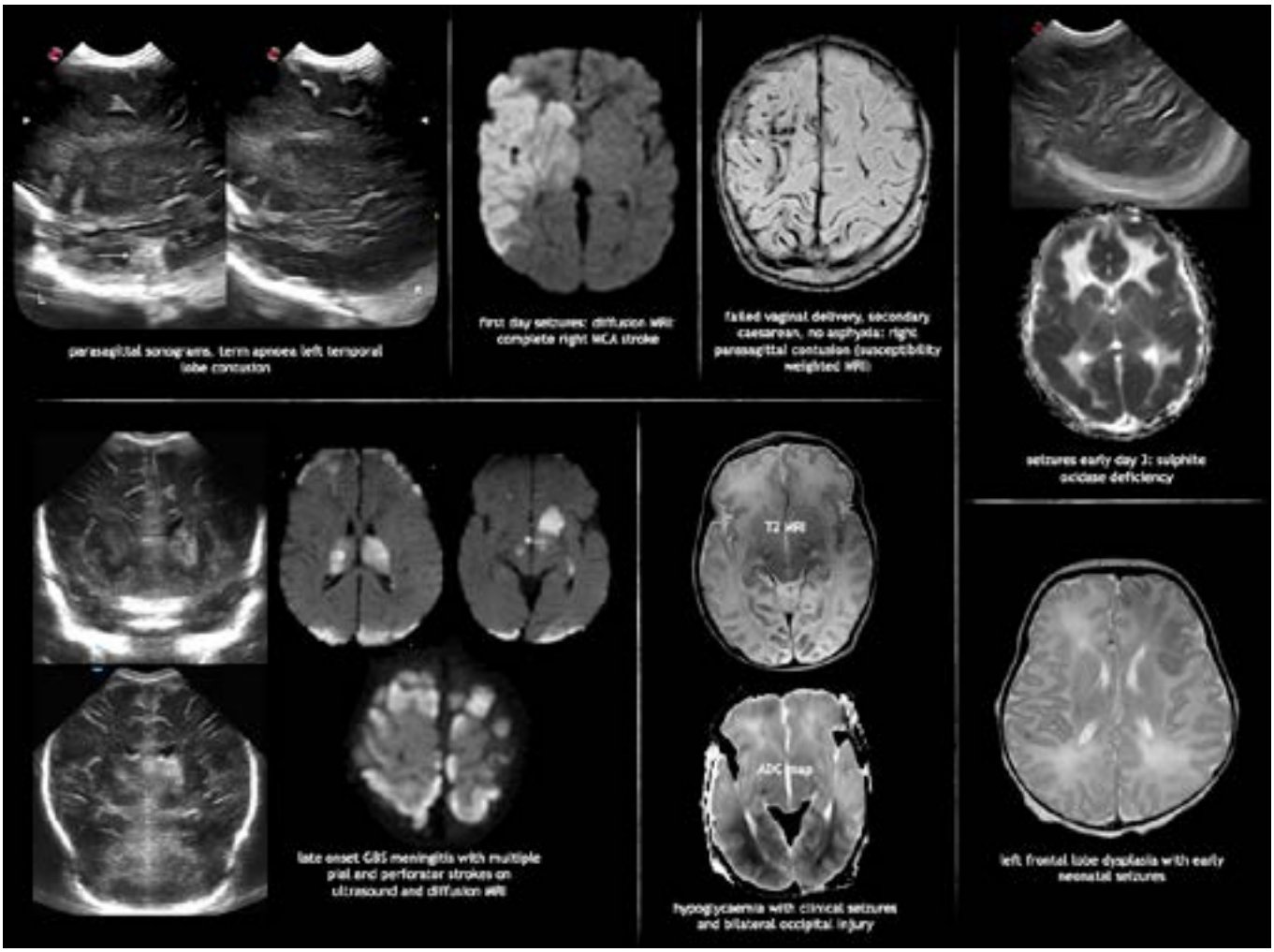
MRI and neonatal stroke

MRI provides the highest anatomic resolution and the best sensitivity to detect acute ischaemia (26). Specific sequences to obtain include diffusion-weighted imaging (from insult to about 7 days later), T1- and T2- weighted imaging, and susceptibility-weighted imaging. A MR angiography of the head and neck should be considered because it can easily be added to the initial MRI evaluation.

T2-weighted images in term infants with neonatal stroke demonstrate a high signal intensity in affected cortical grey matter and white matter during the first week of life, whereas T1-weighted imaging reveals a low signal intensity in the involved cortical grey matter. Between weeks 1-4 after birth, cortical grey matter signal intensity is high on T1- and low on T2-weighted imaging (i.e., cortical highlighting). Serial MRI confirms that in neonates with PAIS, the onset of injury is around the time of delivery. Tissue breakdown is maximal around 6 weeks. Three-site involvement of the hemisphere, the basal ganglia and the posterior limb of the internal capsule is strongly associated with later contralateral hemiplegia irrespective of the size of the infarct.

Diffusion-weighted imaging is used to depict cytotoxic oedema and provides image alterations within hours of the initial injury (27). Visualization of the lesion using diffusion-weighted imaging is best observed within the first 2-4 days from the moment of the initial injury. In the acute stage intensity changes are seen along the pyramidal tract. This phenomenon has a prognostic value especially at mesencephalic and pontine level and is referred to as pre-Wallerian degeneration. The extent of such acute corticospinal changes may predict the severity of the hemi-syndrome. Recruitment of ipsilateral tracts may predict maintenance of function in the affected limbs. Advanced post-acquisition quantification of diffusion tensor imaging data allows mapping of white matter connections, so called tractography. Tractography can refine subjective prediction of motor dysfunction.

Figure 2 : *Cerebral ultrasounds and MRI pictures related to neonatal seizures*



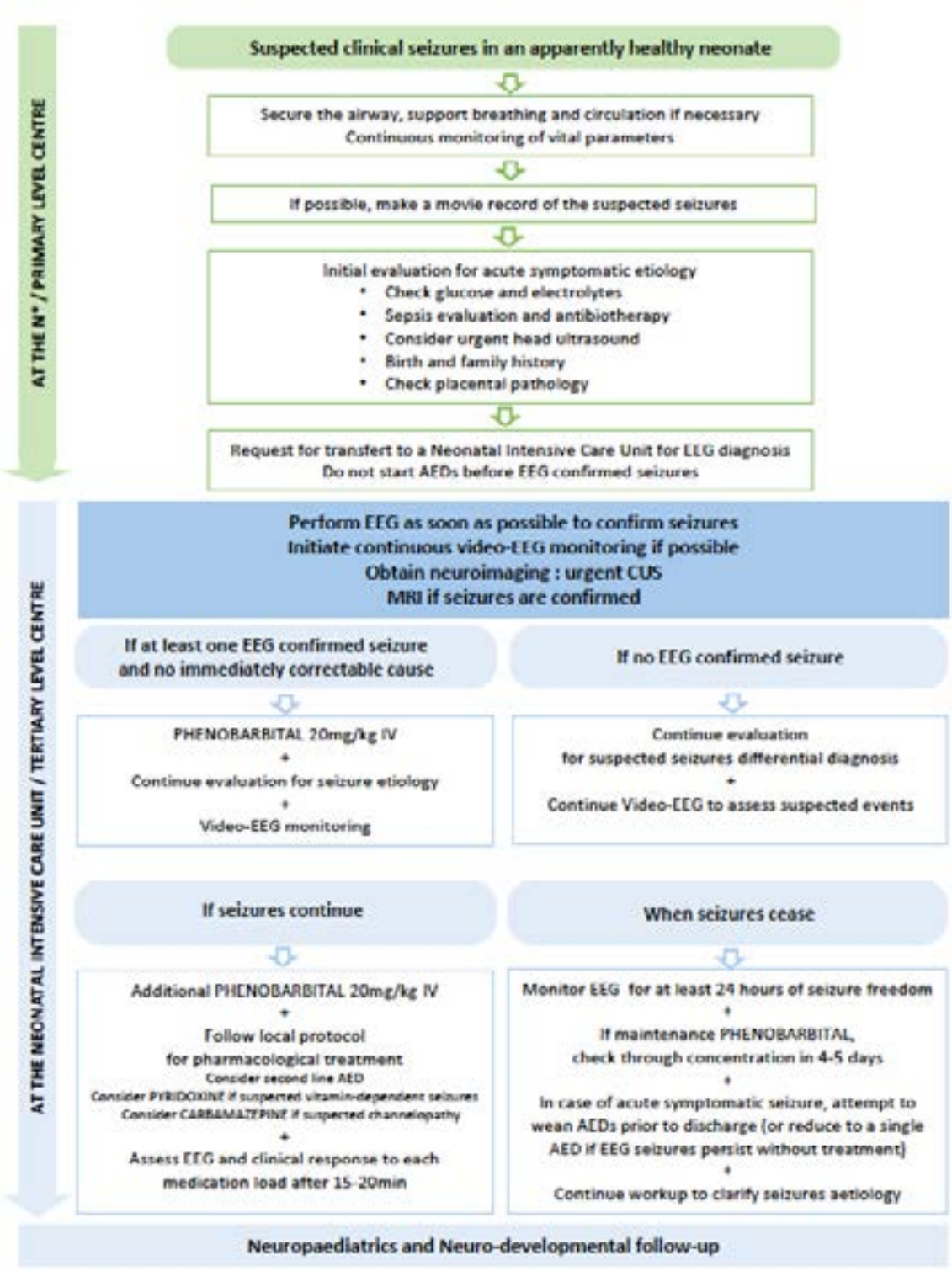
Treatment and algorithm of care in case of acute symptomatic seizures

Whilst being a rare neurological disorder, NS are associated with a high risk for severe brain lesions, epilepsy in childhood as well as cerebral palsy and cognitive impairment (28). Accurate recognition, appropriate diagnosis and early treatment are therefore of utmost importance (6). A protocol for the management of suspected NS is proposed in Figure 3.

The evaluation and treatment of a newborn infant with suspected seizures must occur simultaneously (6). As during any neurologic emergency, the first step involves accurate management of the airway, breathing and circulation. Priority should be given to the identification of easily correctable causes such as electrolyte disturbances or hypoglycaemia (3,29). If infection is suspected, cultures of blood, urine and cerebrospinal fluid should be obtained as soon as feasible, to promptly initiate antibiotics or antiviral medication (3). Every case of NS should be discussed with a tertiary level centre and transfer must be considered to provide cerebral monitoring using (video)-EEG, as well as accurate imaging to establish a diagnosis. In 2011, the American Clinical Neurophysiology Society (ACNS) developed specific guidelines on neonatal monitoring with conventional EEG (20). The guidelines state that electrophysiological monitoring must be proposed to every newborn with suspected seizures if correction of the underlying aetiology cannot be quickly obtained.

For high-risk neonates (e.g., with hypoxic-ischaemic encephalopathy or intra cranial haemorrhage) treatment with AEDs should be started immediately after suspected seizures, without waiting for EEG results (3,6,29). If the diagnosis

Figure 3 : *Assessment and treatment algorithm of neonatal seizures. (Based on Shellhaas 2019, Glass 2019 and Soul 2018)*



is unclear, treatment may be continued until EEG seizures are confirmed. Once seizures are recorded on EEG, prompt treatment is indicated (3,29).

Early treatment of NS with AEDs improves outcome (11). However, overtreatment may be harmful as side effects of AEDs may include hypotension, respiratory depression, and arrhythmia (11). Moreover, chronic use of AEDs is associated with cognitive and memory impairment in children (30). The decision to initiate AEDs therefore not only depends on the aetiology but also includes the seizure burden, i.e., the duration of electrographic seizures in a given period. A long seizure burden is associated with poor outcome (12). It is generally considered that rare and brief seizures may not require immediate treatment but require more prolonged EEG monitoring. A seizure burden higher than 30-60 seconds per hour is considered as a threshold to initiate treatment (22).

Discussion on treatment options is beyond the scope of this paper. The aim of AEDs is not only to resolve the acute seizure activity, but also to reduce the severity of acute brain injury and ideally to decrease the incidence of later epilepsy and/or neurologic disability (7). Hereto, multiple treatment algorithms exist worldwide, as current evidence does not suggest the superiority of one particular AED. It is therefore imperative that neonatologists and paediatric neurologists develop hospital-specific, consensus-based practice pathways for neonatal seizure evaluation and treatment (3). Phenobarbital remains the most frequently used first-line treatment for NS, but its efficacy is only about 50% (3,6). The use of concomitant AEDs for NS is thus common, with phenytoin, levetiracetam, midazolam and lidocaine being the most commonly used second- or third-line therapies. The choice of any association of AEDs must be based on the type of NS, its aetiology, the mechanism of AED action to target synergy and possible adverse effects (e.g., the association of phenytoin and lidocaine should be avoided because of possible cardio-depressive effects). For some conditions, the use of a specific pharmacological treatment is indicated. For example, in vitamin-dependent epilepsies one should consider pyridoxine, pyridoxal-phosphate or folinic acid. Carbamazepine has been shown to be effective for the control of seizures in case of *KCNQ2* channelopathy. Such "targeted" therapy highlights the importance of an early diagnosis of the underlying aetiology based on an appropriate analysis of the clinical context, the EEG features of the seizures, as well as the laboratory, genetics, and imaging workup by a specific trained team.

Conclusion

Seizures in the newborn represent the manifestation of an important cerebral pathology and need urgent diagnosis and treatment. Seizures can be subtle in nature and easily missed. An accurate description of the initial critical symptomatology may suggest the diagnosis at an early stage. Conversely, treatment of seizures without neurophysiological documentation may rule out the diagnosis. A good surveillance on maternity ward is therefore of utmost importance. The policy of early discharge from our maternity wards requires us to train midwives who monitor newborn infants at home.

Conventional multi-channel EEG with time-locked video is the gold standard in establishing a diagnosis for neonatal seizures and is essential to guide treatment. It must be initiated as soon as possible.

Conventional MRI combined with diffusion imaging is mandatory to identify the origin of the pathology.

An organised network between midwives, paediatricians, neonatologists, and neuro-paediatricians is the only way to guarantee optimal management of seizures in the newborn.

Conflict of interest

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

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Management of hypoxic-ischemic encephalopathy – current issues for the paediatrician

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Keywords

Perinatal asphyxia, hypoxic-ischemic encephalopathy, therapeutic hypothermia

Abstract

Perinatal asphyxia (PA) is defined as the deprivation of oxygen occurring around the time of birth. Hypoxic-ischemic encephalopathy (HIE) is an encephalopathy due to PA. Perinatal asphyxia and HIE are still associated with high morbidity and mortality rates. The use of therapeutic hypothermia (TH) commencing preferably within the first 6 hours of life – currently the only scientifically validated treatment modality for HIE – has been proven to reduce the mortality rate and disability. We discuss pathophysiology, diagnosis, neuroimaging, treatment, the impact of PA and TH on pharmacology, follow-up, and some remaining questions of PA and HIE. The purpose of this article is to guide the general pediatrician in selecting the patients for neuromonitoring and TH and inform them about the tools for outcome assessment and early intervention for those with high risk for impaired neurodevelopmental outcome.

Introduction

Perinatal asphyxia (PA) is defined as the deprivation of oxygen occurring around the time of birth. Hypoxic-ischemic encephalopathy (HIE) is an encephalopathy due to PA (1). In industrialized countries, its incidence is estimated to 1-5/1000 births (20-30/1000 in developing countries) (2). Mortality remains high (10-15%) and 25% of the survivors will develop a neurological impairment such as cerebral palsy, developmental delay, blindness, deafness, seizures and long-term neurological disability during childhood (1).

The therapeutic gold standard for moderate and severe forms of HIE is therapeutic hypothermia (TH) starting preferably within 6 hours of life for a duration of 72 hours. Randomized controlled studies have shown a significant reduction in death and disability at 18 months and improved neurodevelopmental outcome at 6-7 years (1). Therapeutic hypothermia is currently the only effective, and scientifically validated treatment for HIE, with a number needed to treat of 7 (1).

The purpose of this article is to summarize what is known about HIE and TH, useful for the general pediatrician taking care of newborns at delivery. We discuss pathophysiology, diagnosis, neuroimaging, treatment, the impact of PA and TH on pharmacology, and follow-up. In addition, the indications for transfer to a neonatal intensive care unit (NICU) in the context of PA, as well as unanswered questions about future perspectives, are discussed.

Pathophysiology of HIE

The pathophysiological mechanisms behind HIE are complex and can be divided in 3 phases (Figures 1 and 2) (3). The first phase of primary energy failure results from cerebral blood flow interruption (i.e. the primary neuronal insult) with reduced supply of oxygen and glucose and leads to an anaerobic metabolism as well as immediate neuronal death by necrosis. A transient recovery of cerebral oxidative metabolism after resuscitation maneuvers, i.e. the latent phase, precedes a secondary phase of delayed, progressive failure of oxidative metabolism, typically starting after 6-8 hours (3). During this secondary neuronal insult, there is secondary energy dysfunction leading to mitochondrial collapse, cytotoxic oedema, increased production of free radicals, inflammatory mediators (neuroinflammation) and excitatory neurotransmitters. This leads to delayed neuronal apoptosis and extensive programmed cell death (3, 4). These events resolve over approximately 72 hours. A tertiary phase describes the ongoing effect on brain connectivity, maturation, and myelinization. These events could last between weeks to years after the perinatal insult and can explain the broad range of long-term neurological sequelae described in the affected patient population (3).

Diagnosis of HIE

Hypoxic-ischemic encephalopathy is a specific diagnosis that applies when a neonate suffers from an encephalopathy that is highly suspected to be due to a hypoxic-ischemic event. The causes of this event can be subdivided into maternal, placental, cord-related, foetal, traumatic and postnatal factors. A difference is made between an acute, severe event (sentinel event) such as umbilical cord prolapses, placental abruption or uterine rupture resulting into a possible near total asphyxia, or less severe events often leading to subacute, partial asphyxia (5).

An asphyxiating injury is often accompanied by systemic hypotension, leading to multi-organ failure. A newborn with neonatal encephalopathy (NE) can present with an abnormal state of consciousness, abnormal behaviour, respiratory difficulties, seizure activity, poor tone or posturing and absent reflexes. In cases where HIE is the cause of NE, the clinical signs of encephalopathy appear immediately after birth or within the first few hours of life.

Since a sentinel event is not always present peripartum, determining HIE as being the cause of a NE is not always straightforward and the differential diagnosis of NE should be kept in mind. Other aetiologies for NE such as multiple perinatal strokes, metabolic abnormalities, brain anomalies or infections are the more common differential diagnosis and must be quickly excluded.

The criteria for inclusion in the TH protocol are found in Figure 3. TH is currently recommended only for *neonates > 35 weeks of gestational age (GA)*

Figure 1 : *Flow chart showing the mechanisms contributing to each phase of the evolution of neonatal encephalopathy over time. From Davidson et al. Update on mechanisms of the pathophysiology of neonatal encephalopathy (3). Reprinted with permission from Elsevier.*

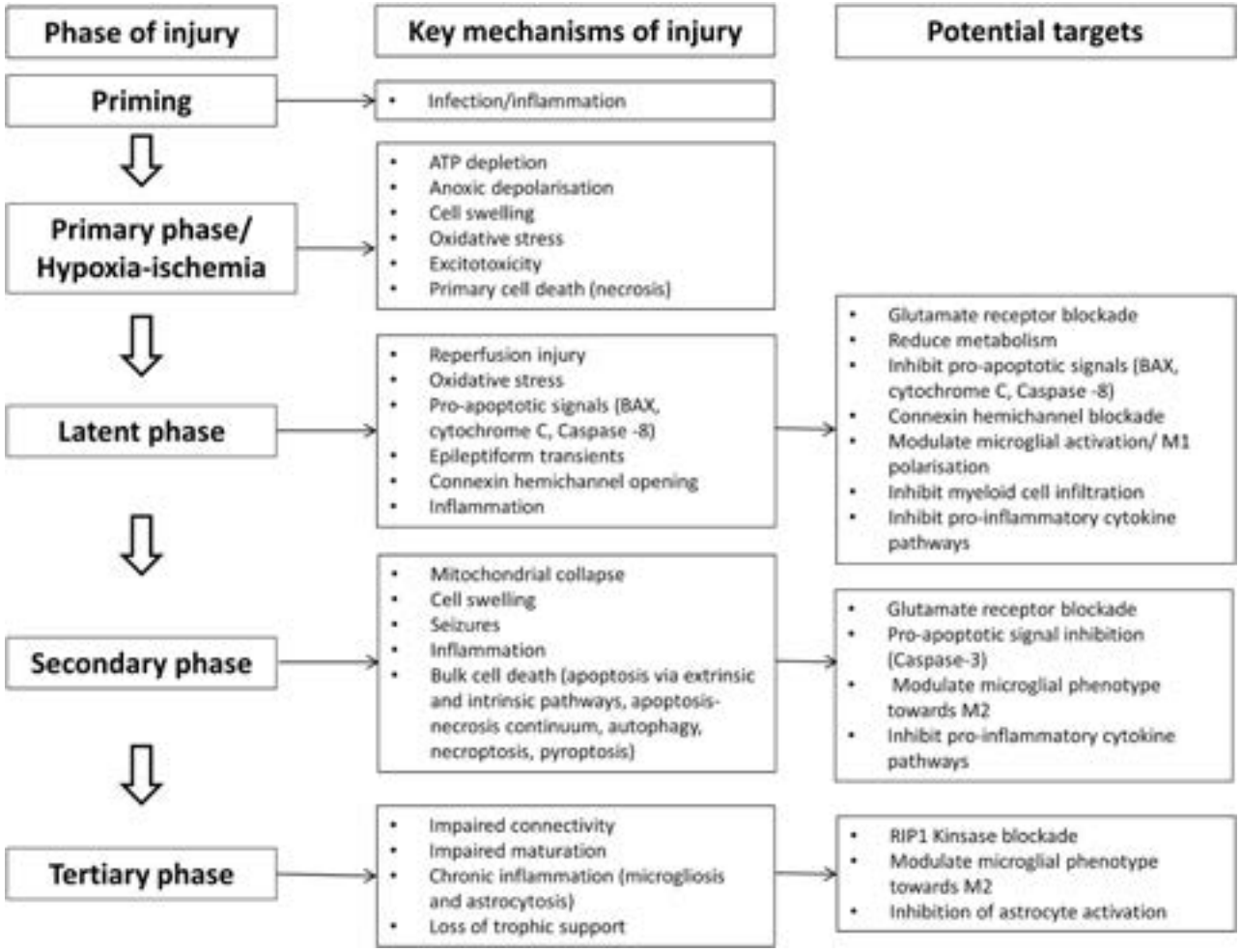


Figure 2 : *Pathophysiology of hypoxic-ischemic encephalopathy – First and second phase. Figure courtesy from Cornette et al. (30).*

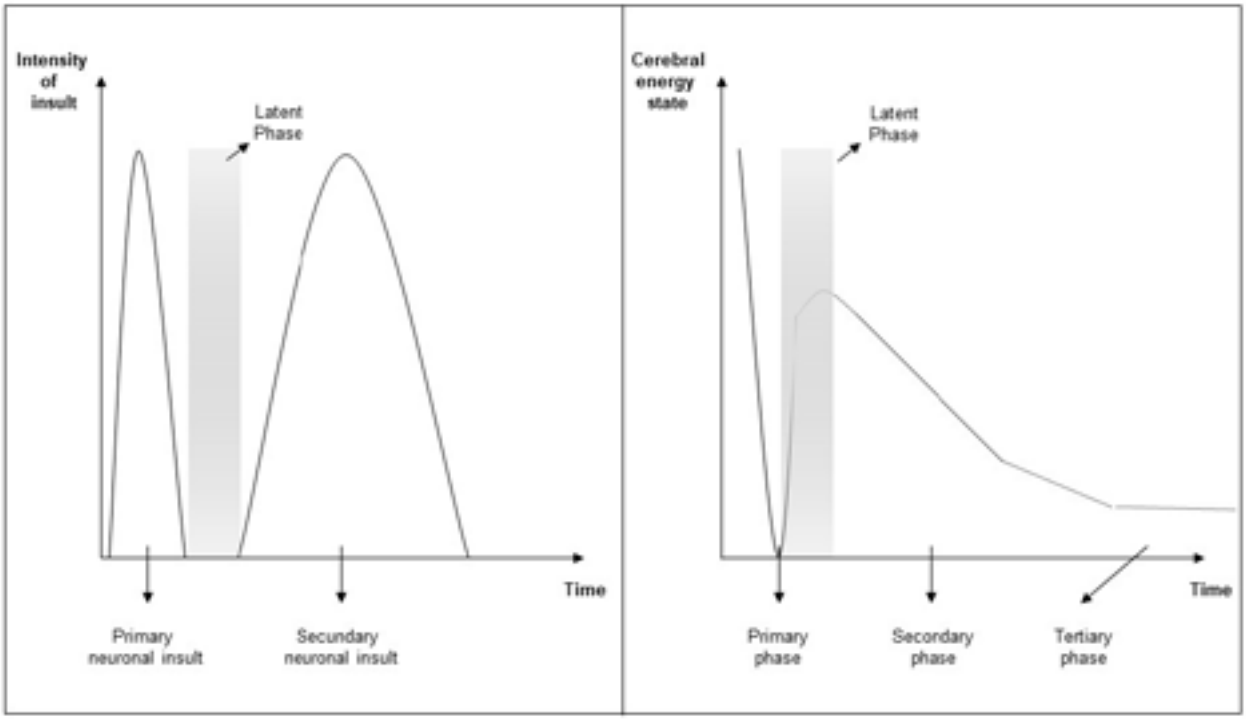
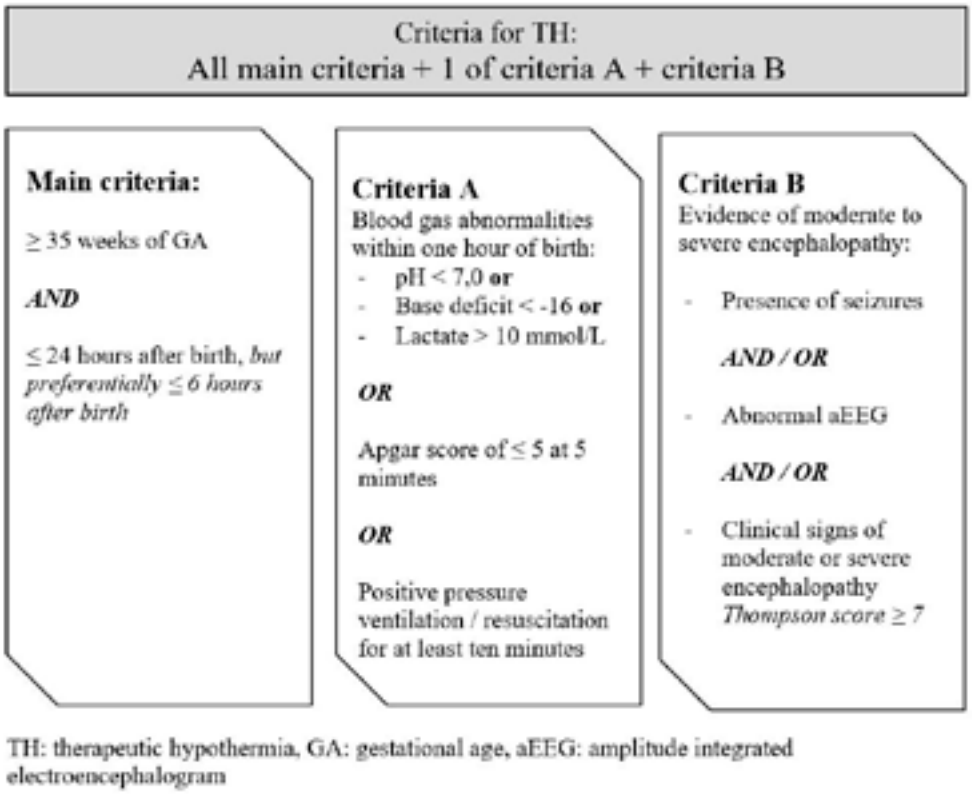


Figure 3 : *Criteria for therapeutic hypothermia.*



TH: therapeutic hypothermia, GA: gestational age, aEEG: amplitude integrated electroencephalogram

(although some centres are now including neonates as early as 34 weeks GA) *and > 1800 g* (6)**.**

The *criteria for peripartum asphyxia* in TH studies, with each enrolled neonates with at least one of these criteria, consist of:

- Blood gas abnormalities on cord blood or within one hour of birth or after resuscitation for postnatal collapse: pH < 7.0 or base deficit < -16 or lactate □ 10 mmol/L
- Apgar score of ≤ 5 at 5 minutes
- Positive pressure ventilation / resuscitation for at least ten minutes

While the criteria for PA can be established bedside, and are based on objective evidence, establishing the degree of encephalopathy is more complicated. However, the *presence of an abnormal neurological examination* after PA supports the presence of HIE. Depending on the severity of the primary injury, and the presence of (evolving) brain damage, the clinical picture may evolve during the first hours after birth. Early recognition of moderate to severe encephalopathy is primordial to select eligible neonates for timely referral for TH. Careful clinical examination and especially the use of available clinical scoring systems, can distinguish between mild, moderate and severe encephalopathy. In addition, neuromonitoring devices like electroencephalogram (EEG) / amplitude integrated electroencephalogram (aEEG) are available to explore cerebral activity, in support of the HIE diagnosis. Both the clinical as well as the neuromonitoring tools are further described below.

Clinical diagnosis of HIE based on clinical scoring systems

The presence and severity of HIE can be estimated by 2 scoring systems: the modified Sarnat scale (Table 1) and the Thompson score (Table 2).

The Sarnat scale distinguishes 3 stages of HIE. The scale was first published in 1976 and it was intended to facilitate the formulation of neurologic outcome. This scoring system is to be used at 24 hours after birth and implies the use of EEG (7). Currently, a modified Sarnat scoring system can be used to diagnose the severity of HIE within the first hours after birth based on clinical examination alone (8).

However, the (modified) Sarnat score, although still widely used by general paediatricians, leaves much to individual interpretation of certain clinical criteria and is often misinterpreted. In a NICU environment, the Thompson score, a practical and more objective point system, is therefore preferred to determine the degree of encephalopathy and to decide whether the neonate should be subjected to TH. A good correlation with the Sarnat scoring system has been described. The Thompson score consists of clinical assessment of nine signs with a maximum score of 22. A Thompson score ≥ 7 between 1 and 3 hours of age suggests a moderate to severe clinical encephalopathy and is used as a criterion to start with TH (Figure 3, Table 2) (9). If there is doubt about possible HIE, or in case of a Thompson score of 5 after one hour which increases during the next hour a transfer to a NICU is recommended.

Neurological assessment of the newborn should be done as early as possible and should be repeated during the first hours of life to assess a detrimental progression of the encephalopathy.

Diagnosis of HIE based on neurophysiology

An early EEG on admission can provide insight in the cerebral activity of asphyxiated newborns. Term newborns who suffered from peripartum hypoxia often show EEG patterns in line with the severity of the hypoxic moment. Usually, the amplitude and the continuity of the background pattern are impaired for the first 6 to 8 hours of extra-uterine life, and then improve or worsen with the possibility of the emergence of seizures. Several classifications of EEG patterns in the asphyxiated newborn have been established on these features. The most commonly used are the French 4-grade classification and the Murray classification (10, 11). When using the French classification, hypothermia is indicated for scoring equal to or above grade 2.

Unfortunately, full EEG acquisition is not available in all NICUs 24 hours a day. Optimal application of the equipment, and interpretation of the recording require specific neurophysiologist expertise. Therefore, aEEG is an easily

Table 1 : *Modified Sarnat scoring system. Predominant clinical features in stage 2 and/or stage 3 are an indication to start with therapeutic hypothermia. From Sarnat et al. Sarnat grading scale for neonatal encephalopathy after 45 years: an update proposal (8). With permission from Elsevier.*

Clinical Feature	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Spontaneous movement	Frequent symmetrical	Decreased	Absent
Autonomic system	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable (loss of heart rate variability)
Gastrointestinal motility	Normal or decreased	Increased; passing meconium	Variable
Primitive reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong	Weak; incomplete	Absent
Tonic neck	Slight	Strong	Absent
Olfactory response	Strong	Weak	Absent
Myotendon stretch reflex	Brisk	Brisk	Absent
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Normal or mild distal flexion	Strong distal flexion	Intermittent decerebration, fisting, thumb adduction
Central tone	Normal	Decreased	Flaccid

available, alternative technique. The aEEG trace is obtained by an algorithm calculated from a standard 2 or 4-electrode EEG acquisition. This cot side technique is now worldwide in use for the inclusion in the TH protocol and the brain monitoring of the asphyxiated newborn during the process. The visual analysis of an aEEG can be done bedside and is based on the lower and upper margins (voltages) of the recorded band (Table 3 and Figure 5). The level of the lower margin provides information on the EEG background. The bandwidth variation informs on the reactivity of the brain activity and the existence of a sleep-wake cycle. Marked and sudden changes of the lower margin and bandwidth suggest the occurrence of seizures (Figure 5). Several classifications for aEEG interpretation exist. Most often used is the classification of Al Naqeeb revised in 2006 by Hellstrom-Westas (12,13). According to these classifications, it is now accepted that the return of a sleep-wake cycle before 12 hours of life or a normalization of the background pattern within the first 6 hours of life are associated with a favorable neurological outcome. Therefore, aEEG represents an important tool to include patients in the TH protocol, to diagnose the occurrence of seizures, to monitor the effect of anti-epileptic drug treatment, and to assess evolution of cerebral activity over time (10).

Neuroimaging in HIE

Although cranial ultrasound can still play a role in the full-term infant with HIE, brain magnetic resonance imaging (MRI) is the method of choice to identify brain lesions and lead to a prognosis (14). Diffusion-weighted imaging (DWI) obtained between days 4 and 7 after the insult are most informative. DWI is based on the molecular diffusion of water and it best illustrates the cytotoxic oedema and, consequently, cell death. Brain swelling, even if initially severe, disappears by the second week after the insult and the DWI "normalizes". Therefore, brain MRI sequences (T1, T2 and DWI) are ideally performed after the cooling and the rewarming periods between days 4 and 7 (14).

Different patterns of brain injury have been described according to the severity and duration of the hypoxic-ischemic insult. They can be classified into two main patterns.

- The basal ganglia-thalamus (BGT) pattern affects the central grey nuclei and perirolandic cortex. This pattern is most seen after an acute and intense hypoxic event (e.g. cord prolapse, placenta abruption, etc.). At birth, newborns are severely depressed and need resuscitation. Neonates with the BGT pattern tend to be severely handicapped and suffer from motor disorders and learning difficulties. Depending on the severity of the BGT injury and the involvement of the posterior limb of the internal capsule (PLIC), the neurological prognosis varies (14).

- The watershed predominant (WS) pattern of injury is seen following prolonged partial PA. In this pattern, the lesions affect the white matter located in the junctional territories of the anterior, middle and posterior

Table 2 : *Thompson scoring system. A Thompson score of ≥7 is an indication for therapeutic hypothermia.*

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
Consciousness	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	Normal	Infrequent < 3/day	Frequent > 2/day	
Posture	Normal	Fisting / cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent / bites	
Respiration	Normal	Hyperventilation	Brief apnoea	Apnoea / IPPV
Fontanel	Normal	Full	Tense	

Figure 4 : *Clinical setting of therapeutic hypothermia. Figure courtesy from Cornette et al. (26).*

cerebral arteries. In the more severe case, the overlying cortex is also involved. The lesions can be unilateral or bilateral, anterior and/or posterior. Neurological manifestations at birth may be mild and do not always meet the criteria for cooling. Children with the WS pattern are more at risk of cognitive deficits, language delay and/or behavioral problems (14).

Treatment of HIE

Therapeutic hypothermia involves actively reducing the body temperature to 33.5 degrees Celsius during 72 hours, which acts as a neuroprotector (see Figure 4 for the setting). Neither deeper cooling (32°C) nor a longer duration of TH showed any benefit (15). The hypothermic period is followed by controlled rewarming (increase of temperature with 0.5°C per hour) up to 36.5°C. Subsequently, a temperature of 36.5°C is maintained for 24 hours. According to the currently available Flemish-Dutch guidelines, start of the hypothermia treatment is possible within the first 24 hours after birth, but preferably before 6 hours of age (6).

Hypothermia may modify cells programmed for apoptosis, leading to their survival. It may also protect neurons by reducing cerebral metabolic rate, attenuating the release of excitatory amino acids and lowering production of toxic nitric oxide and free radicals. TH aims to limit this delayed apoptosis by decreasing cerebral energy metabolism (5 to 8% per degree) and cerebral blood flow (and consequently cerebral edema). A specific action on the excitotoxic cascade and the activation of neuroprotective genes have also been demonstrated (4).

There is increasing preclinical evidence that late, neurorestorative interventions have potential to improve the overall outcome. In the so-called "hypothermia plus" studies, TH is combined with the administration of an extra molecule that shows to be neuroprotective in animal studies. For example, the free radical antagonist melatonin as well as the anti-excitotoxic gas Xenon, might be able to extend the therapeutic window for hypothermia, potentially by suppressing free radical release and excessive glutaminergic activity during the early phase of recovery from hypoxia-ischemia (3, 16). An ongoing study in which several Belgian units participate combines TH with the administration of allopurinol (or placebo) in the first 30 minutes of life (ALBINO trial, www.albino-study.eu). Allopurinol is a xanthine oxidase inhibitor and, if administered early after the insult, it reduces the production of oxygen radicals and brain damage in experimental, animal and preliminary human studies of cerebral ischemia. Furthermore, trophic factors such as EPO or IGF-1 can cross the blood-brain barrier and could boost neurogenesis (3, 16). Finally, studies in which mesenchymal stem cells are administered by intranasal route are promising, as such may enhance brain plasticity (3).

Impact of asphyxia and hypothermia on pharmacology

Neonates with PA treated with TH often need multiple drug therapy. Asphyxia and hypothermia both influence physiology, and consequently also pharmacokinetics (PK) and pharmacodynamics. Their impact on the 4 main PK steps (absorption, distribution, metabolism and excretion) is described in a recent review (17). Absorption data are limited since the intravenous route

Table 3 : *Amplitude-integrated electroencephalogram classification*

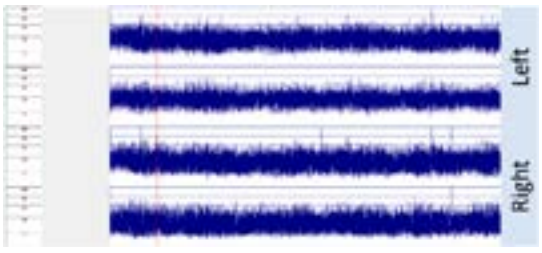
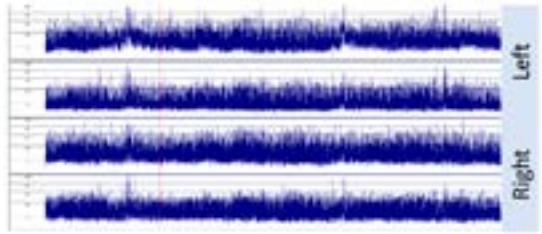
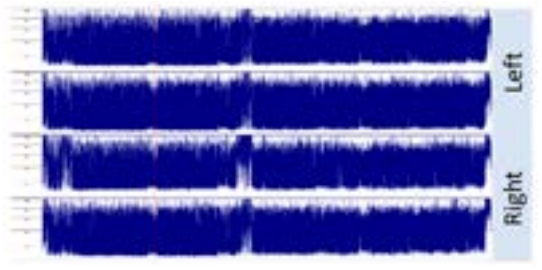
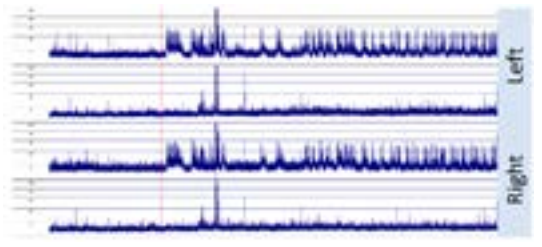
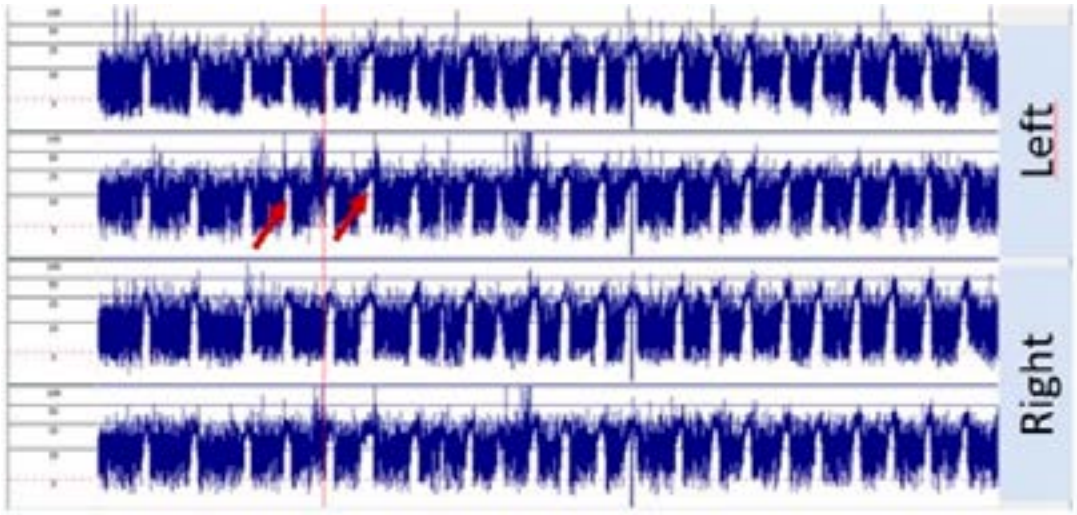
al Naqeeb classification (1999) (12)	Hellström – Westas classification (2006) (13)	aEEG typical tracing
Normal: lower limit > 5 µV and upper limit > 10 µV	**Normal:** continuous trace of normal voltage, sleep wake cycling lower margin > 5 µV and upper margin > 10 µV	
Moderately abnormal: lower margin ≤ 5 µV and upper margin > 10 µV	**Discontinuous:** lower margin < 5 µV and upper margin > 10 µV	
	Burst suppression: lower margin < 5 (0-1) µV and upper margin > 25 µV	
Severely abnormal: lower margin < 5 µV and upper margin < 10 µV	**Low voltage:** lower margin < 5 µV and upper margin < 10 µV	
	Flat trace: isoelectric trace < 5 µV	

Figure 5 : *Amplitude-integrated electroencephalogram (aEEG) in an asphyxiated newborn, day 1. The trace is discontinuous with the lower margin of the aEEG band < 5µV. Each rise in the lower margin indicates a seizure episode (2 examples indicated by red arrows).*



is usually applied during TH (18). Volume of distribution can increase (+30% for ampicillin), decrease (-37% for morphine) or remain unchanged during hypothermia. While knowledge on the impact of PA and TH on renal drug excretion increases, the mechanisms explaining impact on drug metabolism need further research (18). Overall, clearance of drugs undergoing metabolism (e.g. morphine) is often decreased in this population. Decreased clearance is most pronounced for renal drug elimination, like aminoglycosides (gentamicin -25 to -35%, amikacin -40%) (17, 19) or beta-lactam antibiotics (17). The renal impact is also obvious in physiology data. Serum creatinine values at birth up to 48h are higher in neonates with PA and TH compared to reference 50th centile values. After 48h a declining trend towards high(-normal) creatinine is observed (20). Based on above mentioned examples it is clear that adapted dosing for some compounds during TH is recommended, to avoid drug accumulation and toxicity. Therapeutic drug monitoring for selected drugs, and observation of clinical effects in this setting, are needed to further individualize dosing.

Follow-up

The current rate of death or disability following TH at 33.5°C for 72 h for moderate/severe HIE is 29% of whom 23% of survivors were identified with cerebral palsy (1). Assessment of the severity of brain damage and prediction of outcome is essential to determine intensive care management and to ensure adequate parental counselling.

In general, outcome corresponds to the severity of clinical grading of encephalopathy, and moderate to severe grades will have the highest rates of disability and mortality (1, 5). Many predictors have been studied to evaluate the prognosis for the individual patient, including clinical history, EEG/aEEG, near-infrared spectroscopy and MRI (11,13,21-23). It is necessary to remember that HIE is a dynamic process and the greatest prognostic accuracy for predicting long-term neurological outcome is likely to be obtained by combining repeated clinical examination with neurophysiological tests, as well as brain MRI in the first week of life, whether or not the neonate is treated with TH.

It is important to inform parents of their neonate's situation as soon as possible, and meetings with the parents should be repeated regularly. This permits them to fully understand the current situation of their child and offers them a sense of control and safety (24). Parents are initially often in a state of shock, and they need clear information particularly regarding the diagnosis of HIE and the treatment decisions that might be made within hours of arrival in the NICU (25). As the end of the hospital stay approaches, it is also very important to organize and explain to parents the follow-up program for these children.

Remaining questions

The key issue remains whether we should use TH for mild encephalopathy and inclusion beyond 6 hours of life.

Therapeutic hypothermia initiated before 3 hours of life has been shown to be more effective than TH initiated between 3 and 6 hours of life. Although TH initiated between 6 and 24 hours of life may have benefit, its effectiveness is still uncertain (6, 26). If, unfortunately, it has not been possible to start TH before 6 hours of life, we should still consider it up to 24 hours, depending on the evolution of the clinic and the complementary information (biological and neurophysiological) (6)

Furthermore, 50% of HIE develop mild encephalopathy that does not meet the criteria for TH. Their outcome was previously considered as normal but several studies have shown that approximately 20-25% of these patients have an unfavorable short-term and long-term outcome (with significant reduction in IQ and language skills, neuropsychological difficulties, autism, epilepsy, visual and sensory loss and higher rates of learning impairment) (27). Brain imaging of these neonates with mild encephalopathy may show detectable abnormalities on MRI, even after TH (28). However, meta-analyses have failed to determine the benefit of hypothermia in this category of patients (29).

In any case, whenever there is some doubt about the severity of HIE, discussing the case with a NICU immediately after birth is essential. This may lead to a timely referral to a NICU with EEG-expertise to help grading the HIE and to decide whether to cool or not.

Conclusion

Hypoxic-ischemic encephalopathy remains a major cause of neonatal mortality and long-term neurodevelopmental sequelae in industrialized countries. Therapeutic hypothermia has been proven to reduce the mortality rate and disability of the term and near-term neonates presenting with moderate or severe HIE in the context of perinatal asphyxia. Timely discussion and transfer to a NICU is therefore imperative for any neonate with perinatal asphyxia in whom there is doubt about the indication for therapeutic hypothermia.

Conflicts of interest statement

The authors of this review declare that they have no conflict of interest. They do not have any affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this review.

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The management of the late preterm and term newborn with early onset infection anno 2022

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Keywords

Early onset sepsis, newborn, management

Abstract

Early onset sepsis (EOS) is a common source of admission to a neonatal intensive care unit (NICU). Identifying children at risk for EOS remains essential but challenging because of aspecific clinical signs and poor predictive value of blood tests. Although the incidence of EOS has decreased over the past twenty years, primarily due to the introduction of intrapartum antibiotic prophylaxis, many children with low risk of EOS are evaluated and are treated unnecessarily. This leads to a separation of mother and child, an increase in health care costs, not to mention the side effects of antibiotics in future childhood. We conducted a review of the literature regarding the latest guidelines, inflammatory markers and tools that can help us in the evaluation and management of newborns at risk of EOS. The goal of this article is to discuss an evidence-based approach to the assessment and management of newborns > 35 weeks presenting with signs of possible EOS. An emerging trend is serial clinical examination which is promising to reduce newborn assessments and treatment. In all cases, EOS are unpredictable and clinical vigilance is essential over time.

Introduction

Early-onset sepsis (EOS), defined as sepsis with positive blood or cerebrospinal fluid culture occurring between birth and 72 hours of life occurs in 0.3-1/1000 infants born at ≥ 35 weeks' gestation (1-11).

EOS can result in severe outcome or death and remains a significant source of morbidity. Studies report a mortality rate of approximately 2-4% in newborns born ≥ 35 weeks (2,11). The incidence of EOS varies by country, local neonatal center, prophylactic antibiotic therapy practices, gestational age and the presence of symptoms or risk factors (2,8-11).

EOS is acquired before or during the delivery and results from a vertical transmission (12). The most common pathogens causing EOS among term and late-preterm are Group B *Streptococcus* (GBS) (40-45%) and *Escherichia coli* (10-15%). Other less common pathogens include Gram-positive cocci (predominantly group *Viridans streptococci* and *Enteroccoccus spp.*), Gram-negative pathogens (5%), *Staphylococcus aureus* (≈3-4%) and *Listeria monocytogenes* (≈1-2%) (1-4,7,12,14).

Intrapartum antibiotic prophylaxis (IAP) in mothers with GBS colonization reduces neonatal EOS due to GBS significantly but not due to *E. coli* (7).

Peripartum risk factors (table 1) account for 10-20% of deliveries and are similar for *E. coli* and GBS or other common bacteria responsible for EOS (1-3,7,8,12-15).

Clinical manifestation of EOS is often non-specific, subtle and may mimic noninfectious disease (12). Recent studies in the US reported that 13% of all term newborns were evaluated for EOS using the CDC guidelines of 2010 and that 11% of them were treated empirically with antibiotics while only 0.04% of the newborns in the study had a blood culture confirmed infection (16). Even if we are all aware of the high risk of mortality and morbidity associated with EOS, recent research has shown the negative effects of unnecessary antibiotherapy such as the increase of antibiotic resistance or the disruption of the neonatal microbiome that may lead to obesity, asthma, autoimmune disease, inflammatory bowel disease and neurological disorders (12,17). Inaccurate EOS evaluation or empirical antibiotherapy also leads to maternal-infant separation with negative effects on bonding and breastfeeding with

Table 1: Risk factors of EOS

- Maternal colonization with GBS
- Prolonged rupture of membranes (>18h before delivery)
- Chorioamnionitis *
- Prematurity (<37 gestational weeks)
- Maternal GBS bacteriuria during the current pregnancy
- The history of a newborn with invasive GBS disease
- Inadequate intrapartum antibiotic prophylaxis **

* Now called maternal intra-amniotic infection according to the new recommendations by the American College of Obstetricians and Gynecologists (ACOG) in 2020). Suspected intra-amniotic infection based on ACOG is defined as "maternal intrapartum fever > 39°C or maternal temperature between 38°C and 38.9°C in combination with one or more criteria as well as maternal leukocytosis, purulent cervical drainage, or fetal tachycardia") and occurs in 1-10% of full term births (13).

** The adequate IAP is penicillin G, ampicillin or cefazolin, and administration should be done more than 4H before delivery. Vancomycin or clindamycin used in high risk cases for penicillin anaphylaxis is not adequate IAP. These antibiotics can have some protection but are not the first recommended because not enough evidence of protection. They are considered inadequate, as is the dose is done <4h before delivery (13).

increased formula supplementation, frequent blood samples and insertion of intravenous lines, potential antibiotic resistance, extension of hospital stay and costs that could have been avoided (1,2,6,10,15-17).

Diagnosis

Clinical signs and symptoms

According to the literature, most newborns with EOS become symptomatic within 12 to 24 hours of life (14). Newborns have a low risk of developing EOS if they are asymptomatic at birth and have an even lower risk if adequate intrapartum antibiotic prophylaxis was given during labor (1,4,10). Clinical evaluation is the strongest predictor of EOS.

The initial symptoms of EOS can be focal signs of infection or unspecific symptoms (table 2) like tachypnea with retractions, nasal flaring or grunting mimicking a transient tachypnea of the newborn, which makes it very hard for physicians to withhold the beginning of antibiotherapy in some situations (1,6,7,10,13,15). In borderline situations, it is essential to reevaluate the newborn and to eventually confirm the clinical improvement and that the antibiotics are not necessary.

Table 2. Clinical signs of sepsis

Neurological signs and behavior	Temperature instability	Respiratory instability	Hemodynamic instability
Lethargy Altered muscle tone (floppy baby) Irritability, bulging fontanel Seizures, neonatal encephalopathy Poor feeding	Fever Hypothermia	Signs of respiratory distress with polypnea, grunting, apnea Need of supplemental oxygen Non-invasive support (e.g. CPAP) or invasive support with mechanical ventilation Persistant pulmonary hypertension	Tachycardia, Bradycardia Hypotension Prolonged blood capillary refill time Blood pressure support (e.g. inotropic agents)

Blood tests

Common diagnostic tests such as C-reactive protein (CRP) and complete blood count have been used routinely in the evaluation of EOS but have poor sensitivity and low predictive value in case of newborn infants (1,7,10,13,15).

First of all, abnormal white blood cell (WBC) count, neutropenia in particular, has been highlighted in newborns who were exposed in utero to an inflammatory process (e.g. in case of premature rupture of membranes) instead of an infectious process but also in cases of maternal preeclampsia or placenta insufficiency while thrombocytopenia is not an early sign of infection in a neonate (2,12,18). Table 3 shows upper and lower limits of neutrophils count (19). Immature to total neutrophil count is the hematologic marker that has the highest positive predictive value (15,17). The values of WBC will also vary naturally during the first 12 hours of life (12).

With regards to CRP, its increase will appear only after hepatic synthesis has started and may increase in response to various stimuli. Therefore CRP should not be tested or at least, in case of normal value, not be taken into account in the early process of a potential infectious disease (12). If tested, the predictive value is improved if it is obtained after 4 hours of life (according to several studies, at least 6 to 12 hours of life) (15).

Both blood markers have a high negative predictive value. Even in the presence of clinical symptoms and risk factors, serial negative CRPs taken after 12 hours of life rules out sepsis. Thus, serial measurements are more informative than single values but should be reserved for symptomatic newborns. Serial measurements of normal values can reassure the physician to avoid starting or to allow for the discontinuation of the antibiotics in case of therapy (2,12,17).

Some other inflammatory markers (such as procalcitonin) have been suggested to help physicians to determine whether or not an infectious process is in progress. The use of IL-8, a proinflammatory cytokine which rises earlier than CRP in the course of neonatal infection, has proven added value in the diagnosis and treatment of neonatal EOS, but is of no clinical value at this moment in Belgium due to the lack of reimbursement (20).

Table 3. Upper and lower limits of neutrophils/mm3 over time according the study report by Schmutz and al. (19)

Timing of neutrophil count	Neutrophil count (x10^9/L)	
	Gestation 28-36 weeks	Gestation > 36 weeks
at delivery	1.0 - 10.5	3.5 - 18
at 6-8 h after birth	3.5 - 25	7.5 - 28.5
at 72h-240 h after birth	0.8 - 12.5	2.7 - 13

* The results of this study showed higher upper limits of neutrophils counts compared to Manroe's traditional chart in 1979 or Mouzinho report in 1994 (chart for <36 weeks) but similar upper limit value compared to Carballo's study in high-altitude. The difference between Manroe and this study can be possible explain by modern method of counting of neutrophils (old vs new) and variations in altitude.

Culture

Blood culture or cerebrospinal fluid (CSF) culture is the confirmatory diagnostic tool. Generally, a minimum of 1ml of blood is required in a pediatric blood culture bottle to increase sensitivity and ideally 2 samples (from 2 different sites) should be taken (2,12,17). If the newborn has a central catheter, one of the blood samples should be taken from the vascular catheter (12). In case of intrapartum antibiotic prophylaxis (IAP) the density of pathogens in the blood are decreased so a volume of >1 ml blood might increase the sensitivity (21).

According to several studies, there is no effect of IAP on the timing of blood culture positivity, with a median time to positivity < 24 hours (2). There is no need for an anaerobic culture bottle.

Urine culture is not indicated and gastric aspirates or body surfaces cultures are not recommended because of sub-optimal sensitivity and specificity and because of their poor predictive value for infection (12,15).

Placental culture will inform the physician to which bacteria the newborn has been exposed in utero, but will not necessarily indicate a true infection. Acute or chronic intrauterine inflammation might be highlighted by the anatomopathological analysis of the placenta (12).

Management of the newborn > 35 weeks

Approach for the symptomatic newborn

In case of clinical signs of sepsis, it is necessary to start a full diagnostic evaluation regardless of risk factors or IAP (15). It has been demonstrated that newborns exposed to IAP with confirmed EOS were more often symptomatic at birth than unexposed newborns (4).

Full diagnostic evaluation should include a full blood cell count, CRP and a blood culture (min 1ml or 2ml if IAP). A lumbar puncture (LP) should be done if the newborn has signs suggesting meningitis or if there is a strong suspicion or proven sepsis, but only if the child is stable enough to tolerate the procedure (2,22). A repeat LP should be done after 24-48 h of therapy if CSF culture is positive or if there is no response to the initiated treatment. In case of respiratory symptoms, a chest X-ray should be done and an endotracheal culture should be taken in case of intubation even after initiation of antimicrobial therapy. All cultures should preferably be sampled before antibiotherapy is initiated, but antibiotics should never be delayed in case of difficult sample (e.g. septic shock patient).

In case of an isolated clinical sign (e.g. isolated tachypnea in the first hour of life, isolated temperature after a long labor, epidural anesthesia, isolated maternal fever,…), diagnostic evaluation can be postponed but a clinical re-evaluation must be done in the first 1 or 2 hours of life and midwifes and/

or nurses should be fully informed and aware of signs that would need an earlier medical intervention.

Following the diagnostic evaluation, empirical antibiotherapy (ampicillin/amoxicillin or penicillin + aminoglycoside) should be started with weight and gestational age adjusted doses (13). Third or fourth-generation of cephalosporin drugs are reserved for suspected meningitis. In case of rapid recovery or absence of arguments for a sepsis it may be possible to stop antibiotics. Serial evaluation of biomarkers like CRP and WBC counts may help physicians to decide how long antibiotherapy should be continued.

Two negative CRPs (< 10 mg/L) at an interval of at least 24h rule out sepsis with a specificity of 99.7% and should be a strong argument for the discontinuation of the antibiotics unless there is evidence of site-specific infection (2,17).

It would be reasonable to perform 2 serial CRP levels at 12h and at the time of the aminoglycoside trough level. When the 2 serial CRP levels are below 10 mg/L (negative) and blood culture remains negative after 24h incubation, the antimicrobial therapy can be stopped when the clinical condition is stable or improved. This would be probably in more than 50% of the neonates with suspected neonatal EOS. A recent study showed that time of positivity of blood culture was < 24 hours in most children and occasionally 36-48h (23). So in case of absence of positive blood culture, physicians should consider stopping antibiotherapy after 24 and 36h if there is no other argument for sepsis. However, a positive CRP will not confirm the presence of an infection and should not be an argument to extend the duration of antibiotherapy in a well-appearing newborn with negative cultures whatever the risk factors that had been highlighted (17). In these neonates with "clinical" infection a switch after 48 hours of IV antimicrobial therapy to oral therapy has not only been proven to be safe, it also decreases hospital stay and increases breastfeeding success because the neonate will not be separated from the mother (24,25). In these children oral amoxicillin instead of ampicillin is the first choice due to its high oral bioavailability. The duration of antibiotherapy varies between 5 and 21 days (table 4).

Table 4. Duration of antibiotherapy

	Duration of antibiotherapy
Proven sepsis*	5 to 10 days
Gram positive meningitis	14 days
Gram negative meningitis	21 days

*In case of "proven" sepsis, duration of antibiotherapy will depend on the results of the cultures and on the clinical evolution of the infant. Usually in case of positive blood culture, antibiotherapy is continued for a period of 5 to 10 days pending the clinical and CRP evolution. Indeed, in case of uncomplicated sepsis, when CRP becomes negative (e.g. at day 5) and the patient's clinical condition is improved, antimicrobial therapy can be stopped without the risk of relapse (30).

Approach for the asymptomatic newborn

The management approach of an asymptomatic newborn is highly challenging. In the words of Richard A. Polin in 2021, "early onset sepsis: finding a needle in a haystack" (9). Indeed, the management of these babies remains controversial and heterogenous (13,14).

Several guidelines have been published in the last twenty years by various committees worldwide (e.g. American Academy of Pediatrics (AAP), United States Center for Disease Control and Prevention (CDC), National Institute for Health and Clinical Excellence from United Kingdom (NICE)) in order to evaluate treatment and generate algorithms for managing newborns with risk factors or clinical symptoms (14,22). Nevertheless, we should not forget that even newborns with no risk factors may develop EOS (e.g. GBS EOS can occur with negative GBS carriage). We will need to consider the balance of risk and benefit before starting an empiric antibiotherapy.

We have several options for assessing the risk of EOS and evaluating the need for a diagnostic evaluation and further for an eventual treatment:

Categorical risk assessment: this algorithm is based only on standard perinatal risk factors to identify babies at high risk of EOS. This approach was recommended by the first consensus and guideline published in 1996 by CDC. In 2014 a Belgian guideline was published (15). With these guidelines, any well-appearing newborn from a mother with suspected chorioamnionitis would receive an empirical treatment until proven otherwise, and those with prolonged rupture of membranes (PROM) with inadequate IAP would be subjected to laboratory evaluations. With the low risk of EOS, the estimated number needed to treat (NNT) well-appearing babies born to mothers with suspected chorioamnionitis, is > 450 (16,26). Unnecessary evaluations and empiric treatment of well-appearing newborns with low risk resulting from these guidelines make this approach outdated (13,14,27).

A. Multivariate risk assessment: the neonatal EOS calculator is a tool whose purpose is to reduce laboratory testing or empiric treatment by helping physicians to evaluate the risk of EOS. This free online calculator (https://neonatalsepsiscalculator.kaiserpermanente.org/) was developed by Puopolo and Escobar at Kaiser Permanente in California in 2012 and was then modified over time. This tool, based on the incidence of EOS in each institution, gestational age of the newborn, highest maternal antepartum temperature, time from membrane rupture to delivery, maternal GBS status and the type of intrapartum antibiotherapy, estimates the baby's individual risk of EOS caused by any pathogen in the first 24 hours of life for babies of more than 34 weeks.

Depending on the clinical status of the newborn, an evaluation of the risk of EOS is reported and a clinical recommendation is suggested. The advantage of this tool is that the first evaluation only includes objective data and not a clinical diagnosis of maternal chorioamnionitis (2).

A recent meta-analysis conducted by Achten et al. (2019) showed that there was a reduction in laboratory testing and empirical treatment after the implementation of the EOS calculator in comparison with conventional strategies (6). Nevertheless, rates of missed cases of EOS were comparable to those that were observed when categorical risk assessment is used.

According to the main study on the use of the EOS calculator, "2.6% of all term and late-preterm neonates received antibiotics in the first 24 hours of life" (11).

However, with the use of the calculator, all patients classified in the category " clinical illness" are indicated to receive antibiotherapy. The calculator could still overestimate EOS, because simply having non-invasive CPAP breathing support without oxygen falls into this category. E.g. a baby born at 39 week' gestation supported with non-invasive CPAP because of transient tachypnea, does not necessarily need antibiotic therapy but the calculator will recommend it based on the "clinical illness". This child could very well be monitored clinically in the NICU and the need for antibiotic therapy could be reassessed within 2 hours of admission.

Literature has shown that implementation of the calculator in units reduced antimicrobial use around 50% without an increase in undiagnosed EOS cases (5,6). However, there are no specific data to evaluate if this approach would be safe in Belgium.

It should be noted that a selected American population was used to develop the mathematical model for prediction of the calculator. Since the local incidence will be different for other populations and will influence the final score and the threshold to treat (the probability of missing a case will increase if we use a lower EOS incidence) and since the GBS screening policy and thus the method of observation time of newborns may be different elsewhere, generalizing this tool to other health care settings outside the US or to at-risk populations with higher EOS local incidence would probably not be recommended (5,6,14).

The calculator is thus helpful but it does not replace the clinician and can still result in over-treatment. Clinical monitoring remains essential even when the baby is allocated in routine care (5).

Studies comparing the calculator method and repeated clinical examinations should be carried out (currently a multicenter prospective Italian study is underway).

B. Serial clinical examinations: Since the vast majority of infants developing EOS will be symptomatic within the first 24 hours of life, serial clinical examinations have become an emerging trend in the management of well-appearing newborns. This strategy, regardless of any risk factor, results in the evaluation and potentially the treatment of newborns who develop signs of illness during the first 48h of life (2,13).

Several studies reported that serial physical examinations every 4 to 6 hours through 48 hours of age lead to a significant decrease in the use of antibiotherapy, laboratory tests and blood cultures and this without a delay in the initiation of antibiotic treatment in case of infection (1,2,4,10,14, 28). Nevertheless, this approach requires a lot of resources: sufficient medical and trained nursing staff, clear protocols with optimal assessment (structured vital signs – heart rate, respiratory rate, temperature, protocols that will define which parameters and which abnormal signs require assessment by a physician). The decision to start antibiotics will be left to the discretion of the physician. Much larger studies will be needed to assess safety and use in comparison with the EOS calculator.

Conclusion

EOS is rare but because of the potential consequences of incorrect diagnosis and treatment, it is often over diagnosed and over treated. Clinical signs are aspecific and can mimic another benign illness. Laboratory tests lack specificity and sensitivity. It is important to keep in mind that antibiotic treatment will save a newborn's life in case of sepsis but will have long-term side-effects in case of unnecessary administration. Therefore, physicians will have to consider the risk/benefit balance when initiating antibiotherapy and should ask themselves whether it is necessary to continue the antibiotics when sepsis is not confirmed.

In the same way, unnecessary evaluations will result in parental concerns, mother-infant separation with parental anxiety, delayed breastfeeding, higher financial costs and longer hospital stay.

Different approaches are possible (categorical risk assessment, sepsis calculator or serial clinical examinations). Each approach has its advantages and disadvantages, and to date none can ensure perfect case detection. Clinical vigilance is essential with repeated physical evaluations leading to the best risk/benefit balance. Large-scale studies comparing different strategies are recommended for better practice and avoiding unnecessary antibiotics.

Ultimately, we can say that not all EOS are predictable. Thus, clinical evaluation remains an essential part of the early diagnosis (27,28).

Conflict of interest

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

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An update on congenital CMV

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Abstract

Congenital cytomegalovirus (cCMV) infection is an important cause of lifelong sequelae such as neurodevelopmental impairment and sensorineural hearing loss (SNHL). Although many questions regarding this disease have been resolved, many topics are still under discussion. Counseling of (future) parents is therefore challenging.

This narrative review aims to give an overview on diagnosis, management, treatment and prevention of cCMV in pregnant women and their babies in order to help the clinician in counseling and making a decision for referral.

Introduction

Nowadays, when talking about "the virus" many people can only think of coronaviruses. However, with an incidence of 0.5-2% worldwide, being the main cause of non-genetic sensorineural hearing loss (SNHL) and an important cause of neurodevelopmental problems, congenital cytomegalovirus (cCMV) might be called "the virus" in perinatology.

CMV is a member of the family of *Herpesviridae*, which have the ability to stay latently present in the body after a primary infection. Transmission occurs through contact with infected bodily fluids (urine, saliva, vaginal secretion, semen, breastmilk) or blood-contact (transfusion or organ transplantation). The seroprevalence in women of childbearing age is around 50 % in developed countries and even higher in developing countries. In immunocompetent adults and children, CMV infection usually does not cause severe symptoms. However, when a CMV infection occurs during pregnancy, there is a risk of transferring the infection to the fetus. Such is possible in women without pre-existing immunity against CMV (primary infection), but also in women with antibodies from a previous CMV infection by reactivation of the virus or infection with a different strain of CMV (non-primary infection) (1).

Prenatal diagnosis

Routine antenatal screening for CMV is currently not recommended in pregnancy, which was also emphasized in a knowledge report of the Belgian Health Care Knowledge Centre (KCE) in 2015 (2). This is partly due to the fact that CMV does not meet some of the criteria for screening tests. However, the current lack of effective prenatal treatment also contributes to the current recommendation (1, 3). Women are tested in case of flu-like symptoms or if prenatal ultrasound is suggestive of cCMV infection (3). Possible signs on fetal ultrasound are intra-uterine growth retardation, fetal ascites, hydrops fetalis, oligohydramnios, microcephaly, intracerebral calcifications and echogenic bowel (1).

The gold standard for determining maternal primary CMV infection is serologic testing, with IgG and IgM being the preferred option (4). If CMV IgG is detected in combination with CMV IgM, it is important to determine the moment of infection. The CMV IgG avidity assay is considered a primary tool for this purpose. IgG avidity increases with time: infections with low-avidity IgG are considered recent infections (3-4 months), while a high avidity index is present in case of past infections (3). The presence of CMV IgM and low-avidity IgG is very effective in diagnosing primary CMV infection during pregnancy (4). Until now, there are no validated tools (serological or virological) to diagnose secondary CMV infections in a precise manner (1, 5). Maternal serology screening can be falsely reassuring as it will not always identify non-primary infections.

Once seroconversion is diagnosed, a thorough follow-up of the pregnancy is mandatory to identify the (seriously) affected children. Identifying which foetuses are affected, and to what extent, is challenging. Structural foetal ultrasound, amniocentesis for culture or PCR and prenatal MRI all have their role in diagnosing cCMV and predicting its outcome (4). The sensitivity of prenatal diagnosis techniques varies depending on the population selected, the gestational age at the time of the investigation and the gestational age at the time of infection (5).

Prenatal ultrasound can help detecting structural or growth abnormalities that may suggest foetal infection, but many of these findings are non-specific for CMV (intra-uterine growth retardation, echogenic bowel, ventriculomegaly, calcifications, hepatosplenomegaly) (1, 4).

Amniocentesis is commonly used to diagnose foetal infection. It must be performed after 21 weeks of gestation and at least 6 weeks after maternal infection (5). If CMV-DNA PCR on amniotic fluid is positive, the diagnosis of congenital CMV infection is confirmed (high specificity). However, a negative PCR on amniotic fluid does not rule out congenital CMV infection (low sensitivity). In order to exclude false-negative CMV PCR on amniotic fluid, confirmation of diagnosis by neonatal testing is essential, since neonatal testing has a much higher sensitivity. Hence, future parents must be counselled on the importance of neonatal testing and need to be aware of the fact that a positive result on amniocentesis does not provide any information on future cognitive development of the infant and severity of sequelae (4). Cordocentesis has the same sensitivity and specificity as amniocentesis but the risk of complications is higher, which makes amniocentesis the preferred diagnostic technique (5).

The use of prenatal MRI has increased over the last years. Prenatal cerebral MRI is a valuable tool adding information to fetal ultrasound if performed at the right time (> 32 weeks of gestation) and if interpreted by people who

are experienced in evaluation of foetal brain imaging (6, 7). Appropriate integration of foetal MRI into prenatal diagnostics can lead to a more accurate counselling and/or more appropriate management (6).

Prenatal management

Over the years, several prenatal therapeutic options have been studied, such as immunoglobulins and valaciclovir during pregnancy. No conclusive results have been published so far. Hence, since further studies on the different therapeutic options are still warranted, prevention of CMV infection plays a key role, e.g., vaccines and hygiene measures.

Valaciclovir during pregnancy

The question rises if prenatal treatment with valaciclovir could improve the prognosis of infants affected with cCMV. Recent research indeed shows a possible advantage of treatment with valaciclovir during pregnancy, especially if the treatment is given at an early stage of infection and in the first trimester (8). However, since the majority of CMV infections are subclinical, this would mean that early-pregnancy serologic screening should be performed on all pregnant women in order to identify the CMV infection early.

Valaciclovir during pregnancy is classified as a group B drug, which means there is no clear evidence of risk in humans. However, given the lack of large controlled safety studies on this topic, reliable and definitive conclusions cannot be drawn (9).

Immunoglobulins

Administration of hyperimmune globulin monotherapy before the 24th week of pregnancy did not show an amelioration in neonatal outcome (10). Currently, trials with a combination of valaciclovir and hyperimmune globulins show promising results (11).

Vaccines

The first attempt to develop a vaccine against CMV infection began in the 1970s. In 2000, the Institute of Medicine in the USA gave CMV vaccine the highest priority within the vaccine development program and stimulated the development of several vaccine candidates. The development of such a vaccine is complex, due to the nature of CMV protective immunity (antibodies and T-Cell responses) and the capacity of CMV to remain latent in the body. In order to prevent congenital infection, the vaccine should be able to protect both seronegative women from primary infection and seropositive women from reinfection and reactivation (12). Several CMV vaccine candidates are in different stages of development, of which the more promising ones appear to be able to express several antigens. The different strategies of vaccination have yet to be elucidated (pregnant women, universal vaccination of 12-year-old boys and girls, vaccination of seronegative women of child-bearing age).

Education of pregnant women

Although the various clinical trials on vaccines seem promising, none will be available immediately. Hygiene information and education of pregnant women is therefore currently the most effective strategy for prevention of CMV infection (13). CMV is transmitted by direct contact with bodily fluids (urine, saliva, etc.) and can remain on soiled surfaces for a few hours. Children, mainly under 6 years old (with a peak between 1 and 2 years old), are the main vectors of the disease. An effective strategy to reduce maternal CMV infection in future mothers is raising their awareness of the risk of cCMV and the existence of possible strategies to prevent such infection. Possible prevention consists of simple hygiene measures, especially in women who already have children or work with young children (14).

To aid this education, several media (video, brochures, etc.) are available: the CDC has published hygiene measures for pregnant women on its website, and in Belgium both the ONE (Office National de l'Enfance) and Kind en Gezin have published brochures in French, Dutch and English to educate women on the prevention of congenital CMV infection.

Postnatal Diagnosis of cCMV

Identification of infants with congenital CMV (cCMV) infection

At this point, no universal neonatal screening is performed. Hence, testing for CMV in neonates is only recommended in case of the presence of any sign indicative of intra-uterine CMV infection or after known maternal seroconversion.

Until recently viral isolation and culture from urine was the gold standard for diagnosing cCMV infection. Since PCR on urine has high sensitivity (100%) and specificity (99%) and the results are more rapidly obtained than cultures, this is now the preferred diagnostic technique. One urine sample is sufficient to confirm the diagnosis (3). CMV PCR testing of saliva is an alternative technique and easier to perform. Saliva samples should be taken immediately before feeding in breastfed newborns, and confirmed with urine, as false-positive results have been reported (18). A study by Exler et al. found that overall concordance of CMV DNA detection in neonatal saliva and urine is 91% and that PCR in saliva compared to urine, showed a positive predictive value of 73% (15). If available, screening with PCR on saliva and confirmation with PCR on urine is the least invasive, but most reliable method.

The PCR on urine can only be performed during the first 3 weeks of life. After this age, there is a possibility that a postnatal infection (e.g. through breastmilk) is detected. So, in case of diagnosis after 21 days, congenital CMV infection must be confirmed by detection of PCR CMV-DNA on the dried blood spot (neonatal screening card) (3, 16).

Diagnostic work-up in the newborn

As soon as congenital CMV is confirmed in the neonate, a thorough clinical examination and diagnostic work-up should be performed, consisting of laboratory testing, cranial imaging, hearing screening and ophthalmological evaluation. This will allow to identify the consequences of fetal infection and to classify the infection as being symptomatic or asymptomatic. Those additional investigations should be performed within the first 4 weeks of life in order to be able to offer treatment within the optimal window of opportunity.

Clinical examination

All congenitally infected neonates should be thoroughly examined at birth for the most common signs of cCMV infection: small for gestational age, hepatomegaly, splenomegaly, petechiae, microcephaly and jaundice/ hyperbilirubinemia. If any of these symptoms is found, the child is considered symptomatic.

Many other signs and symptoms at birth have been reported in case reports, such as respiratory distress syndrome, congenital nephrotic syndrome, nephritic syndrome, hypothyroidism, cardiac problems, intestinal malrotation with positive intestinal CMV biopsy, osteitis and cutaneous presentations such as perineal papules erosions and ulcers.

Laboratory testing

Laboratory testing should be performed with hematocrit, leucocyte and thrombocyte count, AST (aspartate-aminotransferase) and ALT (ala-aminotransferase). Determination of the viral load can be performed although its clinical value remains unclear. Although there seems to be a higher viral load in symptomatic infants compared to asymptomatic infants, no clinically relevant relation between viral load and neurodevelopmental or hearing outcome has been described so far (17). Further studies on the significance of blood viral load are warranted.

Cranial Imaging

Since cCMV can affect the central nervous system (CNS), a thorough assessment for CNS involvement is necessary. Experts agree that every child should have at least a cranial ultrasound at birth. Whether or not MRI should also be performed in every child, remains unclear (18). Although a cranial ultrasound performed by an experienced pediatric radiologist or neonatologist is very effective in showing cystic lesions, calcifications, ventriculomegaly and cerebellar abnormalities, other abnormalities (white matter lesions, polymicrogyria, lissencephaly, hippocampal dysplasia and cerebellar hypoplasia) are better detected by MRI (10). Although no international consensus exists on the use of both MRI and cranial ultrasound in the diagnostic work-up of all children with cCMV, we believe that MRI provides valuable additional information on central nervous system involvement and that it could be beneficial to perform both in every neonate with cCMV. Recently, a new MRI severity score was published helping with early prediction of long-term neurological sequelae (19).

Hearing screening

Sensorineural hearing loss (SNHL) is the most common problem in cCMV with up to 20% of asymptomatic newborns having congenital or late-onset SNHL (20). Therefore, all CMV-infected infants should have an audiological screening, preferably by auditory brainstem response. Any deviation of ³ 20 dB is considered abnormal and should be evaluated by an ear-nose-throat specialist.

Ophthalmologic screening

In all infants with cCMV a fundoscopy should be performed to detect chorioretinitis and/or optic atrophy, which occurs in about 10% of symptomatic babies (21).

Classification asymptomatic and symptomatic cCMV

After all investigations have been performed, the classification symptomatic/asymptomatic can be made based on all results. This classification has an impact on the decision for treatment, the way follow-up is planned and the way parents are counselled concerning long-term outcome. According to the literature, about 10-15% of live-born infants with cCMV are classified as symptomatic after birth.

Recently, it was suggested that the symptomatic children should be classified as mildly, moderately or severely symptomatic (18). It is essential that a uniform definition of symptomatic and asymptomatic cCMV infection is used worldwide. Whether SNHL should be part of this definition remains a matter of debate amongst various research groups. Being the most common sequela, SNHL should be included in the definition of symptomatic cCMV according to recent American guidelines (22).

Figure 1 describes the criteria for classification in mildly, moderately and severely symptomatic cCMV as adapted from the European expert consensus statement in 2017, with isolated hearing loss being part of this criteria (18).

Therapy

Every (severely) symptomatic child is eligible for treatment with valganciclovir. Almost 20 years ago Kimberlin et al. published the first clinical trial on anti-viral treatment of infants with symptomatic congenital CMV infection. The infants were treated with ganciclovir 6 mg/kg/dose every 12 hours intravenously for 6 weeks. Despite significant loss to follow-up, 21 of 25 treated infants (84 %) showed either amelioration or normalization of hearing loss versus 10 of 17 infants in the control group (59%). Safety evaluations showed neutropenia as the main toxicity. Additionally, the positive effects of ganciclovir on neurodevelopmental outcome persisted after 1 year of age.

Several years later dose-finding studies for the oral pro-drug of ganciclovir, valganciclovir, were performed. Oral dosage of 16 mg/kg/dose valganciclovir every 12 hours showed a comparable pharmacokinetic profile compared to IV ganciclovir. The major advantage of this administration route is the fact that there is no need for a central venous catheter and therefore, no need for hospitalization during treatment.

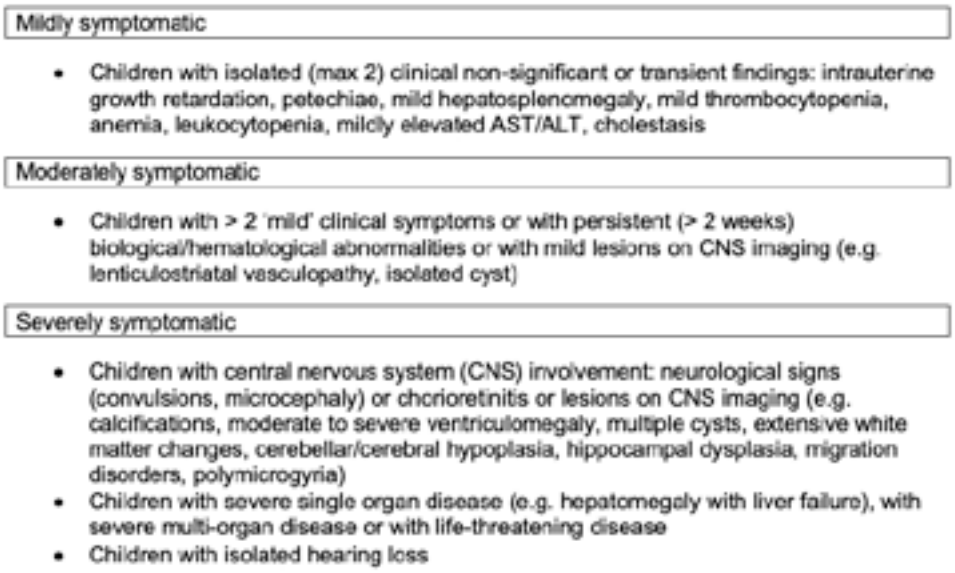
The possibility to give oral medication also re-opened the discussion on the duration of therapy. Kimberlin et al. suggested that the positive effect of 6 weeks of antiviral treatment seemed to wane over 2 years. They observed that viral loads became detectable again shortly after cessation of therapy. Studies indeed suggest that hearing outcomes at 24 months are better if complete viral suppression is achieved within 14 days after starting treatment and maintained for the rest of the treatment. However, clinical relevance of this effect has been questioned (17).

A randomized controlled trial addressed the question whether 6 months of valganciclovir was superior to 6 weeks of treatment. Although best-ear hearing after 6 months was similar in both groups, hearing was more likely to improve or to remain normal at 12- and 24-months follow-up in the group having received 6 months of therapy (73%) versus 6 weeks of therapy (57%, $p = 0.01$). Additionally, the group that was treated for 6 months had better neurodevelopmental scores at 24 months (evaluated by Bayley-III). Severe neutropenia was comparable in both groups and reversible in all cases (23). Since the intended effect of treatment (amelioration of best-ear hearing and amelioration of neurodevelopmental outcome) is more convincing in the 6-month treatment group, current state of the art is to treat infants for 6 months with valganciclovir, unless severe side effects necessitate an earlier discontinuation.

Of importance is that all studies were performed exclusively in infants with a gestational age above 32 weeks who were less than 1 month old when treatment was started.

For asymptomatic infants, expert consensus remains not to treat the infection in order to avoid exposure to the potential risks of valganciclovir administration, such as neutropenia, liver dysfunction (mostly transient) and possible gonadal toxicity and carcinogenicity (observed in animal models). However, since asymptomatic infants also show a risk of hearing deterioration, research is needed to explore possible treatment strategies for these children. Recently, a retrospective cohort study including infants and children with asymptomatic cCMV and later hearing loss, who received treatment with valganciclovir after the neonatal phase (mean age at start of treatment 53.3 weeks, range 12-156 weeks) showed best-ear hearing improvement in 90.8% of treated infants. Short-term adverse effects were limited (only 4.4% transient hematological changes), and long-term adverse effects were not reported (24). In this context, the results are awaited from an ongoing phase 2 open-label trial (ClinicalTrials.gov Identifier: NCT03301415 - USA), in which asymptomatic infants are treated with valganciclovir during

Figure 1 : *Criteria for classification in mildly, moderately and severely symptomatic cCMV (Adapted from the European expert consensus statement in 2017 (18))*



4 months in order to prevent later hearing loss.

Long-term outcome

Disabilities due to cCMV are estimated to be more common compared to any other well recognized conditions such as Down syndrome, spina bifida or fetal alcohol syndrome (25). Around 20% of infected neonates will suffer neurodevelopmental and/or audiological sequelae. Both symptomatic as well as asymptomatic children can develop sequelae, with a higher risk in the symptomatic group (Figure 2). Approximately 40% to 60% of infants with symptomatic cCMV will have permanent sequelae due to the disease: most commonly SNHL, followed by cognitive impairment, chorioretinitis and cerebral palsy. In infants with asymptomatic cCMV at birth, 10-15% will develop sequelae, mainly SNHL. Conflicting results are published concerning the risk of having neurodevelopmental and behavioral problems in infants with asymptomatic cCMV (26, 27). Additionally, no predictors of adverse outcome in asymptomatic cCMV could be identified (1, 25).

Sensorineural hearing loss

Hearing loss is the most common sequela in both symptomatic and asymptomatic cCMV. It is unclear whether late-onset SNHL is caused by viral reactivation or by the immunological host response. A review by Goderis et al. showed that 12.6% of all children with cCMV (1/3 of symptomatic children and 1/10 of asymptomatic children) experience hearing loss. Among symptomatic children, the majority have bilateral loss. In the asymptomatic group unilateral hearing loss is more common.

SNHL in cCMV infected children is characterized by fluctuations, progression and often delayed-onset. It can be unilateral or bilateral and can be severe to profound with need of hearing amplifications or cochlear implants. About 6% of infected children need a hearing aid or cochlear implant ranging from 29-44% to 1-3% in symptomatic and asymptomatic neonates, respectively (1).

The risk of delayed onset and progression of hearing loss in all cCMV children emphasizes the need for a long-term follow-up. Timely diagnosis and management is essential to improve hearing outcome (25).

Neurodevelopmental outcome

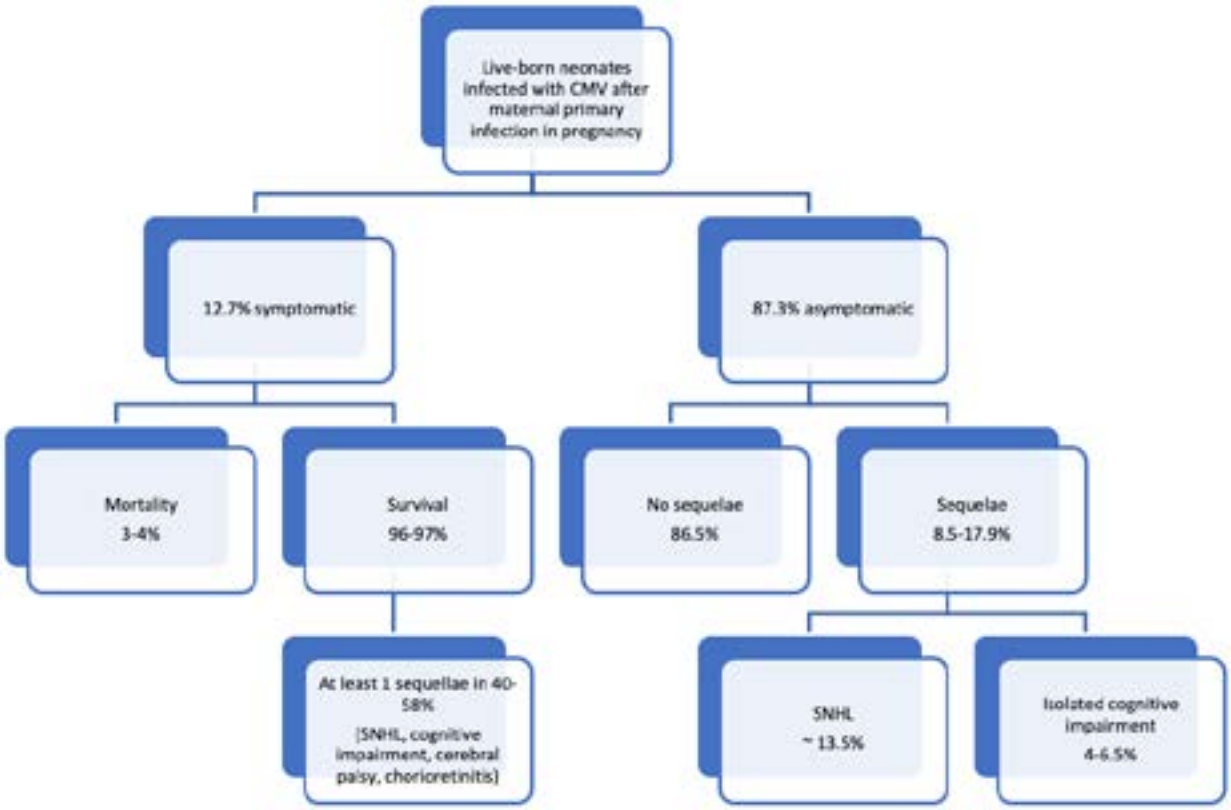
Congenital CMV is the leading infectious cause of neurodevelopmental delay: compared to CMV-negative children, CMV positive children are twice as much at risk to develop long-term impairment up to the age of 6 years (28). Cognitive impairment (mental delay, speech impairment), motor impairment (cerebral palsy, fine motor problems, epilepsy, hypotonia) and neurobehavioral impairment (autism spectrum disorder, attention deficit disorder) have all been described in children with cCMV. Since children with hearing loss have a higher risk of developing vestibular dysfunction, this may also cause motor problems. An interesting finding is the suggestion of a relationship between autism spectrum disorders and cCMV. However, a meta-analysis in 2018 could not confirm this association (29). Further studies on this topic are warranted. Presence of severe abnormal neonatal imaging (MRI and cranial ultrasound) is most predictive for poor outcome. It also has been suggested that gestational age at seroconversion and the classification at birth might correlate with outcome (1). cCMV infection seems to be more severe in newborns born to pregnant women with first trimester infection and if classified as symptomatic at birth. However, both symptomatic and asymptomatic newborns with cCMV infection can develop long-term sequelae, particularly in the behavioral and communicative areas, independently from the trimester of maternal infection (27). This is important in counselling parents.

Topics of discussion

Primary versus non-primary infection

For a long time, primary maternal infections were assumed to have a more significant impact on the fetus than non-primary infections. More recent data, however, have indicated that preconceptional maternal presence of CMV IgG is not protective against CMV-infection related fetal damage or later hearing loss. Differences in natural history and long-term prognosis of cCMV disease according to maternal primary versus non-primary CMV infection are not clearly documented (30, 31). Results from a recent meta-analysis indicate that neither symptomatic infection at birth nor the development of long-term sequelae were significantly correlated to the type of infection (32). Although

Figure 2 : *Frequency of sequelae in infants with cCMV after primary maternal infection. (Adapted from Leruez-Ville et al (2020) and Dollard et al (2007)) (1, 35)*



preconceptional seroimmunity might provide protection against intra-uterine transmission of CMV, once fetal infection occurs the risk of developing symptoms and sequelae is similar in both primary as well as non-primary infection (31).

Universal versus targeted screening

Alternative technologies for universal screening are currently evaluated. Due to widespread utilization in neonatal screening for other conditions, there has been much interest in using dried blood spots (DBS) taken at birth for CMV screening. However, screening DBS is less sensitive than PCR testing of saliva, with a sensitivity ranging between 28 and 100%, and is contingent upon the method of extraction and DNA amplification and the patient group selected. The recent standardization of viral DNA extraction and innovative PCR techniques have led to improved sensitivity of DBS screening to around 80%. A potential limitation in the use of DBS is that only 80–90% of congenitally infected infants have detectable CMV in their blood soon after birth. Despite this, the sensitivity of DBS screening has been shown to adequately detect those infants most at risk of developing SNHL. Stored DBS can be used to diagnose cCMV retrospectively (3, 33).

An alternative approach could be testing infants who do not pass their newborn hearing screening. A large-scale study led to identify 57% of the infants with CMV-related SNHL in the neonatal period. Additionally, the costs associated with targeted neonatal screening look favorable compared with other screening programs. However, this targeted approach would miss those CMV-positive infants who pass the newborn hearing test but are still at risk for late-onset SNHL (34).

The development of new techniques such as quantitative nucleic acid amplification tests (QNAT) and the generalization of PCR assays on urine or saliva samples, less expensive and less affected by transport and storage, could be the most effective approach for use in widespread newborn screening programs (16).

Conclusion

Congenital CMV is the most common congenital infection worldwide with an important impact on child, parents and society. Although many questions regarding this disease were answered, many topics are still under discussion and remain to be explored.

It is of utmost importance that when a child is diagnosed with cCMV, all additional investigations are performed in a timely manner so that therapy can be offered if eligible. A thorough follow-up until the age of 6 years, both audiologically and neurodevelopmentally, is recommend in every child with cCMV. Ideally, investigations and follow-up should be performed in a center with experience on cCMV.

Conflict of interest

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

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Non-invasive ventilation in the neonate: guidelines for the general pediatrician

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Keywords

Preterm, respiratory distress, ventilation

Abstract

Respiratory distress is a frequent problem in preterm and full term neonates. Even though invasive ventilation is necessary in certain situations, adequate knowledge and experienced use of non-invasive ventilation may be sufficient for a large group of neonates.

In this review article, we discuss the recent scope on non-invasive ventilation in late-preterm neonates and propose guidelines on the respiratory support of preterm neonates from 32 weeks of gestation on, not necessarily needing admission to a neonatal intensive care unit.

Introduction

Premature birth is associated with lung immaturity and pulmonary disease is the most important cause of morbidity in preterm neonates. Respiratory distress syndrome, transient tachypnea, apnea of prematurity and persistent pulmonary hypertension are among the most common pulmonary diseases in newborns.

For a very long time, invasive mechanical ventilation was the primary treatment of choice for respiratory insufficiency. Nevertheless, during the last decades, it became clear that invasive mechanical ventilation increases the risk of bronchopulmonary dysplasia (BPD), possibly leading to severe and long-term respiratory and neurologic consequences.

Important advances in neonatology in relation to pulmonary support include therapy with antenatal corticoids and surfactant replacement. Antenatal corticosteroids are given to accelerate fetal maturation in case of risk of preterm birth. Surfactant became a revolutionary treatment for respiratory distress syndrome, leading to better compliance of the lungs and less hypoxic respiratory failure. The combination of all of the above resulted in as significant decrease in mortality and prematurity related morbidity as well as a more prominent position of non-invasive ventilation in neonatal care. Consequently, the last decade showed an increasing interest for non-invasive ventilation modes, giving rise to more knowledge about the different systems and their indications (1,2).

In this review, we would like to discuss the recent scope on non-invasive ventilation in late-preterm neonates and propose guidelines on the respiratory support of preterm neonates from 32 weeks of gestation on, not necessarily needing admission to a neonatal intensive care unit.

Neonatal respiratory distress

The two most common pathologies among newborns are respiratory distress syndrome and transient tachypnea of the newborn (3).

Respiratory distress syndrome or hyaline membrane disease is the most common cause of respiratory distress in preterm neonates. As the type II alveolar cells are immature and produce less surfactant, the surface tension of the alveoli is increased and lung compliance is decreased. This leads to atelectasis causing respiratory distress (retractions, grunting), hypoxia and respiratory acidosis. The typical X-ray shows homogenous opaque infiltrates and air bronchograms. Symptoms might be very scarce at first but increase in the hours after birth when stocks of surfactant become depleted. Endogenous surfactant synthesis will start after 72-96 hours and clinical symptoms can then decrease. However, atelectotrauma and ventilator induced lung injury have well been described and need to be avoided by early intervention.

Transient tachypnea of the newborn is a benign and mostly self-limiting condition caused by residual pulmonary fluid in the alveolar and interstitial space. This is a clinical and radiological diagnosis (parenchymal infiltrates, sunburst sign, intralobar fluid accumulation) more frequently seen in babies of male gender, with macrosomia and after cesarean section. Symptoms can last from a few hours to about 48 hours.

It is important to be aware that during the initial course or during the treatment, especially in the course of hyaline membranes disease, lung damage resulting into chronic lung injury can occur. In case of a sudden onset of respiratory distress with increasing need for oxygen, in a previously stable patient, a pneumothorax needs to be suspected. Other factors causing respiratory distress (infection, persistent pulmonary hypertension, peripartal asphyxia, inborn metabolic disorders, congenital heart disease, …) need to be considered in presence of clinical factors raising suspicion.

In at risk or early symptomatic patients, non-invasive ventilation therapy as a therapy for respiratory distress needs to be started as early as possible. This will significantly reduce the risk for progressive atelectasis.

For further details and guidelines on delivery room management, we refer to the article on the new guidelines in the delivery room developed elsewhere in this issue.

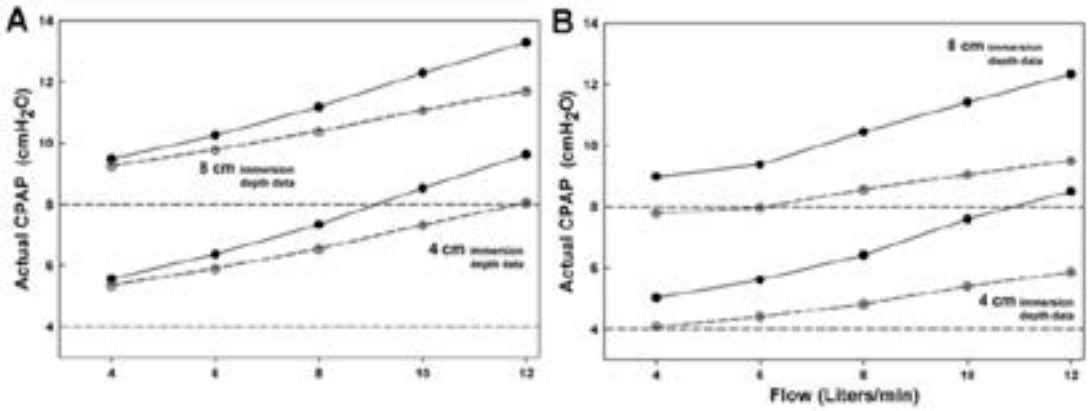
After stabilization in the delivery room, the further choice of respiratory support in the neonatal unit needs to be based upon the newborn's needs and diagnosis.

Modalities for non-invasive ventilation

Nasal CPAP

Nasal CPAP delivers continuous positive airway pressure, preventing alveolar

Figure 1: *The relation between given flow and expiratory limb depth with no and small leak, demonstrating the influence of a good seal on the level of pressure and given support; adapted from Kahn et al. (4)*



Actual B-NCPAP under no leak (*A*) and small leak (*B*) conditions shown for 4 and 8 cm expiratory tubing immersion depth in water. Pprong (•); Pprox (○); Pdistal (small dot). Note that Pprox and Pdistal overlap.

collapse and thus ensuring better gas exchange by stabilizing the functional residual capacity and reducing pulmonary shunts. It also decreases airway resistance and splints the pharyngeal airway, thereby reducing the work of breathing, incidence of apnea and airway collapse (5).

Continuous positive airway pressure was first studied in 1971 by Gregory et al with positive effects in the treatment of respiratory distress syndrome.

CPAP is preferably started immediately after birth while reabsorption of fetal lung fluid and establishment of functional residual capacity are occurring. During the transfer from the delivery room to the neonatal unit, positive pressure should be maintained in case of respiratory distress and this even if there is no need for oxygen supplements.

Two types of CPAP exist: continuous flow and variable flow CPAP.

In continuous flow CPAP the expiratory limb is submersed in a water seal or obstructed by a valve providing the positive end expiratory pressure. The continuous flow is delivered via a flow meter with oxygen blender, heated and humidified. One of the systems providing continuous flow CPAP is also known as bubble CPAP. Figure 1 shows the relation between given flow and expiratory limb depth with no and small leak. It demonstrates that the level of pressure is influenced by the possible presence of a leak on one side and flow on the other side. This might lead to low PEEP (positive end-expiratory pressure) and ineffective support, or to administration of actual pressure which is above the target with risk of lung injury, especially when there is no leak (4,5).

In variable flow CPAP, continuous pressure is generated directly into the nostril or a 'pre-chamber' positioned immediately in front of nasal prongs. A jet of blended oxygen-air is injected towards the nares to provide constant positive pressure. If more inspiratory flow is needed, the venturi action allows additional inspiratory flow. A fluidic flip during spontaneous expiration flips the flow around, leaving via the expiratory limb. The constant but variable gas flow maintains a continuous positive airway pressure, allowing active expiration. This system is also known as Jet-CPAP, or Infant Flow as it's a widely used brand, and reduces the work of breathing as well as increases the lung recruitment.

Nasal CPAP interfaces include mostly nasal masks, prongs or a nasopharyngeal tube (Figure 2) (6,7).

Complications of CPAP are secondary to the pressure administered into the lungs, to the interface irritation directly damaging the nose and to accumulation of air into the stomach and gastro-intestinal tract.

The (excessive) pressure can cause alveolar rupture and air leak syndromes e.g. pneumothorax or pulmonary interstitial emphysema. The positive pressure can also reduce venous return, increase pulmonary vascular resistance and reduce cardiac output. As mentioned above and shown in figure 1, the actual given pressure can exceed the wanted pressure in case of no leak and patients who are very active, moving or crying. In these situations, the given PEEP can increase dramatically and the risk of lung injury rises severely.

The nasal mask or prongs can be too large or too small, or they can cause too much pressure on the nasal area resulting in erosions or necrosis. It requires considerable dedication and skills to apply the nasal interface in a way avoiding complications and still ensuring seal. When trying to increase the seal, there is also a risk of depression of the facial bones. Neonates younger than 30 weeks of gestation are at higher risk of nasal injury than (near) term babies. Very meticulous nursing care is required in order to avoid serious injury and application of barrier dressings is advised. (Figure 3)

Furthermore, as CPAP blows continuous pressure through the nasopharyngeal cavity there is need for the placement of a nasogastric tube to be able to decompress the stomach (8).

Humidified and heated high flow nasal canula (HHHFNC)

HHHFNC delivers humidified and heated gas flow at rates higher than the demanded inspiratory flow. This ensures a variable positive end-expiratory pressure. HHHFNC also reduces dead space and nasopharyngeal airway resistance resulting in decreased work of breathing and more efficient gas exchange.

Practically, the system comprises a flow generator, an air-oxygen blender and a heater-humidifier, all providing flow through bi-nasal prongs. Flow rates range from 2 till 3 liters per kilogram per minute and gas is delivered at 37 degrees and 100% humidity.

The advantages of HHHFNC are the increased comfort for the neonate and the parents, less nasal trauma in comparison with CPAP devices or invasive ventilation and the easy use for the caretaker (9,10).

An important limitation is the variable and consequently less reliable positive end-expiratory pressure.

Nasal interfaces

As mentioned before, an important aspect about noninvasive ventilation in neonates are the interfaces used to deliver the flow and oxygen, if needed. In the case of CPAP, the seal they provide is of major importance. However, in all modes of noninvasive ventilation, the comfort and risk of nasal trauma play a significant role. Masks and prongs are usually alternated in CPAP, while HHHFNC uses a non-sealing interface with protective skin pads. Another interface, gaining popularity, is the RAM cannulaÒ developed by Dr. Ramanathan (11,12). It was first designed for oxygen delivery only, but is now also validated for the administration of high flow therapy and for nasal ventilation (conventional and High Frequency Ventilation). The RAM cannula

Figure 2: *Nasal interfaces*
A CPAP interfaces: nasal mask, nasal prongs (left panel) and nasopharygeal tube (right panel)
B. High flow interfaces: RAM cannula (left panel) en Optiflow® nasal cannula (right panel)

is made of flexible and soft material with thin-walled nasal prongs leading to an increased diameter of the inner prongs. This decrease in airflow resistance results in the ability to provide some degree of positive pressure ventilation, although less efficient compared to known CPAP-devices.

Non-invasive ventilation: other mechanisms

Other modalities for non-invasive ventilation exist.

BiPap (Bi-level nasal CPAP) provides unsynchronized PEEP combined with cycles of low additional pressure at low rate.

NIPPV, nasal intermittent positive pressure ventilation, ensures higher peak inspiratory pressures at a faster rate, resulting in higher tidal volumes and increased functional residual capacity. The inspiratory flow used in NIPPV is not synchronized, forming the most important disadvantage of this ventilation mode (13,14). Earlier studies demonstrate reduced work of breathing when using synchronized non-invasive ventilation, as well as less need for intubation or reintubation and reduced central apneas.

NivNAVA (Noninvasive Neurally Adjusted Ventilation Assist) ventilation supports the respiration in a synchronized way by detecting the diaphragmatic movements using a specialized orogastric tube lined with sensors. Based on the patient's electromuscular signal, pressure support is administered and a back-up inspiratory flow will follow if a set apnea time had passed.

Nasal high-frequency oscillation ventilation applies an oscillatory pressure waveform to the airways using a nasal interface, enhancing alveolar recruitment and CO2 elimination. Although less used in clinical practice, animal models showed promising results.

As these ventilatory modalities are mainly used in neonatal intensive care units, we will not discuss them further.

To CPAP or to High Flow

As High Flow is easier to use and causes less nasal trauma, the question rises whether it can serve as an alternative to CPAP. Several studies have been performed in search of an answer to this question. Yoder et al (n=432) found no difference in efficacy and safety as initial support; they saw however a significant rate of nasal trauma due to CPAP devices (15). The HIPSTER trial (Roberts et al, n=564) and Murki et al (n=272) noted a significantly higher failure rate in the HHHFNC group with good response to rescue therapy with CPAP (16,17). Nasal trauma and pulmonary leaks were on the other hand higher in the nCPAP group. The recently published HUNTER trial (n=754) confirmed that among preterm babies of more than 31 weeks of gestation, the use of HHHFNC as a primary support was inferior to CPAP with a significantly higher incidence of intubation (10). On the other hand, studies showed significantly better scores on the COMFORT scale in groups with HHHFNC compared to groups treated with nCPAP (Spentzas et al, n=46) (9).

In our opinion, in late preterm infants it is of major importance to start respiratory support early enough. With a team trained in its use, CPAP is preferable for neonates with moderate to severe respiratory distress. In cases of mild distress with little need for oxygen, high flow can serve as an alternative. (Table 1)

Table 1: Comparison between characteristics, side effects and goals of CPAP and HHHFNC

CPAP	HHHFNC
Constant PEEP	Less reliable PEEP
Maintenance of FRC and less airway collapse	Washout of nasopharyngeal dead space
Higher success rate in RCT	Higher failure rate and need for intubation in RCT
More nasal trauma	Less nasal trauma
Knowledge of device and good seal is necessary for adequate therapy	Easy use
More air leak syndromes	Possible air leak syndromes

Adjunctive management

Beside the respiratory management, the patient should be managed in an optimal environment to allow for better stabilization.

First, respiratory drive can be optimized with caffeine therapy if evaluated insufficient (18).

As much as possible, the patient should be kept in a calm and stimulus free condition ensuring minimal touch protocol. Careful attention must be paid to the limitation of unnecessary noise and light. The patient should be placed in a comfortable position, e.g. swaddled, in a suitable nest or skin to skin if the parents are available and the infant is stable.

Metabolic stability (glucose, temperature) must be maintained to limit energy consumption. This includes evaluation for the need of IV glucose infusion even if minimal feedings can be started early. As early as possible, minimal enteral feedings should be initiated (10-20 ml/kg/d) to optimize maturation and function of the gastrointestinal tract.

Detection and management of other non-respiratory complications (infection, feeding intolerance, pain, hemodynamics…) need to be evaluated but are out of the scope of this article.

Timely referral to NICU

As we speak about late preterm neonates with respiratory distress, the need for escalation of care needs to be noticed in a timely matter. More specifically we address the cases where neonates on non-invasive ventilation suffer from increasing respiratory distress and/or increasing need for oxygen. Early communication between neonatal (intensive) care wards is of major importance. The indication for surfactant therapy to treat RDS (currently set on worsening when FiO2 >0.30 on CPAP pressure of at least 6 cm H2O according the European guidelines (19) needs to be foreseen ensuring timely referral to a tertiary hospital with neonatal intensive care unit.

Conclusion

Non-invasive ventilation has a prominent role in the respiratory support of late preterm and term neonates. The two most used devices are nasal CPAP and HHHFNC. Early respiratory support in the delivery room with CPAP is important and the decision between above named modalities needs to be made based upon diagnosis, the patient's needs and team competence.

Disclosure

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

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Late preterm pathologies and prognosis

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Abstract

Infants born between 34 weeks 0 days and 36 weeks 6 days of gestation are called late preterm infants (LPTi). This group accounts for the majority of preterm infants.

Late preterm birth is associated with a higher risk of immediate clinical problems in a wide variety of organ systems. This includes the need for respiratory support, gastro-intestinal immaturity, hypoglycemia, hypothermia and hyperbilirubinemia. There are also more long-term morbidities with higher risk for neurodevelopmental problems and chronic respiratory and metabolic pathologies.

Therefore, this group is associated with high societal, emotional and financial costs. They require special attention during hospitalization and follow-up. Developing a structural care program in maternity and neonatal units can be useful.

Epidemiology

The past decades, there has been a significant increase in preterm births, especially late preterm births. Evolution in obstetric care pursues a decrease in very preterm and extremely preterm births, resulting in an increase in late preterm births. Changing maternal demographics and maternal health (e.g. higher maternal age, more obesity worldwide, …) are also possible explanations. In 2020, 7 to 8 percent of births in Belgium are premature. Late preterm infants represent one third to three quarters of this population (1-4). In singleton births, four to six percent of all deliveries occur between 34 and 37 weeks. In multiple gestation, approximately 40% of the children are born late preterm (3,4).

Late preterm infants have substantially lower mortality rates and less severe morbidities compared to very and extremely preterm infants. However, their disease burden should not be underestimated. The mortality rates among late preterm infants are 2 to 3 times higher compared to term infants (5,6). Overall morbidity rates in late preterm infants are even 7 times higher than in term infants (22% vs 3%). Given their immature respiratory and hemodynamic status, late preterm infants are at higher risk for any form of resuscitation support in the delivery room. They have higher rates of admission to NICU and have more rehospitalizations (6,7). Therefore, the terminology has changed from 'near term' infants to 'late preterm' infants to emphasize their significant immaturity and associated mortality and morbidity. They are associated with high societal, emotional and financial costs, due to their large absolute number (5,6).

In most cases (50-75%) late preterm birth occurs due to spontaneous labor or premature rupture of membranes. Potential risk factors are higher maternal age, smoking, low socio-economic status, multiparity and medically assisted reproduction (5).

Late preterm delivery is medically induced in 30% of the cases because of maternal and/or fetal conditions (5). Possible fetal indications include intra-uterine growth restriction, oligohydramnios, monochorionic twins or complicated multiple gestation. Maternal conditions are either pre-existing (e.g. hypertension, diabetes with vascular complications,…) or pregnancy related (e.g. preeclampsia, cholestasis, poorly controlled gestational diabetes,…). Uterine and placental anomalies (e.g. placenta praevia, placenta accreta, prior uterine rupture,…) can also lead to late preterm delivery (8).

Respiratory complications

An efficient gas exchange requires cleared and ventilated alveolar spaces and an increase in pulmonary blood flow to match ventilation and perfusion (7,9). In LPTi, the pulmonary development is still immature, at terminal saccular stage. This stage is characterized by maturation of dense alveolar saccules into thin, mature and more easily ventilated alveoli. Type II pneumocytes also become more prominent at 34 to 36 weeks of gestation. They are the source of pulmonary surfactant, reducing surface tension at the air-water interphase and facilitating expansion of the alveoli. In addition, pulmonary capillaries begin to bulge into the space of each terminal sac to increase pulmonary blood flow (9).

Late preterm infants more often have symptoms of respiratory distress (e.g. transient tachypnea, respiratory distress syndrome, pulmonary hypertension, pneumothorax,…) than term infants. This increases the length of neonatal stay in one third of these infants and the need for oxygen therapy, respiratory support and surfactant replacement is higher compared to term infants (6). Relative risks of nasal continuous positive pressure or mechanical ventilation requirements are respectively 9 and 5 times higher.

The incidence of respiratory problems in late preterm infants has a strong age-related trend. More than 20% of infants born at 34 weeks have respiratory distress compared to 7% in infants born at 36 weeks' gestation (1,7).

Antenatal betamethasone therapy decreases the rate of respiratory morbidities (1,6). However, this therapy is not routinely recommended for impending late preterm deliveries. The positive effect on the mild and frequently self-limiting respiratory morbidities doesn't always outweigh the side effects (e.g. impaired growth, hypoglycemia, …) and unknown long-term effects (10).

Transient Tachypnea of the Newborn (TTN)

TTN is defined as a late clearance of lung fluid from the alveolar space. The incidence in late preterm infants is up to 4% (7). Several explanatory mechanisms are proposed. Late preterm infants have weaker respiratory muscles and more inadequate surfactant production. This ensures that insufficient inspiratory pressures are generated, which can lead to insufficient lung aeration (11). Sodium channels in the lung epithelial cells play a role in the clearance of lung fluid. As their expression is gestational age-related with a peak expression at term gestation, late preterm infants are more at risk to develop TTN (7).

During active labor, sodium channels are activated by increased fetal epinephrine and steroid concentration. Therefore, preterm infants born by cesarean section in absence of labor and "vaginal squeeze", are more at risk to develop TTN (7).

Respiratory Distress Syndrome (RDS)

RDS is the result of qualitative and/or quantitative deficiency of pulmonary surfactant. Preterm infants have both an immature surfactant system and a quantitative deficiency (7,9). Uterine contractions enhances surfactant production, therefore birth by cesarean section in absence of labor is a risk factor for developing RDS (7).

The incidence of RDS in late preterm infants is 8 to 13-fold higher than in term infants (7).

Apnea of Prematurity

During the last 6 weeks of gestation, significant changes occur within several brainstem regions. These changes contribute to a synchronized and coordinated breathing with maturation of the upper airways and lung volume control, laryngeal reflexes, chemical control of breathing and sleep-wake cycle. Immaturity of these brainstem regions may result in apnea of prematurity. Late preterm infants are thus more at risk for central apnea (7,9). Obstructive apnea also occur at greater frequency as late preterm infants have highly compliant chest wall and upper airways who tend to collapse when the diaphragm contracts (7).

Persistent Pulmonary Hypertension of the Neonate (PPHN)

Late prematurity is a significant risk factor to develop PPHN as late preterm infants have an increase in smooth muscle cells in the walls of pulmonary blood vessels. This leads to increased pulmonary vascular resistance and eventually shunting and ventilation-perfusion mismatch (9). The presence of RDS is a risk factor due to alveolar atelectasis (7).

The overall incidence of PPHN in late preterm infants is 0.4%, compared to 0.08% in term infants. In infants with respiratory morbidities, the incidence in the late preterm group is 0.94%, compared to 0.11% in term infants (9).

Pneumothorax

Pneumothorax is more present in late preterm infants, due to the structurally immature and less compliant lungs and (invasive) ventilation support (6).

Management

As a result of these multiple risks for pulmonary complications, a close clinical monitoring is needed in late preterm infants. When signs of respiratory difficulties arise (immediately after birth or in the first hours of life), cardiorespiratory monitoring and appropriate therapy must not be delayed (6).

Gastro-intestinal complications

Gastro-intestinal problems occur in one third of all late preterm infants, compared to 7% of term infants (6). Feeding difficulties are the primary reason for prolonged hospital stay in LPTi (6, 7, 12). Poor weight gain, dehydration and failure to thrive are frequently seen in LPTi (7, 12). Possible explanations can be categorized in following domains.

Firstly, late preterm infants have an important oral motor hypotonia and are rapidly fatigued resulting in difficult persistent latching and suckling. They often require feeding support and time to reach full enteral feeding is significantly longer (6,7,12). Their orobuccal, breathing and feeding coordination is also immature with a higher risk of choking (7,12). Observing feeding moments is therefore important. If a discoordination is present, an early consultation with a speech therapist can be useful (6). Because of their delayed gastric emptying, LPTi also have a higher frequency of gastroesophageal reflux, which can contribute to reducing food intake (7).

Secondly, breastfeeding is frequently complicated due to both inappropriate lactogenesis in the mother following maternal pregnancy complications and latching difficulties in preterm infants. Given the normal delay in full maternal milk supply, breastfeeding problems can initially go unrecognized until a larger amount of breastmilk is required. This may lead to an inadequate intake resulting in failure to thrive (6).

The incidence of initiation and maintenance of breastfeeding in late preterm infants is significantly lower than in term infants. Therefore, both support and education from lactation consultants and kangaroo or skin-to-skin care are crucial (12).

Lastly, the nutritional requirements of late preterm infants have not been specifically evaluated. Higher energy expenditure and thus higher nutritional needs are expected, as derived from those of very preterm infants (8). Close monitoring of weight is essential to evaluate the need for active nutritional support (parenteral nutrition, gavage feeding, fortifiers, supplements, …) (7,12). The requirements for vitamins, minerals and trace elements are also likely to be higher in LPTi, but insufficient data is available to make concrete recommendations. The incidence of vitamin D deficiency is higher in LPTi suggesting that higher vitamin D supplementation could be useful. Late preterm infants are also at risk for developing iron deficiency and associated microcytic anemia because of their lower iron stores related to the shorter duration of pregnancy, lower birthweight and multiple blood sampling (12). A better neurological development is also seen in late preterm infants who receive early routine prophylaxis (13). Tubules of LPTi excrete a significantly higher amount of sodium compared to tubules of term infants, due to an immature renal function (14). This may play a role in the presence of failure to thrive in LPTi as serum sodium is correlated with weight gain. Monitoring is thus recommended.

Metabolic complications

Hypothermia

Neonates rely on non-shivering thermogenesis to maintain body temperature. Brown fat, which is produced from the 28th week of pregnancy, is the source of this thermal regulation, together with hormonal regulation. Efficiency of temperature regulation is therefore dependent on gestational age and is defined by the amount of brown fat and the maturity of the hypothalamus. In addition, preterm infants have more heat loss because of a higher surface area to weight ratio, less white adipose tissue and an immature epidermal barrier (15). Rigorous monitoring of the temperature and prevention of heat loss is of importance. In the first hours, this might be supported by early skin-to-skin contact with one of the parents, thorough drying of the skin and the use of caps and warm blankets. During the rest of the hospital stay, close follow up and adjustment of room temperature and clothing remains important. Incubators, warming beds or heat tables decrease the risk of temperature instability. Skin to skin contact is still advised during the whole hospitalization.

Hypoglycemia

Late preterm infants have reduced glycogen stores and an immature hepatic glycogenolysis and gluconeogenesis in combination with inappropriately high secretion of insulin. The sudden discontinuation of maternal glucose supply after birth may therefore cause hypoglycemia when there is an insufficient metabolic response. Limited enteral intake due to immaturity, higher glucose need (hypothermia, infection, hypoxia), less alternative energy sources (intrauterine growth restriction) or higher circulating insulin in case of unbalanced maternal diabetes may further contribute to the higher risk of hypoglycemia (15). Therefore, systematic monitoring of the glycemia is recommended in late preterm infants during the first 24 hours of life as well as early feedings and support of breastfeeding. In some situations, transient intravenous glucose administration might be needed to insure proper levels of serum glucose (16).

Hyperbilirubinemia

Due to an immature liver function with slower bilirubin conjugation and increased enterohepatic circulation, jaundice occurs more often and can be more prolonged in late preterm infants. Concurrent infections or feeding difficulties with secondary dehydration can further increase the risk of hyperbilirubinemia.

The blood-brain barrier in late preterm infants is more permeable. This, in combination with lower circulating albumin, can make them more vulnerable for neurological complications at lower bilirubin levels (17).

Guidelines for phototherapy incorporate those risks and a lower threshold for initiation of therapy is recommended in late preterm infants (18).

Infectious complications

The late-preterm infant is more vulnerable for infections because of an immature immune system, less transplacental maternal antibodies and associated comorbidities.

The innate as well as the adaptive immune system is less developed in preterm infants, partly because of a deficient production of immunoglobulins, complement proteins and a less effective cellular response to infections (19).

An infant is protected with passive immunity by transplacental passage of antigen-specific immunoglobulins in the third trimester. This transfer increases with fetal age, so preterm and late preterm infants have lower levels of circulating maternal IgG's. The use of human milk is therefore crucial to support the preterm infants' immature immune system after birth. It contains high concentrations of secretory IgA and IgG as well as human milk oligosaccharides and many other immunomodulatory components. These components are suggested to compensate for the deficiencies in the neonatal immune system (20).

Higher incidence of intrauterine inflammation in preterm infants as well as the need for vascular access and respiratory support devices further increase the risk of infections like sepsis and pneumonia in this vulnerable population (19).

Neurological complications

Brain weight at 34 weeks is only 65% of that of the term baby. Between 34 and 40 weeks of gestation, the brain experiences significant growth and development with intense synaptogenesis, dendritic arborization and myelination. The cortical surface growth is exponential at those ages with the development of sulci (21,22).

Ultrasound screening is not always routinely performed in late preterm infants because of the low prevalence of acute neurological problems. However, intraventricular hemorrhage does occur more often than in term infants (0.41% vs. 0.09%). Therefore imaging should be done on clinical suspicion and with low threshold (23).

Long term complications

Different studies reported that late preterm infants have a threefold increased risk for cerebral palsy compared with term infants and are also more vulnerable for minor psychomotor impairments such as cognitive difficulties, language and praxis problems, social interaction disturbances and attention-deficit disorders (21,23,24).

At preschool age, two studies report significantly lower communication and gross motor scores for late preterm infants, both at 12 month corrected age and at 3 years of age (25,26).

At school age, a descriptive meta-analysis reported a moderate deficit concerning neurological impairment, school skill and requirement of early intervention program (27). However, these differences were only significant for infants with a complicated neonatal course and not significant for babies with an easy neonatal course (24-27).

Late preterm infants have a higher respiratory vulnerability than term infants, even in the absence of acute respiratory impairments after birth. Within the first years of life, they have a higher incidence of respiratory interventions and need respiratory support more frequently. Late preterm gestation is also associated with asthma as the lung function of these infants is compromised with a persistent decreased forced expiratory flow and forced vital capacity with a higher residual volume (8).

The incidence of an Apparent Life Threatening Event (ALTE) and sudden infant death syndrome (SIDS) is also higher in late preterm infants compared to term infants (8-10% vs <1% for ALTE and 1,36/1000 vs 0,69/1000 for SIDS) (7).

This group also has a higher risk for respiratory infections in the first two years of life. Because of this vulnerability, they benefit from an adapted vaccination scheme. In Belgium, a supplementary dose of conjugated pneumococcal vaccination is administered at the age of 12 weeks and the booster vaccinations of 15 months are given at 12 months of age. Influenza vaccination is recommended for infants older than 6 months. Passive immunization for RSV with palivizumab is recommended in late-preterm infants with more than 48 hours of respiratory support in the NICU if they are less than 6 months old at the beginning of the RSV season.

To further protect this population, influenza and pertussis vaccination is advised for family members and caretakers of infants <6 months of age.

In adulthood, higher incidences of arterial hypertension, obesity and metabolic syndrome have been described (1,5,23). Preventive measures should be taken where possible.

Conclusion

It is important to recognize the increased risk for complications in the late preterm infant and try to avoid them. This can be done antenatally by interdisciplinary consultation to correctly indicate the need for preterm delivery and betamethasone administration. Postnatally it is important to implement preventive measures and monitor for known complications including respiratory adaptation difficulties, hypothermia, hypoglycemia and to initiate appropriate treatment where necessary.

This group of infants also requires a specific and close follow-up as they are at higher risk for long-term neurodevelopmental impairment and other chronic problems. Developing a structured care program after discharge can therefore be useful for both acute and chronic impairments. At the same time focusing on non-separation between parents and infants can facilitate bonding and benefit breastfeeding. It is important to keep mother and child together as much as possible by stimulating kangaroo care and creating units with the possibility of rooming-in (28).

Disclosure

There is no conflict of interest for any of the authors.

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Parental participation: essential for developmental care but challenging in neonatal wards

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Introduction

Premature babies, born at less than 37 weeks gestational age, represent 7% of births in Belgium. According to the degree of prematurity and severity of associated illnesses, the special needs of preterm infants are provided in neonatal units, ranging from non-intensive wards to high-tech neonatal intensive care units (NICUs). Despite progress in neonatal care, which have led to increased survival, premature infants are at risk of developing long-term morbidities such as complex cognitive dysfunctions, behavioural disabilities, and socio-emotional problems. These developmental morbidities do not only affect the most immature, but also moderately and late preterm infants born between 32 and 37 weeks of gestational age. To enhance neurobehavioral outcome, neonatal units try to implement developmental care policies. One of the key features of most developmental strategies is parental involvement and participation in the care of their baby. Yet, it remains one of the biggest challenges. It requires considering parents as primary caregivers and partners in clinical decision-making.

Principles of Family and Infant Centered Developmental Care (FICDC)

Throughout the hospitalization, preterm infants can be overwhelmed by lighting, noise, painful procedures, handling, and parental deprivation. Brain growth and establishment of neuronal networks occur during the NICU stay. Exposure to environmental stressors can have long-term neurodevelopmental repercussions. Parents of a preterm or a sick neonate, far from the joy of an expected normal pregnancy, very often live a stressful experience. Beside the fear of prematurity-associated comorbidities, the complexity of care delivered in neonatal units, requiring experienced professionals, can be very intimidating (1). The staff, who represents authority and expertise, can interfere with parents' perception of their child, and significantly alter their role (2). Consequently, parents may fear the proximity with their fragile babies and feel insecure or incompetent in providing them care and support (2). Sometimes, parental experience of stress is so unbearable that anxiety, depression or a post-traumatic stress disorder can arise, which can influence the relationship with the baby (3,4). This adversely impacted parent-infant relationship can be associated with poor long-term developmental outcomes, emotional instability, and child abuse (5).

Since the pioneering work of Heidelise Als in 1982, developmental care practices have been implemented in NICUs worldwide to decrease the stress in preterm and sick infants and promote their well-being, growth, and optimized neurological and behavioural outcome. They consist of a range of interventions including postural support, pain management, lactation and breastfeeding support, sleep protection, skin-to-skin contact (SSC), and observation of baby cues to favour individualization of care (6). Such strategies can only be successful if parents are fully recognized in their fundamental role and integrated in the decision-making process, funding the base for Family and Infant Centered Developmental Care (FICDC). This concept emerges from the evolution of the parental role in the last decades in neonatal wards. In the past, parents were considered as visitors having to respect limited visiting hours and without any active function in their baby's care. Today, most neonatal units adopt unrestricted parental access, promote SSC, and encourage participation in care and decision making. Albeit diverging in terms of theoretical concepts, the mainstay of all FICDC policies is welcoming parents and families in the neonatal units and actively involve them in the daily care of their baby (5). FICDC has short- and long-term benefits for the infant and the family (6). On top of technology in neonatal units, FICDC has also favoured survival and better integration of the fragile baby in the family (5).

Evolving to a FICDC unit requires fundamental changes in the daily approach to babies and their families. Parents are the constant in the child's life, whereas services and personnel fluctuate (1). The staff must emphasize the importance of parental presence for the short and long-term development of their child. As such, parents must be regarded as primary caregivers. Health care workers should involve them as partners in clinical decision-making. This implies a flexible staff that supports the crucial role of parents by bringing continuous assistance, adequate information, and individualized psychosocial support (6). Whilst parents involved in the treatment of their child feel more confident, health care professionals can have the feeling that parents interfere with their function. Therefore, FICDC policies must be clear and provide emotional and financial support to meet family and staff needs (1).

Benefits of parental participation

Physical and emotional closeness through sensorimotor interactions is crucial for the mother-infant bond, thereby helping regulate the infant's physiology and behaviour in the short term and its capacity to adapt in the future. Among different modalities of physical closeness, SSC, as a marker of parental participation, is medically safe and has the strongest evidence for a positive impact on the infant's health (7). Several clinical studies, mainly in the context of Kangaroo Care, compiled in meta-analyses including thousands of low-birth-weight infants have investigated the short- and long-term benefits

of SSC (7–9). As compared to conventional care, early and sustained SSC participates in the attenuation of pain during procedures, cardiorespiratory stability, and prevention of hypoglycaemia and hypothermia (8). At the time of discharge from the hospital, low-birth-weight infants are more likely exclusively breastfed and exhibit better growth profiles including head circumference (7,8). Moreover, SSC reduces the risk of sepsis and mortality in this fragile population, albeit the effect might be more pronounced in low-income countries (7,8).

Nurturing care interventions as Newborn Individualized Developmental Care and Assessment Program (NIDCAP) or continuous day and night family presence were also associated with a decreased risk of bronchopulmonary dysplasia and better general development in a Swedish setting (10,11). As a result, the possibility for parents to stay 24 hours a day decreased the length of NICU stay (11). Indeed, integration in the daily care of their baby may empower parents and favour their readiness for the transition from the NICU to home, thereby attenuating the financial impact of prematurity (3). The association between increased parental participation via SSC and improved outcomes needs further investigation but might involve combined effects of genome, epigenetics, microbiome, and anti-inflammatory properties of breastfeeding (11,12).

In addition, SSC is a moment belonging exclusively to parents, during which all neuroprotective care practices can be provided. SSC helps parents' sensitivity allowing a better understanding of the child's needs, bonding and later attachment between the parents and their baby. Parents also feel more confident and competent in parenting. Other benefits for the parents themselves include a decrease in stress, anxiety, and depression (13). A meta-analysis of 22 randomized controlled trials (RCTs) concluded that NICU interventions focused on FICDC seem to be the most promising ones in reducing parental stress (14). By contrast with the abundant literature assessing the benefits of parental participation for the mother-infant dyad, much less attention has been paid to fathers. They tend to be less present than mothers in neonatal wards, but they do not have to be considered as second level parent (15). Postpartum depression in fathers is a reality, with feelings of inadequacy and uselessness when compared to the maternal nursing role. Involvement of fathers in supporting breastfeeding may provide an opportunity to bond with their newborn. Their attitudes can influence mothers' breastfeeding decisions (16).

With regards to neurodevelopmental outcomes, SSC positively impacts developmental, cognitive, and emotional outcomes (17). While providing SCC, parents indeed promote the neurodevelopment of their baby by singing, reading to them, performing massages, protecting sleep, and preventing or reducing pain during procedures (8). Therefore, creating an environment that favours communication and minimizes distractions is meaningful (15). In a retrospective cohort study including about one hundred of extremely preterm infants, higher duration of SCC was associated with a better language score at 12 months, while cognitive scores remained unchanged (17). During the follow-up of an RCT comparing continuous SCC and standard care, prematurely born adults having benefited from SCC show better intellectual quotient scores, school performances, and social skills (18).

When results of RCTs were gathered in systematic reviews, the effectiveness of NICU interventions on neurodevelopment appears disappointing. Indeed, there is limited evidence supporting a positive effect of NIDCAP on behaviour and movement of preterm children at 5 years of age, with no significant effect on cognition (19). Another meta-analysis evaluating NIDCAP effectiveness on neurodevelopment failed to show significant benefits likely due to the lack of large, good quality trials (20). Overall, meta-analyses in the setting of developmental care might be difficult to interpret because of large variations in NICU interventions, limited number of RCTs, different target populations, precluding the identification of the most effective intervention (21). Beside differences between studies in terms of quality and inclusion criteria, this might also reflect the fact that parental participation, while being primordial for the infant's health, might not be enough *per se* to counteract all the detrimental effects of prematurity.

Barriers and facilitators to parental participation

Despite the benefits of parental participation, including parents in the everyday care remains a challenge for neonatal units. Identified obstacles to parental presence are numerous and strongly vary depending on geographical origin, as reflected by a prospective survey involving 11 NICUs across Europe (22). These differences might reflect variations in neonatal unit infrastructures, culture of care provided by the staff, hospital visiting policies, sociodemographic characteristics of parents and families, and social benefits offered in each country.

The infrastructure of neonatal units and policies of parental visits can strongly affect the participation and presence of families. With regards to FICDC, unrestricted access of parents to their baby is essential. Having access to a reclining chair or bed, a bathroom and kitchen can offer a better comfort and help parents stay around the clock (4). Having a place where the parents can gather and meet with family or friends can encourage them to spend more time in the unit.

Recent data have suggested that the presence of single rooms instead of an open-bay design could promote parental presence and contribute to their psychological well-being (23). Single rooms can be designed as family rooms, which allow the presence of siblings (4,22). Nevertheless, the existence of single rooms might increase maternal stress, which has been ascribed to a feeling of isolation and higher responsibility regarding the infant (24). The reason for these discrepancies between studies is unclear but might emphasize that other factors, such as the lack of adequate support from the staff and/or specific socio-demographic conditions, can overcome the benefits of staying in a single room.

The contribution of socio-demographic factors to parental participation is inconsistent in the literature (15). While the presence of siblings is a common limitation, other predictors of reduced parental participation have been highlighted such as the lack of income, long distance between the hospital and the residence, parent's health issue, and lower level of maternal education (16,22,24). In some instances, cultural and religious factors can be relevant to understand parents' and staff's reactions as gender assumptions and the presence of fathers (4). Another limiting factor for parental participation in neonatal wards is the infant's health condition and the degree of medical support provided. As such, more neonatal comorbidities and medical interventions correlate with less parental visits and duration of holding (24). This underlines the fact that high level of stress can make parents fear the proximity of their baby.

Because parental stress is a marker of parental involvement, addressing parents' psychological needs and supporting them emotionally during the hospital stay is critical to favour long-term bonding between infants and their families. Therefore, beside emotional, and empathic support, social workers and psychologists represent an added value to support family organization and/or provide financial assistance (4,5). Among social measures, the limited duration of paternity leave can explain, at least partially, the under participation of fathers (16). The length of paternity leave strongly varies from one country to another: it can only last a couple of days in some European regions, whereas it extends up to several months in Germany and Sweden. In countries providing longer paternity leave, fathers are more involved. Moreover, the perception that fathers have of their own function influences their participation during the hospital stay: the more they have the feeling that their presence is as essential as that of mothers, the more they will get involved in their baby's care (16).

Finally, as healthcare professionals have a role of educators, coaches and facilitators of care and bonding, their behaviour can significantly influence parental participation. On the one hand, the medical staff can be very intimidating for parents because they assert their authority and act to control the relationship in a protective attitude (1). On the other hand, for caregivers who are often highly stressed by monitoring and treatments, hour shifts, and the lack of available staff, the process of implementation of FICDC can be overwhelming. Moreover, depending on the infant's health status, the staff can fear or hesitate to propose parents to help for daily caregiving activities (25). The lack of experience and clear guidelines on developmental care measures makes implementation more complex. The efficacy of implementation can

vary greatly if the general policy in the neonatal unit establishes FICDC as a standard of care or a caring practice (25).

Involving parents and families in the practice: the starter pack

Considering principles of FICDC that have been integrated in paediatric care for the last decades, Table 1 summarizes concrete actions that can be implemented for children with special health needs, their families, and medical staff (1). Unlike older children hospitalized in a paediatric ward, the newborn admitted to the neonatal unit does not have time to fully integrate the family structure (1). Thus, the first contact in the neonatal ward can be very scary for parents. It is important to favour infant-parent interactions before explaining the medical condition and equipment (5). Parents must be involved progressively, without forcing them. The staff should privilege this first contact, making a positive moment to help build a secure emotional relationship. More than just hands-on care, the staff should coach parents based on respect and dignity, information sharing, participation, and collaboration. Parents must be informed about the importance of their presence and involvement in the provision of care. This implies that the NICU staff should be trained and properly informed on neuroprotective developmental care for preterm infants and the importance of family. For such unit changes to occur, creating guidelines is essential (4). Having a unit policy on parents and family involvement, to which all the staff adheres, is an important tool to promote the implementation of FICDC. Coaching and training parents can represent a considerable time investment for the staff at the beginning. Yet, as parents become more confident and increasingly involved in caregiving and feeding of their baby overtime, the workload of the nursing staff decreases (3).

Regular and clear communication between parents and staff is a corner stone to change from a system-centered where rules are imposed, to a FICDC approach that provides families the possibility to determine what works best for them (4). Because the information can be difficult to understand, especially the first days after birth, it must be repeated, consistent and clear (26). Having a limited number of reference staff as a care team for the infant can favour collaboration and make the parents feel as equals and partners. Their active participation in medical rounds improves communication, enhances collaboration with the medical team, and increases satisfaction. When parents feel recognized as partners and not simple visitors, they feel supported and have a sense of control over the situation (16). When parents and all the members of the multidisciplinary team find their place in the continuity of FICDC, satisfaction increases for families and the NICU staff. Finally, parent-to-parent support is often highly appreciated and might be beneficial for implementation and perpetuation of FICDC.

Since space and privacy can influence parent-infant closeness (27), NICU infrastructures are often presented as a limiting factor for the implementation of FICDC. However, the Group of Reflection and Evaluation of the Environment of Newborn with the French Society of Neonatology (GREEN) and the French parents' associations concluded that the sensory content of the environment might be more meaningful than the design of the ward (28). Single rooms offer many benefits but are not always the solution for families or staff because they offer privacy but are also a source of isolation (29). In a meta-analysis including 1850 preterm infants, no differences were observed regarding anxiety, infant-parent bonding or self-efficacy between open bay units or single-family rooms, even if there are other benefits as higher parental presence, higher rates of breastfeeding, and lower rates of sepsis (30). Anyways, in many infrastructures moving to a single-family room unit is often unrealistic. Alternatively, inexpensive adaptations for open bay units can be suggested to facilitate parental presence by providing a specific place with folding screens, comfortable chairs, and/or beds allowing an overnight access. Nonetheless, the negotiation of space and place can be very challenging in open bay units and acknowledging the ownership of a place gives the feeling of being respected as a primary caregiver (26,27). Efforts to create a calm atmosphere are also essential since parents as infants can be overwhelmed by the light and noise in the unit (26).

When considering FICDC, family is far broader than just the parents. Siblings should not be forgotten. They can feel neglected since their parents spend a long time in the neonatal unit. They must be informed, and be able to

Table 1: Summary of elements to facilitate the implementation of family-centered care.

Principles of family-centered care	Concrete actions
Sustained family-infant relationship	· Unrestricted access · Specific and comfortable place nearby the infant · Welcoming siblings and other family members
Parent-professional collaboration	· Regular and clear communication · Partnership relation · Staff as facilitator of bonding
Support family strength and individuality	· Individualized care · Respect cultural and social diversities · Enhance parent and infant competences · Give parents a sense of control
Sharing information on an ongoing basis	· Parent enrolment in medical rounds · Recognize parents as partners
Parent peer support	· Create a parent advisory board · Work with parent associations · Parent groups
Understanding and incorporating developmental needs	· Staff training on age-appropriate care · and risks of inappropriate stimulations · Parent coaching · Acknowledge the benefits of parental presence
Emotional and financial support for families	· Unit psychologist and social worker · Activities for siblings · Catering / parking facilities / transport facilities
Flexible, accessible, and responsive health care for families	· Clarify parents and staff roles and expectations · Attention to power relationships · between parents, nurses, and physicians · Ask families what is important for them
Implementing policies and programs to provide support for the staff	· Considering FICDC as a standard of care · Allow investments for infrastructure and staff · Clear guidelines and staff training

visit, and participate according to their age and personality. Parents of a hospitalized newborn can decide who they consider as family members. Hence, grandparents, other family members, or close friends can be crucial resources for psychological support and precious logistical assistance.

Several programs and resources supporting the implementation of FICDC are available. For example, the 'Family and Infant Neurodevelopmental Education program®' or the 'Close Collaboration with Parents Training Program®' have been created to guide neonatal units and caregivers in establishing this collaboration. The European Foundation for the Care of Newborn Infants (EFCNI) has recently published standards of care for newborn health and emphasizes the primary role of parents in the provision of care (https://www.efcni.org/). They state that: (i) parents must have unrestricted access to the neonatal ward; (ii) continuous SSC should be promoted; (iii) family needs should be recognized and supported; and (iv) a parental advisory board can help implement FICDC.

Conclusion

Integrating parents in the care of their newborn optimizes developmental protective measures. Parents learn to read their infants' cues and are a warranty for the individualization of care. Parental involvement, combined with a respectful and thorough communication that favours a partnership with the NICU staff, allows an increased general satisfaction. However, evaluating the effects of these interventions in clinical studies remains difficult. In the future, the development of standardized outcome sets evaluating FICDC interventions would be useful to determine the most adapted ones and allow better quality large trials (9). Finally, the one-size-fits-all approach cannot be given for FICDC. Each neonatal unit should identify its own barriers and enablers including physical environment, healthcare worker beliefs, clinical practice, and characteristics of parental presence. Adherence to local guidelines and search for creative solutions for space and unit design are needed to boost a change in practice.

Conflict of interest

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

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Figure

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Care of the Extremely Low Gestational Age Newborns after NICU discharge

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Keywords

extremely premature, follow-up, neurodevelopmental impairment, complex care

Abstract

Extremely low gestational age newborns, born before 28 weeks of gestation, have a significant risk for medical complications and developmental disabilities, stressing the need to closely follow their health and development. In Belgium, the neurodevelopmental follow-up of these infants is organized according to a RIZIV-INAMI Convention. On the order hand, the general pediatrician also has an essential role in the prevention and diagnosis of complications and in supporting the families. This article provides an overview of the short- and long-term complications these children can present with.

Highlights

- The increasing survival rate in extremely preterms underlines the importance for a close multi-disciplinary follow-up even up until adolescence.
- About 7% develops CP, one fifth has a motor delay at 2 years corrected age, increasing up to one third exhibiting motor skills deficits at preschool age accompanied with a greater risk for DCD
- Cognitive problems are often accompanied by shortcomings in executive functioning and/or behavioral problems.
- Retinopathy and cerebral visual impairment are common visual problems and can further impact their development.
- A three to four-fold increase in psychiatric problems, especially ADD and ASD with a phenotype characteristic for preterms marked by inattention, anxiety and social difficulties
- Parental mental health is crucial for attachment and later cognitive and behavioral development

Introduction

Improvements in neonatal intensive care have been associated with increased survival rate of extremely low gestational age newborns (ELGANs), who are born before 28 weeks of gestation. Nevertheless, about half of those children will present chronic health disorders or complex neurodevelopmental impairments (NDI) in a way that largely exceeds the occurrence of those impairments in term newborns. Moreover, most children do not present an isolated medical problem but a range of physical, neurological and /or emotional difficulties. Those difficulties do not only impact the child, but also the family well-being.

The general pediatrician plays an important role in coordinating primary care, medical subspecialties and neurodevelopmental follow-up (1). Improvements in mortality and morbidity have been made possible thanks to proactive treatment of those babies during Neonatal Intensive Care Unit (NICU) stay and probably the same in follow-up will help them too. This article focuses on following developmental outcomes of ELGAN: growth, feeding behavior, motor outcomes, cognitive, learning and language disabilities, neurovisual disorders, behavioral and psychiatric disorders and parental mental health. Those aspects can have cumulative effects on the development of the child. Early, accurate diagnosis and treatment is important to improve outcome in the sense that injured or compensatory neural networks can develop over time.

Developmental care and family integrated care in neonatal units

Recent research has highlighted the role of the NICU environment and individualized care to influence short- and long-term outcome of ELGANs. Neonatal units evolve into units based on Developmental Care, Family Centered Care and coupled Care while still offering high level of medical assistance. Following this principle, the Neonatal Individualized Developmental Care and Assessment Program (NIDCAP) was established in Belgium since the 1980s. NIDCAP aims to promote the development of premature babies by including and supporting parents in understanding their child's behavior while avoiding separation between mother (also the father) and child, reducing stress related to environmental factors and adapting care procedures.

It is widely accepted that parental mental health is an important factor affecting child development. For human newborns direct skin-to-skin contact from birth, which leads to emotional connection, is essential for developing secure attachment. Maternal-neonate separation prevents these critical processes for secure attachment from taking place (2). Safe, stable, and nurturing relationships during childhood are important protective factors in child development. The support of an adult who helps to make the child feel safe, as a co-regulator in early development and as a sensitive, responsive parent later on, is an effective protective factor that may build resilience. This attitude begins from the NICU admission (3).

Medical care after discharge

After discharge from a NICU, close medical attention is recommended during the first years of life, especially when the infant is leaving the hospital with nutritional or respiratory support. In any case, *growth and development* should be assessed to detect and address possible feeding difficulties, respiratory problems, and severe NDI. Regular (medical) check-ups are

highly appreciated by the families, especially when the general pediatrician can easily appeal on a multidisciplinary support team. As the infant grows up, the need for respiratory and feeding support decreases (1). Moreover, in Belgium, a RIZIV-INAMI Convention proposes 4 neurodevelopmental evaluations on fixed time points of 4, 12 and 24 months corrected age and 5 years in order to detect NDI and organize support and treatment. Content of the RIZIV-INAMI Follow-up convention is listed in figure 1 and table 1.

Neurodevelopmental outcome refers to cognitive, neurologic, motor, behavorial and/or sensory outcome. Severe NDI is defined as the presence of one or more of the criteria described in table 2 and can be diagnosed in most cases at the end of the second year of life (1). Nevertheless, individual prognostic value of this assessment is not as predictive as expected. Some children diagnosed as having severe NDI at the age of 2 years, might be classified as having mild impairment at the age of 8 years which can be attributed to early therapy and parental guidance.

Moreover, developmental disabilities are often only diagnosed later in childhood, but may still have a significant impact on the child's participation and quality of life.

Table 3 depicts the necessary parameters to collect at NICU discharge and key points of medical surveillance later in life.

Growth and feeding problems

ELGANs have increased caloric and nutrients requirements compared to term newborns making them at risk for inadequate growth. *Growth impairment* at birth and/or at corrected term age, including poor head growth, has been associated with impaired cognitive and motor performance. On the other side, excessive weight for length exacerbates the risk of metabolic syndrome at adulthood. Breast milk is the best nutritional option, but correct fortification or mixed formula feed is sometimes necessary to assure optimal growth (4). Food diversification is proposed between 4 and 6 months corrected age. Optimal growth curves for ELGANs are still discussed. Nevertheless, using the corrected age until 2 years of age at least is mandatory.

After discharge and through the first years of life, ELGANs have been found to have more *feeding difficulties* than term born babies such as swallowing difficulties, excessive duration of meals, difficult transition to solid food. Such feeding difficulties impact the growth evolution and form a massive stress factor for the parents (1). Prolonged ventilation, feeding gastric tube, nociceptive stimulation of the face can disturb the maturation of suck and swallow rhythms. However, neurologic impairment can also interfere with oral motor function. Hence, children exhibiting oral motor dysfunction need to be referred to a feeding specialist as soon as possible.

Motor disorders and risk of cerebral palsy

Preterm infants often present brain injuries, of which diffuse white matter injury is most common and observed in 50-80% of the cases (5-7). Brain damage makes these infants more vulnerable for NDI, of which *cerebral palsy (CP)* is the most impairing outcome (8). The overall estimated prevalence of CP in preterm infants is 6.8%, but this increases with decreasing gestational age (GA) (9).

As CP is a clinical diagnosis, the detection is mostly based on the combination of clinical and neurological signs, but abnormal neuroimaging can further endorse the diagnosis. Early predictive signs (before 5 months corrected age) are abnormal neonatal neuro-imaging (86-89% sensitivity) and/or motor dysfunction observed with the Prechtl Qualitative Assessment of General Movements (98% sensitivity) and/or Hammersmith Infant Neurological Examination (90% sensitivity)(10). The combined use of these clinical assessments further increases the diagnostic accuracy. After the corrected GA of 5 months, clinical observations including the inability to sit independently by the age of 9 months, hand function asymmetry, or the inability to take weight through the plantar surface (heel and forefoot) of the feet are signs, identified by high-quality evidence, that further standardized investigations for the detection of CP should be initiated. For more information on the current evidence for the early and accurate diagnosis of CP, we refer to the published clinical guidelines (10).

Ninety-four percent of the preterm infants with CP have the spastic form (73% bilateral, 21% unilateral), while only 6 % has predominantly non-spastic characteristics (dyskinesia/ataxia) (11). Due to the ongoing development and maturation of the brain as well as the possibility of plasticity, it is strongly recommended to start as early as possible with early motor interventions in which parental involvement is highly recommended (10). Importantly, children with only a suspected diagnosis of CP should be referred as well for early intervention while refining the diagnostic process (10).

Fortunately, in most cases, prematurely born children will not develop CP. Nevertheless, *deficits in motor skills* remain a common feature. A prevalence of 20.6% of overall motor delay is reported up to 2 years corrected age with mild delays (18%) being more common than moderate-to-severe delays (8.6%) (9). However, these early assessments appear to be poor predictors for motor outcome at preschool age, since the same review reported a higher prevalence of overall motor difficulties in pre-school aged children (36%). This difference is partially due to the fact that a more sensitive test is used at pre-school age requiring more motor control and coordination to perform the tasks successfully. In case motor deficits are persistent and compromise functional independence in daily life, this might be classified as Developmental

Figure 1 : *Inclusion criteria of the RIZIV-INAMI neurodevelopmental follow-up convention*

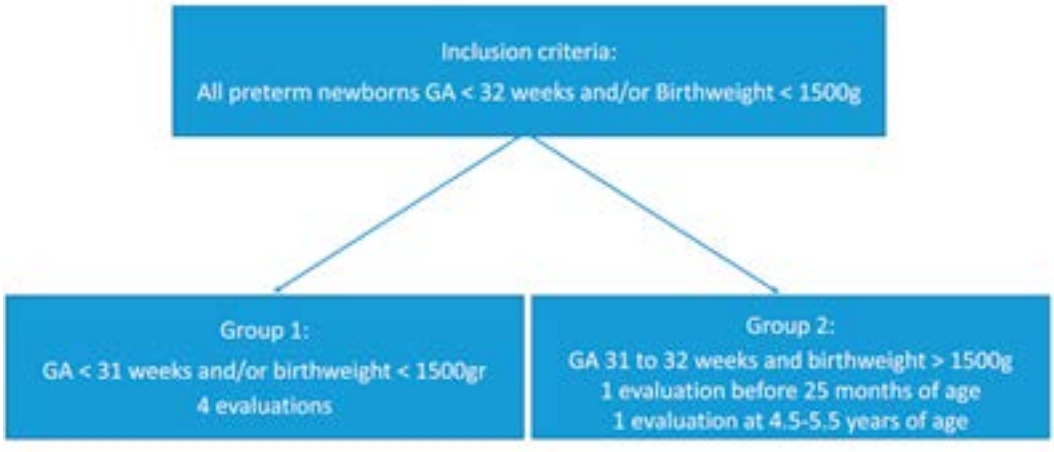

Table 1: schematic overview of the RIZIV-INAMI Follow-up convention

	Time-points of follow-up			
	3-6 months corrected age	**9-13 months corrected age**	**22-25 months corrected age**	**4.5 -5.5 years**
Neuropaediatrician / neonatologist	Collect visual and auditory evaluations	Collect visual and auditory evaluations	Growth Collect sensory evaluations	Growth, Collect sensory evaluation
Physiotherapist	AIMS and BSID-III motor scale	AIMS and BSID-III motor scale	BSID-III motor scale	Beery VMI and M-ABC-2
Psychologist	Parental well being	BSID-III cognitive scale and language scales	BSID-III cognitive scale and language scales	WPPSI IV
Speechtherapist	/	/	/	CELF-Preschool2 NL ELO, N-EEL (Chevrier Muller) or Exalang FR
Social assistant	yes	yes	yes	yes

Abbreviations: AIMS, Alberta Infant Motor Scale; BSID-III, Baley Scales of Infant and Toddler Development third version; VMI, The Beery-Buktenica Developmental Test of Visual-Motor Integration, 6th Edition; M-ABC-2, Movement Assessment Battery For Children second version; CELF, Clinical Evaluation of Language Fundamentals.

Coordination Disorder (DCD). DCD is a neurodevelopmental disorder characterized by 4 criteria: 1) motor skills are delayed and uncoordinated given the child's age and motor experience 2) which persistently interferes with their daily live performance, 3) and cannot be explained by any medical, neurodevelopmental, psychological, or social condition, nor by cultural background, and 4) these symptoms arise early in childhood (10). ELGAN survivors have been reported to have a 3 to 10-fold increase risk for developing DCD compared with the prevalence of of 5%-6% in the general population (12,13). Hence, awareness for the occurrence of this neurodevelopmental disorder in ELGAN children is warranted. For more information on the current clinical guidelines regarding DCD, we refer to the recently published clinical practice recommendations (12)which included a total of 10 293 infants. The pooled prevalence of cognitive and motor delays, evaluated with developmental tests, was estimated at 16.9% (95% confidence interval [CI] 10.4–26.3.

Cognitive, language and learning disabilities

ELGAN children have an increased risk for cognitive and learning disabilities. Within the RIZIV-INAMI Follow-up convention, the *intelligence profile* is only captured during the final assessment at 4.5-5.5 years of age with a proper cognitive test such as the Wechsler Preschool and Primary Scale of Intelligence Test (WPPSI). At the earlier time points, developmental scales with a cognitive subscale, such as the Bayley Scales of Infant and Toddler Development-Version III, are often used to examine the cognitive development. Based on such developmental scales, a meta-analysis has reported an overall cognitive delay of 16.9%, with mild delays being more common (14.3%) than moderate-to-severe delays (8.2%) (9). However, this meta-analysis did not exclusively included infants born before 28 weeks of GA but also included infants born between 28 and 32 weeks of GA. Nevertheless, as in accordance with motor deficits, cognitive and learning disabilities also increase with decreasing GA (9).

Based on cognitive tests at a later age, moderate-to-severe delays occurred in 14.7% of the cases (9). However, this number is based on only two studies, and the occurrence of mild delays could not be calculated by the meta-analysis.

When performing the WPPSI, ELGAN children appear to have greater weaknesses in working memory and perceptual reasoning than verbal comprehension and processing speed abilities. Therefore, it is especially important to realize that, beyond the overall IQ score, it is above all the heterogeneity of the subscales that is highlighted (14). Moreover, their intelligence profile can be highly heterogeneous, underlining the importance to look beyond the overall IQ-score.

Besides intelligence profile, *cognitive development* is also crucial for school performance and executive functioning. It is therefore important that adaptations are made at school to support these patients. The need for individualized support at school increases with lower GA; e.g. 50% at 24 weeks GA, 13% at 26 weeks GA (15). The support needed also varies according to the difficulties presented. For example, mathematics seems

Table 2: Definition of Severe neurodevelopmental impairment (NDI) (1)

At two years of age	- Cognitive delay based on scores on standardized cognitive tests that are 2 standards deviations below the mean. - Moderate to severe cerebral palsy, defined as a score of more than 2 on the Gross Motor Function Classification System. - Bilateral hearing deficit requiring amplification. - Severe visual impairment with visual acuity <20/200 with the best correction, in the better seeing eye.
Later in life:	- No international agreement; severe NDI is based on the same definition than at 2 years or one of the complications noted below **:** - Consider severe behavioral disorders: autism spectrum disorders, attention deficit disorders, anxiety - Severe learning disabilities - Developmental coordination disorder - Cerebro-visual-impairment

to be particularly difficult, which seems in ELGAN-children to be related to underlying difficulties with executive function and working memory, rather than number estimation in term born children. Strategies to optimize learning are related to attentional strategies and favoring sequential information management.

Specific *language* studies show that ELGANs have lower scores than children born at term and those born between 28 and 36 weeks.

Problems in language acquisition appear in the early childhood period. The RIZIV-INAMI Follow-up convention only involves a language test by a professional speech therapist at around 5 years of age, which is quite late. Children who present language retardation usually have already been diagnosed and oriented to follow speech therapy. However, there is a strong relationship between language deficit and cognitive difficulties. It is therefore important to identify as soon as possible specific language impairments are present (16). Moreover, communication and language skills, and language pragmatics in particular, should be assessed at each appointment between pre-school age and adulthood.

When the deficit is established, difficulties often persist into school-age and adolescence. In the article of Lee, language and reading skills are associated with the degree of prematurity and studied independently of gender, IQ and socioeconomical status in a population of 9-16 years old children. Language analysis was performed with specific tests according to the field studied. The linguistic processing speed, verbal memory

Table 3: Important information at NICU discharge and childhood

	Important points to check at discharge	Long term medical follow-up
Growth parameters	Weight, length, cranial circumference: *Is there growth restriction, pre- or postnatal?*	Need for growth hormone supply Evaluation around 2-3 years
Clinical status	Respiratory rate, heart rate, saturation, blood pressure: *Chronic lung disease? Risk of hypoxia? Risk of pulmonary hypertension?*	Blood pressure Lung function CT-scan Cardiac ultrasound/catheterization to diagnose Pulmonary Hypertension in case of Bronchopulmonary Dysplasia
Nutrition and feeding	Type- volume-frequency-duration of feeding sessions and incidents: *Quality of growth? Risk for aspiration?*	
Biology	Hemoglobin, reticulocyte count, ferritine, Calcium-Phosphorus-alkaline phosphatases: *Need for vitamins or nutrients supplementation?*	
Immunization	Current immunization (3 doses Pneumococcal vaccination) + Influenza immunization after 6 months RSV prophyllaxis	Current immunization
Vision/hearing status	Eye fundus (retinopathy and treatment) Auditory Evoked potentials at discharge	Annual vision assessments Hearing assessment at 1 and 2 years
Neurodevelopmental status	Cranial imaging through ultrasound +/- MRI: *risk for NDI, risk of hydrocephaly.*	According to clinical evolution Cerebral MRI if indicated Genetic investigations
Neurodevelopmental status	Holding/carrying and/or physiotherapy recommendations	Long term neurodevelopmental follow-up beyond 5 years of age Indication for individual support: physiotherapy, speech therapy,…
Sleep safety	Cardiopulmonary Resuscitation training: *risk for Sudden Infant Death Syndrome*	Polysomnography indications
Day care attendance	Avoid during the first winter: *risk of infections and readmissions.*	School attendance + individual support if needed
Family	Concern about family well-being: Postpartum depression- Parental and siblings support groups	Psychological support of parents if indicated.
Administrative	Major familial Allocations – conventions for special care or feedings	

and reading comprehension are directly proportionally associated with the degree of prematurity. For the receptive vocabulary, syntactic comprehension or reading abilities, GA was not a direct predictor. These impairments seem to be associated with white matter injury caused by the prematurity. Diffuse myelination disturbances represent the majority of cases but focal cystic necrotic lesions of periventricular leukomalacia can also be found even if their prevalence is decreasing compared to diffuse lesions (17).

Neurovisual disorders

Annual visual evaluation is important to diagnose strabismus, refractive errors and visual field defects (prevalence: 25-50%). The most frequently described ophthalmological pathology affecting ELGANs is *retinopathy of prematurity*. This condition impairs vision through direct involvement of the eye.

Visual disturbances are most of the time equated with acuity disturbances resulting from peripheral damage. However, lesions affecting the retro-chiasmatic visual pathways or the cerebral visual areas also generate a visual deficit. Brain lesions in ELGAN children may affect the visual functions of the brain resulting in *cerebral visual impairment* (CVI) (18). CVI is therefore defined as a verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment (19,20). Transmission of the visual information from the retina to the occipital visual cortex is carried out by the optical radiations. These fibers run along the occipital horn of the lateral ventricle within the cerebral white matter, making them prone to damage in case of leukomalacia. The further neural processing of vision occurs via two pathways: the dorsal and ventral stream. The dorsal stream runs from the occipital lobe to the parietal lobe. This stream processes the object's spatial location ('where'-pathway) and is the more vulnerable part (21). The ventral stream goes from the occipital lobe to the temporal lobe and is involved in visual recognition ('what'-stream).

CVI is subdivided into 3 non-independent categories: low level visual deficit, oculomotor disorders (fixation, pursuit, visual capture), and higher level visual perceptual deficits (alteration of the stages of analysis and integration of visual information) (22). Neurovisual disorders have multiple impacts on daily life, school learning and social relationships (23). They are e.g., involved in postural and gestural control, the construction of spatial representations allowing displacements, in object recognition and the learning academic skills such as reading, writing and mathematics. As such, recognition of its early signs before the age of 3 is paramount.

Behavioral problems and psychiatric disorders

Preterm birth is identified as a significant risk factor for *mental health disorders* with a 3- to 4-fold increased risk for mental health issues reported. Attention Deficit Hyperactivity disorder (ADHD) and Autism Spectrum Disorders (ASD) are the most prevalent at school age and adolescence.

A spectrum of *"preterm behavioral phenotype"*, characterized by inattention, anxiety and social difficulties, is often described with presentation ranging from subclinical symptomatology, which is frequent, to overt psychiatric disorder. The association with other comorbidities, particularly cognitive impairment, is mostly present (24). Altered brain development due to biological vulnerability and environmental influences, such as neonatal pain and stress, and non-optimal parental strategies are thought to explain the link between preterm birth and those socio-emotional and mental health problems (25).

ADHD is diagnosed in 17-20% of ELGANs comparing to 5-10% in term peers. Some differences are noticed. The child shows signs of internalizing behavior, is withdrawn or shy. Inattentive behavior is more frequent than hyperactivity. The gender ratio is about 1. It is characterized by the low association with conduct disorders, the weaker association with socio-familial risk, close correlation with medical variables revealing inflammatory processes in the

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EEN STRIKT GECONTROLEERD WATER.
Interview met Arnaud Collignon, Water Ressources Manager bij SPA®, die uitleg geeft over de beschermingsmaatregelen in de stroomgebieden in de Venen en over de uitgevoerde controles om zuiver, zwak gemineraliseerd water met een constante samenstelling te garanderen.

EEN STROOMGEBIED VRIJ VAN MENSELIJKE ACTIVITEIT

AC: *Het beschermingsgebied van het mineraalwater van Spa is meer dan 13.000 hectare groot. Binnen deze perimeter is er geen enkele industriële activiteit, geen landbouw en geen pesticiden, om de zeer hoge zuiverheid van het water te garanderen. Van de bron tot de fles blijft het water in een gesloten circuit en ziet het geen daglicht. Alle materialen die met het water in contact komen, of het nu gaat om leidingen of verpakkingen, worden regelmatig getest en geanalyseerd om te garanderen dat zij inert en niet-verontreinigend zijn. Ook de verpakking garandeert de kwaliteit en de zuiverheid van het water. De productielijnen worden continu gecontroleerd. Al deze procedures en controles, van de bron tot de fles, maken het mogelijk om een water van hoge kwaliteit en met een onberispelijke zuiverheid aan te bieden en te garanderen.*

DAGELIJKSE ANALYSES, UITGEVOERD DOOR EEN ERKEND LABORATORIUM

AC: *Het Spa-water voldoet aan alle vereisten van de Europese regelgeving op dit gebied. Zo wordt het water dagelijks geanalyseerd om zijn microbiologische kwaliteit en chemische samenstelling te evalueren. Het wordt gecontroleerd bij de bron, en voor en na het bottelen. Om uitmuntendheid te garanderen, gaat de controle van het water zelfs verder dan de regelgeving met regelmatige controles op een brede waaier aan microbiologische, fysisch-chemische en organische parameters door het Spadel Laboratorium (gecertificeerd volgens ISO 17025). Bovendien controleren onafhankelijke laboratoria het water regelmatig op de afwezigheid van opkomende verontreinigende stoffen (bestrijdingsmiddelen en hun metabolieten, residuen van geneesmiddelen, hormoonverstoorders, virussen...). Naast de wekelijkse microbiologische controles analyseerde Spadel in 2020 zo'n 53.204 parameters van het Spa-water.*

CRITERIA VOOR HET LABEL "GESCHIKT VOOR DE BEREIDING VAN BABYVOEDING"

AC: *Om het label "geschikt voor de bereiding van voeding voor zuigelingen" te verkrijgen, moet water aan verschillende criteria voldoen: een zeer hoge zuiverheidsgraad, constant in de tijd en een lage minerale samenstelling, wat het geval is voor Spa® Reine omdat het laag gemineraliseerd is met een zeer laag gehalte aan calcium, fluoride, chloride en natrium, maar ook aan nitraten en nitrieten. Spa® Reine beantwoordt perfect aan al deze criteria. Daarom is het water van Spa® Reine de eerste keuze voor baby's en voor moeders die borstvoeding geven.*

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neonatal period (e.g. enterocolitis, sepsis, bronchopulmonary dysplasia...), or with impaired brain growth or maturation. Deficits in working memory and data processing are specifically observed (24-26).

ASD, especially symptoms of impaired social communication, is also associated with premature birth. Twenty percent of a 2 years cohort of ELGANs scored positively on a screening scale for ASD comparing 5% of term newborns. At adolescence, 8% of a cohort of extremely preterm born children was diagnosed with ASD using a standardized assessment protocol compared to 0.6% in a term born cohort. ASD is frequently associated with low cognitive outcome (IQ), but even in an absence of severe NDI prevalence is increased by a forth times. Associated factors are white matter and cerebellar injury while genetic factors are more often found in autistic children born at term (24-26).

At school age, the prevalence of *anxiety* is 3 to 4 times more frequent than in term born: 9% versus 2%. Again, strong association with low IQ is found. The occurrence of depressive symptoms is more controversial (24-26).

In addition to their mental health disorder, those adolescents are more often the subject of *bullying*, which can exacerbate their mental health symptoms.

The management of these mental health disorders is increasingly complex. It requires coordinated care by a child psychiatrist or psychologist including guidance at school.

Parental mental health as a crucial factor in the development of the preterm born child

Maternal mental health is a factor that might be crucial in the prevention of psychopathology in preterm children. Mothers of preterm infants are significantly more likely to experience postpartum depression, anxiety, and posttraumatic stress disorder than mothers of full-term born infants (26). The experience of preterm birth and its consequences may affect the parent's well-being and mental health. Parents whose children need to be admitted to the NICU, experience feelings of shock, uncertainty, fear, guilt, anger, grief, depression, loss of control, blame, helplessness, and anxiety (27). Preterm birth and hospitalization are highly stressful experiences for parents. Preterm delivery interrupts the normal process of becoming a parent and parenting distress seems to persist long beyond hospital discharge, with parents showing ongoing concerns about their child's health and development.

The *caregiving environment* has even been reported to be more influential on the development of infants born preterm compared to those born full-term. It is demonstrated that prematurity may act as a susceptibility factor, enhancing above-average social functioning in the context of low-stress and supportive environments. In addition, a low-stress environment may reduce the cognitive gap between preterm and full-term infants (28,29).

Altogether, this strongly underlines the importance of monitoring parental mental health after preterm birth and the possible strength of interventions supporting the quality of early family interactions.

Adolescence and adulthood

Few follow-up studies expand to adolescence. Differences in *motor performances* persist but consequences thereof on the quality of life seem to regress. *Lower cognitive scores* appear to be conserved over childhood and adolescence and contribute to reduced attainment at school and lower employment opportunities (30).

Health related quality of life and social inclusion remain lower in ELGAN adults, especially in the presence of neurosensory impairments and poor health conditions. However, the gap with term born individuals does not increase with age. Data are nonetheless conflicting. Nevertheless, a lot of adults born extremely preterm report a good quality of life (30).

Conclusion

Improvement in neonatal intensive care management has resulted in an increased survival rate of ELGAN children. However, the risk of medical complications and developmental disabilities increases with decreasing GA, stressing the need to closely follow-up the growth and development of these children, which will facilitate early diagnosis and starting up early interventions. Although these children are only followed until 5 years of age within the RIZIV-INAMI Convention, we recommend to remain attentive for mild developmental disabilities and psychiatric disorders, even up until adolescence. Finally, parental mental health and secure attachment should always be considered, given the impact it has on the child's development.

Disclosure

There is no conflict of interest for any of the authors.

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Lower airway pathology in children with Down syndrome

PhD thesis presented on 16/12/2021 at Antwerp University, Antwerp, Belgium.

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Keywords

Down syndrome, airway malacia, respiratory problems

Abstract/introduction

Down syndrome (DS) or trisomy 21 is a prevalent chromosomal disorder that is associated with a broad spectrum of health problems. In children with DS, both upper and lower airway problems are frequently observed and impose a major health burden on both the patients and their families. In this dissertation, we have tried to provide a systematic overview of the different pulmonary and airway problems encountered in this specific patient population, and to explore certain topics in more detail in an attempt to provide a more patient-tailored clinical approach.

PhD summary

First, we made a scoping review of existing literature concerning (lower) airway problems in children with DS. We systematically searched medical databases (MEDLINE and PubMed) to collect relevant papers and were able to include 60 original studies that met our criteria. These were analyzed and summarized by topic. Though a lot of these reviewed papers were retrospective and some of them lacking control groups, they showed consistent conclusions about all of the discussed topics: In DS, airway anomalies (such as laryngo-, or tracheomalacia but also rare combined anomalies) are significantly more prevalent than in controls and often require a specific approach. Furthermore, respiratory tract infections are usually more severe and associated with an increased need for (prolonged) hospitalization. RSV bronchiolitis is a well-studied example of this. A large proportion of DS children suffers from chronic pulmonary aspiration, that is often silent and results in protracted and difficult-to-treat symptoms. Pulmonary hypertension, recurrent wheeze and some other, rare conditions are more commonly encountered in DS. This calls for an increased awareness and multidisciplinary follow-up (1).

Subsequently, we verified the results from previous small-scale studies concerning the higher prevalence of airway anomalies in our DS cohort. We did this in a retrospective manner and added a comparison to a large control group without underlying conditions. We confirmed the presence of one or more airway anomalies in 72% of pediatric DS patients with chronic or recurrent respiratory symptoms undergoing lower airway evaluation (direct laryngoscopy and/or bronchoscopy). This in contrast to the control group, where only 32% had a similar diagnosis. We most frequently encountered airway malacia and found a very high proportion of children with DS diagnosed with multiple airway malformations (about one in four patients) (2).

Since these airway anomalies are associated with a tendency to airway collapse, the question arose whether they have an effect on obstructive sleep disorders in this already predisposed population. It is common knowledge that there is a very high prevalence of obstructive sleep apnea (OSA) in individuals with DS due to the prominent muscle hypotonia, the narrow upper airways and tendency to obesity. However, data on the clinical relevance of lower airway anomalies is scarce. We retrospectively collected data from full overnight polysomnograms (PSG's) from our DS cohort and compared these between the group with lower airway anomalies and the group with a normal evaluation of the lower airways. We found no significant differences in prevalence of OSA, OSA severity or choice of treatment (when comparing a conservative approach, upper airway surgery or CPAP therapy). When looking at follow-up PSG's, there was an overall good response to OSA treatment, again without significant differences between the DS group with and without airway anomalies. We only found a (not statistically significant) tendency to more persistent OSA among those with lower airway anomalies (3).

As we know from our scoping review, children with DS suffer from more (severe) respiratory tract infections, with a higher need for (prolonged) hospitalization. Besides the evident anatomical predisposition, we explored other possible contributing factors. Given that these children receive more antibiotics and spend a lot of time in hospitals and care facilities, we investigated if there are differences in lower airway microbiota. We used the database from the airway endoscopy study and retrospectively added results from bronchoalveolar lavage fluid (BALF) cultures (when available). We compared the detected microorganisms but found no major differences in lower airway microbial composition between the DS group and the control group, besides a significantly higher proportion of DS children with gram negative bacteria such as *Haemophilus influenzae* and *Enterobacterales* (4).

Extensive literature suggests an inherent immunological dysfunction as another possible cause for this increased infectious burden, as well as for the higher prevalence of several autoimmune conditions in DS. Most frequently described in DS are: lower white blood cell count, lower lymphocyte count and several subtypes, abnormal levels of immunoglobulins, and so on. In the search for immunological parameters that are potentially predictive for recurrent infections, we conducted a prospective, cross sectional study. We compared

white blood cell count and differentiation, lymphocyte subgroups and immunoglobulins G, A and M between DS children with and without recurrent respiratory tract infections (RTI's). None of the tested parameters differed significantly between the two groups when accounting for age. We only observed a non-significant trend towards a higher leukocyte and neutrophil count and lower ratio CD4+/CD8+ in the group with recurrent RTI's, but these proved to be poor predictors. Further research (including functional testing) is required, but we suspect that the higher infectious burden in DS children is largely multifactorial in origin.

Another possible contributing factor that should not be underestimated, is chronic pulmonary aspiration (CPA). This remains a challenging diagnosis that is often made indirectly by detection of gastroesophageal reflux and/or by swallowing studies, all with variable sensitivity and specificity. Literature already suggests a high prevalence of dysphagia in children with DS, but the impact on the lungs is yet unclear. We found promising papers concerning biomarkers in respiratory specimens indicating CPA (mostly in experimental settings), and chose to set up a prospective feasibility study determining a number of these biomarkers in BAL samples, namely: lipid laden macrophage index, amylase, pepsin and bile acids. Though some technical issues still need to be addressed, we believe that our suggested future study protocol could benefit not only patients with DS but also with other comorbidities characterized by cognitive or developmental delay in diagnosing CPA.

Based on the findings of this dissertation, we propose the following recommendations (see table 1) which can be helpful in the care of children with DS and chronic / recurrent respiratory problems. Needless to say, these should be tailored to the needs of each individual patient.

As a final **conclusion**, we would like to emphasize that in DS, there is a complex interplay of different organ systems and comorbidities that at times warrant a multidisciplinary approach. So in addition to an experienced general pediatrician who coordinates everyday care for these children, we believe that there should be a close cooperation with a team of pediatric specialists (such as pediatric pulmonologists, cardiologists, ENT specialists, and so on), in order to provide the most optimal care for children with DS.

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Table 1. : Recommendations for the care of children with DS and chronic / recurrent respiratory problems

> Refer to / seek advice from a pediatric pulmonologist
> Estimate the need for: o **Airway evaluation**: keep a low threshold for complete airway endoscopy (especially when the patient presents with stridor or chronic noisy breathing). o **Polysomnography**: advise a PSG before the recommended age of 4 in case of heavy breathing / snoring, witnessed apneas, excessive daytime sleepiness or behavioral problems. Perform DISE before airway surgery. o **Evaluation of pulmonary aspiration**: refer the patient to a speech therapist to estimate the risk of dysphagia; keep a low threshold for additional swallow and/or GER studies (even in the absence of indicative symptoms). o **Immunological screening**, but keep in mind that also asymptomatic children with DS can have e.g. leuko- and/or lymphopenia. o **Screening for pulmonary hypertension** in consultation with a pediatric cardiologist since no formal guidelines exist; a cautious proposal would be to perform an annual cardiac ultrasound until school age and further every 5 years (also in the absence of cardiopathie congénitale).
> Check the vaccination status; advise influenza vaccine annually and 23-valent pneumococcal vaccine for patients >2y with chronic cardiac or pulmonary disease
> In case of need for anesthesia, keep in mind the risk of difficult intubation due to tracheal narrowing and/or the possible presence of airway anomalies

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Avoidance of bottles during the establishment of breastfeeds in preterm infants

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Question

Does using bottles interfere with breastfeeding success in preterm infants whose mothers want to breastfeed?

Context

Preterm infants usually start milk feedings through gavage tube. Once they are mature enough to co-ordinate sucking and swallowing (often around 32-34 weeks gestation), they can start sucking feeds. Sucking feeds are gradually increased, starting with once a day, with the number of tube feeds decreasing until the sucking feeds alone provide sufficient nutrition for growth and development. During the transition time, mothers may not always be in the hospital to breastfeed and often expressed breast milk or formula is administered by bottle. There is concern that using bottles may interfere with breastfeeding success, possibly due to a difference in sucking action required for the breast compared to an artificial nipple.

This Cochrane review therefore wanted to assess the effects of the avoidance of bottle feeds during the establishment of breastfeeding on breastfeeding success, and to assess the safety of alternatives to bottle feeds.

Criteria for study selection

The review included studies comparing complete avoidance of bottles with use of bottles for preterm infants (<37 weeks gestation) whose mothers planned to breastfeed. In the group avoiding bottles, alternative feeding strategies could be used for complementing or supplementing breastfeeds including gavage tube, cups, spoon, dropper, finger feeding and others. The primary outcomes of interest were full breastfeeding compared with no or partial breastfeeding, and any breastfeeding (full or partial) compared with no breastfeeding at discharge and at three and six months post discharge.

Summary of the results

Seven studies with a total of 1152 preterm infants were included in this review. Five studies used cup feeding as a supplementary feeding method, one exclusively used gavage tube feeding as an alternative and one used a novel teat which was specifically designed to closely mimic the sucking action of breastfeeding. Most studies were conducted in high-income countries with only two studies conducted in middle-income countries and none in low-income countries.

Avoiding bottles may increase the number of infants who are fully breastfed compared with those who are partially or not breastfed at discharge (bottle feeds: 44 per 100 vs avoiding bottles: 64 per 100 (95% CI*: 52-79); NNTB^: 5 (95% CI: 3-11); 1074 infants, 6 studies, low-certainty evidence) and probably increases any breastfeeding compared to no breastfeeding at discharge (bottle feeds: 79 per 100 vs. avoiding bottles: 88 per 100 (95% CI: 84-92); NNTB: 11 (95% CI: 8-20); 1138 infants, 6 studies, moderate-certainty evidence).

Avoiding bottles probably increases full breastfeeding three months after discharge (bottle feeds: 36 per 100 vs avoiding bottles: 57 per 100 (95% CI: 50-65); NNTB: 5 (95% CI: 4-7); 986 infants, 4 studies, moderate-certainty evidence), and may increase full breastfeeding six months after discharge (bottle feeds: 31 per 100 vs avoiding bottles: 51 per 100 (95% CI: 35-73); NNTB: 7 (95% CI: 4-14); 887 infants, 3 studies, low-certainty evidence). The avoidance of bottle feeds may increase the occurrence of any breastfeeding (partial or full) at both three months after discharge (bottle feeds: 60 per 100 vs avoiding bottles: 78 per 100 (95% CI: 60-100); NNTB: 7 (95% CI: 4-25); 1063 infants, 5 studies, low-certainty evidence) and six months after discharge (bottle feeds: 45 per 100 vs avoiding bottles: 56 per 100 (95% CI: 49-63); NNTB: 9 (95% CI: 6-20); 886 infants, 3 studies, low-certainty evidence).

The study with the specifically designed teat showed no difference in breast feeding outcomes. Therefore, of all strategies avoiding bottles, the cup feeding or exclusively tube feeding strategies are the ones that led to greater breastfeeding success. The latter study was of lower methodological quality reducing the certainty around the possible benefits of the exclusively tube feeding strategy. Adherence to cup feeding was poor in one of the studies which could indicate dissatisfaction with this method by staff or parents (or both). However, the remaining four studies did not report dissatisfaction or low adherence.

There were no other benefits or harms associated with avoiding bottles including for length of hospital stay or episodes of infection per infant (both low-certainty evidence).

Conclusion

Avoiding the use of bottles in preterm infants during the transition to breastfeeding probably increases the extent of any breastfeeding at discharge and may improve breastfeeding success up to six months after discharge.

Implications for practice

At the moment, most of the evidence for increasing breastfeeding success is provided by studies using cup feeding as an additional feeding strategy. Whether using tube feeding exclusively to supplement breastfeeding enhances breastfeeding success, is still uncertain and will need more research. The use of a novel teat more closely mimicking the sucking action of breastfeeding did not result in increased breastfeeding success.

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Access the full text of these reviews via the Cebam Digital Library for Health (www.cebam.be/nl/cdlh or www.cebam.be/fr/cdlh)

* **CI:** confidence interval
^ **NNTB:** number needed to treat for an additional benefit outcome

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(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.[5]

gsk

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. coli*cellen door recombinantDNAtechnologie [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) **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] **• Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden [a] 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 [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 1 van de volledige SPK . De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 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). **Bijzondere waarschuwingen en voorzorgen bij gebruik** Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen . Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfuncties. Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door *Neisseria meningitidis* groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. Dit middel bevat minder dan 1 mmol natrium (23 mg) per dosis, dat wil zeggen dat het in wezen 'natriumvrij' is. Terugvinden herkomst Om het terugvinden van de herkomst van biologicals te verbeteren moeten de naam en het batchnummer van het toegediende product goed geregistreerd worden. **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 B-1000 Brussel Madou Website: www.eenbijwerkingmelden.be e-mail: adr@fagg.be **Luxemburg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy - Hôpitaux de Brabois Rue du Morvan 54 511 Vandoeuvre Les Nancy Cedex Tél.: (+33) 3 83 65 60 85 / 87 e-mail **:** crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments 20, rue de Bitbourg L-1273 Luxembourg-Hamm Tél.: (+352) 2478 5592 e-mail: pharmacovigilance@ms.etat.lu Link pour le formulaire: https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html **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** 07/10/2021 (v12). **AFLEVERINGSWIJZE** Op medisch voorschrift.

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A snapshot on current practices and recent trends on vitamin K prophylaxis in term neonates in Flanders

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Keywords

newborn; infant; vitamin K, vitamin K deficient bleeding, prophylaxis

Abstract

A survey on vitamin K prophylaxis for term newborns with responses from 56/59 Flemish maternities and 17/30 midwifery units that do home deliveries unveiled relevant variability. About 50% of maternities use the intramuscular (1-2 mg), about 50% the oral (1-2 mg) route, with 5 different maintenance doses in breastfed infants. Nine/13 recently (<5 years) changed regimens were a switch from oral to intramuscular. Midwifery units only use oral vitamin K, with 6 different regimens. Both paediatricians and midwives reported personal experience with parental refusal of intramuscular (20/54 and 13/15) or any prophylaxis (11/54 and 16/16) respectively.

Introduction

Vitamin K refers to a group of fat-soluble vitamins important for blood clotting, but also of relevance in bone metabolism, endothelial functions and in regulation of blood calcium. Regarding its role in coagulation, Vitamin K is essential in the carboxylation of immature to mature coagulation factors (including factor II, VII, IX or X, but also protein C and S). In neonates, there is a natural tendency to vitamin K deficiency and low reserves because of poor placental transfer, potentially resulting in vitamin K deficient bleeding (VKDB, "haemorrhagic disease of the newborn"), typically subdivided in *early* (day 1), *classic* (day 2-7) or *late pattern* (2-12 weeks) with intracranial haemorrhage as the most feared event (1). Once the infant is beyond the age of 12 weeks, there is sufficient synthesis driven by the intestinal microflora (1).

Initiation of vitamin K prophylaxis in the 1940ies resulted in a significant decrease in VKDB, with subsequent guidelines and implementation of vitamin K prophylaxis, most commonly based on a single intramuscular dose (1 mg) (2,3). These guidelines were largely based on observational studies, further supported by a limited number of randomized controlled trials. More recently, barriers emerged to vitamin K prophylaxis, mainly related to the association of vitamin K prophylaxis and childhood cancer (including leukaemia, central nervous system, renal, hepatic or bone, soft tissue, germ cell tumour) in two consecutive case-control studies, with a higher odds ratio (1.97, range 1.3-3.0) for the intramuscular route (4). However, in subsequent meta-analyses, these findings were never confirmed (2). Another burden relates to the invasiveness and the associated procedural pain. For the Flemish Association of Paediatrics (Vlaamse Vereniging Kindergeneeskunde, VVK), this setting resulted in two equivalent options in their latest guidance (October 2008) on vitamin K of ***either*** a single 1 mg intramuscular at birth, ***or*** 2 mg oral, followed by a weekly dose of 1-2 mg vitamin K when breastfed until 12 weeks of postnatal age (with specific additional advice in the event of fat malabsorption).

More recently, additional comparative data on the efficacy of oral versus intramuscular administration emerged. Among others, Zurynski recently reported on the Australian Paediatric Surveillance program (1993-2017) (5). During the 'oral' route period (1993-1994), the VKDB rate was significantly higher when compared to the 'intramuscular' route period (1995-2017). As the VVK is preparing an update on the vitamin K guideline, we collected a snapshot on the current practices in the Flemish maternities and in midwifery units that take care of home deliveries.

Methods

Following ethical approval of the survey by KU Leuven (MP016741, 10-12-2020), and with the logistic support of the VVK secretary in the GDPR setting (General Data Protection Regulation), an online questionnaire was repeatedly circulated (February-March 2021) to all heads of the relevant departments (paediatrics, neonatology), with an additional search on midwifery units. The questionnaire was focused on the current practices on vitamin K prophylaxis in term cases and on recent changes in practices, and also collected information on experiences with parental refusal.

Results

Responses were received from 56/59 maternities (complete responses in 54), so that we attained a very high response rate (95 %), and from 17 midwife units (on about 30 contacted, response rate 57 %). Table 1 and Table 2 summarize the findings for the maternity wards involved for breastfeeding and formula feeding respectively.

The diversity in dosing regimens did not differ between hospitals with or without neonatal intensive care unit.

Interestingly, 13/54 maternities indicated that their policy has been adapted in the last 5 years. In 9/13, there was a switch from oral to the intramuscular route, while the other 4 adaptations related to changes in dosing regimen. Finally, the 17 responses from midwifery units for breastfed infants are summarized in Table 3. Related to formula fed infants, 2 mg was used in 11 units, 1 mg in 1 unit (+ 3 units, preference of the parents and 2 units not relevant, as formula feeding also never occurs). It is hereby worth to stress that none of these units uses the intramuscular route.

Reports on parental refusal were based on personal experience of the paediatrician or midwife. Experiences with refusal of intramuscular administration or any prophylaxis were reported by 20/54 and 11/54 paediatricians respectively. For midwives, this was reported by 13/15 (intramuscular) and 16/16 (any) respectively. Related to this problem, paediatricians rather focused on the efficacy of the prophylaxis and highly value an updated vitamin K guideline, while midwives focused more on the parental preference and their informed choice to select the administration route.

Discussion

In essence, this snapshot on current practices on vitamin K prophylaxis in term neonates born in Flanders provides a contemporary and reliable overview on the diversity in practices just before the VVK guideline is updated. In our personal opinion, this does provide some key findings, as summarized.

1. Irrespective of how this update will turn out, the current practices are diverse, so that the short hospital stay and the resulting multidisciplinary, multi-unit perinatal care necessitates good coordination and communication. Consequently, a uniform approach could be beneficial to avoid uncertainties or errors resulting in substandard prophylaxis.
2. There are significant differences in practices and opinions between paediatricians and midwifes. Based on the Study centre Perinatal Epidemiology report, the number of home births is rather limited (0.6%), but there is still value to stimulate interaction between both groups (6). Furthermore, independent midwifes are involved in postnatal follow-up at home of both mothers and infants following delivery, either or not after short hospital stay.
3. We suggest that the updated guideline should also contain some guidance, a statement or reflection on how to handle parental preferences and refusal, balancing the benefits of uniformity (within a given organization) to the value of parental preferences and shared decision making.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

We are grateful to the VVK for their secretarial support, and are even more grateful to all responders, as the value of a survey largely depends on the response rate. This paper is a summary of a master thesis youth health care, and this pdf document is available upon request to the corresponding author.

Tables and table legends

Table 1: Dosing regimens used in Flemish maternity wards for breastfed term infants.

route	maternities (n=54)	dosing regimen used	maternities (n= 54)
Intramuscular	29 (54%)	1 mg IM, at birth	28 (52%)
		2 mg IM, at birth	1 (2%)
Oral	25 (46%)	2 mg oral, at birth maintenance, 1-2 mg, weekly	14 (26%)
		1 mg oral, at birth maintenance, 150 µg, daily	6 (11%)
		2 mg oral , at birth maintenance, 25 µg, daily	3 (6%)
		2 mg oral, at birth maintenance, 150 µg, daily	1 (2%)
		2 mg oral, at birth maintenance, unknown	1 (2%)
		2 mg oral, at birth 2 mg oral, day 4-6 and 4-6 weeks	0 (0%)

Table 2: Dosing regimens used in Flemish maternity wards for formula fed term infants.

route	maternities (n=54)	dosing regimen used	maternities (n= 54)
Intramuscular	30 (56%)	1 mg IM, at birth	29 (54%)
		2 mg IM, at birth	1 (2%)
Oral	24 (44%)	2 mg oral, at birth	23 (43%)
		1 mg oral, at birth	1 (2%)

Table 3: Overview of the dosing regimen used in midwifery units for breastfed infants.

	number of units (n=17)	
2 mg oral, maintenance 1-2 mg weekly until 3 months	4	(24%)
3 x 2 mg oral (at birth, on day 4-7 and week 4-6)	4	(24%)
1 mg oral, maintenance 150 µg daily until 3 months	1	(6%)
5 x 2 mg oral (at birth, on day 7 and subsequently monthly)	1	(6%)
2 mg oral (at birth, once)	2	(12%)
based on the preference of the parents, following informed consent	5	(29%)

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Neuroprotective strategies of neonatal encephalopathy in low-resource settings

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Keywords

Infant, Asphyxia Neonatorum, Encephalopathy, Hypothermia, Developing Countries

Abstract

Objective: Perinatal asphyxia followed by hypoxic ischemic encephalopathy is a major contributor to neonatal death. In high-income countries therapeutic hypothermia is the standard of care. However, safety and efficacy of cooling have not been proven in low- and middle income countries, who bear most of the burden of neonatal encephalopathy. This article reviews the entry criteria of cooling in developing countries and the feasibility, safety and efficacy of different low-cost cooling techniques. Furthermore, we discuss whether other neuroprotective therapies could be used.

Methods: We searched in PubMed and other databases for studies regarding entry criteria, low-cost cooling techniques and other neuroprotective therapies for neonatal encephalopathy in low- and middle income countries.

Results: A 5-minute Apgar score less than six and a Thompson score more than six are useful entry criteria for cooling in low-resource settings. Effective cooling was feasible with different low-cost cooling techniques, but a servo-controlled device maintained the most stable temperature profile and seems to be the most safe and easiest to use device. Only a few studies were powered to assess efficacy. None of the studies could show a significant decrease in mortality rate. When the rate of death and developmental delay were combined, they could notice a significant decrease in the hypothermia group. A promising drug to provide neuroprotection in low-resource settings is 2-iminobiotin.

Conclusions: To assess safety and efficacy of therapeutic hypothermia and other neuroprotective drugs in low-resource settings we need more adequately powered clinical trials.

Introduction

Globally, progress has been made in reducing under-five mortality, but the decline in neonatal mortality stays much more behind (1). One of the major causes of neonatal death is perinatal asphyxia followed by hypoxic ischemic encephalopathy (HIE) (2). Therapeutic hypothermia reduces mortality and neurodevelopmental disability after neonatal encephalopathy and is now widely used as standard treatment in high income countries (HIC) (3-5). It is still unknown if cooling would also benefit neonates in low- and middle income countries (LMIC), where the burden of neonatal encephalopathy is about ten times higher (6,7). A systematic review of Pauliah et al. could not show the same significant reduction in neonatal mortality in LMIC as seen in HIC (8). This absence of treatment effect may be due to heterogeneity and poor design of the included studies, inefficiency of low-cost cooling techniques, lack of adequate neonatal intensive care or differences in study populations.

It is therefore important to investigate these different possibilities. Firstly, we identified which entry criteria for hypothermia could be useful in low resource settings. Secondly, we will summarize which low-cost cooling techniques do exist, whether it is feasible to provide accurate cooling with these techniques and whether they are safe and effective. Furthermore, it is also of interest whether other neuroprotective therapies could be used in LMIC. Last, it must be said that prevention still remains the key stone in perinatal asphyxia.

Materials and methods

We searched for relevant literature in medical databases PubMed, Embase, Cochrane and Trip Database. We used the following search terms: infant, newborn, neonate, hypoxia-ischemia, encephalopathy, hypothermia, developing countries, low- and middle income countries. We analysed the literature published before February 2021 and selected relevant literature based on title and abstract. In addition, we searched in the reference list of the selected articles to identify other possible relevant studies. We used the following inclusion criteria: (1) patients are term or near-term infants with perinatal asphyxia followed by HIE born in LMIC (2) intervention with hypothermia (3) outcomes regarding feasibility, adverse effects and/or mortality. A second type of literature that was searched for were articles regarding possible entry criteria for initiation of hypothermia in low-income countries. Thirdly, we searched for relevant literature regarding neuroprotective therapies other than hypothermia.

Results

Literature search

A total of thirteen studies were selected after applying our inclusion criteria. In addition, we included one thesis research. Characteristics of the included studies are shown in Table 1 (9-22).

Entry criteria in LMIC

Perinatal asphyxia and subsequently the presence of encephalopathy are evaluated to see if infants are eligible for hypothermia. Perinatal asphyxia is mostly defined by a 5-minute Apgar score less than six or the need for ventilation for at least ten minutes. To assess neonatal encephalopathy the Thompson score (Table 2) is more usable in developing countries compared to the Sarnat grading system (Table 3) (23-24). It is a quick and simple clinical grading method that requires no comprehensive training and no specific equipment. A study from Horn et al. showed that a Thompson score of more than six is a sensitive predictor of an abnormal 6-hour aEEG (amplitude integrated electroencephalography) or a moderate-severe encephalopathy (25). Biselele et al. stated that the timing of scoring is also important because it changes during the first six hours after birth. They concluded that more newborns will be eligible for hypothermia if Thompson scoring is done within the first three hours (26).

Secondly, it is of great importance to initiate cooling within six hours of birth. In low-resource settings this time frame may have been passed before hypothermia could be started (27). A study in Congo showed that more than

Table 1: Characteristics of the included studies.

Author, year	Country	Sample size	Cooling method	Inclusion criteria	Exclusion criteria
Robertson et al., 2008 (9)	Uganda (LIC)	21 HT 15 ST	Water bottles	- Gestational age ±37 weeks - 5 min Apgar <6 and/or need for resuscitation - Encephalopathy: Thompson score >5	- Apnea or cyanosis - Absent cardiac output >10 min after birth - Birthweight <2kg
Thomas et al., 2011 (10)	India (LMIC)	20	Ice packs	- Gestational age ±35 weeks - 5 min Apgar ≤5, need for ventilation ±10 min or perinatal predisposition to perinatal asphyxia and cord or postnatal blood gas pH <7 or base deficit ±12 - Encephalopathy (modified Sarnat criteria)	- Small for gestational age - Chromosomal or major congenital anomaly - Severely asphyxiated infants
Bharadwaj et al., 2012 (11)	India (LMIC)	62 HT 62 ST	Ice packs	- Gestational age >37 weeks - 10 min Apgar ≤6, need for ventilation ±10 min, fetal distress, organ dysfunction, history of acute perinatal event and arterial blood gas pH ≤7 or base deficit ±12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth - Outborn
Joy et al., 2013 (12)	India (LMIC)	58 HT 58 ST	Ice packs	- Gestational age ±37 weeks - 10 min Apgar ≤5, need for ventilation ±10 min, fetal distress, organ dysfunction, history of acute perinatal event and cord of peripheral blood gas pH ≤7 or base deficit ±12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth - Outborn
Gane et al., 2014 (13)	India (LMIC)	60 HT 60 ST	Ice packs	- Gestational age ±37 weeks - 10 min Apgar ≤5, need for ventilation ±10 min, fetal distress, organ dysfunction and cord of arterial blood gas pH ≤7 or base deficit ±16 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth
Thayyil et al., 2013 (14)	India (LMIC)	33	Phase changing materials	- 5 min Apgar <6 - Encephalopathy: Thompson score >5	
Thomas et al., 2015 (15)	India (LMIC)	41	Phase changing materials	- Gestational age >35 weeks - 5 min Apgar <5, need for ventilation >10 min, cord or postnatal blood gas pH <7 or base deficit >12 - Moderate or severe encephalopathy (modified Sarnat criteria)	
Thomas et al, 2018 (16)	India (LMIC)	103	Phase changing materials	- Gestational age ±35 weeks - Birth weight ±1800 grams - 5 min Apgar <5, need for resuscitation >10 min or cord blood pH <7.0 or base deficit >12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Chromosomal disorder - Major congenital anomaly
Prashantha et al., 2018 (17)	India (LMIC)	33 PCM 29 IP	Phase changing materials and ice packs	- Gestational age ±35 weeks - Birth weight > 1800 grams - 5 min Apgar ≤5, need for ventilation ±10 min or pH ≤7 or base deficit ±12, - Moderate or severe encephalopathy (modified Sarnat criteria)	
Catherine et al., 2021 (18)	India (LMIC)	78 HT 84 ST	Phase changing materials	- Term infants - 10 min Apgar ≤6, need for ventilation ±10 min, fetal distress or organ dysfunction and cord blood pH ≤7 or base deficit ±12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth
Biselele et al., 2014 (19)	DR Congo (LIC)	12	Servo-controlled device	- Gestational age ±36 weeks - 5 min Apgar ≤5 or need for ventilation ±10 min - Encephalopathy: Thompson score ±7	- Congenital malformations - Birth weight < 2000 grams - Symptomatic infection
Oliveira et al., 2018 (20)	India (LMIC)	82	Servo-controlled device	- Birth weight ±1800 grams - Requirement of resuscitation at birth - Moderate or severe encephalopathy (modified Sarnat criteria)	- Born in moribund conditions - Major life-threatening congenital malformations
Enweronu et al., 2019 (21)	Ghana (LMIC)	13	Passive cooling	- Gestational age ±36 weeks - Birth weight ±2000 grams - Postnatal age <24h - 5 min Apgar <6 and need for resuscitation - Encephalopathy: Thompson score ±7 or suspected clinical seizures	- Infants in whom death was felt imminent and infants with major congenital malformations were excluded
Bhat et al., 2006 (22)	India (LMIC)	20 HT 15 ST	Not described	- Severe perinatal asphyxia	

LIC: low income country, LMIC: lower-middle income country, HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs

40% of infants with HIE were inborn or reached the hospital within 6 hours to receive neuroprotective treatment (28). The mean time until admission to the neonatal unit was 1.3±0.2h for the inborn neonates and 2.5±0.3h for the outborn neonates. Thomas et al. reported cooling of inborn and outborn neonates starting at a mean time of respectively 3±1h and 3.5±1h after birth (10). In four other included studies, cooling was started at a mean age of 3.6h, 3.2h, 3.7h and 3.9h (11,13,19,20).

Exclusion criteria are listed in Table 1. Only one study excluded infants with a symptomatic infection (19). It remains unwritten whether a very high Thompson score could be used as an exclusion item. Biselele et al. reported that all neonates with Thompson score of more than 15 died (28). In a study of Horn et al. 75% of the infants with this score died within the first days or had a severely aberrant aEEG (25).

Feasibility of low-cost cooling methods

Different low-cost cooling devices are used for therapeutic hypothermia in studies of LMIC (Figure 1). Feasibility outcomes of the included studies are listed in Table 4.

1. Passive cooling

Passive cooling is a physiological response seen in infants with neonatal encephalopathy and was recently investigated in a Ghanaian study (29,21). Core temperatures between 33-34°C were only maintained in 18±14% of the time during 72h (21). In 71±22% of the time they recorded temperatures above 34°C and excessive cooling with temperatures less than 33°C was seen 11±18% of the time.

2. Water bottles

A feasibility study in Uganda by Robertson et al. used a mattress made of three water bottles filled with cool tap water (25-26°C) (9). To maintain the core temperature between 33-34°C they added or removed sheets, blankets or water bottles. With this simple and inexpensive method (US$10) infants underwent whole-body cooling during 72h. In comparison they also documented to what degree infants with neonatal encephalopathy cool passively. The mean rectal temperature was 33.6±0.69°C in the infants cooled with water bottles and 36.3±0.64°C in the passively cooled infants. Close nursing monitoring was required and water bottles needed to be changed every 8-12h.

3. Ice packs

Two feasibility studies in India worked with cloth covered ice gel packs to achieve hypothermia (10,11). Gel packs were placed over the back, head, abdomen and axillae and could be added or removed when the rectal temperature changed. The packs were obtained from an immunization clinic at no added cost and could be reused. The mean time taken to reach the target temperature was 52±25 minutes in Thomas et al. and 120 min in Bharadwaj et al. During cooling they registered a mean rectal temperature of respectively 32.9±0.11°C and 33.7±1.02°C. The study of Gane et al. also used ice packs and temperature fluctuation above and under 33.5°C was 0.8°C (13). On an average, this technique required four gel packs per infant and packs had to be changed every 3-4h. Furthermore, one nurse was needed for three infants.

4. Phase changing materials (PCM)

Four of the included studies involved the feasibility of whole-body cooling using phase changing materials. When an infant lies on a bed made of PCM, heat is absorbed from the infant and transferred to the materials until it reaches its melting point. A bed made of PCM approximately costs 40 euros and can be reused for at least twenty infants. With this method two studies of Thomas et al. reached the target temperature in 60 and 90 minutes (15,16). The mean rectal temperature during 72h of cooling was 33.44±0.26°C in the study of 2015 and 33.5±0.39°C in the one of 2018. The target temperature was maintained 96.2% and 89.2% of the time, respectively. In Thayyil et al. the median time to reach the target temperature was 30 minutes and mean rectal temperature was 33.5±0.3°C (14). Prashantha et al. compared PCM with ice packs and documented a median time to reach the target temperature of respectively 30 and 35 minutes and a mean core temperature of 33.47±0.33°C and 33.44±0.34°C (17). This technique did not require frequent changes, but nurses still needed to intensively monitor the temperature.

5. Servo-controlled devices

In an Indian study by Oliveira et al. they used a simplified servo-controlled device based on a model used in high-income countries to provide whole-body cooling (20). The cooling device was set at a target temperature of 33,5°C. By simplifying the design costs could be reduced to approximately US$1000. A temperature between 33-34°C was reached after 102 minutes and could be maintained in 95% of the time. Mean core temperature was 33.4±0.2°C. In the Democratic Republic of Congo Biselele et al. used refrigerated gel bags or neofan in combination with a servo-controlled radiant warmer (19). It took 62 minutes to reach a temperature of 33-34°C. The mean core temperature during 72h was 33.76±0.28°C. A servo-controlled device omits the need for manual adjustments, but nurses still need to closely monitor the temperature.

Adverse events

In addition to the feasibility of low-cost cooling devices, we also need to consider their safety. The reported adverse events including their proportions are summarized in Table 5. The most frequent adverse events were thrombocytopenia, sinus bradycardia, coagulopathy, sepsis, shock/hypotension, hypoglycemia and skin changes. The percentage of skin changes was higher when using ice packs as compared to using PCM (17). Only a few of the included studies had a control arm to compare adverse events between therapeutic hypothermia and standard therapy in LMIC. Robertson et al. documented more seizures in the hypothermia group, but seizures cannot be attributed as a complication of cooling (9). Of the 33 infants participating in the study of Thayyil et al. 3 of the cooled infants developed sepsis, but no one in the control arm did (14). When comparing ice gel packs with standard care Bharadwaj et al. and Joy et al. did not find significant differences in adverse events (11-12).

Table 2: Thompson score.

	0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
Level of consciousness	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	None	< 3/day	>2/day	
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± bites	
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)
Fontanel	Normal	Full, not tense	Tense	

Table 3: Sarnat grading system.

	Stage 1 (mild)	Stage 2 (moderate)	Stage 3 (severe)
Level of consciousness	Hyperalert	Lethargic/obtunded	Stuporous
Muscular tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch	Overactive	Overactive	Decreased/absent
Segmental myoclonus	Present	Present	Absent
Suck	Weak	Weak/absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak/absent
Tonic neck	Slight	Strong	Absent
Pupils	Mydriasis	Miosis	Variable
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial/salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/decreased	Increased/diarrhea	Variable
Seizures	None	Common/focal or multifocal	Uncommon
EEG	Normal/decreased	Early low voltage continuous delta and theta, later periodic, seizures focal 1-1.5 Hz spike-wave	Early periodic pattern with isopotential phases, later isopotential
Duration	<24 h	2-14 days	Hours-weeks

Table 4: Feasibility outcomes of the included studies.

Author, year	Cooling method	Mean age at start	Mean time to reach target T°	Mean rectal T°	Maintaining target T° during 72h
Robertson et al., 2008 (9)	Water bottles			33,6±0.69°C (HT) 36,3±0.64°C (ST)	
Thomas et al., 2011 (10)	Ice packs	3.4h	52 min	32.9±0.11°C	
Bharadwaj et al., 2012 (11)	Ice packs	3.6h	120 min	33.7±1.02°C	
Gane et al., 2014 (13)	Ice packs	3.2h		33.5±0.8°C	
Thayyil et al., 2013 (14)	Phase changing materials		30 min	33.5±0.3°C (HT) 36.4±0.5°C (ST)	
Thomas et al., 2015 (15)	Phase changing materials		60 min	33.44±0.26°C	96.2%
Thomas et al, 2018 (16)	Phase changing materials		90 min	33.5±0.39°C	89.2%
Prashantha et al., 2018 (17)	Phase changing materials and ice packs		30 min (PCM) 35 min (IP)	33.47±0,33°C (PCM) 33.44±0.34°C (IP)	
Biselele et al., 2014 (19)	Servo-controlled device	3.9h	62 min	33.76±0.28°C	
Oliveira et al., 2018 (20)	Servo-controlled device	3.7h	102 min	33.4±0.2°C	95%
Enweronu et al., 2019 (21)	Passive cooling			35.0±1.0°C	18±14%

T°: temperature, HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs

Mortality and developmental delay

The mortality rate and neurological outcomes documented in our studies are listed in Table 6. Only three of the included studies had an adequate sample size and a control arm to evaluate the efficacy of therapeutic hypothermia in LMIC (11,12,18). The mortality rate in all of the three studies was lower in the hypothermia group compared to the group with standard care, but none of the results were significant. In the studies of Bharadway et al. and Joy et al. neurological status at discharge was significantly better in the hypothermia group (11-12). Catherine et al. also showed a small but not significant reduction in neurological abnormality (18).

Neurodevelopmental assessment at 6, 12 and 18 months was done by respectively Bharadwaj et al., Gane et al. and Catherine et al. (Table 7) (11,13,18). They could all show significantly less neurological abnormality in the hypothermia group. The number of deaths at follow-up was again lower, but not significant, when infants were cooled. When they combined the rate of death and neurological outcome at 12 months of age Gane et al. noticed a significant decrease that favours cooling (95% CI 0.18-0.68) (13). When the studies of Bharadwaj et al. and Catherine et al. combined their results there were also significantly more survivors without neurological abnormality at discharge (95% CI 1.18-1.88) and at 6-18 months (95% CI 1.17-1.60) when infants were cooled in comparison with standard care (18).

Other neuroprotective therapies

The neuroprotective effect of various drug therapies has been investigated in in-vitro and animal models as well as clinical trials (30-32). Suggested drugs like xenon and erythropoietin are not affordable in LMIC. Xenon, erythropoietin, magnesium and allopurinol are also given on top of hypothermia, making them no better option for use in LMIC. More promising drugs are melatonin and 2-iminobiotin. The neuroprotective effect of melatonin has been documented

Table 5: Adverse effects reported in the included studies.

Author, year	*Cooling method*	*Adverse events*
Robertson et al., 2008 (9)	Water bottles	- seizures (28% HT, 13% ST)
Thomas et al., 2011 (10)	Ice packs	- thrombocytopenia (25%) - sinus bradycardia (25%) - deranged bleeding parameters (20%) - aposteatonecrosis (15%) - hyperglycemia (15%) - hypoglycemia (10%) - hypoxemia (5%) - life-threatening coagulopathy (5%) - many of the infants shivered
Bharadwaj et al., 2012 (11)	Ice packs	- thrombocytopenia (12.9% HT, 8.06% ST) - sepsis (11.3% HT, 9.7% ST) - pneumonia (9.7% HT, 17.2% ST) - hypoglycemia (9.6% HT, 12.9% ST) - shock (8.1% HT, 14.5% ST) - hypocalcemia (6.45% HT, 12.9% ST) - bleeding (6.45% HT, 4.8% ST) - skin changes (6.45% HT, 0 ST) - pulmonary haemorrhage and hypertension (1.6% HT, 4.8% ST) - acute renal failure (1.6% HT, 3.2% ST) - necrotizing enterocolitis (1.6% HT, 1.6% ST) - arrhythmia (1.6% HT, 0 ST)
Joy et al., 2013 (12)	Ice packs	- shock (12.06% HT, 13.79% ST) - hypoglycemia (10.34% HT, 13.79% ST) - bleeding (6.89% HT, 8.62% ST) - bradycardia (3.45% HT, 0 ST)
Thayyil et al., 2013 (14)	Phase changing materials	- sepsis (18% HT, 0 ST) - seizures (47% HT, 44% ST)
Thomas et al., 2015 (15)	Phase changing materials	- subcutaneous fat necrosis (2.4%)
Thomas et al, 2018 (16)	Phase changing materials	- coagulopathy (21.4%) - sepsis (20.4%) - shock/hypotension (18%) - thrombocytopenia (10.7%) - hyperglycemia (8.7%) - hyponatremia, hyperkalemia (5.8%) - hypoglycemia (6.8%) - persistent pulmonary hypertension (4.9%) - subcutaneous fat necrosis (2.9%) - bleeding (1.9%) - leukopenia (1.9%) - arrythmia (1.9%) - acute kidney injury (1%)
Prashantha et al., 2018 (17)	Phase changing materials and ice packs	- thrombocytopenia (51.5% PCM, 51.7% IP) - shock (45.4% PCM, 48.2% IP) - seizures (42.4% PCM, 58.6% IP) - bradycardia (33.3% PCM, 31% IP) - coagulopathy (33.3% PCM, 27.5% IP) - hyponatremia (27.3% PCM, 34.4% IP) - hypoglycemia (24.4% PCM, 37.9% IP) - hyperbilirubinemia (21.2% PCM, 13.7% IP) - hypocalcemia (15% PCM, 6.9% IP) - anemia (12.1% PCM, 24% IP) - hyperglycemia (12.1% PCM, 24% IP) - acute kidney injury (12.1% PCM, 10.3% IP) - persistent pulmonary hypertension (9.1% PCM, 6.9% IP) - bleeding (9% PCM, 13.7% IP) - skin changes (6% PCM, 20.6% IP) - sepsis (0 PCM, 6.9% IP) - cardiac arrhythmia (0 PCM, 3.4% IP) - gangrene of the hand (0 PCM, 3.4% IP)
Biselele et al., 2014 (19)	Servo-controlled device	- shivering (16.7%) - subcutaneous fat necrosis (8.3%)
Oliveira et al., 2018 (20)	Servo-controlled device	- thrombocytopenia (64%) - gastric bleeds (51%) - persistent pulmonary hypertension (14%) - metabolic acidosis (13%) - pulmonary bleeds (12%) - hypoglycemia (1.2%)

HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs

in a few animal studies (33-35). One small clinical trial investigated oral administration of melatonin without additional hypothermia after asphyxia and showed promising results (36). Neuroprotective effects of 2-iminobiotin have also been shown in animal models (37-38). Currently, a Congolese trial is investigating the safety as well as the efficacy of 2-iminobiotin in neonates with moderate to severe perinatal asphyxia born in Kinshasa (39). To date, they could not attribute any of the adverse events to the administration of 2-iminobiotin (40).

Discussion

Perinatal asphyxia followed by hypoxic ischemic encephalopathy is a major contributor to neonatal death (1,2). In high-income countries therapeutic hypothermia has become the standard treatment for HIE, however in low- and middle income countries efficacy and safety of hypothermia have not been proven (8). Since most of the burden of neonatal encephalopathy occurs in LMIC, it is essential to further investigate neuroprotective treatments in low-resource settings.

Entry criteria in LMIC

Before initiation of cooling, inclusion and exclusion criteria in low-resource settings have to be considered. A low Apgar score, requirement for resuscitation and a Thompson score of more than six are useful criteria for inclusion. Whether a very high Thompson score could also be used as an exclusion item remains in discussion. In these circumstances it could be better to discuss the poor prognosis with the parents and to only offer maximal comfort therapy. Perinatal infection is another exclusion criterion which requires some thought. Infections can increase brain vulnerability to hypoxic-ischemic insult and cooling in the presence of it might even be more harmful (41-43). Lastly, hypothermia needs to be started within 6 hours after birth. Lack of proper transportation facilities in LMIC can be a hazard for this entry criterion as well as delays in healthcare provision in the hospital itself. A study in Congo, which has the most daunting infrastructure on the African continent, provided these data and showed that more than 40% of infants with HIE were inborn or reached the hospital within 6 hours to receive neuroprotective treatment (28).

Feasibility of low-cost cooling methods

To provide hypothermia the included studies used passive cooling, water bottles, ice packs, phase changing materials and servo-controlled devices. In order to be effective, the target temperature between 33-34°C must be quickly reached and maintained during the next 72 hours. Wide fluctuations in temperature not only increase the risk of complications when the temperature drops below 33°C, but also compromise the degree of neuroprotection when the temperature rises above 34°C (44). The median time to reach 33-34°C ranged from 30 to 120 minutes. The most stable temperature profile could be maintained by the servo-controlled devices and PCM. With PCM however ambient temperatures below 28°C and intensive nursing are required (14). Cooling using water bottles and ice packs also requires a high nursing input and moreover frequent changing to ensure temperature is maintained within target range. However, most of the neonatal units in LMIC have a shortage of adequate nursing resources which makes it hard to achieve tight temperature control (45). This may offset the cost benefit of an inexpensive cooling method because of the negative consequences of wide temperature fluctuations. Close monitoring of the temperature is also needed with a servo-controlled device, but it is the only device that omits the need for manual adjustments which makes it less labour-intensive. Although it's more expensive (US$1000) compared to the other cooling methods, it seems to be the most safe and easiest to use device in LMIC.

Safety and efficacy

It's hard to draw conclusions about the safety and efficacy in reducing mortality or neurodevelopmental delay of each device, since most of the studies were not powered for this. Overall, the adverse events documented in our included studies were in concordance with studies from HIC (46-49). However caution must be paid when using ice packs because they seem to increase the risk of skin injuries. Shivering was also seen in a few of our studies which could be caused by undersedation or the method of cooling (10). Regarding the efficacy, none of the studies could show a significant decrease in mortality rate. But when the rate of death and developmental delay were combined, three adequately powered studies could notice a significant decrease in the hypothermia group compared to the normothermia group (11,13,18). However developmental scoring in two studies was done at 6-12 months old and may not describe the permanent neurological outcome (11,13). The lack of follow up is a limitation in all of the studies, except for the study of Catherine et al. In the study of Robertson et al. more infants in the cooling group died (9). Two deaths could be caused by infection according to the author. But maybe death was rather due to the severity of the encephalopathy, since all of the seven infants with Sarnat stage III died and six of them were randomized in the hypothermia group.

We urgently need more adequately powered clinical trials to assess whether hypothermia is also beneficial in LMIC. A large trial in India who enrolled 408 neonates with moderate or severe neonatal encephalopathy is currently on his way. It will compare neonates who are randomly allocated to the cooling group using a servo-controlled device or to the standard care group. This study will be powered to examine whether whole body cooling in LMIC can reduce death or neurodisability at 18 months (50).

Other neuroprotective therapies

It is also of interest whether other neuroprotective therapies might result in better outcomes in LMIC because of easier use and less risk of complications. Promising drugs are melatonin and 2-iminobiotin. Melatonin itself is cost-effective and has a good safety profile. Unfortunately, the available intravenous formulation contains ethanol which is not acceptable for neonatal administration. 2-Iminobiotin, a vitamin B7 analogue, is a non-expensive and safe drug that can be easily administered intravenously and stored in higher temperatures. The efficacy of iminobiotin in comparison to standard care is currently investigated in a Congolese study (39). A follow-up study is also planned to evaluate the neurological development in the first 2 years after birth. This cheap, safe and easily administered alternative to hypothermia could be a possible breakthrough in low-resource settings.

Development of potential neuroprotective treatments could be speed up when HIC and LMIC collaborate (27). Tagin et al. discussed the strong potential for complementary contributions between HIC and LMIC. Developed countries have the established expertise in performing medical studies and developing countries have the higher incidence of neonatal encephalopathy.

A broader perspective

It may be wrong to apply cooling without improving prenatal care, obstetrics, monitoring, resuscitation and respiratory management (51). Prenatally, chronic insults like malnutrition and intra-uterine growth restriction may contribute to the higher incidence of perinatal asphyxia (52). Improving prenatal follow-up, nutritional behavior and treatment of underlying diseases are therefore essential, as well as adequate management protocols and qualified personnel during labor. After birth, adequate intensive care support including proper monitoring, mechanical ventilation, sedation and oxygen-use is needed (27). Scaling up quality of obstetric and neonatal care may result in an even greater reduction in asphyxia-related mortality and morbidity (53).

Conclusion

There is a growing body of evidence that providing therapeutic hypothermia to infants with neonatal encephalopathy is feasible using low-cost cooling methods in developing countries. Adequately powered clinical trials are needed to assess whether these cooling methods are also safe and effective in reducing mortality and morbidity. Future studies should also investigate whether neuroprotective drugs, like 2-iminobiotin, might result in better outcomes in low-resource settings. But efforts should also be made in developing preventive strategies and strengthening obstetrics and neonatal care. Developments in the prevention as well as the treatment of neonatal encephalopathy could make a great contribution in achieving the 2030 sustainable developmental goal 3.

Table 6: Outcome at discharge: deaths and neurological abnormality

Author, year	Cooling method	Sample size	Mortality rate	Neurological abnormality
Robertson et al., 2008 (9)	Water bottles	21 HT 15 ST	33,3% in the HT group 6,7% in the ST group	
Thomas et al., 2011 (10)	Ice packs	20	5%	
Bharadwaj et al., 2012 (11)	Ice packs	62 HT 62 ST	4,8% in the HT group 9,7% in the ST group (95% CI 0.13-1.91)	16.1% in the HT group 40.3% in the ST group (95% CI 0.21-0.76)
Joy et al., 2013 (12)	Ice packs	58 HT 58 ST	1.7% in the HT group 6.9% in the ST group (p value 0.17)	36.8% in the HT group 79.4% in the ST group (p value <0.001)
Thayyil et al., 2013 (14)	Phase changing materials	33	24% in the HT group 13% in the ST group	
Thomas et al., 2015 (15)	Phase changing materials	41	Not reported	
Thomas et al, 2018 (16)	Phase changing materials	103	6.8%	
Prashantha et al., 2018 (17)	Phase changing materials and ice packs	33 PCM 29 IP	3.2%	
Catherine et al., 2021 (18)	Phase changing materials	78 HT 84 ST	28,2% in the HT group 34.5% in the ST group (95% CI 0.52-1.29)	33.3% in the HT group 35.7% in the ST group (95% CI 0.61-1.43)
Biselele et al., 2014 (19)	Servo-controlled device	12	16.7%	
Oliveira et al., 2018 (20)	Servo-controlled device	82	18%	
Enweronu et al., 2019 (21)	Passive cooling	13	23%	
Bhat et al., 2006 (22)	Not described	20 HT 15 ST	15% in the HT group 33% in the ST group (p value >0.05)	HT group < ST group (p value <0.001)

HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs, CI: confidence interval

Table 7: Outcome at follow up: deaths and neurological abnormality

Author, year	Cooling method	Age at follow-up	Sample size	Mortality rate	Neurological abnormality
Bharadwaj et al., 2012 (11)	Ice packs	6 months	57 HT 59 ST	5.3% in the HT group 10.2% in the ST group (95% CI 0.14-1.97	3.5% in the HT group 20.3% in the ST group (95% CI 0.04-0.74)
Gane et al., 2014 (13)	Ice packs	12 months	53 HT 50 ST	7% in the HT group 13.8% in the ST group (95% CI 0.16-1.59)	9.4% in the HT group 36% in the ST group (95% CI 0.10-0.65)
Catherine et al., 2021 (18)	Phase changing materials	18 months	76 HT 79 ST	28.9% in the HT group 36.7% in the ST group (95% CI 0.50-1.24)	6.6% in the HT group 21.5% in the ST group (95% CI 0.12-0.79)

HT: hypothermia, ST: standard therapy, CI: confidence interval

Figure 1 : *Figure 1: Low-cost cooling devices. (a) Water bottles. (b) Ice packs. (c) Phase changing materials. (d) Servo-controlled devices. Reproduced with permission of Thayyil Sudhin and Thomas Niranjan (20,45).*

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Editorial Policy

Aims and scope

The Belgian Journal of Paediatrics (BJP) is the Official Journal of the Belgian Society of Paediatrics.

The Belgian Journal of Paediatrics publishes peer reviewed original articles, review articles, short communications and case reports on all aspects of paediatrics. In addition, all official reports of the Belgian Academy of Paediatrics are published in the journal.

The Belgian Journal of Paediatrics aims to connect all Belgian paediatricians with stimulating, scientifically sound, peer-reviewed articles.

The Journal is published quarterly. The journal is available in a printed version and electronic version. The electronic version is accessible through the website of the Belgian Society of Paediatrics at https://bvk-sbp.be/bjp.php .

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AC: *La zone de protection de l'eau minérale de Spa s'étend sur plus de 13 000 hectares. A l'intérieur de ce périmètre, il n'y a aucune activité industrielle, pas d'agriculture, pas de pesticides afin de garantir une très grande pureté des eaux. Depuis la source jusqu'à la bouteille, l'eau reste en circuit fermé et ne voit pas la lumière du jour. Tous les matériaux en contact avec l'eau, conduites ou emballages, sont très régulièrement testés et analysés pour garantir leur caractère inerte et non polluant. Les emballages garantissent également une qualité de l'eau et une pureté préservée. Un suivi continu des lignes de production est assuré. Toutes ces procédures et ces contrôles, permettent d'offrir et de garantir une eau de grande qualité et d'une pureté irréprochable.*

DES ANALYSES QUOTIDIENNES ASSURÉES PAR UN LABORATOIRE AGRÉÉ

AC: *L'eau de Spa respecte en tous points les exigences de la réglementation européenne en la matière. Ainsi, l'eau est analysée quotidiennement pour évaluer sa qualité microbiologique et sa composition chimique. Elle est contrôlée aussi bien à la source qu'avant ou après sa mise en bouteille. Dans un souci d'excellence, le contrôle de l'eau est poussé au-delà de la réglementation avec des contrôles réguliers sur un large éventail de paramètres microbiologiques, physico-chimiques et organiques par le Laboratoire de Spadel (certifié ISO 17025). De plus, des laboratoires indépendants contrôlent régulièrement l'absence de contaminants émergents (pesticides et leurs métabolites, résidus de médicaments, perturbateurs endocriniens, virus,...). Sans compter les contrôles microbiologiques hebdomadaires, Spadel a analysé en 2020 quelques 53.204 paramètres sur les eaux de Spa.*

LES CRITÈRES POUR LE LABEL «CONVIENT POUR LA PRÉPARATION DES ALIMENTS POUR NOURRISSONS»

AC: *Pour bénéficier du label « convient pour la préparation des aliments pour nourrissons », une eau doit répondre à différents critères : une très grande pureté, constante dans le temps et une composition faible en minéraux, ce qui est le cas pour Spa® Reine puisqu'elle est faiblement minéralisée avec une très faible teneur notamment en calcium, fluor, chlorures, sodium mais aussi en nitrates et en nitrites. Autant de critères auxquels Spa® Reine répond parfaitement. Pour ces raisons, Spa® Reine est une eau de premier choix pour la maman allaitante et pour le nourrisson.*

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