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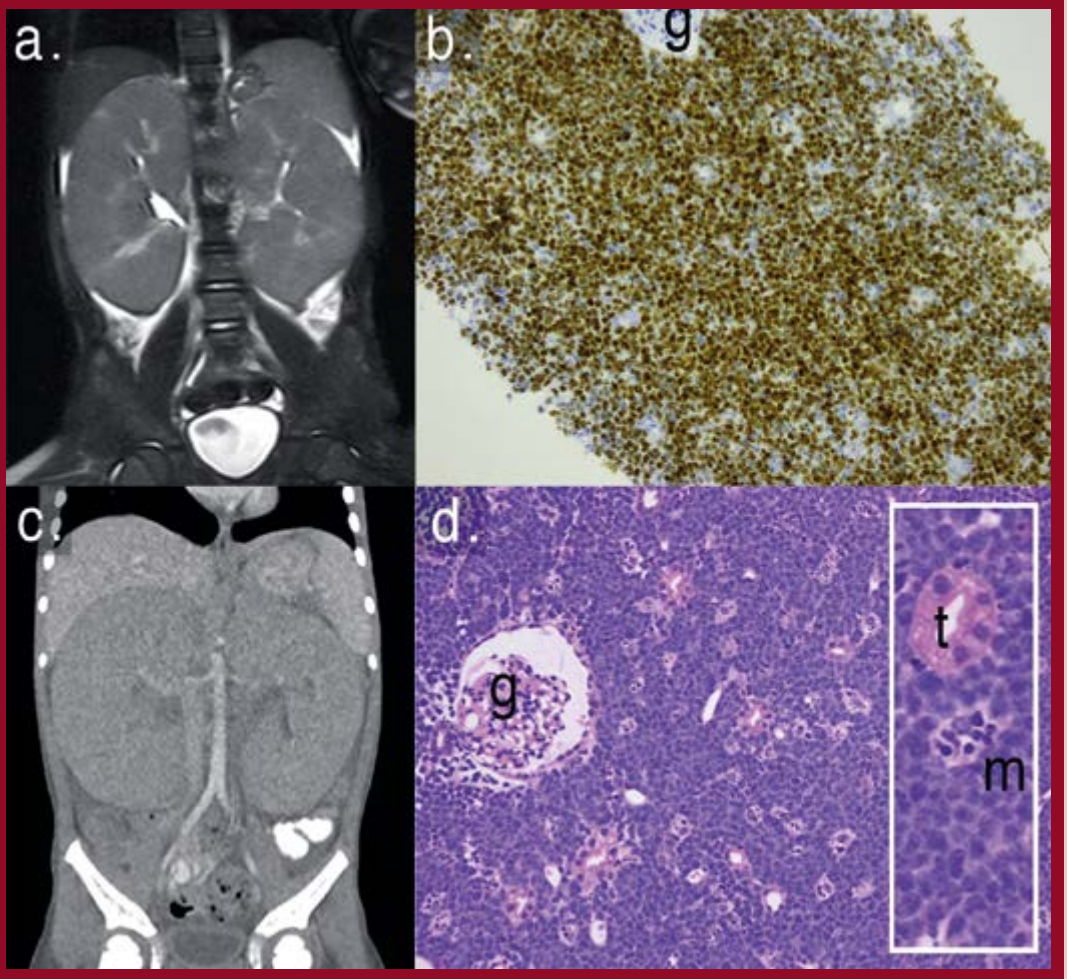

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Société Belge de Pédiatrie

Theme: Pediatric intensive care

Articles

Case Report

Made in Belgium

Short Communication

Vaccination Campaign

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44ste ème Jaarlijks Congres
Congrès Annuel

van de Belgische Vereniging voor Kindergeneeskunde
de la Société Belge de Pédiatrie

44th Annual Congress BVK/SBP

'Guidelines, sometimes law, sometimes not'

SAVE THE DATE
10-11 maart/mars 2016

Theme:

"Guidelines, sometimes law, sometimes not"

Scientific organisation:

Prof. Dr. Yvan Vandenplas
and
UZ Brussel Staff

President BVK/SBP :

Prof. Dr. Anne Malfroot

Venue:

"The Egg" - Rue Bara 175 -1070 Bruxelles Brussels

Logistic organisation: **Act-Wise**

www.bvksbp2016.be

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BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

L'année 2015 s'achève avec dernier numéro du volume 17 de notre revue. Vous y trouverez les rubriques habituelles d'articles originaux et de communications consacrées à des cas cliniques mais aussi la rubrique de plus en plus fournie «made in Belgium». Cette rubrique qui a débuté en 2008 est destinée à rendre compte des thèses défendues par des pédiatres belges ou travaillant en Belgique. Au cours de ces 7 années 24 résumés de thèse ont pu être publiés. Notre revue s'enorgueillit de pouvoir ainsi faire connaître à la communauté pé-diatrique les travaux de jeunes chercheurs dont la qualité scientifique est remarquable et augure de carrières prometteuses.

Deux articles s'inscrivent dans le thème "Soins Intensifs". La coordination de ce thème a été confiée à nos collègues Lars Desmet et Stephan Clément de Cléty et d'autres articles seront publiés ultérieurement afin d'en couvrir les aspects nombreux et multiples.

Une autre rubrique que vous retrouverez avec intérêt concerne notre campagne en faveur de la vaccination. Cette campagne, la deuxième après celle sur «Breastfeeding» fait intimement partie de la mission que nous nous sommes assignée de mettre l'accent sur la prévention et le conseil en matière de santé publique. La campagne «Vaccination» compte 12 articles répartis sur trois ans et s'achèvera au cours de l'année 2016 pour faire place à un autre sujet de campagne respectant la ligne d'utilité publique que nous nous sommes tracée.

Vous retrouverez également le "President's address" tribune dans laquelle notre nouvelle présidente fait part des projets et des lignes d'orientation de la SBP: de nouveaux membres entrent au Conseil d'Administration, de nouveaux statuts ont été publiés et le site web a été entièrement renouvelé… il en avait bien besoin.

Les deux rubriques "Surgeon's corner" et "State of the art" sont absentes de ce numéro et nous les reprendrons à partir de l'année prochaine en tentant de les rendre régulières. Car nous pensons que la chirurgie pédiatrique est intimement liée à notre travail de pédiatre, le dialogue entre médecin et chirurgien étant toujours utile et tout particulièrement en ce qui concerne les enfants à la fois en tant que mesures curatives que préventives. Trois numéros ont pu compter sur des contributions dans le cadre de "State of the art" et cela nous parait une bonne manière de faire le point sur des sujets que nous croyons connaître mais qui bé-néficient de l'expérience des experts que nous sollicitions.

A ce propos ne manquez pas de vous inscrire au prochain congrès annuel de la SBP qui se tiendra les jeudi 10 et vendredi 11 mars 2016 à Bruxelles, organisé par Yvan Vandenplas et son équipe de l'UZ Brussel ave pour thème "Guidelines in Pediatrics". Le programme est riche et varié et eut être consulté sur le site web www.bvksbp.be

Last but not least, notre Journal du pédiatre belge-Tijdschrift van de Belgische Kinderarts" changera de nom à partir de l'année prochaine pour devenir "Belgian Journal of Pediatrics" qui pourra toujours publier des articles en français ou en néerlandais mais encouragera vi-vement la publication en langue anglaise afin de rentrer le plus possible dans les critères nous permettant de poser notre candidature à la reconnaissance par Medline. Cette dé-marche est susceptible d'améliorer notre visibilité et inciter nos jeunes pédiatres en forma-tion à rejoindre notre tribune, organe de notre Société Belge de Pédiatrie.

S. Cadranel et M. Raes

Het jaar 2015 wordt afgerond met het laatste nummer van volume 17 van ons tijdschrift. U vindt er de gebruikelijke rubrieken terug met originele artikels en case reports, maar ook de steeds meer gevulde rubriek "Made in Belgium". Sinds 2008 worden in deze rubriek thesissen van Belgische kinderartsen of in België werkende kinderartsen in het licht te stellen. 24 abstracten werden de afgelopen 7 jaar gepubliceerd. Ons tijdschrift is trots om op die manier onze collega's te informeren over het werk van deze jonge onderzoekers, telkens van een bijzondere wetenschappelijke kwaliteit is en beloftevol voor de toekomst.

Twee artikels hebben betrekking op het thema "intensieve geneeskunde". De coördinatie van dit thema is toevertrouwd aan onze collega's Lars Desmet en Stephan Clément de Cléty. Andere artikels over dit veelzijdig thema worden later gepubliceerd.

Een andere interessante rubriek is onze vaccinatiecampagne. Deze campagne is de tweede na "Borstvoeding" en maakt deel uit van onze missie om te informeren over preventie en advies in de gezondheidszorg. De "vaccinatiecampagne" telt 12 artikels verspreid over drie jaren en zal in 2016 afgerond worden om plaats te maken voor een andere campagne van openbaar nut, in de lijn van onze missie.

In de "President's Address" stelt onze nieuwe voorzitster de projecten en oriëntatielijnen voor van de BVK: nieuwe leden treden aan in de Raad van Bestuur, nieuwe statuten werden gepubliceerd en de website werd volledig vernieuwd ... dat was ook nodig.

De twee rubrieken "Surgeon's corner" en "State of the art" ontbreken in dit nummer. We zullen proberen ze vanaf volgend jaar op een regelmatige basis te hervatten omdat we geloven dat de pediatrische chirurgie nauw verwant is met ons werk als kinderarts, en dat de dialoog tussen arts en chirurg over behandeling en preventie altijd nuttig is, zeker in het geval van kinderen. Drie nummers konden rekenen op bijdragen in het kader van de "State of the art" en dit lijkt ons een goede manier om de te leren van de ervaring van deskundigen over onderwerpen die wij wellicht niet in detail kennen.

Vergeet ook niet in te schrijven voor het volgend congres van de BVK op donderdag 10 en vrijdag 11 maart 2016 in Brussel, georganiseerd door Yvan Vandenplas en zijn team van UZ Brussel met als thema: "Richtlijnen in de pediatrie". Het programma is rijk en gevarieerd en is tevens beschikbaar op de website www.bvksbp.be

Last but not least, ons "Journal du pédiatre belge - Tijdschrift van de Belgische kinderarts" heeft vanaf volgend jaar een nieuwe naam: "Belgian Journal of Pediatrics". Artikels kunnen nog steeds gepubliceerd worden in het Frans of Nederlands, maar we moedigen toch aan om zoveel mogelijk in het Engels te publiceren om zo goed mogelijk aan te sluiten bij de criteria voor de erkenning in Medline. Deze aanpak zal waarschijnlijk onze zichtbaarheid verbeteren en jonge kinderartsen in opleiding aantrekken om in ons tijdschrift te publiceren als orgaan van de Belgische Vereniging voor Kindergeneeskunde.

M. Raes en S. Cadranel

Wij hopen dat onze projecten voor 2016 met succes bekroond worden en wensen u en uw gezin aangename eindejaarsfeesten.
Nous vous souhaitons à vous et vos familles d'excellentes fêtes de fin d'année et formons des vœux pour que ces projets se réalisent avec succès en 2016.

Uw vragen of commentaar

Vos questions ou commentaires

BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

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The President's address

Beste Collega's,

2015 zit er al weer op en heeft plaatsgemaakt voor een nieuw jaar. Ik wens jullie een gelukkig Nieuwjaar met veel geluk en een goede gezondheid, dat blijft het allerbelangrijkste in het leven. Ik wens jullie daarbij ook heel veel positieve energie en veel werkvreugde zodat de obstakels die ons werk vaak meebrengt, met gemak kunnen overwonnen worden.

Terugblikkend naar vorig jaar moet ik toegeven dat onze vereniging een overgangsperiode heeft doorgemaakt door de wissel van het bestuur. Toch zijn we niet blijven stil zitten. De website van onze vereniging werd volledig gerenoveerd en zal nu zeer binnenkort echt in gebruik zijn. Neem alvast een kijk op www.bvksbp.be en suggesties zijn zeker welkom.

Wat betreft het jaarlijks congres van de BVK in maart, de belangrijkste event van onze vereniging, zijn we goed gevorderd, en is het programma van de 44e editie op 10 en 11 maart 2016 in zijn definitieve versie te vinden via een link op onze website of via de congres website http://www/bvksbp2016.be.
Thema is "Guidelines" in de kindergeneeskunde, een actueel en zeer breed onderwerp, we rekenen op uitstekende sprekers, en hebben gezorgd voor een grote variatie aan onderwerpen, en met alle aspecten van een internationaal congres, van posterdiscussies tot plenaire lezingen. We rekenen op leerrijke sessies door dieper in te gaan op bestaande richtlijnen en ze, waar nodig, in vraag te stellen en door aandacht te hebben voor nog te realiseren aanbevelingen. We kunnen nu al verklappen dat het aantal inzendingen voor abstracts een succes was. Tevens kregen we een onverwacht groot aantal inzendingen voor de wetenschappelijke prijzen die nu jaarlijks worden uitgegeven door onze vereniging, de kandidaturen zullen beoordeeld worden door buitenlandse experten. Ook deze inzendingen zullen voorgesteld worden op een zitting tijdens het komend congres.

Tenslotte wil ik jullie, bij het begin van 2016, bedanken voor jullie steun en jullie loyauteit naar de vereniging toe, in goede en in minder goede tijden, door jullie jaarlijks lidmaatschap. Zonder jullie steun kunnen wij niet bestaan.

Mijn beste wensen,

Anne Malfroot
Voorzitter

Januari 2016

Chers collègues,

2015 est déjà passé et nous voilà dans une nouvelle année. Je vous souhaite une bonne et heureuse année et bonne santé, ce qui est la chose la plus importante dans la vie. Je vous souhaite aussi beaucoup d'énergie positive et de satisfaction professionnelle de sorte que les obstacles qu'apporte souvent notre travail puissent être facilement surmontés.

En regardant en arrière, je dois avouer que notre société a traversé une période de transition due au changement du bureau en 2015. Pourtant, nous avons pris le temps de renouveler complètement le site web de notre association qui sera très bientôt réellement en usage. Jetez-y déjà un oeil (www.bvksbp.be). Des suggestions sont certainement les bienvenues.

En ce qui concerne le congrès annuel de la SBP en mars, l'événement le plus important de notre association, nous avons bien avancé. Vous pouvez trouver la version définitive du programme de la 44e édition des 10 et 11 mars 2016 en suivant le lien sur notre site web ou par le site web du congrès: www.bvksbp2016.be.
Le thème est «Lignes directives » en pédiatrie, un sujet actuel et très large, pour lequel nous comptons sur d'excellents orateurs, et avons mis en place une grande variété de sujets, avec tous les aspects d'un congrès international depuis les discussions des communications affichées jusqu'aux conférences plénières. Nous comptons aussi sur des séances éducatives pour approfondir les directives existantes et, si nécessaire, les remettre en question et éventuellement formuler de nouvelles recommandations. Nous pouvons déjà révéler que le nombre d'abstracts reçus a été un succès. Nous avons eu également un grand nombre d'articles pour les prix scientifiques qui sont attribués annuellement par notre association, les candidats seront jugés par des experts de l'étranger. Ces articles seront présentés lors d'une session du prochain congrès.

Finalement, en ce début de 2016, je voudrais vous remercier pour votre cotisation annuelle, gages de votre soutien et fidélité envers notre association, durant les bonnes et moins bonnes périodes. Car c'est grâce à votre soutien, que nous existons.

Mes meilleurs voeux,

Anne Malfroot
Présidente

Janvier 2016

INTRODUCTION

Dear Colleagues,

We are glad to present to you a series of articles on paediatric intensive care, being brought to you in two theme issues in the Journal du Pédiatre Belge – Tijdschrift voor de Belgische Kinderarts.

The timing is not fortuitous. The recent political decisions on the organization of hospital services for children in primary, secondary and tertiary centers contain particular details on the care of critically ill children admitted to a paediatric intensive care unit (PICU).
Moreover, once again, we are now in full RSV season, when we go scrambling for beds to accommodate the peak in admissions of the sickest ones amongst them.

We opted for subjects which could be of interest to every paediatrician, starting with two articles on fluid resuscitation and red blood cell transfusion in the intensive care setting. These will be followed by articles on non-invasive ventilation, acute respiratory distress syndrome, severe sepsis, traumatic brain injury and end-of-life care.

The field has seen impressive advances in the understanding of, and therapy for life threatening diseases. Many randomized controlled trials (RCT) in adult intensive care in the last 20 years have shown the way resulting in a gain in survival.
RCT's in children have concentrated on particularities in childhood. Due to a lower mortality for some diseases, paediatric RCT's focused more on morbidity, using organ dysfunction as the most important outcome feature.
'Less is more' is a common conclusion of this research – gentler ventilation strategies, lower blood pressure targets, later parenteral nutrition, normothermia instead of hypothermia, less transfusion, etc.

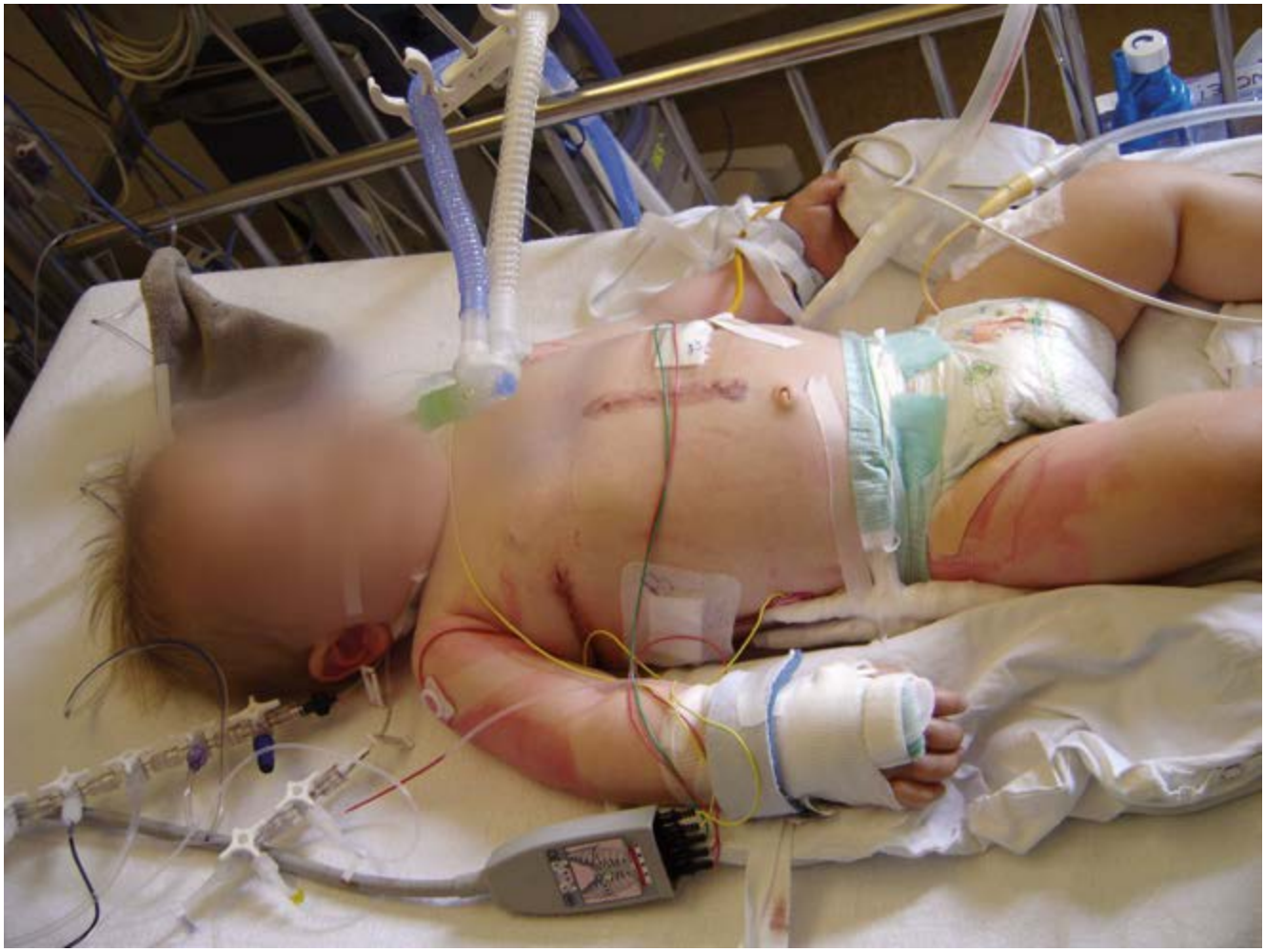
The population admitted to the PICU's has changed, a reflection of what happens on general paediatric wards. PICU's now see more chronic patients with severe co-morbidity, hospital veterans after prolonged neonatal support, lifesaving (cardiac) surgery, transplantation or immunosuppression.
The changes in and uptake of new vaccination strategies have resulted in a drop of some severe community acquired infections, sadly enough to be replaced sometimes by new infections.

In synchrony with the advances in medical care and surgery, the severity of illness and the complexity of care have increased in paediatric intensive care. This has resulted in a professionalization of the teams of nurses, paediatric intensivists and physiotherapists taking charge of these patients.

And what after intensive care ? Data on the long term outcome and psychomotor development after an intensive care stay are just starting to emerge.
Maybe an idea to be reviewed in the Journal in a few years' time.

Lars Desmet

Stéphan Clément de Cléty



Red Blood Cell Transfusion in Critically Ill Children.

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Keywords

red blood cell, transfusion, critically ill, children.

Abbreviations

CO	cardiac output
EPO	erythropoietin
Hb	haemoglobin
Hct	haematocrit
ICU	intensive care unit
O_2	oxygen
MODS	multiple organ dysfunction syndrome
NISHOT	non-infectious serious hazards of transfusions
PICU	pediatric intensive care unit
P_aO_2	partial pressure of oxygen
RBC	red blood cell
S_pO_2	oxygen saturation
TACO	transfusion-related circulatory overload
TRALI	transfusion-related acute lung injury
TRIM	transfusion-related immunomodulation
TRIPICU	Transfusion Requirements in Pediatric Intensive Care Unit

Abstract

The use of RBC transfusion is common in critically ill children given the high incidence of anemia at admission and throughout the PICU stay. The consequence of anemia is a decrease in O2-delivery. The exact Hb threshold at which O2-delivery is impaired is not known and probably not the same for all patients. Severe anemia is associated with worse outcomes. An Hb level below 5 g/dL is associated with an increased risk of death in children and adults. The TRIPICU trial studied the tolerance to anemia in stable critically ill children and demonstrated that a Hb threshold of 7 g/dl could be safely applied in critically ill children. The optimal Hb threshold in unstable critically ill children, neonates scheduled for cardiac surgery, or children with bleeding are currently unknown. RBC transfusions are useful and can be lifesaving. However, there are many risks associated with RBC transfusions. The multiple risks associated with RBC transfusions, include miss-transfusion, transfusion-transmitted infections, and non-infectious serious hazards of transfusions (NISHOT), which can be immune- or non-immune-mediated. The decision to transfuse should therefore be based on evidence of improving or not worsening outcome; but should also be individualised in each patient situation, taking into account the balance between the risk of transfusion and the risk of anemia.

Introduction

RBC transfusions are frequently administered to the critically ill child. Although they are the cornerstone treatment of anemia and blood loss, the decision to transfuse RBC to patients remains a true clinical dilemma. Indeed, both anemia and RBC transfusions are associated with risks and worse outcomes. Anemia is frequent in hospitalised patients especially in the critically ill. Anemia is generally well tolerated. However, some critically ill patients, such as patients with hypoxemia or impaired cardiac output, can be less tolerant to anemia. On the other hand, critically ill pediatric patients are among the largest groups

of blood products users. Due to their underlying condition, these patients are probably also at greater risk of complications and worse outcome when they are transfused. The decision to transfuse has therefore to be individualized in each patient situation, taking into account the balance between the risk of transfusion and the risk of anemia.

In this review we will first address the causes and consequences of anemia and summarise the evidence on the tolerance of critically ill children to anemia. Thereafter we will discuss the benefits and risks of RBC transfusion to finally end with practical recommendations on when, and how much to transfuse in this patient population.

Anemia in the pediatric intensive care unit

Causes and consequences

Anemia is defined as an Hb level below the normal threshold for age. Healthy neonates show a relative polycythaemia. Within the first days of life, erythrocyte production decreases and Hb levels fall to a nadir at about 2-3 months of life. Thereafter, the normal values for Hb gradually increase until adult values are reached after puberty.[1] Anemia is frequent in hospitalised patients especially in the critically ill. In adults, anemia afflicts half of hospitalised patients. A high percentage of children admitted to the PICU are anemic at admission or become anemic during their ICU stay. A large observational study reported a history of anemia within 7 days before PICU admission in 15% of the children. Anemia was present on PICU admission in 33% of children and an additional 41% of the patients became anemic during their PICU stay. In this study, only 26% of the children never became anemic.[2] Anemia seen in the critically ill is the consequence of both an impaired RBC production and an increased RBC loss. Impaired production is caused by a decreased EPO production and responsiveness as well as iron metabolism dysregulation characterised by nutritional deficiency related to reduced intestinal iron absorption, functional iron deficiency related to acute inflammation and chronic disease, and decreased iron availability via suppression of iron release from macrophages. Increased RBC loss is the consequence of an increased RBC destruction and blood loss. Furthermore, blood loss is common in the PICU, both from (peri-operative) hemorrhage and iatrogenic blood loss caused by phlebotomy. The latter is particularly important in pediatric patients because of the small total circulating volume of blood. Finally, many patients receive large amounts of intravenous fluids, which possibly leads to haemodilution.[3,4]

The most important consequence related to anemia is a decrease in tissue O_2-delivery and therefore a reduction of the metabolic reserve. Oxygen, which is mandatory to sustain normal metabolism, needs to be transported effectively from the atmosphere to the tissues. Global O_2-delivery is the amount of O_2 delivered to the whole body from the lungs. It is the product of total blood flow or cardiac output and the O_2-content of arterial blood (CaO_2). This arterial O_2-content is the sum of the O_2 bound to Hb and the O_2 dissolved in the plasma. Most of the O_2 in blood travels bound to Hb; only a minimal amount travels as dissolved O_2. Therefore, the O_2-content of arterial blood (CaO_2) depends primarily on the Hb concentration and arterial O_2-saturation (SaO_2). This means that a drop in Hb or a drop in O_2-saturation as seen in patients with respiratory problems but also in children suffering cyanotic heart disease, will decrease the CaO_2, and require a compensatory increase in cardiac output and O_2-extraction to maintain tissue O_2-delivery.[3]

$$O_2\text{-delivery} = \text{Cardiac output} \times [(1.39 \times Hb \times SO_2) + (P_aO_2 \times 0.03)]$$

Tolerance to anemia: what's the evidence?

There is still a large debate about what are the lowest Hb and critical O_2-delivery level under which O_2-consumption is in jeopardy.[5] Studies performed in hospitalized Kenyan children showed that mortality was significantly higher in patients with Hb levels <5 g/dL, particularly if respiratory distress was present.[4,6] The same observation was made in adults scheduled for bloodless cardiac surgery.[7] It is clear that there is some level of anemia that is dangerous. The exact level is not certain and probably not the same for all patients. At present, an Hb level below 5 g/dL increases the risk of mortality, is the best available evidence on anemia than can be applied in hospitalised children.8 The question remains if this threshold can be applied in critically ill children. The TRIPICU study investigates the tolerance to anemia in stable or stabilised critically ill children. In this study, stable or stabilised was defined as a mean blood pressure not less than two standard deviations below the normal mean for age and if the cardiovascular support (pressors/inotropes and fluids) has not been increased for at least 2 hours. This study shows that critically ill children tolerate anemia well. Indeed, administration of a RBC transfusion to these children when their Hb level drops below 7 g/dL is not inferior to the administration of a RBC transfusion when their Hb level drops below 9 g/dL. Furthermore, such transfusion strategy is associated with an important decrease in exposure to RBC transfusions.[9] Many clinicians think that some subpopulations of critically ill patients need higher Hb thresholds to be transfused. Different subgroup analyses of the TRIPICU study do not support this idea. The subpopulation of patients with *acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)* did not improve when targeting an Hb level above 7 g/dL.[8] A subgroup analysis of the TRIPICU study including patients with *sepsis and septic shock* shows no difference in primary and secondary outcomes between both Hb thresholds.[8,10] A study in critically ill adults yields the same conclusion. This suggests that a threshold Hb of 7 g/dl can probably be safely applied in critically ill children with sepsis. The same conclusion is drawn in postsurgical pediatric patients.[11] A subgroup analysis of the *cardiac surgery* population of the TRIPICU study found the same results.[12] The finding in cardiac surgery patients that a restrictive transfusion strategy is not inferior to a liberal one is confirmed by other studies. In children 6 weeks to 6 years old with a non-cyanotic congenital heart defect that require elective cardiac surgery, a restrictive transfusion strategy (RBC transfusion if their Hb level dropped below 8.0 g/dl) is associated with a shorter hospital length of stay compared to the liberal transfusion strategy (RBC transfusion if their Hb level dropped below 10.8 g/dl). All other outcome measures and the incidence of adverse effects are similar in both RBC transfusion groups.[13] In cyanotic or single-ventricle physiology cardiac children, the comparison of a restrictive (Hb<9.0 g/dL) with a liberal (Hb<13.0 g/dL) transfusion strategy shows that a restrictive transfusion strategy did not affect outcomes.[14]

In *bleeding patients*, RBC transfusion is the fastests mean to increase Hb level. However, in this population, the Hb level is unreliable. It may remain unchanged from baseline immediately after acute blood loss, and will drop considerably only after re-equilibration, which may take several hours. In these patients, the amount and the speed of blood loss are probably the most important determinants. But, in many different situations blood losses are difficult to measure and no bleeding scores are validated in critically ill patients yet.[8] Finally, in *unstable critically ill* patients, there are no hard data on what must be done with respect to RBC transfusion therapy. To date, no absolute Hb threshold that should prompt transfusion exists.[8]

Red blood cell transfusion in the pediatric intensive care unit: benefits and risks

RBC transfusion is the fastest means to increase the Hb level. It is therefore a common and important supportive measure in critically ill children. In a large, multi-centre, prospective study on transfusion practices in critically ill children admitted more than 48 hours in the PICU, almost half of the study population received at least one RBC transfusion. The majority (74%) of the patients received their first transfusion within the first 2 days after their admission to the PICU and only 4% received it after the first week.[2]

Benefits-to-risks ratio of RBC transfusions remains difficult to evaluate. RBC transfusions can be life saving in severe anemic or bleeding patients. However, RBC transfusions should be limited to patients who really need transfusions, for

several reasons. First, RBC transfusions are associated with adverse events, which are frequently underestimated. Overall the most common adverse incidents associated with RBC transfusions are caused by human errors, resulting in the transfusion of an incorrect component or one that does not meet the specific requirements of the patient. Miss-transfusion of blood has become one of the leading causes of death related to blood transfusion.[15] The safety of blood products with respect to transfusion transmitted infectious disease has improved greatly in recent decades. The transfusion risks for HIV, HBV, HCV, and HTLV are extremely low since the introduction of nucleic acid testing that enhances test sensitivity. However, the blood supply is not sheltered from the emergence of new as yet undescribed infectious agents.[16] Presently, non-infectious serious hazards of transfusions (NISHOT), which can be immune- or non-immune-mediated, are of major concern. Short-term non-immune NISHOT include overtransfusion and transfusion-related circulatory overload (TACO). Overtransfusion is of concern, especially in neonates and small children, because of the risk of cardiac overload and/or hyperviscosity, which may impair blood flow and therefore O_2-delivery in small vessels. Evidence shows that mortality increases when Hb >16 g/dL. TACO occurs when a patient is unable to compensate for rapid or high-volume infusions of blood products. Patients predisposed to volume overload, such as those with congestive heart failure, renal failure, and respiratory failure are most at risk to develop TACO.[16] Immune-mediated NISHOT include hemolytic and allergic reactions, transfusion-related immunomodulation (TRIM), transfusion-related acute lung injury (TRALI), nosocomial infections, transfusion-associated graft versus host disease, and allo-immunisation to RBC and HLA antigens.[17] In critically ill patients, TRIM may represent a significant 'second-hit' when added to pre-existing organ dysfunction and/or a systemic inflammatory response syndrome, which may result in TRALI and multiple organ dysfunction syndrome (MODS).[17] This is demonstrated in cardiac surgery patients, where RBC transfusions are associated with an increased pulmonary leak index, an early marker of acute lung injury, and increased inflammatory markers in bronchoalveolar lavage when compared to controls.[18] Additionally, repeated RBC transfusions can lead to iron overload and result in end-organ damage.[17] NISHOT are currently an important cause of transfusion-related fatalities. Furthermore, several studies in children heightened awareness of the dangers of transfusions. Indeed, studies in different subpopulations of critically ill children show an association between RBC transfusion and increased morbidity and mortality. These observational studies demonstrate that RBC transfusions are associated with prolonged mechanical ventilation, PICU and hospital length of stay, and an increased risk of infection.[4] However, association does not mean causality. Today, it is still not known if RBC transfusion is a risk marker or a risk factor of worse outcome. Finally, RBC transfusion is a limited resource. RBCs are scarce due to shrinking of the blood donor pools owing to population age and stringent donor qualifications, and increasing demand from hematological and oncologic diseases, perioperative procedures, and myelo-suppressive therapies.[19] Furthermore, costs associated with RBC transfusions are escalating due to new screening technologies to assure a safe blood supply. Additional factors that may contribute to the steadily increasing costs of blood include processing, collecting, and administering blood and blood components, hospital liability insurance and overhead, recruiting and retaining blood donors, and shortages of trained personnel.[19]

Red blood cell transfusion in the pediatric intensive care unit in practice

When to transfuse?

In critically ill children, evidence exists that unnecessary RBC transfusions can be avoided by considering a lower Hb threshold as trigger to transfuse without worsening patient's outcome. This suggests that all *stable/stabilised critically ill children who are* qualified to be enrolled in the TRIPICU study do not need a RBC transfusion if their Hb level is above 7 g/dl. In the absence of evidence that stabilised *patients with respiratory distress, sepsis or after admitted after surgery*, need higher Hb thresholds, the same Hb thresholds of 7 g/dl can probably be recommended. The study of De Gast-Bakker and the cardiac surgery subgroup of the TRIPICU study putted together suggest that an Hb level above 7 to 8 g/dl is well tolerated in all *stable critically ill children older than 28 days with non-cyanotic heart disease.*[13] *In cyanotic or single-ventricle physiology cardiac patients outside the neonatal period*, it is well tolerated not to give an RBC transfusion to patients as long as their Hb level remains above 9 g/dl.[14] The optimal Hb threshold level in unstable critically ill children, neonates scheduled for cardiac surgery, or bleeding children is currently unknown. In the absence of clear evidence, experts recommend that a patient in haemorrhagic shock should receive a volume of blood products corresponding to the acute blood loss, which must include RBC units, plasma, and platelets; thereafter, the patient should receive blood products to compensate for ongoing blood loss. In unstable critically ill children where evidence is lacking, the only recommendation that can be made with respect to RBC transfusion is to use clinical judgment.[8] Finally, as prevention is better than treatment, efforts must be made to limit the frequency and quantity of blood draws to reduce the need for RBC transfusions. Iron supplementation and erythropoietin have not proven their efficacy in the critical care setting and their potential side effects are not negligible. Currently, there is no evidence to support such practice.

How much to transfuse?

When the decision to prescribe transfusion has been taken, the goal is to transfuse enough RBCs to increase the Hb level and thus the O2-delivery with a minimum of donor exposure, and not too much to avoid overtransfusion, cardiac overload and hyperviscosity. A reliable formula is needed to estimate the volume of blood that must be transfused to achieve a target Hb concentration. There are a number of formulae, each of which takes account of the child's weight, the estimated circulating blood volume, and the Hb concentration or haematocrit of the blood to be transfused.

Volume RBCs to transfuse
= (total blood volume x (target Hb - current Hb))/ Hb of donor unit

Commonly used formulae vary according to the value that is assumed for total blood volume and for the Hb/Hct of each RBC unit. Several formulae underestimate the volume needed to produce a desired rise in Hb and therefore many patients are under transfused and may need to be transfused again, exposing the patient to additional risk and increasing costs. In 2005, Morris and colleagues validated a formula.

This formula is:

Volume of RBCs to transfuse (ml) = 4.8 x weight (kg) x desired rise in Hb (g/dL)

or

Volume of RBCs to transfuse (ml) = 1,6 x weight (kg) x desired rise in Hct (%)

Both formulae are appropriate for supplied RBC units with a median Hct of 70% (Hb of 23 g/dL).[20]

Davies and colleagues validated another formula based on an RBC unit Hct of 60%:

3 x weight (kg) x increment in Hb (g/dL)

Their study showed that 10 ml/kg RBCs gives an Hb increment of 2 g/dL.[21] A number of factors may explain the differences in formulae used. First, the estimate of Hb concentration or haematocrit of the blood unit. Second, stored RBC undergo a progressive loss of viability. After transfusion these older RBC will be taken up and destroyed by the child's reticulo-endothelial system soon after

transfusion. Finally, values for total blood volume are estimated. In conclusion, when the decision to transfuse is taken, a formula can help the physician to know how much RBCs are needed to be transfused to attain the decided Hb goal. However, care must also be taken to reduce the risk of hypervolemia, while minimizing donor exposure.

Conclusion

Anemia is frequent in hospitalised children, certainly when they are admitted to the PICU. Even if anemia is a cause of decreased O_2-delivery, it is usually well tolerated in critically ill children. Nonetheless, anemic children are at increased risk to receive RBC transfusion during their stay. An important cause for anemia during PICU stay is iatrogenic blood loss caused by phlebotomy. Efforts should therefore concentrate to decrease phlebotomy and the volume withdrawn during phlebotomy in order to reduce RBC exposure in critically ill children.

RBC transfusion is an important treatment in case of decreased O_2-delivery as seen with severe anemia and bleeding. RBC transfusions may be life saving but clinicians should not underestimate their potential side effects. In the absence of an easy measurement of O_2-transport, the tricky question is what degree of anemia causes impaired O_2-delivery, and if or how much how RBC transfusion improves it. Most of the evidence is based on the Hb level used as a surrogate of O_2-delivery. For stable non-bleeding non-cyanotic children, restrictive transfusion strategies are not inferior to liberal ones and they are associated with a decrease in RBC use without worsening outcome. When the decision to transfuse is taken, the volume of RBC administered should increase the O_2-delivery adequately without overtransfusion.

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Fluid resuscitation in children.

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Keywords

hypovolemia, shock, fluid resuscitation.

Introduction

Fluid therapy is central in the management of many pediatric diseases ; in this article we will limit ourselves to the most severe diseases that lead to shock.
After early recognition of the signs of shock, effective fluid resuscitation is one of the cornerstones of therapeutic intervention in shock.
However, recent studies have focused attention on the potential risk of excessive fluid resuscitation in septic shock in children .
The challenge for a pediatrician or any other physician is to recognize shock, assess its cause and severity in order to manage it correctly.
We will try to answer the following questions: when, how much and which fluid do we have to give to the acutelly ill child while respecting the old, but so appropriate, Greek proverb: « παν μέτρον άριστον » (all in good measure, everything in moderation).

When ?

Shock is defined as an acute life-threatening circulatory failure with imbalance between oxygen delivery and utilization by the cells, resulting in cellular dysfunction [1].

Early clinical recognition of shock is the first step to successful management of the critically ill child. Clinical diagnosis of shock is made in presence of several signs and symptoms (Table 1 and 2) including tachycardia, altered mental status, impaired perfusion of skin and extremities [2].

Table1 : Signs of shock [5]

	Early shock (compensated)	**Installed shock (Uncompensated)**	**Late Shock**
Signs and symptoms	Tachycardia Mild tachypnea Slightly delayed capillary refill (2-3 sec) Mild irritability	Severe tachycardia Severe tachypnea Respiratory distress Severely delayed capillary refill (> 4 sec) Mottled skin Severe agitation Somnolence Stupor Oliguria	Extreme tachycardia Bradycardia Intensive pallor or cyanosis Irregular respiration Apnea Coma Oligo-anuria
Blood pressure	Normal Orthostatic changes	Hypotension	Severe hypotension
Laboratory	Normal Mild metabolic acidosis Mild lactic acidosis	Moderate to severe metabolic and lactic acidosis	Same + signs of organ dysfunction

Table 2 : Classification of hemorrhagic shock in children [6]

	Class I very mild	Class II mild	Class III moderate	Class IV severe
Percent blood volume loss	<15 percent	15-30 percent	30-40 percent	>40 percent
Heart rate	Normal	Slightly increased	Moderately increased	Markedly increased
Respiratory rate	Normal	Slightly increased	Moderately increased	Markedly increased, markedly decreased, or absent
Blood pressure	Normal or slightly increased	Normal or slightly decreased	Decreased	Decreased
Pulses	Normal	Normal or decreased peripheral	Weak or absent peripheral	Absent peripheral, weak or absent central
Skin	Warm and pink	Cool extremities, mottled	Cool mottling extremities, or pallor	Cold extremities with pallor or cyanosis
Capillary refill	Normal	Prolonged	Markedly prolonged	Markedly prolonged
Mental status	Slightly anxious	Mildly anxious, confused, combative	Very anxious, confused, or lethargic	Very confused, lethargic, or comatose
Urine output	Normal	Slightly decreased	Moderately decreased	Markedly decreased or anuria

An important point to be stressed is that in newborns and children, low blood pressure is a late sign of shock. [3, 4]

In an emergency room, history and clinical examination can determine the origin of the shock (hypovolemic - hemorrhagic, distributive, obstructive or cardiogenic).

The cardinal signs of impaired organ perfusion that must lead to an urgent treatment are tachycardia with altered mental status (anxiety, confusion, irritability, or on the contrary lethargy) associated with increased capillary refill (> 3 sec), mottled or cold extremities and a decreased pulse.
These signs associated with an arterial blood pressure normal for age, characterize compensated shock (blood flow is decreased, normal or even increased but can be maldistributed; vital organ function is frequently maintained).
Without appropriate treatment the situation will lead to low blood pressure and uncompensated shock (with a significant reduction of effective circulatory volume, severe microvascular dysfunction and multi organ dysfunction).
This could result in irreversible shock and death.

The first measures consist of managing the airway, ventilation, and administering oxygen by face mask while obtaining intra-venous or if needed, intra-osseous access for fluid administration after excluding heart failure and/or cardiogenic shock [4].

The goal of fluid resuscitation is to increase effective circulating volume, leading to an increase in organ perfusion pressure, without causing fluid overload.
Clinically, correction of signs of shock should be seen, including normalization of mental status, of arterial blood pressure and pulse pressure, followed by an improved diuresis. [7, 8, 9]
Laboratory signs caused by shock (metabolic and lactic acidosis) will be followed serially and can confirm stabilization of the child.

How much ?

1) Septic shock :

Septic shock is a combination of distributive and hypovolemic shock associated with possible myocardial dysfunction.

The Pediatric Acute Life Support guidelines [4] recommend bolus fluid resuscitation of 20 mL/kg aliquots administered in 5 to 10 minutes, followed by repeat boluses during further emergency management of septic shock to compensate for inflammation related capillary leak and to restore intravascular volume.

For compensated shock, it is recommended to administer 20 mL/kg of isotonic crystalloid over 5 to 20 minutes and to check the response of the patient before administration of additionnal fluid boluses.
For uncompensated shock the first bolus of 20 ml/kg is administrated faster (5 to 10 minutes) and repeated up to three times (60 mL/kg) before starting a vasoactive drugs.

There are several techniques to rapidly deliver the bolus via rapid infusion pumps, inflatable devices or manually with a syringe and a three way stopcock.

Clinical signs of fluid overload such as hepatomegaly and/or pulmonary rales with decreased oxygenation indicate time to stop fluid resuscitation and these should actively be sought for.

After every fluid bolus, the clinical response should be assessed.

Cardiac Output monitoring (PiCCO®) and/or bedside echocardiographic assessment (cardiac output and/or filling, stroke volume variation,…) could be useful for the well trained intensivist to guide fluid resuscitation and avoid volume overload.
Appropriate validation for these measures in pediatrics is lacking though. Further studies are needed to define reliable measures to identify volume responsiveness. [10, 11]

Increased lactic acid (> 4 mmol/L) is usefull to detect uncompensated shock and to predict severity of shock, but some patients with septic shock have normal lactic acid levels. [12]

Most of these recommendations are based upon retrospective studies involving small numbers of children and extrapolation from adult recommendations as the early-goal directed therapy (EGDT) protocols for septic shock. [13, 14]

Some recent studies have cast doubt on EGDT in adults. In children, some studies have questioned the routine of fluid therapy in infected children. [15, 16] This brings to our attention the risks of fluid overload which could increase mortality, respiratory failure and ventilatory days. [17, 18]

2) Hemorrhagic shock

Obviously, localizing and stopping the bleeding is the central feature in the management of hemorragic shock.
Loss of intravascular blood volume associated with clinical signs of shock (Table 2) must be resuscitated as hypovolemic shock, starting with 20 mL/kg crystalloid bolus. Thereafter, if more fluid bolus is needed, transfusion of red blood cell, platelets and fresh frozen plasma should also be considered, depending on the severity of ongoing bleeding and the initial hemodynamic volume response in restoring circulation. [11]

In the particular case of shock associated with acute-on-chronic anemia, blood resuscitation is needed to avoid heart failure and volume overload.

3) Cardiogenic shock

It is vital to recognize cardiogenic shock to avoid worsening heart failure and fluid overload.
In rare instances, a limited careful fluid bolus of 5 to 10 mL/kg over 20 minutes could be useful.
The main initial treatment will be the introduction of inotropes such as dobutamine or epinephrine (catecholamines), or milrinone (a phosphodiesterase inhibitor), and diuretics. [11]

4) Burns

Major burn lead to burn shock. In this situation, delay in vascular access and fluid therapy is associated with increased mortality. [19]
During the first 24 hours, fluid therapy guided by formula as Parkland formula (4ml/kg bodyweight/%TBSA burned) is essential in restauration of organ perfusion. However, such formulas provides insuffisant precision in estimation of fluid requirement.
Fluid therapy should be guided not only by formula but also by clinical response and eventually by echocardiography.
Excessive fluids can increase the risk of acute respiratory distress syndrome, compartment syndrome and increase of burn severity. [20]

Which fluids ?

Cristalloids or colloids ?

This debate is as old as intensive care itself. [21, 22]

There is no evidence demonstrating a difference in the outcome of adult or pediatric patients receiving colloids or crystalloids during fluid resuscitation, except for traumatic brain injury (worse outcome with albumin). [23]

Normal saline (0.9 % NaCl) has been used in most trials, and so is the main crystalloid used in pediatrics but large volumes of normal saline are responsible for hyperchloremic acidosis, impairing renal function, and possibly vascular permeability. [24]
We must note that normal saline is slightly hypertonic despite its 'isotonic' classification.

Balanced solutions as Plasmalyte® or Ringer's lactate® solution (without glucose) (Table3) are more physiologic solutions despite the K+ content (the physiologic level of 5 mmol/L is easily diluted during the perfusion) with less interstitial leakage after large volume administration. [24]

Isotonic solutions with a composition close to plasma can be used for fluid resuscitation instead of normal saline in most clinical settings, except in particular situations of Chloride loss (as in vomiting), or excessive renal sodium losses.

Artificial colloids based on starches have recently been abandoned because of associated acute kidney injury. Albumin, a natural colloid, is still frequently used for volume therapy after cardiac surgery in children, although there is no good evidence supporting its superiority over cristalloids.
Apart from these arguments, colloids are far more expensive than cristalloids.

As usual, additional trials will be needed to specify which resuscitation fluid is optimal in these particular situations in pediatrics.

Table 3 : Example of solutions

	Per Liter	***Plasma***	***NaCl 0,9 %***	***Plasmalyte 148 ou A***	***Hartmann (Ringer-lactate)***	***Albumin 4%***
						Human origin
Na^+	mEq	141	154	140	130	148-154
K^+	mEq	4-5		5	4	0
Cl^-	mEq	103	154	98	109	< 120
Ca^{++}	mEq	5			2,7	
Mg^{++}	mEq	2		3	/	
$HPO_{4^{--}}$	mEq	2,5-6		/	/	> 20
HCO_3^-	mEq	24				
Lactate	mEq	< 2		/	27,7	
Acetate	mEq			27	/	
Gluconate	mEq			23		
pH		7,4	5,1-5,7	6,5-8	6-6,5	
Osmolarite	mOsm	275-290	308	295	273	

Conclusions

Fluid resuscitation saves lifes but the PALS clinical criteria for fluid resuscitation are not based on objective or reproducible haemodynamic studies.

It is obvious that to reverse hypovolemic shock, there should be no delay in fluid therapy. The choice of fluid is secondary to that.
Evidence from the scientific literature is still lacking to define the ideal resuscitation solution, or the optimal amount needed. Criteria for fluid overload are also subject to debate.

The old greek quote 'παν μέτρον άριστον' which means all in good measure or everything in moderation applies in fluid resuscitation too.
What fluid, with what salt and other ions concentration and how much to be effective enough without being deleterious ?

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Severe acute kidney injury as presentation of Burkitt's lymphoma: two case reports and review of the literature.

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Keywords

Acute kidney injury; primary renal lymphoma; Burkitt's lymphoma; nephromegaly.

List of abbreviations

AHT	Arterial hypertension
AKI	Acute kidney injury
CSF	Cerebrospinal fluid
CT	Computer tomography
EBV	Ebstein Barr Virus
GFR	Glomerular filtration rate
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin lymphoma
PRL	Primary renal lymphoma
TLS	Tumor lysis syndrome
US	Ultrasonography
WBC	White blood cell count

Abstract

Acute kidney injury (AKI) is a life-threatening condition and accounts for approximately 2-3% of admissions in pediatric tertiary care centers. Very rarely, AKI is caused by tumor invasion due to a lymphoproliferative malignancy. We report two cases with severe AKI with normal urine sediment as presentation of Burkitt's lymphoma. Clinical examination showed impressive bilateral nephromegaly and hypertension. Blood analysis in both patients indicated severe AKI, without hematological abnormalities. Urine sediment was normal, without hematuria or proteinuria. Abdominal ultrasound demonstrates bilateral renal enlargement (+12SD), with increased corticomedullar differentiation. Magnetic resonance imaging (MRI) demonstrated the presence of a homogenous renal enlargement with features of an infiltrative lesion. Ultimately, microscopic and immunohistochemical analysis of the renal biopsies confirmed the diagnosis of Burkitt's lymphoma in both patients.

Conclusion: We discuss two cases of AKI at a very young age caused by primary lymphomatous renal infiltration due to Burkitt's lymphoma and analyze the literature on this rare condition. The kidney biopsy is mandatory to confirm the diagnosis. Early and aggressive therapy is the key to ensure a good outcome.

Introduction

Acute kidney injury (AKI) is a life-threatening condition that accounts for 2-3% of admissions in pediatric tertiary centers. In the last two decades, incidence is increasing mainly because of the nephrotoxic side effects of new drugs [1, 2].

In cancer patients, AKI is even more common, either secondary to the side effects of chemotherapy or as a direct consequence of malignancy: (1) Volume depletion related to anemia, vomiting or diarrhea can cause prerenal AKI. (2) Obstruction of the urinary tract due to tumor mass is an important postrenal cause. (3) Tumor lysis syndrome (TLS), an intrinsic cause of AKI, is an oncologic emergency resulting in hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia with a risk of cardiac arrhythmias, seizures and death due to multi-organ failure. (4) Renal tumors or malignancies with renal involvement may cause or aggravate AKI [3, 4]. Recently, it has been described that despite the fact that renal tumors in children occur in only 6.64 per million per year (nephroblastoma 90%, renal cell carcinoma 9%), its incidence is increasing [5]. Furthermore, a particular link between cancer and AKI exists in lymphomas. In advanced stage disease, secondary infiltration of the kidneys

is common, but seldom presents with AKI and renal invasion is often diagnosed post-mortem [6]. In addition, only a few cases of primary renal lymphomas (PRL) which seem to originate from the kidneys have been described, however, this is extremely rare in children [7-13]. PRL is less disseminated, but presents always with AKI. Prompt diagnosis is crucial to initiate chemotherapy, to prevent irreversible loss of kidney function.

In this paper, we describe the unusual presentation of two young caucasian boys with AKI and nephromegaly caused by PRL and give an overview of the literature.

Case 1

A four-year-old male presented with a 14-day history of general weakness, anorexia, vomiting and abdominal pain. There was no history of diarrhea or fever. Personal and family history were unremarkable.

Physical examination revealed mild dehydration, tachypnea and malignant arterial hypertension (AHT) (176/119 mmHg; +2SD for sex, age and height is 118/76mmHg). The abdomen was bloated with two non-tender masses in the upper quadrants on palpation.

Biochemical examination revealed hemoglobin of 8.5 g/dL (11.5-13.5 g/dL), white blood cell count (WBC) of 9,200/mm^3 (5,500-15,500/mm^3) and platelet count of 224,000/mm^3 (150,000-450,000/mm3). C-reactive protein was normal. Plasma urea and creatinine were 97 mg/dL (<48 mg/dL) and 2.9 mg/dL (0.26-0.42 mg/dL) respectively. Lactate dehydrogenase (LDH) was 5,860 U/L (135-250 U/L). Uric acid was 8.9 mg/dL (2-5.5 mg/dL), phosphorus level was 1.62 mmol/L (1.45-2.10mmol/L). Urinalysis showed no leucocyturia, hematuria or proteinuria. Urine output was 0.9 ml/kg/h.

Ultrasonography (US) demonstrated hepatosplenomegaly (+3.2SD), and bilateral renal enlargement (right 14 cm (+12SD) and left 13.5cm (+11SD)), with increased corticomedullar differentiation, without hydronephrosis. Magnetic resonance imaging (MRI) confirmed homogenous renal enlargement, with features of an infiltrative lesion (Fig1a). Both the pancreas and the spine were invaded, but cerebrospinal fluid (CSF) was negative for malignant cells.

Since microscopic analysis of bone marrow aspirate was negative, a renal biopsy has been performed. This revealed infiltration by Burkitt's lymphoma: diffuse, medium-sized lymphoid infiltrate, with little basophilic cytoplasm and large nucleoli, combined with small distinct ones could be seen on hematoxylin and eosin stains. Interspersed apoptotic bodies and tingible-body macrophages were present, creating the characteristic starry-sky appearance of Burkitt's lymphoma. The neoplastic cells expressed CD20, CD10, CMYC, but no Bcl2 (Fig1b). FISH analysis showed a t(8;14)(q24;q32). Ebstein Barr Virus (EBV) was not found.

Chemotherapy according to the Inter-B-NHLritux 2010 protocol was initiated. This protocol is a LMB chemotherapy based regimen including cyclophosphamide, vincristine, prednisone, adriamycin, methotrexate, cytarabine and etoposide. During the first week of chemotherapy hemodialysis was required due to TLS. At last follow-up, 26 months after diagnosis, blood pressure and renal US were normal with a glomerular filtration rate (GFR) of 61 ml/min/1.73m².

Case 2

A four-year-old boy presented with lethargy, anorexia, vomiting and weight loss since one month. There was no fever nor diarrhea. He had an unremarkable personal and family history.

Physical examination revealed pallor, mild signs of respiratory distress, distension of the abdomen with hepatomegaly and bilateral nephromegaly, and AHT (139/98 mmHg; +2SD for sex, age and height is 115/74mmHg).

Laboratory evaluation revealed hemoglobin 9.6 g/dL (11.5-13.5 g/dL), WBC-count 13,700/mm3 (5,500-15,500/mm^3) and platelet count 380,000/mm^3 (150,000-450,000/mm^3). Serum creatinine 5.97 mg/dL (0.26-0.42 mg/dL), urea 215 mg/dL (<48 mg/dL) and LDH 758 U/L (135-250 U/L). Uric acid was 12.3 mg/dL (2-5.5 mg/dL) and phosphorus level was 0.94 mmol/L (1.45-2.10mmol/L). Urinalysis reveals no abnormalities. Urine output was 1.2 ml/kg/h.

On US, both kidneys were enlarged (13 cm right and 12,7 cm left; both +10SD) with diffuse aberrant echogenicity, without hydronephrosis. Hepatomegaly, but no splenomegaly was seen. Computer tomography (CT) displayed enlargement of pancreas and both kidneys, without focal lesions (Fig1c). Further staging showed lymphomatous invasion of the spine and supra- and infradiaphragmatic adenopathies. CSF was normal. Bone marrow showed 40% blasts, that weakly expressed CD20 and CD19, but no conclusion could be made.

Renal biopsy confirmed the diagnosis of Burkitt's lymphoma: hematoxylin and eosin stains showed the pathognomonic starry-sky appearance, with expression of CD20, CD10, CMYC and without Bcl2 (Fig1d). FISH analysis identified a IgH-CMYC rearrangement, although classical translocation of t(8;14)(q24;q32)/IGH-CMYC was ruled out. EBV was negative.

After initiating chemotherapy according to the Inter-B-NHLritux 2010 protocol, the patient required hemodialysis due to TLS. At last follow-up, 18 months after diagnosis, blood pressure and renal US were normal with a GFR of 85ml/minute/1.73m^2.

Discussion

We present two cases of AKI caused by primary lymphomatous infiltration of the kidney by Burkitt's lymphoma. Non-Hodgkin lymphoma (NHL) is one of the commonest subtypes of malignancy in children (7%). It develops in lymphocytes and multiple subtypes have been described. Burkitt's lymphoma, named after Denis Parsons Burkitt, is the most prevalent subtype and accounts for approximately 45% of the pediatric cases. It is a poorly differentiated lymphocytic lymphoma, consisting of monoclonal proliferating B-lymphocytes, with a characteristic underlying MYC translocation at 8q24. This translocation is characteristically with a partner immunoglobulin gene that is most often IgH at chromosome 14q32. Occasionally other translocations may be present. This tumor predominantly affects children aged from 5 to 14 years and is probably the fastest growing tumor in humans. As a consequence, more than 70% of the patients present with advanced disease at diagnosis. Thanks to the use of intensive multi-agent chemotherapy, most patients with Burkitt's lymphoma can now be cured, with a five-years event-free survival above 80% [14,15].

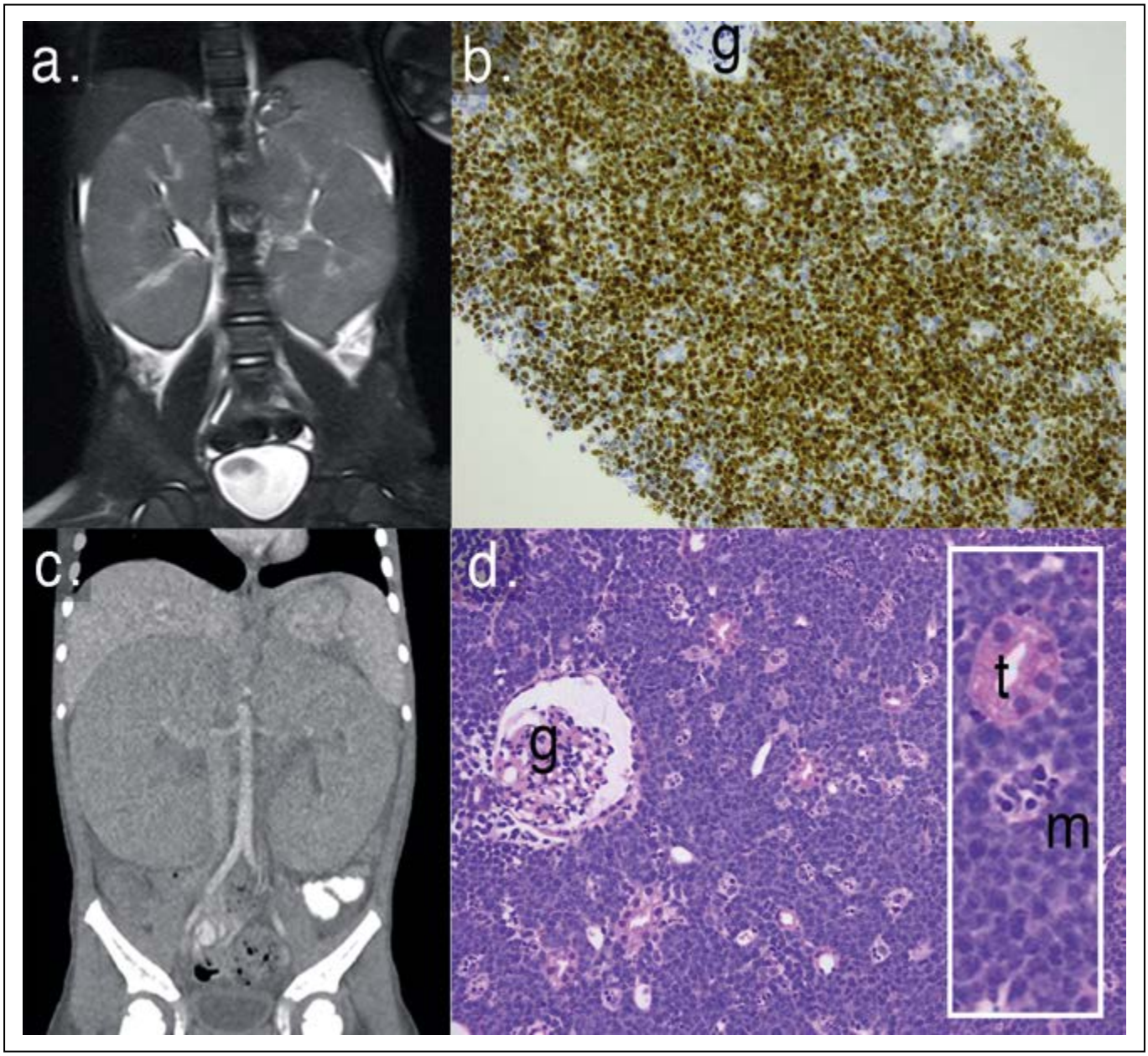
Secondary lymphomatous infiltration of the kidneys is common in NHL. However, AKI as initial symptom is rare. On the contrary, PRL as described in our cases is almost invariably associated with AKI at presentation. Only a few case reports in children have been published [7-13]. The rarity of PRL in children makes it difficult to diagnose.

PRL was first described by Malbrain et al., who suggested some criteria to fulfill the diagnosis: (1) AKI is required at initial presentation; (2) renal enlargement is present without obstruction or extra-renal lymphomatous involvement; (3) diagnosis is made by renal biopsy; (4) other causes of AKI are excluded and (5) chemotherapy provides rapid improvement [16].

While MRI showed infiltration of spine and pancreas in our cases, we believe this had been caused by secondary infiltration due to the aggressively growing tumor starting in the kidney.

PRL as a clinical entity is still being discussed. Indeed, kidneys do not contain lymphatic tissue, which makes it hard to understand how PRL could develop. On the contrary, the pathogenesis of secondary lymphomatous infiltration of the kidney is clear: the primary tumor can spread hematogenously or extends directly from the retroperitoneum. Based on the sparse evidence that exists today, this puzzle cannot be solved. However, the two cases described above approve the kidneys could be the primary organs involved. Thus, it should be clear that a subtype of NHL exists, which presents with renal invasion and concomitant AKI. Disregarding the semantic discussion, the term 'PRL' provides a good description for this specific subtype.

Figure 1



Legend

Fig. 1a Patient 1: A coronal T2-weighted magnetic resonance imaging of the abdomen showing bilateral homogenous, enlarged kidneys.

Fig. 1b Patient 1: Immunohistochemistry staining shows uniform nuclear expression of CMYC in the neoplastic cells, as a consequence of the hallmark translocation t(8;14)(q24;q32), causing dysregulation of the MYC gene, that plays a role in cell cycle progression, apoptosis and cellular transformation (anti-CMYC, x200).

Fig. 1c Patient 2: Computer tomography demonstrates bilateral enlargements of both kidneys without signs of disseminated disease.

Fig. 1d Patient 2: Neoplastic alteration of the kidney by Burkitt lymphoma cells, overgrowing the residual glomeruli (g) and tubuli (t). The cells are medium-sized and uniform in size and shape with several small basophilic nucleoli. The presence of tingible body macrophages (m) gives the tumor the characteristic starry-sky appearance (hematoxylin and eosin, x200; inset x630).

Finally, Törnroth et al. tried to unravel the mechanism of AKI in PRL. In a cohort of 5 adult kidney biopsies compared to 50 adult kidney biopsies from the literature, two patterns of lymphomatous infiltration were distinguished: an interstitial and an intraglomerular/intravascular type. In the first, interstitial proliferation of lymphoma cells causes increased intrarenal pressure, subsequently causing AKI. Renal parenchymal elements are pushed aside, explaining the extreme nephromegaly. The second type causes AKI by obstructing the glomeruli. Obviously, this pattern is associated with proteinuria and hematuria, which resembles glomerulonephritis [17]. In both pediatric cases we described, AKI was caused by the interstitial type and may explain the absence of hematuria and proteinuria.

Conclusion

Although rare, PRL should be considered in children with unexplained AKI and bilateral nephromegaly. Young age does not preclude the diagnosis. When suspected, especially in enlarged kidneys without an aberration in urinalysis, confirmatory renal biopsies should be obtained and therapy should be initiated as soon as possible to avoid irreversible renal impairment.

Acknowledgment

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- COMMUNICATION FROM ASTRAZENECA –

Direct and Indirect Benefits of Vaccinating Children Against Seasonal Influenza

CHILDREN BEAR A HIGH BURDEN OF INFLUENZA AND PLAY A CENTRAL ROLE IN THE TRANSMISSION OF THE DISEASE IN THE COMMUNITY

Influenza viruses infect each year up to 30% of children [1], who often develop complications due to secondary infections like acute otitis media or pneumonia [2]. Young children (under 5 years of age) have consistently shown the highest hospitalizations rates for influenza in Belgium between 2000 and 2007 (86.3/100,000 children) [3]. Mortality remains low in the paediatric population, but can happen in otherwise previously healthy children. In the United Kingdom during the 2003-2004 season, 17 children died of influenza, none had pre-existing risk factors and 14 had no evidence of significant bacterial co-infection [4]. The WHO recognizes since 2012 young children as a risk group for complications of influenza [5].

Children also play a central role in the propagation of influenza throughout the community. In addition to their relatively high infection rate, children can shed virus for >14 days and up to 3 weeks longer than adults; young children can shed virus for up to 6 days before symptom onset, compared with 1 day before through 5 days after symptom onset in adults [6, 7]. Children are also a key vehicle for secondary transmission because of their frequent close contact with large groups of individuals (e.g., at school or day care) [8]. The importance of children in transmitting influenza is highlighted by the sequential shift of peak infection rates from children to adults [8], the apparent interruption of influenza epidemics during school vacations [8], and data suggesting reduced viral transmission with implementation of vaccination programmes among school-aged children [9-11]. It was also observed that school absenteeism often precedes work absenteeism in a community [12].

INDIRECT PROTECTION OF VULNERABLE GROUPS BY VACCINATING CHILDREN – HERD PROTECTION

Protecting children against influenza would not only reduce the high burden of disease in that population, but would also help reduce transmission of influenza viruses in the community, indirectly protecting those who cannot be vaccinated (like the very young children) or those at higher risk of influenza-related complications (like the elderly, or persons with co-morbidities).

Several studies suggest that increased use of influenza vaccine among children could reduce illness in household or community contacts via herd protection, a phenomenon wherein immunisation of a high percentage of a population results in protection for those who are and those who are not vaccinated [13].

In a study in Tecumseh (USA), vaccinating 85% of school age children reduced the occurrence of illness 3-fold compared with a neighbouring community [10]. In Moscow region, vaccinating children in kindergartens and schools resulted in direct protection of the children, but also in indirect outcomes, with 3.4 times fewer episodes of influenza-like illness (ILI) among unvaccinated elderly people compared to communities where children were not vaccinated [14]. In a large study, vaccination with a live attenuated influenza vaccine (LAIV) of approximately 20–25% of children, 1.5 to 18 years of age in the intervention communities, resulted in an indirect protection of 8–18% against medically attended acute respiratory illness (MAARI) in adults above 35 years of age [15]. The same team conducted a study in children 5-18 year-old and observed both direct significant protection against influenza-positive illness and pneumonia and influenza events among vaccinated children (31.5% coverage), and indirect effectiveness against MAARI in unvaccinated children 5 to 11 and adults 35 to 44 years of age [16]. In Canada, a unique community level randomized controlled trial performed in Hutterite communities showed that vaccinating children and adolescents significantly protected unimmunised residents of these rural communities against influenza (reduction of 61% of influenza confirmed illness in the community) [9].

In Japan, an association between vaccination of school-aged children and reduced excess deaths for influenza and pneumonia in the entire population was observed between 1977 and 1987 when influenza vaccination was made mandatory for Japanese schoolchildren and 1994 when the program was discontinued (**Figure 1**) [11]. During this interval, the country experienced an annual reduction of 10,000-12,000 deaths from influenza and pneumonia, despite the limitation of the vaccination program to children and the absence of a national vaccination program for elderly who bear the highest mortality rates. After the end of the program, mortality rates started to increase again, and study authors concluded that **universal vaccination of schoolchildren reduced influenza-associated mortality in the older population by preventing spread of the infection to that susceptible group** [11].

In Europe, QLAIV is approved for children 2 to <18 years of age

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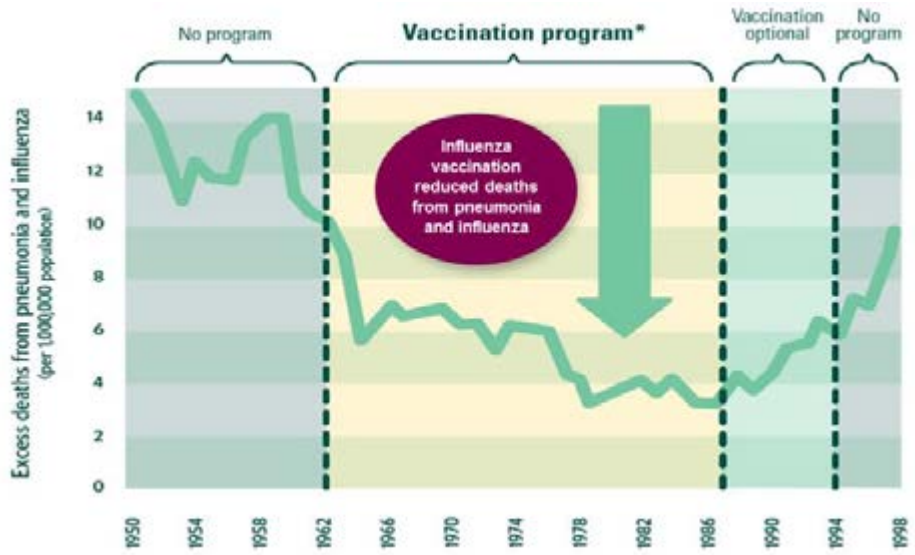
Figure 1. Impact of the influenza vaccination programme of school-aged children in Japan



The green curve represents the five-year moving average of excess deaths attributed to both pneumonia and influenza and all causes in Japan before, during and after the influenza vaccination programme (*) among school-age children (Adapted from [11])

Real world evidence from the UK influenza vaccination programme for children

Several countries recommend vaccination of children against influenza, and in Europe, both Finland and the United Kingdom (UK) have started influenza vaccination programmes for healthy children with a LAIV, based on clinical data showing its superior efficacy compared to inactivated vaccines (87% efficacy against cultured confirmed influenza virus infection, compared to 60% respectively) [17], and a good safety profile [18].

In 2012, the Joint Committee on Vaccine Immunization in the UK decided to extend its flu vaccination policy to children 2-16 years of age based on mathematical models [19, 20] concluding that "*extending the programme to low risk children was likely to be cost effective as this could both provide direct protection lowering the impact of influenza on children and indirect protection lowering influenza transmission from children to other children, adults and those in the clinical risk groups of any age*" [21]. The roll-out is gradual and in the first season (2013-2014) included vaccination of all children aged 2 and 3 years (through primary care services) and primary school-aged children in a limited number of pilot areas. During that first season, the vaccination coverage rates achieved were of 40% among 2-3 year-old children, and 53% in schools on average, and trends were seen for both direct and indirect outcomes of the programme, as measured through various disease indicators like primary care visits and hospitalizations with confirmed influenza virus infection [22].

In 2014-2015, the programme was extended to all children 2-4 year-old and to more pilot areas, including secondary schools. Significant impact of the programme was seen in pilot areas where primary school children (5-11 year-olds) were vaccinated (**Figure 2**) [23]: ***i/*** direct impact was observed in the target group, with statistically significant reductions in primary care visits for influenza-like illness (ILI), emergency department visits and hospital admissions, and non-significant reduction in ICU admissions; ***ii/*** indirect impact in non-targeted age groups (herd protection) was also observed, with a 59% significant reduction of ILI visits in all >17 years, and non-significant trends of reduced primary care visits and hospitalizations among children <5 years of age, and adults. **Similarly to what was observed for the Japanese programme in the 1980's** [11]**, a significant reduction for respiratory excess mortality was observed in the population from primary school pilot areas** [23].

The data from the UK programme are particularly promising given the low vaccine effectiveness observed during the 2014-2015 season due to a major drift of the circulating H3N2 strains compared to the vaccine strains recommended by the WHO.

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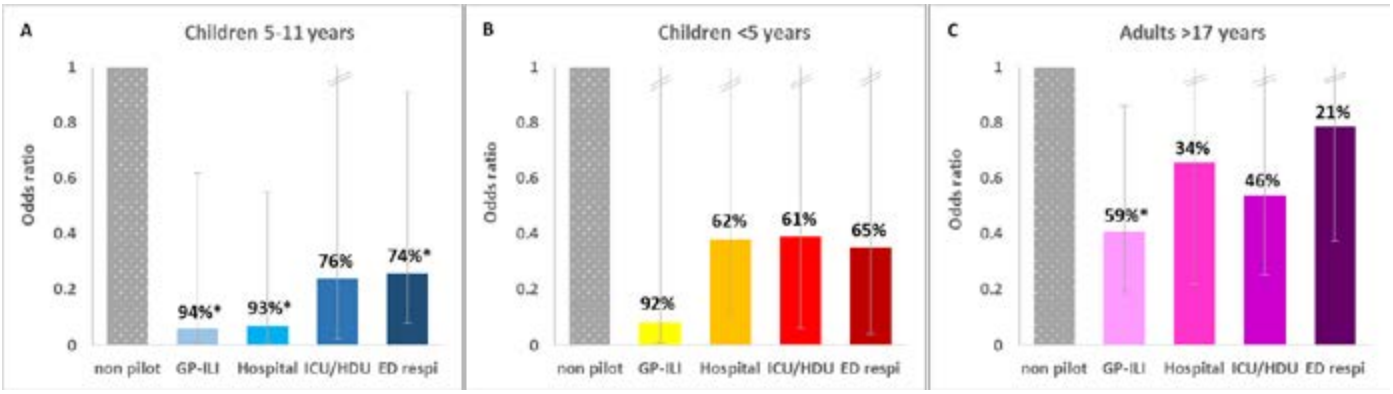
Figure 2. Decreased incidence of primary and secondary care indicators in primary school pilot compared to non-pilot areas in England during the 2014-2015 influenza season



*Odds ratios are provided for different influenza outcomes indicators (GP-ILI – general practitioner visits for influenza-like illness; Hospital – influenza-confirmed hospitalizations; ICU/HDU – influenza-confirmed Intensive care unit/high dependency unit admissions; ED respi – Emergency department attendance for respiratory illness) in the primary school programme target group (**A**) and in non-targeted groups, children <5 years (**B**) and older population (**C**). Percentage decrease of odds ratios are provided for each outcome compared to non-pilot areas (* p<0;05).*

The programme is ongoing throughout the UK, but to date, only England has published outcome data. Nevertheless, the JCVI stated during its meeting in June 2015 that Scotland and Northern Ireland, which vaccinated all primary school aged children in 2014-2015, achieved high uptake rates and experienced a shorter period of flu activity above the threshold level compared to England, which only had pilots, and Wales which did not vaccinate in primary schools [24].

For the current season, 2015-2016, all children 2-6 year-old will be targeted by the programme, together with the continuation of school programmes in pilot areas in England, and all primary schools in Scotland and Northern Ireland.

Conclusion

Children bear a high and under recognized burden of influenza disease and play a key role in the transmission of the disease in the community. Several studies have demonstrated that vaccination of school-age children provides indirect health benefits for the population. Based on such evidence, countries like the UK have decided to include low risk children into their flu vaccination policy. In Belgium, the cost-effectiveness of flu vaccination in children has been evaluated in a study concluding that "*vaccination of children against seasonal influenza can achieve some level of indirect protection*" and that "*a universal influenza vaccination of children is likely to be considered as cost-effective compared to other interventions if vaccination costs would be reduced*" [25]. A new model for Belgium has been developed and recently presented at ISPOR [26], demonstrating both direct and indirect protection benefits of vaccinating healthy children with a quadrivalent LAIV in Belgium. Further analysis are required to assess the cost-effectiveness of a vaccination programme with a LAIV in Belgium.

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Three children with dark discolouration of urine.

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Keywords

alkaptonuria, dark urine, homogentisic acid, ochronosis.

Case report

Two sisters of respectively 7 months and 6 years old, with consanguineous Syrian parents presented with complaints of dark discolouration of urine at the outpatient clinic. This phenomenon existed since their birth. The diapers of the sisters discoloured dark and sometimes black. A third case concerned a 3-years-old Ethiopian boy without medical history who consulted the international adoption consultation. He presented with dark discoloured urine (Figure 1). Physical examination of all three children showed normal growth, development and no apparent pathological signs. None of them had physical complaints. Laboratory results of urine samples of the Syrian children (Table 1) showed increased protein concentration, reduced creatinine concentration and strongly increased protein/creatinine ratios. The laboratory results could not be related to any disease. To explain those divergent laboratory results, quantitative microalbumin levels and qualitative protein in urine, using a dip-stick test strip, were subsequently analysed. Microalbumin was normal and the dip-stick tested negative. A different outcome between the negative dipstick test and the positive laboratory test reveals interference by a substance, which falsely elevates protein levels and falsely decreased creatinine levels. For quantification of creatinine, a second method based on high performance liquid chromatography (HPLC) method was used. The HPLC method showed normal creatinine levels, confirming also falsely decreased creatinine in the routine laboratory analysis. A possible interference by homogentisic acid (HGA) was suspected as a possible cause [1]. Adding one drop of 1.0 M NaOH to fresh urine caused dark discolouration (Figure 1). NaOH accelerates the oxidation and colour change of HGA in fresh urine from colourless to dark urine within a few minutes. This colour change is very suggestive for the diagnosis of alkaptonuria. A very high concentration of HGA measured in the urine of all children (Table 1) confirmed the diagnosis.

Table 1: Laboratory results of urine samples of 2 Syrian sisters

	Syrian girl 6 year	Syrian girl 7 months	Ethiopian boy 3 years	Reference values and units
Total protein#)	2.46	0.93	-	g/L
Microalbumin	9.6	11.3	-	0-30 mg/L
Creatinine in urine#)	2.2	0.7	5.0	mmol/L
Protein#)/Creatinine#) ratio	11.18	13.29	-	0.15-0.30 g / 10 mmol creat.
Dipstick protein in urine	negative	negative	negative	Negative
Creatinine (HPLC)	12.68	1.87	-	mmol/L
Homogentisic acid	22092	9938	-	µmol/L
Homogentisic acid	3320	5314	2024	0-5 mmol/mol creat.

#) Interference of the laboratory method by increased homogentisic acid (HGA) levels

Figure 1:

A. Dark discolouration of urine in underwear
B. Addition of 1.0 M NaOH to fresh urine (left tube) turns urine into dark (right tube) and is suggestive for alkaptonuria.

Discussion

Alkaptonuria is a rare autosomal recessive disorder caused by homozygous or compound heterozygous mutation in the homogentisate 1,2-dioxygenase (HGD) gene on chromosome 3q13 leading to deficiency of the HGD enzyme. According to the Orphanet the prevalence of alkaptonuria is 1-9/1.000.000. HGD is involved in the catabolism of phenylalanine and tyrosine. HGD deficiency leads to accumulation of HGA which is oxidized and polymerized when exposed to air or oxidative reagents and causes urine to turn dark. An accumulation of the dark pigment in connective tissues, such as sclerae and skin, is called ochronosis. This characteristic dark pigmentation usually appears after the age of thirty years. People with alkaptonuria typically develop progressive and severe arthritis, particularly in the spine and large joints, beginning mostly in early adulthood. Damage to heart valves, kidney stones, and prostate stones can be other features of ochronosis.

It has been suggested that a protein restricted diet and a high dose of ascorbic acid reduces the intake of phenylalanine and tyrosine and impedes the oxidation and polymerization of the HGA metabolite. However, it is not clear whether this dietary restriction has a beneficial effect on the prevention of clinical symptoms later in life. Ascorbic acid is believed to prevent the oxidation of homogentisic acid and reduces the binding of HGA to connective tissues. Nitisinone (NTBC) is a potential disease modifying drug which is currently applied only to adults and in a research context for the treatment of alkaptonuria. It inhibits 4-hydroxyphenyl-pyruvate-dioxygenase and reduces significantly formation and accumulation of HGA in connective tissues [2]. Because of the postulated risk on cognitive dysfunction, the use of Nitisinone is not indicated for children with alkaptonuria given the advantages do not outweigh the disadvantages [3].

Conclusion

Alkaptonuria is rare, and less known by pediatricians. Dark discolouration of urine is the characteristic presenting clinical symptom. High HGA levels might falsify laboratory results. Using different analysis methods, right laboratory results can be obtained. Dark discolouring by adding 1.0 M NaOH solution to fresh urine is very helpful to suggest the diagnosis alkaptonuria, but increased HGA is the hallmark for the right diagnosis.
A curative treatment has not been developed yet. Nitisinone is a promising enzyme-inducing drug that reduces the accumulation of HGA in adults. A protein restricted diet with a high dose ascorbic acid intake are currently the best therapeutic options in children. Because alkaptonuria patients are rare, and the development of clinical symptoms is highly unpredictable, it is difficult to determine the moment to start treatment with Nitisinone. Therefore, it has been recommended to follow and to treat these patients in an academic centre.

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Bilateral Cryptorchidism with a Twist.

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Keywords

Cryptorchidism, Disorders of Sex Development, 46 XX male, 46, XX Testicular Disorder of Sex Development, SRY gene

Introduction

Cryptorchidism or the absence of at least one testis in the scrotum, is the most common disorder of the male genitourinary system and is most frequently identified at birth. The testicular descent occurs in the third trimester of gestation: about 30% of the preterm males have an undescended testis, the incidence at term age is estimated between 3 to 9%. [1] Bilateral cryptorchidism is found in 10 to 20% of cases. A spontaneous descent of the testis does not occur after sixth month of life. The persistence of cryptorchidism beyond puberty is correlated to subsequent infertility problems, risk of testicular cancer and a reduction in psychosexual wellbeing. As this condition can induce later morbidity, timely identification and referral for adequate treatment is imperative. [1,3] We would like to present the case of a 15-month old boy who presented with bilateral cryptorchidism and a thin penile shaft, due to a SRY gene translocation, conforming the diagnosis of 46, XX male syndrome.

Case presentation

We present the case of a 15-month old boy who presented with bilateral cryptorchidism. Parental concerns about his penile length in comparison to his six-week-old sibling were the initial motive for checkup at our outpatient clinic.

There were no elements in the history that suggested a severe somatic pathology. He had a normal psychomotor development. He showed a regular growth along the 3rd centile for both weight and height (target height = 176.5 cm, +-8.5 cm). On clinical examination we observed bilateral cryptorchidism, both testes being inguinal and a thin penile shaft with small but normal length (width 9 mm, no reference charts available, length 3 cm, mean 4.7+-0.8 cm, mean 2.5 SD = 2.6 cm).[4] There was no hypospadias.

A biochemical and hormonal work up showed no abnormalities: normal electrolytes, normal thyroid function, normal cortisol levels, LH < 0.1 IU/L, FSH 0.6 IU/L, prolactine 4.7 µg/L, estradiol < 5 ng/L, AMH > 22 .00 ng/mL and a normal 17-hydroxyprogesteron level. An ultrasound of the scrotum confirmed the presence of both testes.

The combination of bilateral cryptorchidism, the thin penile shaft and relative small penis in comparison with his younger sibling was the reason for performing cytogenetic analysis, which showed a 46, XX karyotype. Further testing confirmed a translocation of the SRY gene to the X chromosome and the diagnosis of 46, XX male syndrome was made.

The patient was referred to our Pediatric Endocrinology department for further follow up. He started on a triple cycle of a very low dose of testosterone (25 mg intramuscular once monthly) to promote penile growth. Descent of the testes was not reached: an orchiopexy with biopsies was performed before the age of two. Biopsies showed Sertoli cell only tubuli (Nistal classification type 3), and absence of ovarian tissue. Biopsies were performed to differentiate between 46, XX male syndrome and the 46, XX Ovotesticular Disorder of Sex Development, as a minority of patients with 46, XX Ovotesticular Disorder of Sex Development (previously known as hermaphrodites) are SRY positive [5].

Discussion

Cryptorchidism is the most common congenital abnormality of the genitourinary tract. The diagnosis of cryptorchidism is essentially clinical. Cryptorchidism should be differentiated from retractile or ascending testis due to a cremasteric reflex.

When one or both testes cannot be found at clinical examination, several techniques have been described to assess its presence or location: anti mullerian hormone (AMH) levels, ultrasound, MRI and laparoscopy. [1,2] In case of bilateral cryptorchidism, dosage of AMH allows to confirm the presence or absence of testicular tissue. In case of undetectable AMH, anorchidism is confirmed and surgical exploration is unnecessary. When AMH is detectable, but presence of the testes cannot be confirmed by ultrasound or MRI, a laparoscopy is indicated and has the additional advantage of immediate therapy if the testes are found.

Unilateral or bilateral cryptorchidism in combination with hypospadias or micropenis suggests a disorder of sexual development (DSD) and requires an endocrine and genetic work-up. [1,2,6] In case of hypospadias with unilateral cryptorchidism, the of risk of DSD is 15%, when there is hypospadias with bilateral cryptorchidism this rises to 50%. [7]

The gonadal development is a very precise and very complex matter. To develop a female phenotype with normal ovaries a 46, XX karyotype, but also the presence of genetic factors such as DAX1 and the signaling molecule WNT-4, are necessary. [8] To develop a male phenotype a 46, XY karyotype and, more specifically, an intact SRY (sex determining region - Y) gene, in combination with other factors such as SOX9 are required.

It is thought that the SRY gene plays a role in germ cell development or maintenance and thus differentiation to a male phenotype. [9]

Recombination between the X and Y chromosomes' pseudo – autosomal regions in paternal meiosis can result in XX males or XY females due to win or loss of the SRY gene. [9] These chromosomal rearrangements lead to an aberrant sexual differentiation.

They represent only a part of the disorders of sexual development (DSD) known today, as the term DSD describes a condition in which development of chromosomal, gonadal or anatomical sex is atypical. Further testing in our patient, as shown in Figure 1, confirmed an SRY gene translocation and the diagnosis of 46, XX male syndrome was made.

The 46, XX male syndrome, in the more recent literature referred to as the nonsyndromic 46, XX Testicular Disorder of Sex Development, is a relatively rare genetic disorder. The prevalence is estimated at one in 20,000 to 100,000 males. Approximately 80% of individuals with 46, XX male syndrome are SRY positive and 20% are SRY negative. The majority, about 85%, will present after puberty with male external genitalia ranging from normal to ambiguous, two small testicles without presence of ovarian tissue, gynecomastia,azoospermia, absence of the Müllerian system and a shorter-than average stature.

Approximately 15% of individuals with nonsyndromic 46,XX testicular DSD present at birth with ambiguous genitalia. [9, 13] Testicular histology which have been reported with this syndrome are inconsistent : some have been reported as hyalinization of the seminiferous tubules, absence of the germ cells or absence of the seminiferous tubules, hyalinized seminiferous tubules with Sertoli cells and marked interstitial cell hyperplasia, Leydig's cell hyperplasia or absence of the Leydig's cells. [14, 15]

Pediatric cases are still scarce and are usually diagnosed by chance [11], as diagnosis is usually made in adult life due to further investigations of infertility. In a study by Hofher et al. prevalence of 46 XX male was about 0.4 to 1% of men over 18 years old diagnosed with infertility. [12, 13, 16]

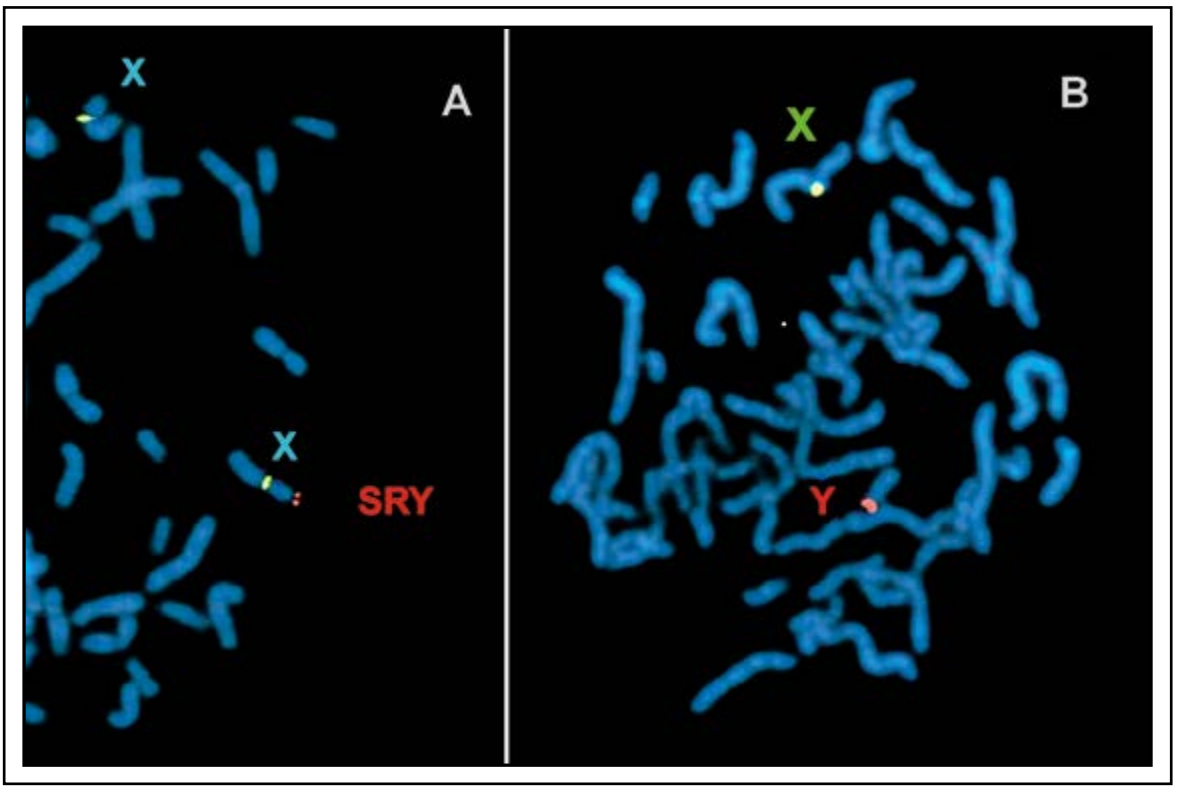
The current guidelines on diagnostic workup of cryptorchidism are quite confined concerning the definition of hypovirilization. The study groups of Gapany et al. and Kolon et al. [1, 2] performed a systematic review of all available guidelines. They concluded to perform a hormonal work up and a karyotype if no testis are palpable or in the presence of other signs of 'hypovirilization', such as hypospadias or micropenis. Our patient did not have hypospadias or micropenis [1, 4, 6], but we did observe a thin penile shaft and therefore performed a karyotype. A strict adhesion to the current diagnostic guidelines would have precluded this workup, mainly because of the unclear definition of hypovirilization.

Not discussed in the guidelines concerning management of cryptorchidism is the anogenital distance (AGD), which to date is mainly used as a biological marker of androgen action in population studies of the effects of environmental chemicals on genital development. A reduced AGD has been associated with hypospadias. [17, 20] The meaning of AGD in DSD is not clear, we did not measure it in our patient. Recent literature in humans has shown that a shorter AGD is associated with a higher incidence of cryptorchidism in male newborns. AGD could serve as a potential biomarker for disruption of androgen action during the male programming window period. Additional studies are needed to conform these findings and to further determine their etiology. [21]

Our understanding of DSD is still growing and guidelines will have to evolve as an early diagnosis and follow-up of these patients can lead to a better quality of life with the offering of orchiopexy, testosterone replacement therapy, in some cases growth hormone therapy [22], mammoplasty, preventive measures concerning osteopenia and psychological support.

Our case report suggests that not only penile length but also penile width is important to take into account when assessing virilization. We would therefore advocate a relaxed interpretation of the term hypovirilization and a more liberal performance of a karyotype in the presence of bilateral cryptorchidism with only discrete signs of hypovirilization.

Figure 1: Panel A : FISH karyotype of our patient, showing the presence of two X centromeres and one SRY gene. Panel B : FISH karyotype of a male control, showing one X centromere and one SRY gene.



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Toename van hypoglycemieën na toediening van een somatostatine-analoog voor hyperinsulinisme: een indirecte aanwijzing voor insulinetoediening in kader van een Munchausen by proxy.

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Keywords

kind, congenitaal hyperinsulinisme, hypoglycemie, insuline, Munchausen by proxy

Abstract

Congenitaal hyperinsulinisme (CH), gekenmerkt door hoge insulinewaarden tijdens een hypoglycemie, is de meest frequente oorzaak van hyperinsulinisme bij kinderen. Onze casus betreft een vijfjarig meisje met recidiverende hypoglycemieën sinds een Nissen fundoplicatie op de leeftijd van 1 jaar. Initieel werd een dumping syndroom gediagnosticeerd, maar de hypoglycemische symptomen persisteerden ondanks acarbose en dieetaanpassingen. Een continue subcutane glucose monitoring bevestigde de multipele hypoglycemieën, voornamelijk postprandiaal. Serum insuline op het moment van een nuchtere glucosemeting (52 mg/dL) bedroeg 8.6 µIU/mL (referentie nuchtere concentraties: 2.7 – 16.5 µIU/mL), met een C-peptide van 1.3 ng/mL (referentie nuchtere concentraties: 0.87 – 3.0 ng/mL). Serum aminozuren, lactaat en ammoniak bepalingen, alsook een CT-scan van de pancreas, waren normaal. Dit leidde tot het vermoeden van CH, waarop genetische testen werden ingezet. Diazoxide werd opgestart, maar gaf geen verbetering. Subcutane toediening van een somatostatine-analoog leidde tot minder frequente hypoglycemieën. Bij de omschakeling naar een langwerkend somatostatine-analoog traden ernstige hypoglycemieën met bewustzijnsverlies op. Op dat moment werd een verhoogd serum insuline (47.4 µIU/mL) met een laag C-peptide (0.24 ng/mL) geobjectiveerd. Dit leidde tot het vermoeden van exogene insulinetoediening, wat toegegeven werd door de moeder. Ze verklaarde daarenboven sinds verscheidene jaren intermittent sulfonylurea gegeven te hebben aan haar kind.
Exogene insulinetoediening moet steeds overwogen worden in de differentiaaldiagnose van recidiverende en onverklaarde hypoglycemieën met hyperinsulinemie, zeker indien de episodes verergeren na toediening van somatostatine-analogen, welke de insulinemie bij exogene insulinetoediening kan verhogen. De verborgen toediening van zowel orale sulfonylurea als subcutane insuline bemoeilijkt de diagnose van Munchausen by proxy.

Abstract

Congenital hyperinsulinism (CH), characterized by inappropriate normal insulin levels during hypoglycemia, is the most frequent cause of hyperinsulinism in children. A five-year-old girl was investigated for recurrent episodes of hypoglycemia since the age of one year. A dumping syndrome after Nissen surgery had been diagnosed previously, but hypoglycemic symptoms persisted after acarbose administration and dietary changes. At the moment of a borderline fasting hypoglycemia (53 mg/dl) serum insulin was 8.6 mUL/L and C-peptide was 1.33 µg/L. Serum amino acids, lactate, NH3 and CT scanning of the pancreas were normal. A urine screening for sulfonylurea was negative. Diazoxide therapy was started, without any improvement. Less frequent hypoglycemic episodes were seen after switching to a subcutaneous somatostatin analogue. A severe hypoglycemic episode, leading to loss of consciousness, was witnessed after a switch to a longacting somatostatin analogue. At that moment, an increased serum insulin (47.4 mIU/L) in combination with a low normal C-peptide level (0.08 nmol/L) was found. This led to the suspicion of exogenous insulin injection, which was confessed by the mother. Furthermore, administration of sulfonylurea from presentation until start of somatostatin therapy was mentioned by the mother, explaining the initial elevated C-peptide and insulin levels.
Surreptitious insulin injection should be considered in the differential diagnosis of recurrent and unresponsive hypoglycemic episodes, especially in case of more severe hyperinsulinemia occurring after a somatostatin analogue administration, known to increase the level of exogenous insulin. Simultaneous dosage of C-peptide and insulin levels is the key in differentiating exogenous from endogenous hyperinsulinism.

Casusbeschrijving

In januari 2011 zagen we een vijfjarig meisje dat zich presenteerde met recidiverende hypoglycemieën sinds de leeftijd van 1 jaar na het uitvoeren van een Nissen fundoplicatie wegens een ernstige gastro-oesofageale refluxziekte. Een orale glucose tolerantietest (OGTT) liet een dumping syndroom vermoeden. Een behandeling met acarbose had een wisselend effect op de postprandiale glycemie. Daarnaast vertoonde de patiënt een voorgeschiedenis van chronische bronchitis bij een tracheomalacie en astma, waarvoor ze behandeld werd met budesonide, salbutamol en montelukast, en een idiopatische hematurie zonder afwijkingen op nierbiopsie. Bepalingen van nuchtere glycemie, serum elektrolyten en basale hormonen (ACTH, cortisol, GH, insuline, C-peptide) waren normaal. Een echo van de lever en een OGTT waren normaal.

Bij een verlaagde glycemie van 52.9 mg/dL werd een insulinewaarde van 8.6 µIU/mL en een C-peptide van 1.32 ng/mL gemeten. Serum aminozuren, lactaat en ammoniak bepalingen alsook een CT-scan van de pancreas waren normaal en ketonurie was afwezig. Er werd gestart met een behandeling met diazoxide (10mg/kg/dag) en genetisch onderzoek naar congenitaal hyperinsulinisme werd ingezet .

De bepaling van de vrije vetzuren (0.99 mmol/L) en β-hydroxybutyraat (0.24 mmol/L) was normaal en in de urine konden geen sulfonylurea teruggevonden worden. Er werden geen mutaties in het *HNF4A, KCLJ11 of ABCC8* gen teruggevonden.

Van november 2012 tot december 2013 werd diazoxide vervangen door subcutane sandostatine-inspuitingen en in september 2014 werd geswitched naar langwerkende somatostatines gezien de persisterende hypoglycemieën.

Bij een glycemie van 38.0 mg/dL werd een serum insuline van 47.4 µIU/mL en een C-peptide van 0.24 ng/mL gemeten. Op dit moment kwam het vermoeden van de exogene toediening van insuline door de moeder en werd een transfer naar de pediatrische intensieve zorgen zonder de aanwezigheid van de moeder geregeld. Daar werd een snelle normalisatie van de glycemie zonder enige behandeling geregistreerd. De moeder gaf toe aan haar dochter de afgelopen 2 jaar insuline toegediend te hebben, ontvreemd uit het woonzorgcentrum waar ze werkte, voorafgegaan door intermittente sulfonylurea toediening.

Discussie

Wat begon als een tweede advies omtrent recidiverende hypoglycemieën evolueerde van een zoektocht naar de oorzaak van hyperinsulinisme naar het bewijzen van een Munchausen by proxy (MBP). Gedurende drie jaar werden multipele investigaties uitgevoerd en tevergeefs verscheidene medicaties uitgetest. De paradoxale toename van hypoglycemieën bij opstart van een langwerkend somatostatine-analoog en de contrasterende insuline/C-peptide verhouding leidde finaal tot de diagnose van exogeen hyperinsulinisme.

De oorzaak van hyperinsulinisme is bij kinderen niet altijd met zekerheid te achterhalen. Genetische bevestiging van een congenitaal hyperinsulinisme is immers niet altijd mogelijk, terwijl de beeldvorming van een insulinoom initieel normaal kan zijn. [1] Anderzijds kan de opsporing van kortwerkende sulfonylurea in de urine daags na toediening negatief zijn en meten niet alle immunoassays exogeen insuline. [2] De verborgen intermittente toediening van zowel orale sulfonylurea als subcutane insuline bemoeilijkten de diagnose van exogeen hyperinsulinisme in onze casus.

In de literatuur kunnen slechts een aantal casussen teruggevonden worden waarbij een zorgverlener insuline toedient aan een kind, met slechts één casus waarbij exogeen insuline was voorafgegaan door toediening van sulfonamides. Bij de behandeling van volwassenen met een onderliggende neuro-endocriene tumor, maligne insulinoom of maligne mesenchymale tumor, werd het fenomeen van verergerende hypoglycemieën bij de overschakeling op langwerkende somatostatines vastgesteld. [3, 1, 4] Bij gezonde proefpersonen werd een verlengde werking van exogeen insuline na toediening van een somatostatine-analoog gedocumenteerd. [5] Ons laboratorium gebruikte de Roche ECLIA insuline kit, welke een kruisreactiviteit met Actrapid® vertoont.

Drie casusbeschrijvingen uit 1999 (Bappal et al), 2008 (Dejoie et al) en 2010 (Green et al) rapporteren de acute presentatie van een jong meisje (3.5, 2 jaar en 8 weken oud) met respectievelijk lethargie, convulsies en nogmaals lethargie gevolgd door recurrente hypoglycemieën. Urine analyse toonde geen ketonen, geen afwijkingen van de organische zuren, noch de aanwezigheid van een oraal antidiabeticum. Bloedresultaten waren initieel normaal. Maar net zoals in onze casus zorgde de triade van een laag c-peptide en hyperinsulinemie op het moment van een hypoglycemie voor de bevestiging van MBP. Dejoie et al en Green et al maakten gebruik van immunoassays om de synthetische insuline-analogen te detecteren in het bloed: ze vergeleken daarvoor stalen van patiënten met stalen van niet-diabetische individuen en individuen met type 1 diabetes. In alle casussen was er een familielid met diabetes die behandeld werd met insuline. [2, 6, 7]

Wat opvalt is dat personen met MBP in de verschillende case reports enkele gemeenschappelijke karakteristieken vertonen. Zo gaat het vaak om een vrouwelijk persoon, vaak een familielid, meestal de moeder. De persoon die insuline toedient heeft in zijn directe omgeving de mogelijkheid om ongemerkt aan insuline te geraken: door een familielid met diabetes mellitus of een werkgerelateerde context. Een ander typisch kenmerk is dat op het moment dat er een vermoeden is dat de verzorger de ziekte zou kunnen veroorzaken, deze persoon overschakelt op een andere methode of een andere medische subdiscipline raadpleegt voor andere symptomen. In deze casus werd eerder een nierbiopsie uitgevoerd in het kader van onverklaarde hematurie. Achteraf gaf het meisje toe dat haar moeder via een vingerprik bloed in de urine druppelde.

Vaak wijst de discrepantie in de laboresultaten in de richting van MBP. Slechts op het moment dat het mogelijk is om het kind te isoleren van de ouder wordt de diagnose duidelijk. Deze casus toont aan dat de weg naar de diagnose van MBP moeilijk is en van lange duur kan zijn.

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Diagnosing serious infection in acutely ill children in ambulatory care*.

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Background:

Acute infection is the most common presentation of children to ambulatory care.[1] In contrast, serious infections, such as meningitis, pneumonia, sepsis, and pyelonephritis, are rare and often present at an early stage.[2] Clinical prediction rules and near patient testing might aid early recognition of those serious infections and adequate referral to avoid complications or death. Previous research has shown that a decision tree based on signs and symptoms can effectively rule out serious infection in children, although only a small amount of all children testing positive might actually have a serious infection.[3] To reduce the number of false positives, point-of-care (POC) tests might be useful, providing an immediate result at the bedside. The most probable candidate is C-reactive protein.[4] Every clinician should reassure anxious parents of children with self-limiting illnesses.[5] The improvement of diagnostic algorithms, the addition of technological devices and the sensible use of safety netting procedures could improve prognosis of seriously ill children.

Methods:

This thesis focusses on this clinical prediction rule and evaluates whether it has diagnostic value in different urgent-acces settings, such as general practice, pediatric outpatient clinic and the emergency department. First, we externally validated clinical prediction rules, identified by a systematic review, in 7 urgent-access datasets, as well as comparing these results to recent findings in other studies.[6] After zooming in on the diagnostic value of the clinical prediction rules based on vital signs with potential to differentiate serious infections from the majority of self-limiting illnesses in an inpatient pediatric setting in the UK,[7] we focused our analyses on the validation of the decision tree based on signs and symptoms in a new but similar population in Flanders.[8] We examined the analytical accuracy and user-friendliness of a POC test after careful selection of a device that meets all our requirements.[9] Finally we explored the added value of the selected POC CRP test in a prospective diagnostic accuracy study in three different ambulatory care settings: general practice, outpatient pediatric clinic, and the emergency department.[10]

Results:

We found that the clinical prediction rule, based on the physician's gut feeling that something is wrong, a child experiencing shortness of breath and a temperature above 40°C, effectively rules out any serious infection in the general practice setting and that adding a point-of-care CRP test improves this prediction rule, avoiding additional unnecessary referrals for additional testing or admission to hospital. In the specialist setting (emergency department or outpatient clinic) we suggest a new clinical prediction rule, based on the CRP-level in combination with clinical signs and symptoms to perform initial triage of children presenting with an acute illness.

Discussion:

The incidence of serious infections has declined over the past few years, amongst other reasons, due to vaccination strategies and improvements in neonatal care. Before a clinical prediction rule can be implemented in routine care, it has to go through several stages of development and testing.[11-13] A single test will never reach perfect sensitivity and specificity in real life. To tackle the ever-present clinical uncertainty, physicians often put a safety net in place, informing parents when to re-contact and which alarm signs are relevant to monitor.[14-17] We have put an emphasis on these issues and offer a perspective for future developments in the field of point-of-care testing in serious infections in pediatric primary care.

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Neonatal pharmacology: Towards improved predictability.

Summary of the PhD Thesis of Anne Smits
Promotor: Prof. Dr. K. Allegaert, Co-promotor: Prof. Dr. J. de Hoon

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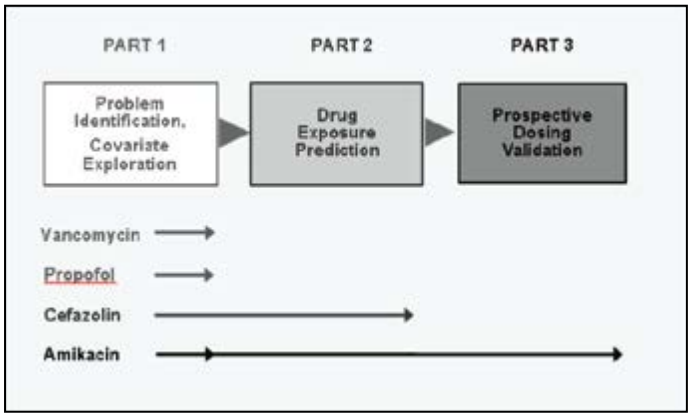
Keywords

Clinical pharmacology, neonate, covariates.

Summary

Clinical pharmacology has the intention to predict drug effects based on pharmacokinetics (PK, concentration/time relationship) and pharmacodynamics (PD, concentration/effect relationship). The general principles hereby used also apply to neonates. However, fast developmental changes in neonatal life result in extensive inter- and intra-individual PK/PD variability, making both clinical care and research in these patients more challenging. The aim of this doctoral thesis is to improve drug exposure predictability in neonates based on PK and/or PD studies of commonly used -but still insufficiently understood- drugs in this population. The research sequence presented in Figure 1, reflects the 3 main parts of the thesis. Subsequently, each part will be discussed separately.

Figure 1: Schematic overview of the 3-step general objective of this thesis and the compounds studied. Arrows along the compounds indicate the part in which they are investigated



PART 1: Exploration of covariates contributing to inter-individual variability in drug exposure in neonates.

Although vancomycin is used for more than 50 years in neonatal intensive care units, there is no optimal dosing regimen yet. We reported up to 70% of vancomycin routine trough levels below the target level (10 mg/L), despite the use of published dosing regimens. This is just an illustration of the extent of unanticipated problems in neonatal drug exposure. Small (low birth weight, current weight) and immature [low gestational age, postmenstrual age (PMA)] neonates, seemed to be most prone to display subtherapeutic vancomycin exposure in this retrospective study [1].

Similar, knowledge on disposition of drugs at an effect site or deep body compartment in neonates is limited. Therefore we collected and quantified amikacin concentrations in epithelial lining fluid of ventilated neonates. The highest amikacin concentration measured was reached between 6-14.5 h after administration, which is delayed compared to adults [2].

Besides antimicrobial drugs, we also explored covariates of propofol disposition in neonates. This short acting anesthetic drug is used in our unit as premedication for (semi)elective invasive procedures. Using 24 hour urinary propofol metabolite profiles, postnatal age (PNA) turned out to be the main driver of propofol metabolism [3]. The limited contribution of glucuronidation to propofol metabolism was in line with other reports of glucuronidation in early life. Based on the link between phenotypic glucuronidation and propofol clearance, and on the fact that bilirubin also needs glucuronidation, we explored if indirect hyperbilirubinemia served as a predictive biomarker to anticipate further reduced propofol clearance in neonates. Since both iso-enzymes (UGT1A1 for bilirubin and UGT1A9 for propofol) involved display a similar maturational pattern, this hypothesis seemed reasonable. However, it turned out that PMA and PNA as covariates were most optimal to predict clearance, irrespective of the presence of hyperbilirubinemia [4]. This can be explained by the fact that neonatal jaundice is the final result of either increased production or decreased elimination. Elevated bilirubin, respiratory distress syndrome, hemodynamic instability are all characteristics most often seen in the first days of life. Since we use propofol for (semi)elective endotracheal intubation in these neonates, without appropriate propofol dosing regimens, a prospective dose-finding study with simultaneous assessment of propofol PD (sedation and relaxation state, vital signs) was conducted. Based on a preliminary analysis, a trend towards lower single intravenous bolus propofol doses compared to previous reports was documented, while clinical recovery after the propofol bolus takes time. Based on continuous vital sign data, safety was assessed with only a moderate decrease in blood pressure and a short decrease in peripheral and cerebral oxygen saturation.

PART 2: Integration of covariates to improve drug dosing and drug exposure prediction.

Integration of covariates, explaining variability in neonatal PK and/or PD processes, in drug dosing regimens can improve drug exposure prediction. This was illustrated with cefazolin, a first-generation cephalosporin used as prophylactic agent for surgical procedures. Based on a population PK model, covariates of neonatal cefazolin disposition were determined, taking into account saturable (i.e. concentration dependent) protein binding [5]. Since the unbound fraction of a drug is responsible for drug (side)effects, we encourage both the determination and implementation of protein binding data in PK/PD models. The unbound cefazolin fraction in neonates is higher compared to adults and is in part explained by covariates PMA, albuminemia, total cefazolin concentration and unbound cefazolin concentration [6]. Pooling of our cefazolin protein binding data with published adult cohorts revealed that besides anticipated covariates (albuminemia, total cefazolin concentration, unbound cefazolin concentrations), also the patient subgroup contributes to variability in unbound fraction across different populations [7]. Monte Carlo simulations (i.e. a statistical tool to evaluate and predict drug exposure) using our neonatal cefazolin data, indicated that lower cefazolin doses could be used while still reaching a predefined PD target for effective prophylaxis. Based on this analysis, a weight-and age-based model-derived cefazolin dosing regimen for neonates was proposed [5]. Although this dosing regimen should theoretically result in improved cefazolin exposure in NICU patients, prospective validation by a clinical trial is needed.

PART 3: Prospective validation of model-based dosing regimens in neonates.

In the last part of this thesis, amikacin, an aminoglycoside, was used to document how such a prospective dosing validation can lead towards improved predictability of drug exposure in neonates. A previously published amikacin population PK-based dosing regimen was prospectively validated using 1195 routine serum therapeutic drug monitoring (TDM) results. Overall, target peak (>24 mg/L) and trough values (<3 mg/L) were attained in most patient groups. Specific subgroups who would benefit from an additional dosing adaptation were identified. Consequently, this prospective validation effort ended with the proposal of a new, improved dosing regimen, which in turn needs adequate evaluation and subsequent validation (Table 1) [8]. This at least illustrates that optimizing pharmacotherapy needs to be considered as a continuous research process, in which every result announces the beginning of a new exploration.

Throughout this scientific journey, it became obvious that many gaps in neonatal clinical pharmacology still remain to be explored. Nevertheless, the results obtained in this doctoral thesis yield a small contribution to bridge some gaps. Besides improvements in compound-specific pharmacotherapy for neonates, our observations also provide a basis to further explore PK/PD patterns of other compounds or in other special patient populations.

Table 1: Proposed amikacin dosing regimen for neonates (with postnatal age ≤ 30 days) after prospective validation. [8]

Current bodyweight (grams)	PNA <14 days	PNA ≥14 days
0-800	16 mg/kg/48h	20 mg/kg/42h
800-1200	16 mg/kg/42h	20 mg/kg/36h
1200-2000	15 mg/kg/36h	18 mg/kg/30h
2000-2800	15 mg/kg/36h	18 mg/kg/24h
≥2800	15 mg/kg/30h	18 mg/kg/20h
The dosing interval is prolonged 10 hours, when ibuprofen is co-administered or when asphyxia is diagnosed/considered by the treating physician. Duration of the intravenous infusion is 20 minutes. PNA= postnatal age.		

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Short Communication

Hypersensitiviteit pneumonitis bij kinderen : Casuïstiek en bespreking van de literatuur.

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Keywords

hypersensitiviteit pneumonitis, extrinsieke allergische alveolitis, chlld

Abbreviations

ACE : Angiotensin converting enzyme
ANA : Anti-nucleaire antistoffen
ANCA : Anti-neutrofiele cytoplasmatische antistoffen
Anti-CCP : Anti-cyclisch citrulline peptide antistoffen
BAL : Broncho-alveolaire lavage
HP : Hypersensitiviteit pneumonitis
HRCT : Hoge resolutie computertomografie

Inleiding

Hypersensitiviteit pneumonitis (HP) ofwel extrinsieke allergische alveolitis ontstaat als gevolg van een overdreven immunologische reactie op inhalatie van microbiële (fungale, bacteriële of protozoaire micro-organismen) en dierlijke antigenen (glyco-proteinen). De meeste frequente uitlokkende antigenen bij kinderen zijn afkomstig van vogels (o.a. dons), of zijn van fungale oorsprong, o.a. actinomyceten.[1,2] Gezien de inflammatoire respons niet enkel beperkt is tot de alveoli maar ook de terminale bronchioli en het interstitium omvat, spreekt men tegenwoordig over 'hypersensitiviteit pneumonitis' i.p.v. 'extrinsieke allergische alveolitis'.[1,2] Bij volwassenen is dit ziektebeeld vrij goed gekend met als prototype de 'duivenmelkerslong' [3]. Bij kinderen is hypersensitiviteit pneumonitis een zeldzame aandoening, waardoor de diagnose niet voor de hand liggend is. De differentieel diagnose van diffuse longziekte is zeer breed en omvat meer dan 200 verschillende aandoeningen [4] Er zijn veel verschillende classificatiesystemen ter beschikking. Een classificatie volgens leeftijd is het meest bruikbaar bij kinderen [4,5]. Bij kinderen onder de 2 jaar wordt diffuse longziekte meer frequent gezien in kader van aanleg- of ontwikkelingsstoornissen, zoals bijvoorbeeld alveolocapillaire dysplasie, of in kader van surfactant dysfunctie aandoeningen. Bij kinderen ouder dan 2 jaar wordt diffuse longziekte meer frequent gezien bij systeemaandoeningen, zoals juveniele reumatoïde artritis, systeemlupus, sarcoïdosis of vasculitiden. Infecties (atypisch of opportunistisch), toxische inhalaties, roken en hypersensitiviteit pneumonitis zijn echter ook mogelijke differentieel diagnoses bij oudere kinderen [4,6]. Een uitgebreide (expositie-) anamnese is dan ook aangewezen.

Casus

Een meisje van 7 jaar oud met Algerijnse origine, geboren in België, werd verwezen door de kinderarts wegens vermoeden van interstitieel longlijden. Sinds een aantal maanden waren er op- en afgaande symptomen van koorts, hoesten, polypnee en gewichtsverlies. Verder had ze een blanco medische voorgeschiedenis. De ouders zijn niet consanguin. Vader heeft astma. De andere siblings zijn gezond.

Bij klinisch onderzoek zagen we een tenger meisje (gewicht < p3) met milde hyperinflatie en tachypnee (50/min), maar een zuivere longauscultatie. In rust had ze normale saturaties maar bij milde inspanning was er desaturatie tot 60-70%.

RX thorax toonde een diffuus reticulonodulair longbeeld met tevens wazige infiltraten in beide middenkwabben. Een CT Thorax toonde diffuus verspreide centrilobulaire, micronodulaire matglasverdichtingen (zie figuur 1, panel A en B). Op echo cor waren er geen tekens van pulmonale hypertensie. Bloedonderzoek toonde een normaal hemogram, ionogram en LDH maar een mild gestegen CRP (11 mg/L) en sedimentatie (57 mm/u) evenals een uitgesproken hypergammaglobulinemie (30 g/L). Een uitgebreide serologie voor infecties was negatief: negatieve serologie voor EBV, CMV, *Hepatitis C, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumoniae, Adenovirus* alsmede een negatief *Aspergillus* antigen. Ook een intradermo was negatief.

Een auto-immuunscreening was evenmin afwijkend: negatieve ANA, ANCA, reumafactor, anti-CCP en anti-glomerulaire basaal membraan antilichamen, en een normaal ACE. Er was geen proteinurie, hematurie of leucocyturie en ook oftalmologisch onderzoek toonde geen afwijkingen passend bij systeemziektes.

Bij bronchoscopie waren er geen macroscopische afwijkingen. Analyse van het broncho-alveolair (BAL) vocht toonde een lymfocytaire ontsteking met een CD4/CD8 ratio van 0.7.

Bacteriële en fungale kweken bleven negatief evenals PCR's voor *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis* complex, *Adenovirus, RSV*, humaan metapneumovirus, *Pneumocysitis jiroveci en Legionella pneumophila*.

Uit de expositie-anamnese werd blootstelling aan vogels (parkieten) alsook schimmels (vochtproblemen in de slaapkamer) weerhouden. Wegens vermoeden van hypersensitiviteit pneumonitis op basis van de kliniek, anamnese en radiologisch beeld werden precipitines (IgG) voor vogels (duif, papegaai en parkiet) alsook voor schimmels afgenomen. Deze laatsten waren sterk verhoogd, met name voor *Alternaria alternata* en *Aspergillus fumigatus* (112 mg/L en 194 mg/L respectievelijk). Het resultaat van de longbiopsie bevestigde de diagnose met de bevinding van interstitiële ontsteking van het lymfohistiocytaire type met aggregaten van histiocyten en granuloomvorming.

Als behandeling werd gestart met methylprednisolone 2 mg/kg/dag met gradueel verbeteren van het klinisch beeld. Er werd contact opgenomen met de overheidsdienst Gezondheid en Milieu die een inspectie, meting en sanering uitvoerden in de gezinswoning.

Discussie

HP is bij kinderen een zeldzame aandoening en onze kennis is voornamelijk gebaseerd op het ziektebeeld bij volwassenen en op 'case reports' of beperkte 'case series' bij kinderen. De prevalentie in volwassen populaties wordt geschat tussen de 1 tot 20% van de blootgestelde individuen.[1] Tussen 1960 en 2005 werden 95 casussen van HP bij kinderen beschreven.[2] Een recent rapport beschrijft een reeks van 23 Duitse pediatrische patiënten. [2]

De kliniek van deze ziekte omvat een spectrum, onderverdeeld in een acute, een subacute en een chronische vorm. De acute vorm wordt getypeerd door een griepaal beeld (koorts, malaise, myalgie) en respiratoire symptomen (niet – productieve hoest, dyspnee en tachypnee). Het ontstaan is zeer abrupt, binnen de 4 tot 12 uur na expositie. Deze vorm is vaak niet progressief en spontane recuperatie is te verwachten enkele dagen na het stoppen van de expositie. De subacute vorm vertoont een meer sluimerend verloop wat betreft het ontstaan van dyspnee, vermoeidheid en hoest. Respiratoire symptomen zijn meestal mild of afwezig bij subacute HP. De chronische vorm ontstaat door een continue, laaggradige blootstelling aan de geïnhaleerde antigenen. Zeer traag is er toename van dyspnee, hoest, vermoeidheid en gewichtsverlies. Digitale clubbing is aanwezig in 20 tot 50% van de patiënten. Deze vorm gaat vaak gepaard met progressieve longfibrose en cor pulmonale [1]. Het interval tussen expositie en ontstaan van de symptomen kan variëren van maanden tot jaren. Bij onze patiënte past de anamnese en kliniek bij een acute vorm bij eerste symptomen nadien evoluerend naar een subacute vorm.

De diagnose van HP is niet eenvoudig en is gebaseerd op een suggestief klinisch verhaal, het herkennen van expositie aan oorzakelijke antigenen, en een samenspel van klinische, radiologische, biochemische en pathologische bevindingen.

Hoge resolutie CT (HRCT) draagt in belangrijke mate bij aan de diagnose van HP, met een specificiteit tot 81% in volwassen populaties [1]. Deze kan normaal zijn bij acute HP, maar zal meestal een beeld tonen van diffuse matglasverdichtingen en/of kleine centrilobulaire noduli. [1,2] De aanwezigheid van specifieke IgG antilichamen voor het expositie-antigen (precipitines) is een teken van blootstelling maar niet van ziekte. Echter een positieve test is complementair bij de diagnose van HP. Hier tegenover staat dat negatieve precipitines de diagnose van HP niet uitsluiten [4]. In de chronische vorm van HP is de aanwezigheid van een polyclonale hypergammaglobulinemie beschreven [1], en al werd dit niet weerhouden in een pediatrische populatie [2] was dit wel bij onze patiënte aanwezig.
BAL toont meestal een verhoogde cytose (meestal > 20 miljoen op 100 ml BAL vocht), met een overwegend lymfocytaire formule (>50%). [1,2] Studies bij volwassenen toonden een relatieve predominantie van CD8+ T cellen aan met lage CD4/CD8 ratio (tussen de 0.5-1). [1] De studie van Griese et al [2] toonde daarentegen een verhoogde CD4/CD8 ratio aan in kinderen. Daarom wordt niet aangeraden om de CD4/CD8 ratio te gebruiken als diagnostisch criterium. [1]

Longhistologie bij HP toont een milde tot sterke inflammatie met toename van de lymfocyten, voornamelijk T-lymfocyten en macrofagen, t.h.v. de alveolaire septa en alveoli. Ook typisch zijn de niet-verkazende histiocytaire granulomata.

De differentiële diagnose van HP omvat een breed spectrum van interstitieel longlijden (ILL). De richtlijnen wat betreft diagnostiek van ILL stellen een stapsgewijze oppuntstelling voor, te starten met de minst invasieve onderzoeken.[4,6] Het Europees protocol voor diagnose en behandeling van diffuse longziekte bij kinderen stelt voor te starten met HRCT. Zo niet diagnostisch wordt er overgegaan naar bloedanalyses, bronchoscopie en pas in een laatste stap longbiopsie.[4] In principe kan de diagnose van HP gesteld worden op HRCT maar gezien de zeldzaamheid en nog onvoldoende kennis over deze pathologie bij kinderen, zal frequent worden overgegaan naar een longbiopsie ter confirmatie. [2,4]

De eerste stap in de behandeling van HP bij kinderen is expositie aan het oorzakelijk antigen te vermijden. Wat de medicamenteuze behandeling betreft adviseren de meeste richtlijnen het gebruik van systeemcorticoïden. Toedieningswijze (oraal, intraveneus of inhalatie), dosis of duur van therapie zijn sterk uiteenlopend . [2,4,6,7] In de studie van Griese et al. [2] wordt het nut van corticoïden in twijfel getrokken. Cardoso et al. [8] beschrijft een reeks pediatrische patiënten met HP en ondersteunt het belang aan van systemische corticoïden als behandeling in de subacute en chronische vorm mede om evolutie naar fibrose tegen te gaan. Prospectieve klinische studies zullen dit verder moeten uitklaren.

De prognose van HP is wisselend en is afhankelijk van het subtype, ziekteduur, intensiteit van antigenexpositie, APO afwijkingen en mogelijks genetische factoren. Aanwezigheid van fibrose op HRCT en longbiopsie is geassocieerd met een povere prognose factor.[1] De richtlijnen adviseren patiënten klinisch op te volgen 1, 2, 3, 6 en 12 maanden na diagnose, en nadien enkel jaarlijkse controles te voorzien zo een gunstige evolutie. Er wordt geadviseerd om beeldvorming, met voorkeur RX thorax ter beperking van stralingsbelasting, uit te voeren bij diagnose, 6 maanden en 12 maanden na diagnose.[4] Spirometrie met diffusiecapaciteit draagt niet zozeer bij tot diagnose, maar kan een goede parameter zijn voor het opvolgen van ziekteprogressie. Bij oudere kinderen wordt geadviseerd om dit minstens éénmaal jaarlijks op te volgen. [1,2,4] Het periodisch bepalen van precipitines kan dienen als marker van blijvende antigen-expositie. Een studie van McSharry et al. [9] toonde een afname van de precipitines bij 7 duivenmelkers die na diagnose van HP hun beroep hadden stopgezet. Er werd geen medicamenteuze therapie gestart, enkel expositie werd gestaakt. Halfwaardetijd van de precipitines was 95 dagen, een driemaandelijkse opvolging zou dus optimaal zijn. In de literatuur vonden we echter geen gegevens omtrent een eventueel effect van steroïdentherapie op precipitine-waarden.

Het is onduidelijk waarom enkel bepaalde individuen bij blootstelling aan een antigen HP zullen ontwikkelen. De aard van het antigen, de hoeveelheid inhalatie, intensiteit en frequentie van blootstelling alsook de immunologische reactie van het individu spelen hier in mee. Een genetische susceptibiliteit wordt vermoed. [1,10]

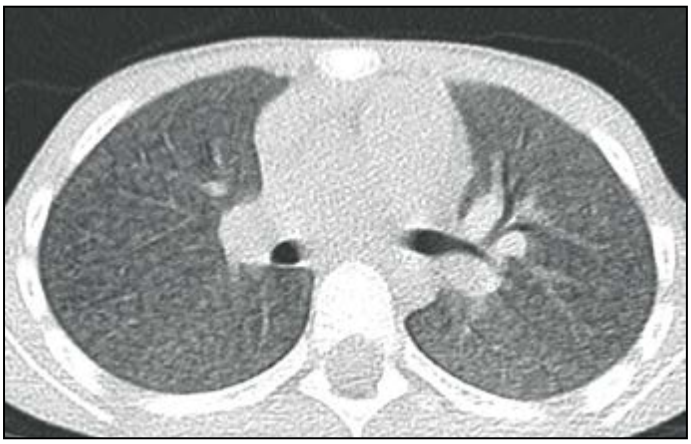
Familiaal voorkomen van HP wordt beschreven maar dit kan ook te maken hebben met de gezamenlijke expositie. Sommige HLA types worden geassocieerd met het ontwikkelen van HP (HLA-DQw3, HLA-A11, A2, DR7, DR9, B8). [8,10] Uiteraard is de frequentie en distributie van HLA-allelen populatie-bepaald en wordt typering ook enkel in studieverband uitgevoerd.

Conclusie

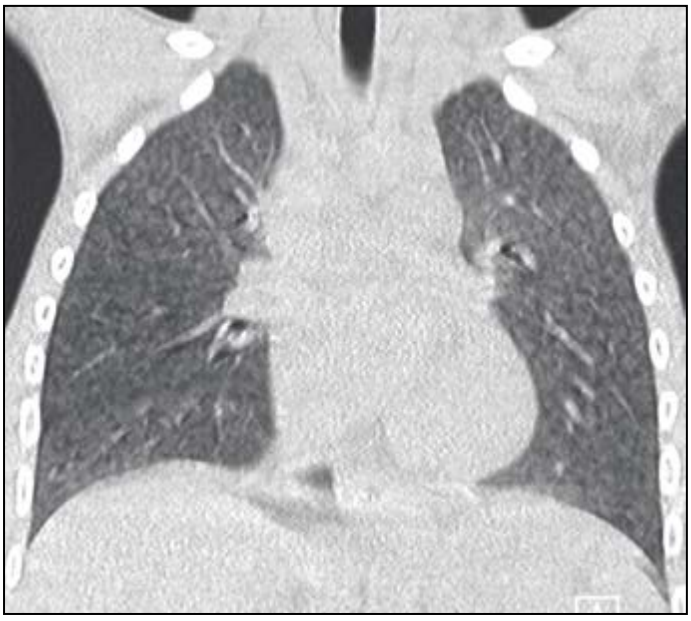
De diagnose van HP bij kinderen is moeilijk en wordt dikwijls laattijdig gesteld, ondanks de aanwezigheid van karakteristieke symptomen bij presentatie. Bij een beeld van interstitieel longlijden moet dus ook bij kinderen HP worden opgenomen in de differentieel diagnose. Een gerichte en uitgebreide expositie-anamnese is hierbij essentieel. Het vermijden van antigen-expositie is de eerste stap in de therapie. Het gebruik van corticoïden is meestal de eerste stap van de medicamenteuze behandeling. Prospectieve dubbelblind studies zijn nodig om het nut hiervan en van mogelijke alternatieven aan te tonen.

Figure 1 A & B.
Thorax van de patiënte toonde diffuus verspreide centrilobulaire, micronodulaire matglasverdichtingen.

Panel A.



Panel B.



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Rotavirus vaccinatie: Beoordeling van de implementatie in België.

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Inleiding

Rotavirus gastroenteritis staat gekend als een democratische ziekte, dwz dat wereldwijd elk kind voor het de leeftijd van 5 jaar bereikt heeft, zal te maken krijgen met een symptomatische rotavirusinfectie [1]. De incidentie van rotavirus gastroenteritis gevallen in geïndustrialiseerde landen en ontwikkelingslanden is vergelijkbaar [2]. In geïndustrialiseerde landen is deze infectieuze aandoening verantwoordelijk voor hoge morbiditeitscijfers, het merendeel van de sterfgevallen komen voor in ontwikkelingslanden vanwege een moeilijkere toegang tot de gezondheidszorg [3]. In 2008 was dit virus verantwoordelijk voor ongeveer 450.000 sterfgevallen binnen de groep van kinderen jonger dan 5 jaar.

Vaccinatie is de beste optie om de ziekte te voorkomen aangezien dit uiterst besmettelijk virus bestand is tegen de klassieke sanitaire maatregelen. Momenteel zijn er 2 verschillende orale vaccins goedgekeurd door de Europese autoriteiten. Beide vaccins bevatten levend afgezwakt virus, maar verschillen in aantal virusstammen die vervat zitten en in het aantal dosissen die toegediend worden. Rotarix (Glaxosmithkline Biologicals, Rixensart, België) is een humaan monovalent vaccin (G1P [8] virusstam) waarvoor 2 dosissen nodig zijn, het gerecombineerde humaan-bovine pentavalente RotaTeq vaccin (G1, G2, G3, G4, P [8]-stammen) (Merck & Co., Inc., Whitehouse Station, NJ, USA) wordt gegeven in 3 dosissen.
Het **implementeren van een nieuw vaccinatieprogramma binnen het huidige preventiekader** biedt de opportuniteit om nauwkeurig bepaalde indicatoren op te volgen als **toetsing voor het vaccinatiebeleid**.

Beleid

Sinds oktober 2006 is rotavirusvaccinatie voor alle zuigelingen in België aanbevolen door de Hoge Gezondheidsraad en terugbetalingsmodaliteiten zijn in voege sinds november 2006. Deze modaliteiten werden in 2007 aangepast nadat een tweede specialiteit beschikbaar werd in België. Er is momenteel een partiële terugbetaling van kracht, waarbij ouders per dosis 11,8 euro remgeld op zich nemen. Afhankelijk van de toegediende specialiteit wordt een 2-dosis of 3-dosis schema gevolgd. Binnen de huidige richtlijnen worden zuigelingen gevaccineerd vanaf de leeftijd van 8 weken, een tweede dosis wordt 4 weken later toegediend en een eventuele derde dosis volgt nog eens 4 weken later. De vaccinatie moet beëindigd zijn voor de leeftijd van 6 maanden, vanwege een vermoeden van een verhoogd risico op intussusceptie bij vaccinatie boven deze leeftijd en om de zuigelingen zo vroeg mogelijk te beschermen.

Impact

Dit doctoraatsonderzoek nam aanvang met de beschrijving van **de impact van het rotavirusvaccinatieprogramma op de ziektelast** en de **seizoenaliteit van de incidentie**, kort na introductie van beide vaccins op de Belgische markt.

De impact werd berekend aan de hand van het aantal laboratorium-geconfirmeerde gevallen van rotavirus gastroenteritis, zoals gerapporteerd door het nationaal netwerk van peillaboratoria van het Wetenschappelijk Instituut voor Volksgezondheid (WIV). Deze publiek beschikbare surveillance gegevens werden gebruikt om de temporale distributie van rotaviruspositieve gevallen tijdens een pre- en post-vaccinatieperiode te vergelijken. Voorts werden resultaten betreffende ziekenhuisopnames vanwege rotaviruspositieve gastroenteritis tijdens deze periodes samengebracht en besproken.

Het aantal gerapporteerde rotavirus gastroenteritis gevallen tijdens het eerste jaar post-vaccinatie (juli 2007-juni 2008) komt overeen met het minimum aantal gevallen dat gemeten werd over de ganse pre-vaccinatieperiode (1999-2001 en 2005-2006). Deze daling wordt ook geobserveerd in de 2 daaropvolgende seizoenen, waarbij in 2008-2009 50% minder gevallen werden gerapporteerd in vergelijking met het minimum aantal gevallen over de ganse pre-vaccinatieperiode. Er is een opmerkelijke verschuiving (ongeveer 4-6 weken) van de start en piek van het rotavirusseizoen en deze verschuiving is eveneens aanwezig tijdens de 2 volgende post-vaccinatieseizoenen (2008-2009 en 2009-2010) [4].

Doeltreffendheid

In een tweede fase werd de **doeltreffendheid van beide beschikbare vaccins "in real life situation"** gemeten, waarbij de focus lag op het voorkomen van ziekenhuisopname omwille van ernstige rotavirus gastroenteritis bij jonge kinderen in België.
Voor de evaluatie van de doeltreffendheid van rotavirusvaccinatie werd een prospectieve, ziekenhuisgebaseerde, multi-centrum, gematchte case-controle studie uitgevoerd (= RotaBel studie), gebaseerd op het Wereld Gezondheidsorganisatie (WHO) generisch protocol voor de monitoring van de impact van RV vaccinatie op de ziektelast van gastroenteritis. Zowel voor cases als controles werd informatie over demografie, medische voorgeschiedenis (inclusief vorige ziekenhuisopnames vanwege gastroenteritis), voedingspatroon,

socio-economische situatie en vaccinatiestatus verzameld via een vragenlijst bij de ouders en via nazicht van het medisch dossier en de vaccinatiekaart. Voor de cases werden ook klinische gegevens opgevraagd over de huidige

$$\left(1 - \frac{\text{kans om gevaccineerd te zijn binnen de cases}}{\text{kans om gevaccineerd te zijn binnen de controles}}\right) \times 100$$

gastroenteritis episode. De doeltreffendheid (%) werd geschat via volgende formule, afgeleid van Orenstein en collega's [5]:

De resultaten van de case-controle studie tonen aan dat rotavirusvaccinatie uiterst doeltreffend is in de preventie van ziekenhuisopname voor rotavirus gastroenteritis bij jonge kinderen in België. Ongeveer de helft van de kinderen die opgenomen werden vanwege een ernstige rotavirus gastroenteritis (n=99; 48%), hadden minstens 1 dosis rotavirus vaccin gekregen, tegenover 91% (n=244) van de controlekinderen (P<0.001). De doeltreffendheid van 2 dosissen van het monovalente rotavirusvaccin is 90% (95% betrouwbaarheidsinterval 81% tot 95%) en is vergelijkbaar bij de verschillende onderzochtte leeftijdgroepen (3-11 maanden: 91% en ≥12 maanden: 90%). Bij een kwart van de rotaviruspositieve kinderen (25%) werd een co-infectie met noro-, astro-, en of adenovirus aangetroffen. De werkzaamheid van de vaccinatie bij deze kinderen was 86% (95% betrouwbaarheidsinterval 52% tot 96%) [6]. De distributie van de infecterende genotypes is significant gerelateerd met de vaccinatiestatus (p<0.001), waarbij de G2P [4] rotavirusstam proportioneel vaker werd aangetroffen bij gevaccineerde kinderen. De G2P [4] rotavirusstam was verantwoordelijk voor 52% van alle zieke gevallen, de werkzaamheid van het vaccin tegen deze stam bedraagt 85% (95% betrouwbaarheidsinterval 64% tot 94%) [7].

Vaccinatiegraad

Daarnaast werd de **dekkingsgraad van het vaccin** onderzocht, bij **jonge Vlaamse kinderen**, samen met de **tijdigheid van toediening en redenen van onvolledige vaccinatie**. Deze resultaten werden vergeleken met de gegevens van andere zuigelingenvaccins die eveneens aanbevolen zijn, maar gratis aangeboden worden.

De couverturegegevens voor rotavirusvaccinatie werden geëxtraheerd uit de Vaccinatiegraadstudie 2012, zoals aangevraagd door het Vlaams Agentschap Zorg en Gezondheid en uitgevoerd door onze onderzoeksgroep, volgens een EPI-gebaseerde survey methode.

Uit een selectie via de "two-stage cluster sampling" methode namen in totaal 874 gezinnen met een kind geboren tussen 1 juli en 16 oktober 2010 deel aan de studie. De deelnemers beantwoordden een vragenlijst en verstrekten vaccinatiegegevens uit het vaccinatiedocument van het kind tijdens een huisbezoek. Nadien werden deze gegevens voor zover mogelijk aangevuld met vaccinatiegegevens geregistreerd in Vaccinnet, Vlaanderens online bestelsysteem voor vaccins, en met vaccinatiegegevens beschikbaar bij de behandelende arts. Op deze gegevens werd tevens een studie uitgevoerd naar het verschil in couverture, zoals gemeten via de beschreven methode en de couverture, zoals bekomen door enkel gebruik te maken van Vaccinnet.

De vaccinatiegraad voor 2 dosissen van het rotavirusvaccin in Vlaanderen, gemeten in 2012 bij kinderen tussen 18 maanden tot 24 maanden, was 92.2% (95% CI: 90.2-93.8). Slechts 8 kinderen (1%) werden gevaccineerd na de toegelaten leeftijd van 26 weken. Bij 57.3% van de gevaccineerde kinderen werd vastgesteld dat de eerste dosis reeds vertraagd werd toegediend (ie vanaf de leeftijd van 9 weken). Onvolledige vaccinatie van het kind bleek vaak een bewuste keuze van de ouders te zijn. Via multipele logistische regressie werden volgende beïnvloedende factoren voor onvolledige vaccinatie bepaald: woonachtig in de provincie Antwerpen, werkzoekende moeder, aanwezigheid van 3 of meer oudere zussen/broers binnen het gezin. De resultaten van de vaccinatiegraadstudie tonen aan dat de uptake van het rotavirusvaccin zeer hoog is, reeds 4 jaar na de start van het programma. Toch zien we dat de dekkingsgraad iets lager is in vergelijking met de dekkingsgraad van de andere vaccins die aanbevolen zijn voor zuigelingen. Mogelijks is dit te wijten aan de partiële terugbetaling van het rotavirusvaccin, terwijl de overige zuigelingenvaccins gratis aangeboden worden [8].

Voor het berekenen van de vaccinatiegraad kunnen verschillende gegevensbronnen aangewend worden. In Vlaanderen wordt gebruik gemaakt van Vaccinnet, een web-gebaseerd bestelsysteem, dat gekoppeld is met een immunisatie-databank. Deze databank kan aangewend worden om heel snel de vaccinatiegraad binnen een bepaalde doelgroep te berekenen, op voorwaarde dat de gebruikers van het systeem (i.e. de vaccinatoren) nauwgezet de gegevens aanvullen. Voor het rotavirusvaccin is dit een grote uitdaging aangezien dit vaccin niet behoort tot de gratis aangeboden vaccins voor zuigelingen en daardoor buiten de klassieke bestelwijze (gebruikmakend van Vaccinnet) valt. Een vergelijk van de vaccinatiegraad, zoals berekend volgens de bovenbeschreven survey enerzijds en anderzijds gebruikmakend van Vaccinnet, toonde aan dat de arbeidsintensieve survey studies nog steeds een accurater beeld geven van de couverture voor de zuigelingenvaccins. Zoals verwacht, is het geobserveerde verschil in couverture van het rotavirusvaccin groter dan voor de overige zuigelingenvaccins binnen het basisvaccinatieschema (79.5% versus 92.2%) [9].

Barrières voor vaccinatie

Gegevens uit de RotaBel studie gaven aan dat er mogelijks een sociale gradiënt zit in de uptake van het rotavirusvaccin. Ter aanvulling van de reden van onvolledigheid van vaccinatie, werd een onderzoek uitgevoerd naar **mogelijke ongelijkheid in rotavirusvaccinatie "uptake"**, al dan niet geïnduceerd door de gedeeltelijke terugbetaling van het vaccin.

Voor dit doel werd gebruik gemaakt van demografische en socioeconomische gegevens van de kinderen gehospitaliseerd vanwege rotavirus gastroenteritis, behorend tot bovengenoemde doeltreffendheidstudie. Van deze kinderen is de vaccinatievoorgeschiedenis gekend, zijnde de rotavirusvaccinatiestatus en het aantal DTP-dosissen die toegediend werden. Aangezien beide vaccins op hetzelfde tijdstip worden toegediend, fungeert deze laatste variabele als benadering van het aantal vaccinatiemomenten waarop tevens een rotavirusvaccin kon toegediend worden. De socioeconomische status van deze kinderen werd bepaald aan de hand van het opleidingsniveau van de moeder enerzijds en anderzijds via het mediaan inkomen op niveau van statistische sector (=welvaartsindex). De bivariate associatie tussen deze variabelen en enerzijds de rotavirusvaccinatiestatus en anderzijds het aantal gemiste kansen werd getoetst dmv Chi^2-test. De resultaten tonen aan dat zowel niet-vaccinatie als gemiste vaccinatiekansen significant gerelateerd zijn aan een lager opleidingsniveau van de moeder, de associatie met de welvaartsindex was niet significant. We kunnen stellen dat financiële drempels geen rol spelen in de keuze om niet te vaccineren, maar mogelijks is de vaccinatieprocedure, waarbij een voorschrift noodzakelijk is, te omslachtig en wordt dit aangesterkt door een lagere perceptie van het risico van de ziekte.

Rol van borstvoeding op de werkzaamheid

Een tweede en laatste luik van het onderzoek focust zich op de lacunes die momenteel nog aanwezig zijn op het niveau van de werkzaamheid van het vaccin. Het is reeds aangetoond dat de werkzaamheid van de huidig beschikbare rotavirusvaccins heel wat lager ligt in ontwikkelingslanden, vergeleken met geïndustrialiseerde landen. Verschillende factoren kunnen hiervan de oorzaak zijn, waaronder de mogelijke interferentie van maternale antistoffen, oa aanwezig in de borstvoeding. De mogelijke invloed van borstvoeding op de werkzaamheid van deze vaccins wordt momenteel nagegaan in een klinische studie, uitgevoerd in zowel België als Vietnam. Ter ondersteuning van deze samenwerking werd reeds een pilootstudie uitgevoerd naar de **prevalentie van rotavirus antilichamen**

in borstvoeding en het **in vitro inhiberend effect op de virustiters van het vaccin**.

De studie naar de prevalentie van rotavirusspecifieke antilichamen in de borstvoeding van Vietnamese moeders toont aan dat moeders afkomstig uit het stedelijk gebied hogere titers aan rotavirusspecifieke antilichamen doorgeven aan hun kinderen. Ondanks het feit dat er slechts heel lage titers aan virusneutralizerende antilichamen konden gedetecteerd worden in de borstvoedingsstalen, was de in vitro virusneutralizerende activiteit van deze stalen wel hoog, wat implicaties heeft voor het toedienen van het orale vaccin aan zuigelingen die op dat moment borstvoeding krijgen [10].

Conclusie

België beschikt over een goed draaiend rotavirusvaccinatieprogramma, hetgeen tot uiting komt in een substantiële daling van het aantal gerapporteerde rotaviruspositieve gevallen. Deze daling is te danken aan de combinatie van een goede werkzaamheid van de beschikbare vaccins en een grootschalige toediening aan de doelgroep. Al dient er nog aandacht besteed te worden aan de tijdigheid van toediening en kan de vaccinatiegraad nog enkele percentages hoger geraken indien enkele logistieke procedures aangepakt worden.

Op internationaal vlak, met name in de ontwikkelingslanden, zal het onderzoek zich verder richten op het identificeren van die factoren die een verlaagde werkzaamheid van de vaccins veroorzaken.

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Académie Belge de Pédiatrie en 2015.

1. Accord national médico-mutualiste.

À partir du 1er Janvier 2015 : 18% d'économies pour tout ce qui concerne l'article 13 (28,6 millions €)
Pour les pédiatres : monitoring ambulatoire demeure inchangé, monitoring au département : aux soins intensifs la date d'entrée et décharge seront considérés comme "un jour" (13 millions). La plupart des services de soins intensifs pédiatriques sont mis sous « soins intensifs » et non sous la Pédiatrie.
Économies de monitoring : 5 millions d'économie sur le monitoring de TOUTES les disciplines ; pour la pédiatrie il s'agira d'une économie partielle. Les économies prévues concerneront 3% du budget de la pédiatrie (150 000 € sur 5 millions). L'économie a été réalisée de manière linéaire sans tenir compte des observations formulées par les pédiatres.
N40 se réduit à N24.

2. Nomenclature monitoring.

Présentation par Dr J Marchand de la Convention monitoring cardiorespiratoire pour nourrissons à domicile : les nouveaux accords sont entrés en vigueur depuis le 01/04/2015. Il y a peu de preuves scientifiques pour justifier les indications pour lesquelles la polysomnographie et le suivi à domicile sont utilisés. L'incidence de la mort subite est descendue à max. 40 cas par an en Belgique.

Le monitoring à domicile demeure possible pour :

- prématurés à haut risque de moins de 31 semaines ou moins de 1,5 kg : plus de prix par jour mais un prix forfaitaire fixe (800 euros) sans possibilité de prolongation.
- syndromes poly formatifs: critères : pathologie + polysomnographie anormale (critères idem); forfait un peu plus élevé.
- prématurés entre 31 et 36 semaines, avec bradycardies, apnées lors des dernières semaines et une polysomnographie anormale.
- ALTE (tolérés, mais finira par éventuellement disparaître)

Ne sont plus couverts par l'INAMI : frères et sœurs, les enfants de mères toxicomanes, ...

Si l'enveloppe prévue de 2,4 millions est dépassée, le taux fixe pour le monitoring sera réduit.

Situation actuelle : 12 centres de référence ; dans le nouvel accord : tous les NICU's peuvent faire une demande au centre de référence
Il n'y a pas de limitation dans l'exécution de polysomnographie, mais seulement pour ce qui est mentionné ci-dessus un monitoring-CR peut être commencé.

3. Programme de soins de pédiatrie : situation dans les différentes régions.

Le VVK a eu une entrevue avec le ministère de Van Deurzen (région flamande) qui surtout écouté et ils attendent pour se prononcer à ce sujet la réponse du Conseil d'Etat. En résumé : pas de mouvement.

- La Flandre ne fait pas appel aux différents services de pédiatrie et attend la décision du Conseil d'Etat. Attitude actuelle de ministre Van Deurzen: examiner des projets pilotes élaborer un nouveau décret pour le programme de soins de base: autre niveau dans les hôpitaux régionaux comprenant une maternité de 500-600 accouchements avec lits pédiatriques de base, mais plus un minimum de 15 lits nécessairement occupés de 70%...
- Wallonie: modèles en circulation. Les services de pédiatrie doivent présenter un manuel multidisciplinaire au collège: compliqué car trois ministres (Demotte- Marcourt- ...) veulent deux centres tertiaires en Wallonie (régions de Liège et de Charleroi) et 2 à Bruxelles.

4. Sous-spécialités.

Les textes pour les différentes sous-spécialités sont prêts notamment pour pneumologie, gastro, endo, néphro et cardiologie qui ont été approuvés (pour la 2ième fois) au printemps de 2015 par le Conseil de la Santé. Depuis lors il n'y a eu aucune ré-action du Cabinet.
Fin novembre, une lettre recommandée a été envoyée au ministre qui a renvoyé un accusé de réception comprenant de vagues promesses. En début 2016 l'Académie et le Collège entreprendront une action conjointe.

Représentation chirurgiens pédiatriques (Belaps, président M Miserez)

L'Académie de pédiatrie soutient un texte sur la reconnaissance de la chirurgie pédiatrique. L'absence de "néonatologie" dans le programme de soins de pédiatrie provoque des problèmes pour des disciplines telles que les chirurgiens pédiatriques. Le Haut Conseil de la Santé reconnait bientôt la chirurgie de l'enfant comme une compétence spéciale avec une formation séparée après les quatre ans de tronc commun.

Proposition du Président de rassembler des arguments pour que la consultation du pédiatre puisse mieux être financée en raison du peu d'actes techniques. L'académie trouve que la priorité devrait être donnée à la revalorisation de l'acte intellectuel.

Consultations :
Pédiatre € 36,75
Interniste € 40,05
Cardiologue € 36,74
Pneumologue € 38,53
Rhumatologue 55 & €
Neurologue € 53,76
Psychiatre € 46,15

5. Raccourcissement du séjour en maternité.

Risque : moins bon suivi pour l'enfant, moins de revenus pour le pédiatre et, finalement coûts plus élevés pour les soins de santé. Le rôle de pédiatre doit être repensé. Proposer que ce projet soit suivi par le collège mère/enfant car cela semble une fausse économie.

6. La prescription électronique.

Difficulté provient du fait qu'il n'y a pas de puce dans les nouvelles cartes ISIS. Le nouveau-né doit avoir une carte d'ID en cas de prescription électronique. Proposition de poser une question parlementaire.
- Dossier médical général : les avantages et inconvénients sont brièvement discutés. Le problème est que le pédiatre n'est pas autorisé/ne peut pas rédiger un DMG.

Samenvatting Academie 2015.

1. Nationaal Akkoord artsen ziekenfondsen

Vanaf 1 januari 2015: 18% besparingen voor alles dat valt onder artikel 13 valt (28.6 miljoen euro)

Voor kinderartsen : ambulante monitoring blijft, monitoring op de afdeling : op intensieve zorgen zal opname en ontslag dag als "één dag" beschouwd worden (13 miljoen). Voor de meeste pediatrische diensten valt Pediatrische Intensieve Zorgen onder Intensieve Zorgen en niet onder dienst Pediatrie.

Besparingen monitoring: 5 miljoen besparing op monitoring voor ALLE disciplines; de besparing op pediatrie zal uiteraard slechts een deel ervan bedragen. De geplande besparingen zouden 3% van het budget pediatrie bedragen (150.000 € op 5 miljoen). De besparing is unidirectioneel doorgevoerd, en er werd geen rekening gehouden met opmerkingen van de kinderartsen.

N40 wordt gereduceerd naar N24.

2. Nomenclatuur monitoring.

Conventie cardiorespiratoire thuismonitoring voor zuigelingen : toelichting door Dr. J Marchand.

De nieuwe akkoorden gaan in vanaf 1/4/2015. Er is weinig wetenschappelijke evidentie voor de indicaties waarvoor polysomnografie en thuisbewaking nu wordt aangewend. De incidentie van plotse dood (wiegedood) is gedaald naar max. 40 gevallen per jaar in heel België.

De mogelijkheid tot thuisbewaking blijft bestaan voor :
High risk prematuren minder dan 31 weken of minder dan 1.5kg : geen dagprijs meer, een forfait (800 euro), verlenging niet meer voorzien
Polyformatieve syndromen : criteria : pathologie + abnormale polysomnografie (criteria idem) ; forfait iets hoger
Prematuren tussen 31-36 weken, met brady's, apneu's tijdens laatste weken en afwijkend polysomno
ALTE (getollereerd, maar zal op termijn mogelijks verdwijnen)

NIET meer terugbetaald door RIZIV: siblings, kinderen van druggebruikende moeders, …
Indien de voorziene enveloppe van 2.4 miljoen overschreden wordt, zal het forfaitair bedrag per monitoring dalen
Huidige situatie : 12 referentiecentra ; In het nieuw akkoord : alle NICU's kunnen aanvraag tot referentiecentrum indienen
Er is geen beperking in het uitvoeren van polysomnografie, maar enkel bij bovenstaande kan er een CR-monitoring opgestart worden.

3. Zorgprogramma Kindergeneeskunde : situatie in de verschillende regio's.

Het VVK had ene gesprek met Ministerie Van Deurzen die vooral heeft geluisterd. Er is een afwachtende houding gezien men uitspraak Raad Van State afwacht. Samengevat: geen beweging.

- Vlaanderen geen oproep naar de verschillende pediatrische diensten, men wacht op de uitspraak van de Raad Van State. Huidige houding Minister Van Deurzen: kijkt voor pilootprojecten, nieuw decreet voor een basiszorgprogramma: Ander niveau van echelonering….in regionale ziekenhuizen met materniteit 500-600 bevallingen met pediatrische basisbedden, maar NIET min. 15 bedden die noodzakelijkerwijs 70 % bezet zijn…
- Wallonië: templates rondgestuurd en diensten pediatrie moesten een 'manuelle multidisciplinaire' insturen, naar COLLEGE: gecompliceerd want 3 ministers (Demotte- marcourt-…) (willen 2 Waalse tertiaire centra –regio Liege en regio Charleroi- en 2 in Brussel).

4. Subspecialiteiten

Teksten zijn opgesteld voor de verschillende subspecialiteiten. De teksten voor pneumo, gastro, endo, nefro en cardiologie werden door de Hoge Gezondheidsraad (voor de tweede maal) positief geadviseerd in het voorjaar van 2015. Sindsdien is er (opnieuw) geen (re)actie van het kabinet.
Eind november werd een aangetekend schrijven naar de minister gestuurd, waarop een bericht voor ontvangst en vage beloftes voor antwoord werd ontvangen. Begin 2016 wordt verder gezamenlijke actie voor Academie en College ondernomen.

Vertegenwoordiging kinderchirurgen (Belaps, voorzitter M Miserez)

De academie van Pediatrie steunt een tekst over de erkenning van de Kinderchirurgie. De afwezigheid van "neonatologie" in het zorgprogramma Pediatrie veroorzaakt problemen voor disciplines zoals de kinderchirurgen. De Hoge GezondheidsRaad erkent weldra de kinderchirurgie als bijzondere bekwaamheid met een aparte opleiding na 4 jaar "truncus communis"

Voorstel van de voorzitter om argumentatie op te bouwen dat de raadpleging kinderarts beter gefinancierd dient te worden, wegens gebrek aan technische prestaties. De academie stelt dat de prioriteit moet uitgaan naar de revalorisatie van de intellectuele acte.

Raadpleging	Kinderarts	36.75 €
	Internist	40.05 €
	Cardiologie	36.74 €
	Pneumoloog	38.53 €
	Rheumatologie	55.& €
	Neurologie	53.76 €
	Psychiatrie	46.15 €

5. (Ver)Kort verblijf op materniteit

Risico: minder goede opvolging kind, minder inkomsten pediater, en uiteindelijk grotere kost voor de gezondheidszorg. Rol kinderarts moet herdacht worden. Vraag stellen dat het college moeder/kind dit project opvolgt. Lijkt een valse besparing.

6. Elektronisch voorschrift

Moeilijkheid is dat er geen chip is in de nieuwe isis-kaarten. Pasgeborene moet identiteitskaart kunnen krijgen als het voorschrift elektronisch moet zijn. Voorstel om parlementaire vraag te stellen.
- globaal medisch dossier: voor en nadelen worden kort besproken. Probleem is dat algemeen pediater geen GMD mag/kan opstellen.

Instructions aux auteurs

LANGUE Français, Néerlandais, Anglais

1e PAGE
- mentionner tous les auteurs avec les institutions et l'adresse e-mail du 'Corresponding author'
- Il est absolument indispensable de mentionner les Key-words (maximum 4)

MANUSCRIPTS
- articles courts, maximum 7 pages dactylographiées sans double interligne, maximum 20 références
- comprenant:
  - **Abréviations:** rangées alphabétiquement
  - **Résumé:** en Anglais, maximum 250 mots
  - **Introduction:** situer le problème à la lumière d'une courte bibliographie
  - **Population, Méthodes et Statistiques:** les méthodes utilisées et sujets étudiés (âge, sexe, nombre de sujets)
  - **Résultats**
  - **Discussion et Conclusion:** doivent être courtes sans répéter tous les résultats déjà connus.
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Journals. Chiba Y, Minagawa T, Mito K, et al. Effect of breast feeding on responses of systemic interferon and virus-specific lymphocyte transformation in infants with respiratory syncytial virus infection. J Med Virol 1987: 21: 7-14.
Books and monographs. Stiehm ER, Fulginiti VA. Immunologic disorders in infants and children. Philadelphia WB Saunders 1973.
Chapter in book. Holt PG, Turner KJ. Regulation of IgE synthesis in man and experimental animals. In Lessof MH, Lee TH, Kemeny DM, eds. Allergy, an international textbook. New York John Wiley 1987: 69-87.
Article by DOI Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. Doi:10.1007/s001090000086

- **Figures et tableaux:** reproduire des figures ou tableaux est possible uniquement après l'accord de l'éditeur de l'article original

SHORT COMMUNICATION :
- maximum 1500 mots, 6 références, 1 figure ou 1 tableau

CASE REPORT :
- maximum 500-700 mots, 6 références, 1 figure ou 1 tableau
- bien détailler l'histoire clinique
- souligner les détails qui suggèrent le diagnostic à l'examen clinique

RESEARCH LETTER :
- maximum 500 mots, 5 références, 1 figure ou 1 table

LETTER TO THE EDITOR
- maximum 300 mots, 3 références

Tous les articles doivent être envoyés par e-mail au secrétariat du Journal du Pédiatre Belge (HYPERLINK «mailto:bvk-sbp@uz.kuleuven.ac.be" bvk-sbp@uz.kuleuven.ac.be) et ne seront publiés qu'après 'peer review'

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Richtlijnen voor de auteurs

TAAL Nederlands, Frans, Engels

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- vermelding van alle auteurs, instellingen, en e-mail adres van de 'Corresponding author'
- vermelding van key-words (maximum 4) is noodzakelijk

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- korte artikels van maximum 7 getypte pagina's, zonder dubbele regelafstand, maximum 20 referenties
- bestaande uit :
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  - **Abstract:** in het Engels, maximum 250 woorden
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  - **Populatie, Methoden en statistieken:** de gebruikte methoden en bestudeerde kinderen (leeftijd, geslacht, aantal)
  - **Resultaten**
  - **Discussie en Conclusie:** moeten kort zijn zonder te herhalen wat reeds in de Resultaten is gegeven.
  - **Referenties:** rangschikken volgens vermelding in de tekst in arabische cijfers. Vermelding van max 6 auteurs, indien meer, 3 auteurs et al.

Journals. Chiba Y, Minagawa T, Mito K, et al. Effect of breast feeding on responses of systemic interferon and virus-specific lymphocyte transformation in infants with respiratory syncytial virus infection. J Med Virol 1987: 21: 7-14.
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- **Figuren en Tabellen:** Figuren en tabellen overnemen kan enkel na toestemming van de uitgever van de originele publicatie

SHORT COMMUNICATION
- maximum 1500 woorden, 6 referenties, 1 figuur of 1 tabel

CASE REPORT
- maximum 500-700 woorden, 6 referenties, 1 figuur of 1 tabel
- anamnese zeer goed detailleren
- de klemtoon leggen op het stellen van de diagnose (bv. een goede tabel of Rx)

LETTER TO THE EDITOR
- maximum 500 woorden, 5 referenties, 1 figuur of 1 tabel

BRIEVEN AAN DE UITGEVER
- maximum 300 woorden, 3 referenties

Alle bijdragen moeten per e-mail verstuurd worden naar het secretariaat van het Tijdschrift van de Belgische Kinderarts (HYPERLINK «mailto:bvk-sbp@uz.kuleuven.ac.be" bvk-sbp@uz.kuleuven.ac.be) en kunnen enkel na 'peer review' worden gepubliceerd.

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