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ORIGINAL ARTICLE

Retrospective Cohort Study

Serial physical examinations, a simple and reliable tool for managing neonates at risk for early-onset sepsis

Alberto Berardi, Anna Maria Buffagni, Cecilia Rossi, Eleonora Vaccina, Chiara Cattelani, Lucia Gambini, Federica Baccilieri, Francesca Varioli, Fabrizio Ferrari

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Abstract

AIM

To investigate whether serial physical examinations (SPEs) are a safe tool for managing neonates at risk for early-onset sepsis (EOS).

METHODS

This is a retrospective cohort study of neonates (≥ 34 wks' gestation) delivered in three high-volume level Ⅲ birthing centres in Emilia-Romagna (Italy) during a 4-mo period (from September 1 to December 31, 2015). Neonates at risk for EOS were managed according to the SPEs strategy, these were carried out in turn by bedside nursing staff and physicians. A standardized form detailing general wellbeing, skin colour and vital signs was filled in and signed at standard intervals (at age 3, 6, 12, 18, 36 and 48 h) in neonates at risk for EOS. Three independent reviewers reviewed all charts of neonates and abstracted data (gestational age, mode of delivery, group B streptococcus status, risk factors for EOS, duration of intrapartum antibiotic prophylaxis, postpartum evaluations, therapies and outcome). Rates of sepsis workups, empirical antibiotics and outcome of neonates at-risk (or not) for EOS were evaluated.

RESULTS

There were 2092 live births and 1 culture-proven EOS (*Haemophilus i*) (incidence rates of 0.48/1000 live births). Most newborns with signs of illness (51 out of 101, that is 50.5%), and most of those who received postpartum antibiotics (17 out of 29, that is 58.6%) were not at risk for EOS. Compared to neonates at risk, neonates not at risk for EOS were less likely to have signs of illness (51 out of 1442 *vs* 40 out of 650, $P = 0.009$) or have a sepsis workup (25 out of 1442 *vs* 28 out of 650, $P < 0.001$). However, they were not less likely to receive empirical antibiotics (17 out of 1442 *vs* 12 out of 650, $P = 0.3$). Thirty-two neonates were exposed to intrapartum fever or chorioamnionitis: 62.5% ($n = 20$) had a sepsis work-up and 21.9% ($n = 7$) were given empirical antibiotics. Among 216 neonates managed through the SPEs strategy, only 5.6% ($n = 12$) had subsequently a sepsis workup and only 1.9% ($n = 4$) were given empirical antibiotics. All neonates managed through SPEs had a normal outcome. Among 2092 neonates, only 1.6% ($n = 34$) received antibiotics; 1.4% ($n = 29$) were ill and 0.2% ($n = 5$) were asymptomatic (they were treated because of risk factors for EOS).

CONCLUSION

The SPEs strategy reduces unnecessary laboratory evaluations and antibiotics, and apparently does not worsen the outcome of neonates at-risk or neonates with mild, equivocal, transient symptoms.

Key words: Sepsis; Group B streptococcus; Intrapartum antibiotic prophylaxis; Newborn; Prevention

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Core tip: The management of asymptomatic neonates at-risk for early-onset sepsis (EOS) remains a challenge. Algorithms based on the threshold values of risk factors result in a large number of uninfected newborns being evaluated and treated. In a 4-mo, multicenter retrospective cohort study, we evaluated a strategy based on serial physical examinations (SPEs) instead of sepsis workup. We studied 2092 neonates. Among 216 neonates initially managed through SPEs, only 12 (5.6%) had subsequently a sepsis workup; only 4 (1.9%) were given empirical antibiotics. All neonates had a normal outcome. SPEs is a simple and reliable tool for managing neonates at risk for EOS.

Berardi A, Buffagni AM, Rossi C, Vaccina E, Cattelani C, Gambini L, Baccilieri F, Varioli F, Ferrari F. Serial physical examinations, a simple and reliable tool for managing neonates at risk for early-onset sepsis. *World J Clin Pediatr* 2016; 5(4): 358-364 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/358.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.358

INTRODUCTION

Infections are a leading cause of neonatal mortality. Exposure to neonatal infection is a large contributor to cerebral injury and long-term disabilities in survivors, especially in the case of preterm neonates[1-4]. Early-onset sepsis (EOS) is transmitted (during delivery or shortly before) from a mother who is colonized at the genital site[2,5]. EOS may be diagnosed on the basis of nonspecific clinical signs and the isolation of a pathogen from sterile sites. EOS is typically defined as sepsis occurring within the first 3 or 7 d after birth[3]. Seven days is typically used for Group B streptococcus (GBS) sepsis[6,7], that remains a leading cause of EOS[1,2]. Universal screening for GBS in late pregnancy and the administration of intrapartum antibiotic prophylaxis (IAP) have led to a striking decline in GBS EOS (from 1.8 cases per 1000 live births in 1990 to 0.25 in 2013 in the United States)[8,9].

The initial symptoms of sepsis are often subtle, but the clinical course may be fulminant, so that neonatologists often initiate antibiotic treatment as soon as there is the slightest clinical suspicion of EOS. There is currently no diagnostic test that can confirm or rule out neonatal sepsis with an acceptable sensitivity and specificity[10,11]. Evidence-based recommendations have been insufficient to date, and neonatal management remains challenging. Guidelines often recommend administering empirical antibiotics to well-appearing neonates at risk of EOS (WAARNs)[12-14]. Algorithms are usually based on the assumption that the presence of maternal risk factors (RFs) implies a higher neonatal risk of EOS. However, most data regarding RFs for EOS have been obtained before the era of IAP. As clinical signs are a sensitive indicator of neonatal sepsis[15]. The 2010 revised Centers for Disease Control and Prevention guidelines recommend observation (instead of laboratory testing) for WAARNs born full term. A sepsis workup is recommended for neonates born after prolonged membrane rupture ($\geqslant$ 18 h) and inadequate IAP (duration shorter than 4 h prior to delivery). A sepsis workup and empirical antibiotics are recommended for chorioamnionitis-exposed neonates[7]. However, concerns have arisen that unnecessary antibiotics contributes to the development of antimicrobial resistance. A selective use of antibiotics in the highest risk patients is now a universal goal[16]. With the aim of further reducing unnecessary testing and antibiotics, some authors have more recently proposed alternative approaches (based on physical examination) to managing WAARNs[17-20].

In Emilia-Romagna (Italy) a GBS Prevention Working Group was set up in 2003 and active GBS surveillance was started. An efficient antenatal screening strategy for the prevention of EOS has been successfully implemented over the years[21,22].

Since 2009 clinicians have managed WAARNs by relying on serial physical examinations (SPEs) rather than on laboratory tests[23,24]. Since its introduction, this strategy has apparently been safe, so that an increasing number of infants at a higher risk of EOS (*i.e.,* late preterm neonates, or neonates born with chorioamnionitis) have been gradually managed through the SPE strategy.

The purpose of this retrospective study was to

confirm that the SPE approach was safe for all WAARNs and was not associated with unnecessary antibiotics. Current data concerning SPEs in WAARNs are limited, especially in neonates exposed to chorioamnionitis at birth, and further data supporting this strategy are needed.

MATERIALS AND METHODS

This is a retrospective cohort study of infants delivered during a 4-mo period (from September 1, to December 31, 2015) at three high-volume, level Ⅲ, regional centres (Azienda Ospedaliero Universitaria Policlinico, Modena; Azienda Ospedaliero Universitaria Policlinico, Parma; and Arcispedale S.M. Nuova, Reggio Emilia) in Emilia-Romagna (an Italian region with about 40000 live births/year). In this region, prevention of GBS infections have led to a decline in the incidence of GBS EOS, which in recent years has decreased to 0.19/1000 live births[23].

Definitions

Inadequate IAP refers to ampicillin or cefazolin given less than 4 h prior to delivery. Risk factors for EOS: These include GBS bacteriuria identified during the current pregnancy, a previous GBS-infected newborn, preterm birth (< 37 wks' gestation), rupture of membranes ≥ 18 h, intrapartum fever ≥ 38 ℃, that is a surrogate of chorioamnionitis[7]. Well-appearing refers to neonates with risk factors for EOS without any clinical symptom of sepsis at age 0-6 h. At-risk newborn is defined as an infant whose mother is GBS colonized or has risk factors for EOS. Culture-proven EOS: Isolation of a pathogen from a normally sterile body site (blood or cerebrospinal fluid) within 72 h of birth and clinical signs and symptoms consistent with sepsis[2,3]. Suspected EOS is defined as the presence of clinical signs and symptoms consistent with sepsis[1-3] plus an abnormal complete blood count and/or elevated C-reactive-protein levels in the absence of a positive blood culture. Ruled out sepsis: Neonates with signs of illness who rapidly recover without antibiotic treatment.

Antenatal screening and management of neonates, before and after the introduction of the SPE strategy

In accordance with the Centers for Disease Control and Prevention guidelines[7,13], women with prenatal GBS colonization or risk factors (see below) should be given IAP. Up to 2008, WAARNs underwent a limited laboratory evaluation (complete blood count - CBC - with differential, blood culture and C-reactive protein)[13]. Since 2009 a new strategy (SPE) for managing WAARNs has been implemented[23,24]. A standardized form detailing information on vital signs and general wellbeing was included in the medical records of WAARNs managed through the SPE strategy (see below). Three independent reviewers reviewed all charts of neonates (≥ 34 wk gestation) delivered in the 3 participating centres and abstracted data (gestational age, mode of delivery, GBS status, risk factors for EOS, duration of IAP, postpartum evaluations, therapies and outcome). The results of standardized forms detailing SPEs were also reviewed. To maintain patient confidentiality, the spreadsheets submitted to the principal investigator did not include any data that would have allowed identification of patients or caregivers.

SPE strategy

Full-term and late preterm WAARNs who received inadequate or no IAP are managed through SPEs, without any laboratory evaluations. This strategy is carried out in turn by bedside nursing staff, midwives and physicians. It is based on the relief of simple vital signs, these may be easily detected by medical and non-medical staff. Each examiner fills in and signs a standardized form (detailing general wellbeing, skin colour - including perfusion and the presence of respiratory signs) at standard intervals (at age 3-6-12-18-36-48 h) (Figure 1). The standardized form is then included in the records of the newborn. Nursing staff and midwives give notification to clinicians when signs of illness develop. As we experienced in our clinical practice, every evaluation requires a maximum of 1 to 2 min. SPE has proven very sensitive for the early detection of all cases of EOS, not only for GBS sepsis.

Neonates with mild or equivocal symptoms during the first hours of life (*i.e.,* neonates born by caesarean section with mild tachypnea that resolves spontaneously within a few hours) are closely observed, but do not necessarily undergo a sepsis workup or receive empirical antibiotics. Antibiotics are given after the collection of blood samples and (when possible) cerebrospinal fluid cultures. WAARNs are not discharged home before age 48 h.

From 2009 to 2012, SPEs were performed on WAARNs ≥ 35 wks' gestation. However, intrapartum fever/chorioamnionitis-exposed neonates or neonates with ≥ 2 risk factors underwent sepsis workup and were given empirical antibiotics[24]. Because of its apparent safety, in 2013 this SPE strategy was extended to all WAARNs ≥ 34 wks' gestation, regardless of RFs.

Statistical analysis

Analyses were performed using STATA/SE 11.2 for Windows; continuous variables were expressed as the mean ± standard deviation or median and range; categorical data were expressed as numbers (percentages). Statistical analyses were performed using the χ^2 test and Mann-Whitney test for independent samples, when appropriate. A P value < 0.05 was used as a threshold for statistical significance.

RESULTS

During the study period there were 2092 newborns with ≥ 34 wks' gestation; the median gestational age was 39 wk (25^{th}-75^{th} IQ range 38-40) and median birth weight was 3920 g (25^{th}-75^{th} IQ range 2980-3590).

Demographics

Table 1 shows the demographics of neonates according

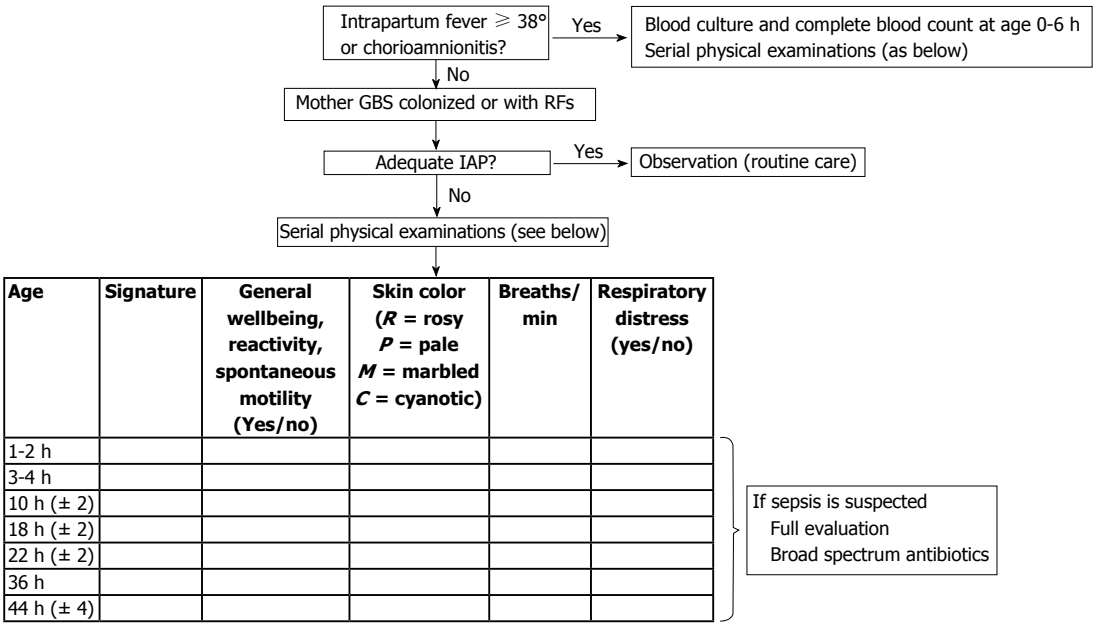

Figure 1 The neonatal management approach for neonates at risk for early-onset sepsis. Full evaluation includes blood culture and complete blood count, C-reactive protein, chest X ray and lumbar puncture. GBS: Group B streptococcus; IAP: Intrapartum antibiotic prophylaxis; RFs: Risk factors.

Table 1 Demographics from the sample of 2092 birth records

Mothers	*n* = 2092
Antenatal screening, *n* (%)	1923 (91.9)
GBS culture-positive, *n* (%)	392 (20.4)
Mothers with risk factor, *n* (%)	578 (27.6)
GBS bacteriuria during pregnancy, *n* (%)	116 (5.5)
Previous infant with GBS disease, *n* (%)	1 (0.05)
Preterm delivery (34 to 36 wks' gestation), *n* (%)	123 (5.9)
Intrapartum fever ⩾ 38 ℃, *n* (%)	32 (1.5)
Membrane rupture ⩾ 18 h, *n* (%)	254 (12.1)
Vaginal delivery, *n* (%)	1507 (72)
IAP administration, *n* (%)	771 (36.8)
IAP given more than 4 h prior to delivery, *n* (%)	470 (61.0)
IAP given to culture-positive women, *n* (%)	341 (87.0)
Gestational age, weeks, median, (IQ)	39.0 (38-40)
Birth weight, g, median (IQ)	3290 (2980-3590)

IAP: Intrapartum antibiotic prophylaxis; GBS: Group B streptococcus; IQ: Interquartile range 25th-75th.

to maternal colonization, risk factors, and IAP administration. Approximately 27% of neonates had at least 1 risk factor for EOS, and 20% were born to mothers with a positive GBS screening. The vast majority of them received IAP (which in most cases was given more than 4 h prior to delivery).

Neonates exposed to intrapartum fever/chorioamnionitis

Thirty-two neonates were intrapartum fever/chorioamnionitis-exposed. Seven of 32 had signs of illness (of which 4 at age 0-6 h and 3 at age 7-24 h). Twenty out of 32 (62.5%) had a sepsis workup, but only 7 (21.9%) were given empirical antibiotics. All had a normal outcome and none of them had culture-proven sepsis.

Neonates at risk and not at risk for EOS

Figure 2 presents data for neonates at risk (or not) for EOS and details of neonates with signs of illness, sepsis workup and empirical antibiotics. Most newborns with signs of illness, and most of those who received postpartum antibiotics were not at risk. However, compared to neonates at risk, neonates not at risk for EOS were less likely to have signs of illness (51 out of 1442 *vs* 40 out of 650, $P = 0.009$) or have a sepsis workup (25 out of 1442 *vs* 28 out of 650, $P < 0.001$), but not less likely to receive empirical antibiotics (17 out of 1442 *vs* 12 out of 650, $P = 0.3$). Among 18 at-risk neonates with signs of illness at age 0-6 h, 9 had mild, equivocal and transient symptoms and were kept under observation without further evaluation; the remaining 9 neonates underwent a sepsis workup.

WAARNs and SPEs

Among the 2092 newborns, 216 (10.3%) initially WAARNs were managed through SPEs; only 12 of 216 (5.6%) had a sepsis workup (because of respiratory signs in most cases) and 4 of 216 (1.9%) were given antibiotics. Sepsis was ruled out in the remaining 8 neonates who had a sepsis workup (as neonates recovered promptly without any antibiotic treatment).

Neonates treated with antibiotics

Postpartum antibiotics were given to 34 (1.6%) of the 2092 neonates, of whom 5 (0.2%) were asymptomatic (they were given antibiotics because of risk factors for EOS) and 29 (1.4%) had signs of illness (respiratory signs in 23 out of 29 neonates). Nine required oxygen support (chest X-rays were consistent with pneumonia in 4 cases), none received nasal CPAP or mechanical ventilation. Twelve of the 29 neonates (41.4%) presented with symptoms at age 0-6 h. One of them had culture proven sepsis (caused by *Haemophilus i.*) The baby was born at 35 wks' gestation to a GBS-negative mother

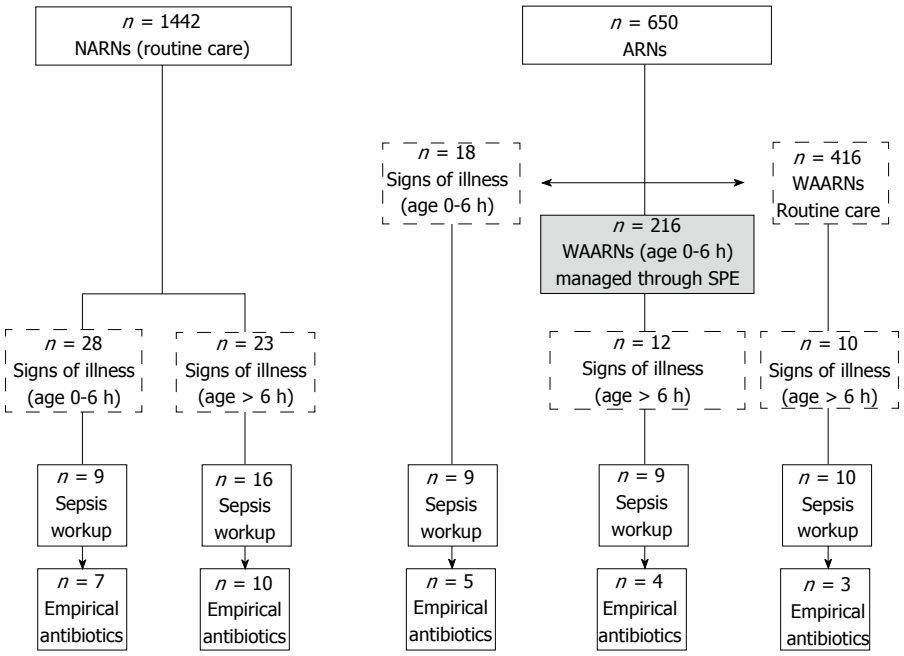

Figure 2 Neonates at risk or not at risk for early-onset sepsis: Signs of illness, sepsis workup and empirical antibiotics. Neonates delivered *via* a planned caesarean section are included among NARNs. ARNs: Neonates born to GBS-positive mothers or with risk factors; NARNs: Neonates born to GBS-negative mothers without risk factors; SPE: Serial physical examinations; WAARNs: Well-appearing at-risk neonates; GBS: Group B streptococcus.

and was given no IAP. Seventeen of the 29 (58.6%) presented with symptoms at age 7 to 63 h. Four of these 17 neonates had been managed initially through the SPE strategy (Figure 2).

All 34 neonates who were given postpartum antibiotics had a sepsis workup before treatment (all had blood culture obtained; 11 underwent also lumbar puncture), and all had a normal outcome, without brain lesions at ultrasound scanning (when performed).

DISCUSSION

Since IAP has become a standard of care, the management of WAARNs has remained a challenge for clinicians. Laboratory tests currently available have poor specificity, low positive predictive value and lack sufficient accuracy for guiding the decision as to whether neonates should be treated with antibiotics[10]. Most guidelines for neonatal management rely on studies carried out prior to the era of IAP. However, IAP leads to a substantial reduction of the risk of EOS. Recent studies show that algorithms based on the threshold values of risk factors may result in a large number of uninfected newborns being evaluated and treated; or they may fail to identify many newborns who require early treatment[11,18,19]. Therefore, new data are necessary in order to develop alternative approaches.

More recently, methods to stratify the risk of EOS by combining different maternal RF groups and clinical examination of newborns have been devised[25]. It is however unclear what impact these methods have on preventing the occurrence of sepsis or what impact they have on the number of asymptomatic newborns unnecessarily treated with antibiotics. Such methods still recommend empirical antibiotics for some WAARNs. A recent study aimed at evaluating the impact of this strategy among 2094 newborns found that 5.3% of full-term neonates were given empirical antibiotics, but more than 40% of them were asymptomatic[26].

A second controversial issue concerns the management of chorioamnionitis-exposed neonates. Early studies reported that most failures of IAP (up to 90% of cases) occur in such neonates[27]. However, recent data show that less than 50% of failures of IAP are tied to chorioamnionitis[28] and the risk of EOS is strongly dependent on gestational age[11]. Because most asymptomatic chorioamnionitis-exposed neonates are born full term, the number of neonates to be evaluated and treated empirically (number needed to treat) in order to prevent one infection may be high (60-1400 newborns) and antibiotic treatment might not be justified for full-term neonates[29].

In the current study, the low incidence of culture-proven EOS (0.48/1000) was the result of high rates of maternal prenatal screening and IAP. No cases of GBS-EOS occurred in the study period. This finding is consistent with regional data, which clearly show a continuous decline in GBS-EOS over the years, thanks to the implementation of the prevention strategy[23].

Most newborns had symptoms at birth or in the first few hours of life, and most had apparently no risk factors for EOS. Under our approach, neonates with mild or equivocal, initial symptoms or asymptomatic neonates with risk factors for EOS underwent SPEs without sepsis workup. Furthermore, only approximately 2/3 of neonates exposed to intrapartum fever or chorioa-

mnionitis had a sepsis workup and only 21% (neonates with signs of illness) were given antibiotics. We could not calculate the number needed to treat, as we had no cases of EOS among initially asymptomatic neonates managed through SPEs.

This less invasive approach has resulted in very few infants (1.6%) treated with antibiotics. Nevertheless, no cases of EOS were missed, as all neonates had a sepsis workup (including blood culture) prior to administering antibiotics. Furthermore, none of the newborns had complications or a worse outcome because of this strategy. By providing strong assurance that frequent examinations actually are performed, this strategy seems safe, reliable and easy to perform.

This study has major limitations, firstly the small sample size of neonates in study. EOS has become rarer than in the past, therefore larger population is required in order to better define neonatal risks. This is especially true for intrapartum fever/chorioamnionitis-exposed newborns, who represent approximately 1% in our population. However, starting from 2003, we recommended an SPE-based approach for the entire region, but the GBS-EOS surveillance network has to date reported no cases of delayed diagnosis. Moreover, our study addresses neonates aged 0-72 h, and we could not exclude that some newborns have fallen ill after the first days of life. However, our approach does not seem to increase the risk of subsequent complications[24].

In conclusion, our study suggests that the SPE strategy may reduce unnecessary laboratory evaluations and antibiotics, apparently without worsening the outcome. However, larger studies are needed to validate this strategy.

COMMENTS

Background

There are insufficient evidence-based recommendations for managing well-appearing neonates at-risk for early-onset sepsis (EOS). Algorithms based on the threshold values of risk factors may result in a large number of uninfected newborns being evaluated and treated; or they may fail to identify many newborns who require early treatment.

Research frontiers

New data are necessary in order to develop alternative approaches.

Innovations and breakthroughs

In this 4-mo, multicenter retrospective cohort study, we studied 2092 neonates, of which > 30% were at-risk for EOS; 216 neonates were initially managed through a strategy based on serial physical examinations (SPEs) instead of sepsis workup. Only 12 (5.6%) had subsequently a sepsis workup and only 4 (1.9%) were given empirical antibiotics. All neonates managed through SPEs had a normal outcome. Among 2092 neonates, only 1.6% (n = 34) were given antibiotics (all but 5 had clinical symptoms consistent with sepsis). Most of them were not at risk for EOS.

Applications

A strategy based on SPEs reduces unnecessary sepsis workup and antibiotics, and does not worsen the outcome.

Terminology

SPEs are carried out in turn by bedside nursing staff, midwives and physicians. at standard intervals (at age 3-6-12-18-36-48 h). A standardized form (detailing general wellbeing, skin colour - including perfusion and the presence of respiratory signs) filled in and signed by the staff is then included in the records of the newborn.

Peer-review

The reviewed article raises important topic of newborn babies potentially at risk of early infection (EOS) because of maternal Group B streptococcus colonization or the existence of other risk factors or the presence of non-specific signs of infection. At the same time, as the authors point out, the real risk for a newborn - in the era of intrapartum antibiotic prophylaxis - is not so common in the group of term and late preterm infants. Driven by concern about the excessive use of antibiotics, as well as exposing the infant to pain when performing laboratory tests, the authors propose a clinical observation in the form of repeated physical evaluation every few hours in the first days of life. It is well-written.

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ORIGINAL ARTICLE

Retrospective Study

Packed red blood cell transfusions as a risk factor for parenteral nutrition associated liver disease in premature infants

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Author contributions: D'Souza A and Valencia G provided the neonatal clinical care in the nursery assisted in the collection of the data and critically reviewed the manuscript after completion; Algotar A created some of the figures, participated in writing of the final manuscript and critically reviewed the manuscript after completion; Pan L collated all of the data collection and organization, created some of the figures, and participated in writing an earlier draft of the manuscript; Schwarz SM assisted in the analysis of the data, performed the statistical analysis, supervised the creation of the figures and critically reviewed the manuscript after completion; Treem WR designed the study, supervised the collection of the data and participated in the analysis of the data, and had input into the final draft of the manuscript, he also critically reviewed and edited the manuscript after completion; Rabinowitz SS reanalyzed the data and wrote the final draft of the manuscript, he oversaw the entire completion of the project.

Institutional review board statement: This study was approved by the Institutional Review Board of SUNY Downstate Medical Center.

Informed consent statement: As this was a retrospective chart review, informed consent was waived by the institutional review board.

Conflict-of-interest statement: None of the authors involved in this study have any conflicts of interest.

Data sharing statement: No additional data are available.

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Abstract

AIM

To determine if packed red blood cell transfusions contribute to the development of parenteral nutrition associated liver disease.

METHODS

A retrospective chart review of 49 premature infants on parenteral nutrition for > 30 d who received packed red blood cell (PRBC) transfusions was performed. Parenteral nutrition associated liver disease was primarily defined by direct bilirubin (db) > 2.0 mg/dL. A high transfusion cohort was defined as receiving > 75 mL packed red blood cells (the median value). Kaplan-Meier plots estimated the median volume of packed

red blood cells received in order to develop parenteral nutrition associated liver disease.

RESULTS

Parenteral nutritional associated liver disease (PNALD) was noted in 21 (43%) infants based on db. Among the 27 high transfusion infants, PNALD was present in 17 (64%) based on elevated direct bilirubin which was significantly greater than the low transfusion recipients. About 50% of the infants, who were transfused 101-125 mL packed red blood cells, developed PNALD based on elevation of direct bilirubin. All infants who were transfused more than 200 mL of packed red blood cells developed PNALD. Similar results were seen when using elevation of aspartate transaminase or alanine transaminase to define PNALD.

CONCLUSION

In this retrospective, pilot study there was a statistically significant correlation between the volume of PRBC transfusions received by premature infants and the development of PNALD.

Key words: Packed red blood cell transfusion; Neonatal intensive care unit; Parenteral nutrition associated liver disease

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Core tip: The etiology of parenteral nutrition associated liver disease (PNALD), a commonly encountered morbidity in the neonatal intensive care unit (NICU) remains unknown. Potentially hepatotoxic packed red blood cell (PRBC) transfusions are routinely administered in this setting. Whether PRBC transfusions increase the prevalence of PNALD is a clinical question that has not been systematically investigated. This pilot study demonstrated that in a cohort of NICU infants who received greater volumes of PRBC, there was a significantly higher prevalence of PNALD. Further investigations to define the exact risk are warranted to minimize NICU stays, costs, and future liver damage.

D'Souza A, Algotar A, Pan L, Schwarz SM, Treem WR, Valencia G, Rabinowitz SS. Packed red blood cell transfusions as a risk factor for parenteral nutrition associated liver disease in premature infants. *World J Clin Pediatr* 2016; 5(4): 365-369 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/365.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.365

INTRODUCTION

Preterm infants are among the most highly transfused patient populations, in part because of the presumption that packed red blood cells (PRBC) improve oxygen delivery[1]. Approximately 38000 premature neonates receive more than 300000 transfusions annually[2]. PRBC transfusion guidelines are based on expert opinion, rather than evidence-based data, and vary among practitioners, institutions and clinical situations[3,4]. The increased susceptibility of neonatal intensive care unit (NICU) patients to develop anemia requiring blood transfusions is attributable to multiple factors. These include prematurity itself, nutritional deficiencies, iatrogenic blood loss, and other medical conditions commonly seen in the NICU such as sepsis, hemolysis, bleeding disorders, and surgery[5].

Although PRBC transfusions are believed to be helpful in the NICU[6], they have been implicated in the development of bronchopulmonary dysplasia, acute lung injury, necrotizing enterocolitis (NEC), intraventricular hemorrhage, and retinopathy of prematurity[7,8]. Multiple transfusions may result in iron deposition leading to dysfunction in the liver, heart and other organs[9-14]. Because RBC life span in preterm infants is shorter, accelerated cell breakdown results in even greater degrees of hepatic iron deposition. Efforts to decrease transfusion requirements in low birth weight infants include utilizing erythropoietin in the first 48 hour of life[15]. This hematopoietic agent has been suggested to have a neuroprotective effect in newborns[16].

Parenteral nutrition (PN) is another recognized risk factor contributing to hepatobiliary dysfunction in newborn infants[17-20]. The clinical spectrum of parenteral nutrition-associated liver disease (PNALD) encompasses cholestasis, cholelithiasis, elevated transaminases, steatosis, fibrosis, biliary cirrhosis, portal hypertension and, potentially, hepatic failure[18]. Although PNALD's pathogenesis may be multifactorial, omega-6 fatty acids in PN regimens now appear to be the primary etiologic agent[19]. Additional risk factors include prematurity, other nutrient excesses or deficiencies, sepsis from the central line, decreased enterohepatic circulation, intestinal stasis, and bacterial overgrowth[20].

The published literature most often defines PNALD in this setting as a direct bilirubin (db) > 2.0[20,21]. As this was a pilot study to provide preliminary data on predicting hepatobiliary disease in the premature infant, transaminase values were also examined. While alanine transaminase (ALT) has been considered a more specific marker for liver dysfunction, aspartate transaminase (AST) has recently been employed as part of a derived AST/platelet ratio index, to predict liver pathology in infants with intestinal failure[22] and biliary atresia[23].

Most low birth weight infants, especially sicker babies, are unavoidably exposed to multiple risk factors associated with hepatobiliary dysfunction, including PN and PRBC transfusions. This retrospective study was conducted to determine if there was any preliminary evidence suggesting that the volume of PRBC transfusions received was associated with the subsequent development of PNALD in this population.

MATERIALS AND METHODS

This retrospective chart analysis was performed as part of a study of 49/51 premature infants maintained on PN

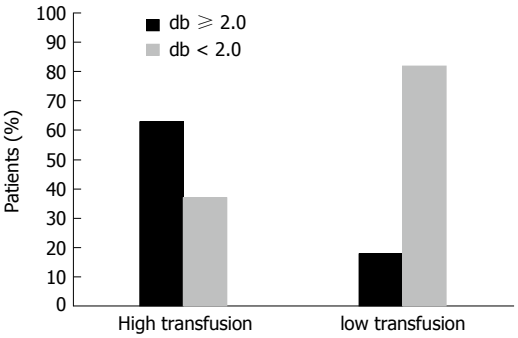

Figure 1 The number of patients that reached peak direct bilirubin ⩾ 2.0 (black bar) or direct bilirubin < 2.0 (grey bar). They are shown for both the low transfusion (total PRBC volume < 75 mL) and the high transfusion (total blood volume ⩾ 75 mL) groups (high transfusion *vs* low transfusion $P < 0.01$). db: Direct bilirubin.

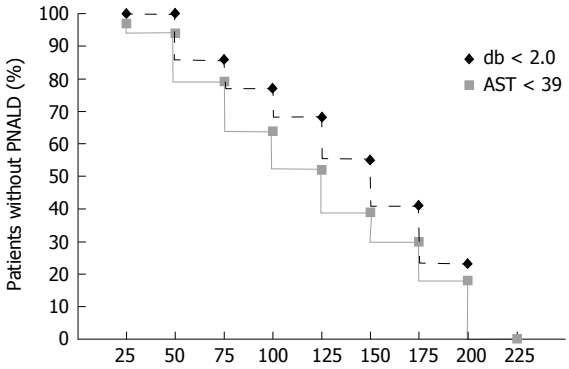

Figure 2 Kaplan-Meier plots tracking the onset of parenteral nutrition associated liver disease by the direct bilirubin and aspartate transaminase criteria as a function of total packed red blood cell transfused. PNALD: Parenteral nutrition-associated liver disease; db: Direct bilirubin; AST: Aspartate transaminase.

> 30 d, at the Children's Hospital at Downstate, State University New York, Downstate Medical Center. Two patients, one with cystic fibrosis and one with Hirschsprung disease (disorders independently associated with cholestasis), were excluded from analysis. In these 49 infants, we assessed the timing and volume of PRBC transfusions, and PNALD was primarily defined as a db level > 2.0 mg/dL[20,21].

One of the authors, SMS performed all of the biomedical statistics. Kaplan-Meier plots estimated the amount of PRBC transfused to attain PNALD onset by this db criterion. Similar analyses were performed for elevation of AST and ALT as alternative markers of PNALD. Proportional hazards regression analysis used age at PNALD onset as the dependent variable, and cumulative RBCs as the time dependent predictor of interest. Potential confounders were cumulative days on TPN (time-dependent) and birth weight. Odds ratios, hazard ratios (HR) and confidence intervals (CI) are reported. This study was approved by the Institutional Review Board of SUNY Downstate Medical Center.

RESULTS

In this cohort of 49 NICU infants, 21 (43%) reached the endpoint of PNALD, defined by a db > 2.0 mg/dL. To analyze any potential role of PRBC transfusions in the development of PNALD, the study population was subdivided into high and low transfusion groups. The subgroups were defined by the median volume transfused in this study cohort, specifically transfusion volumes of ⩾ 75 mL (high) or < 75 mL (low). Employing this cut off value, 27/49 (55%) infants were in the high transfusion group and 22/49 (45%) were in the low transfusion cohort.

Figure 1 shows the relationship between transfusion volume and PNALD, as defined by a db > 2.0 mg/dL. Among the 27 high transfusion infants, 17 (64%) developed PNALD, while PNALD was seen in only 4/22 infants (18%) in the low transfusion group. Further, among all infants who developed PNALD, 17/21 (81%) received PRBC ⩾ 75 mL while only 10/28 (36%) received < 75 mL PRBC volumes ($P < 0.001$). The calculated odds ratio for developing PNALD, based on being in the high verses low transfusion group, was 7.6 (95%CI: 2.01-29.1).

Kaplan-Meier plots provide another perspective on the relationship between PRBC transfusions and PNALD (Figure 2). With cumulative transfusion volumes of 126-150 mL, the prevalence of db > 2.0 mg/dL reached 50%. All infants who were transfused > 200 mL PRBC demonstrated PNALD. Regression analysis showed neither birth weight nor cumulative time on TPN were significant predictors of these endpoints, when used as linear covariates (data not shown). However, cumulative PRBCs were a significant predictor of db ⩾ 2.0 with an estimated HR associated with each additional 15 mL/kg transfused of 1.09 (95%CI: 1.00-1.19). After controlling for birth weight and PN duration, PRBC volume transfused remained a predictor of reaching the primary end point of db ⩾ 2.0. The HR related to incremental PRBC transfused volumes approached significance for each 15 mL/kg (HR = 1.11, 95%CI: 1.00-1.23, $P = 0.053$). However, when the NEC cases were excluded, the transfusion effect on db ⩾ 2.0 became statistically significant ($P = 0.026$).

Five of the 49 infants in our study developed NEC. Of these five infants, three also had culture proven sepsis, and two of these three exhibited PNALD. Of the two infants with NEC but without sepsis, both demonstrated PNALD. Overall, 11/17 study subjects with culture proven sepsis demonstrated PNALD. Employing elevated transaminases, AST and ALT, to define PNALD yielded results similar to those based on db ⩾ 2.0. PNALD was seen in 67% of the cohort based on AST elevations and in 41% based on ALT elevations. Of the 33 infants with AST-defined PNALD, 70% were in the high transfusion and 30% were in the low transfusion cohorts. Similarly, among the cohort of 20 infants with PNALD defined by elevated ALT, 75% were in the high transfusion and 25% were in the low transfusion groups. Similarly to db PNALD, the odds ratio for developing PNALD based on high *vs* low PRBC transfusion was 6.9 (95%CI: 1.78-26.7) if defined by AST, and was 4.2 (95%CI: 1.21-14.9) if

defined by ALT.

DISCUSSION

Although potentially lifesaving, blood transfusions are associated with risks in the NICU[7,8]. Several studies have attempted to better define indications for transfusion in NICU babies[24,25]. Previous investigations have sought to develop transfusion protocols, to achieve an acceptable balance between the risks and the benefits of transfusing preterm infants[1,7,25]. The PINT trial concluded that a higher hemoglobin threshold for transfusions in the NICU resulted in a greater number of transfusions without any added benefit, when compared to a restricted hemoglobin threshold[26]. In the present review of 49 premature infants on TPN, transfusion of $\geqslant$ 75 mL PRBC represented a significant risk factor for developing PNALD. If this relationship is confirmed in larger studies, the potential benefits of PRBC transfusions could be balanced with the associated risk of developing liver disease.

The pathogenesis of hepatotoxicity secondary to both PRBC transfusions and PN includes injury secondary to the generation of hepatic reactive oxidative stress (ROS)[26-30]. Since no effective mechanisms allow for excretion of parenteral iron, repeated transfusions can yield secondary Iron overload[27]. The primary sites for iron overload toxicity are those tissues where iron is stored, with liver being the main target[28]. One of the most important recognized mechanisms of liver injury in this setting is free radical mediated oxidative damage[29]. Preterm infants are especially vulnerable to this insult, as a higher proportion of their iron remains unbound to transferrin, leading to increased ROS[30]. Malonylaldehyde (MDA), a byproduct of hepatic ROS, has been employed as a marker of oxidative stress. Elevations of this compound are associated with chronic transfusion states, such as thalassemia and sickle cell disease[31]. Emerging evidence has also implicated oxidative damage as a factor in PNALD[32,33]. Animal models of PNALD using weanling rat[32] and infant rabbit[33] have correlated severity of liver injury and hepatic MDA content with time on PN.

Several important limitations are associated with this pilot study. This retrospective analysis involved a relatively small number of representative NICU patients. Additionally, the cohort was heterogeneous, as subjects were included over a wide range of gestational ages. Other potential comorbidities, previously identified as PNALD risk factors, were unable to be controlled. If this small study group were to be further subdivided, the numbers would not provide meaningful data. Finally, because this is a small cohort, the higher PRBC transfusions volumes associated with PNALD may actually be secondary to coexisting conditions which are the true primary risk factors for this condition.

In conclusion, our pilot study supports the hypothesis that repeated PRBC transfusions increase the risk of PNALD in NICU infants. This preliminary observation is being presented to stimulate further studies employing larger NICU databases. Access to this information could yield a series of well-defined PRBC transfusion recommendations and/or guidelines based on specific characteristics in this vulnerable cohort.

COMMENTS

Background

Parenteral nutrition is commonly associated with liver disease in the neonatal intensive care unit (NICU). There are a variety of factors that have been described as risk factors for this problem including prematurity, time on parenteral nutrition, sepsis, prolonged periods without enteral nutrition and necrotizing enterocolitis. Packed red blood cells transfusions which can generate reactive oxygen species especially in the livers of premature neonates are a potential trigger for this morbidity.

Research frontiers

Whether the transfusion of packed red blood cells is an actual contributor to the incidence of cholestatic liver disease in the NICU infant receiving parenteral nutrition has not been systematically investigated.

Innovations and breakthroughs

This retrospective pilot study compared a cohort of NICU infants on parenteral nutrition who had received more than the median volume of packed red blood cell transfusions to a second cohort from the same nursery at the same time who received less than the median value. Higher volumes of transfusion led to a statistically significant increase in the prevalence of liver disease in this study as defined by elevated direct bilirubin, by elevated aspartate transaminase and by elevated alanine transaminase.

Applications

This preliminary observation should now be investigated in larger cohorts of NICU infants. If these results are confirmed, then guidelines addressing the safety of packed red blood cell transfusions in the NICU can be developed.

Terminology

NICU: Neonatal intensive care unit; PRBC: Packed red blood cells; PNALD: Parenteral nutrition associated liver disease.

Peer-review

A small and succinct study, while it has some limitations, which are well acknowledged by the author. There are some interesting and statistically significant within this study.

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ORIGINAL ARTICLE

Retrospective Study

Clinical profile and outcomes of pediatric endogenous endophthalmitis: A report of 11 cases from South India

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision, editing, and final approval of the final version.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Aravind Eye Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Abstract

AIM

To study the clinical profile and outcomes of pediatric endogenous endophthalmitis from a tertiary eye hospital in South India.

METHODS

A total of 13 eyes of 11 children presented to us with varied symptoms and presentations of endogenous endophthalmitis, over a five-year period from January 2010 to December 2015 were studied. Except for two eyes of a patient, vitreous aspirates were cultured from all 11 eyes to isolate the causative organism. These eleven eyes also received intravitreal injections. All patients were treated with systemic antibiotics.

RESULTS

Two cases had bilateral endophthalmitis. Ages ranged from 4 d to 11 years. Five cases were undiagnosed and treated, before being referred to our center. Ten of the 13 eyes underwent a core vitrectomy. The vitrectomy was done at an average on the second day after presenting (range 0-20 d). Five of the 11 vitreous aspirates showed isolates. The incriminating organisms were bacteria in three and fungus in two. An underlying predisposing factor was found in seven patients. At a mean follow-up 21.5 mo, outcome was good in 7 eyes of 6 cases (54%), five eyes of four cases (38%) ended up with phthisis bulbi while one child died of systemic complications.

CONCLUSION

Endogenous endophthalmitis is a challenge for ophtha-

lmologists. Early diagnosis and intervention is the key for a better outcome.

Key words: Pediatric; Endogenous endophthalmitis; Outcomes; South India; Fungal

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Core tip: It was a retrospective study of 13 eyes of 11 children with endogenous endophthalmitis, where a detailed evaluation of the clinical profile including the presenting symptoms, signs, incriminating organisms and outcomes were studied.

Murugan G, Shah PK, Narendran V. Clinical profile and outcomes of pediatric endogenous endophthalmitis: A report of 11 cases from South India. *World J Clin Pediatr* 2016; 5(4): 370-373 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/370.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.370

INTRODUCTION

Endogenous endophthalmitis is a rare, but highly destructive infection of the eye, in which the pathogenic organisms reach through the systemic circulation. Studies have shown that endogenous endophthalmitis accounts for 2% to 8% of all endophthalmitis cases[1,2]. It is even rarer in children, and constitutes only 0.1% to 4% of all endogenous endophthalmitis cases[2,3]. In children it may masquerade as uveitis, pre septal orbital cellulitis, congenital glaucoma, conjunctivitis or retinoblastoma. It can also occur as a rare complication of neonatal sepsis. In a particular series in India from a tertiary hospital for every 1000 live births, 1 case of endophthalmitis was seen[4]. The incidence of neonatal endophthalmitis from the United States is about 4.42 cases per 100000 live births[5]. The reasons for the high incidence of endophthalmitis in Indian population may be because of more immunocompromised, poor hygiene and high rates of infection secondary to antibiotic resistant microbes[4]. We report a series of 11 chidren presenting with endogenous endophthalmitis at our institute over a period of five years.

MATERIALS AND METHODS

This is a retrospective study of 13 eyes of 11 children who presented at Aravind Eye Hospital, Coimbatore with signs and symptoms of endogenous endophthalmitis. After taking a detailed history from all the patients, a through ocular examination was done. Visual acuity was taken for all cooperative cases. This was followed by through anterior examination using slip lamp biomicroscopy. Fundus examination was done with indirect ophthalmoscopy. B scan ultrasonography was done for all cases with a hazy media. Short general anesthesia was administered to children who very not cooperative for a through ocular examination. Cases with severe infection were immediately posted for vitreous biopsy with or without core vitrectomy with intravitreal antibiotic injections. All were given systemic antibiotics. All vitreous aspirates were cultured at the microbiology department of Aravind Eye Hospital, Coimbatore. A thorough systemic examination was undertaken with the help of a paediatrician to look for any precipitating factors. A good outcome was defined as maintenance of ocular anatomy with functional vision at the end of treatment.

RESULTS

Two cases had bilateral disease. There were 5 females and 6 males. The mean age was 43 mo (range 4 d to 132 mo). Ten cases (91%) presented with swelling, pain and redness in the eyes. Ten of the 13 eyes underwent a vitreous biopsy with core vitrectomy and intravitreal antibiotics injection. One patient underwent only a vitreous tap with lens aspiration for a lens abscess with intravitreal antibiotics. Two eyes of another patient who suffered from a multifocal retinochoroidal infiltrate secondary to septic arthritis recovered with systemic antibiotics alone. Eleven vitreous aspirates were cultured to isolate the causative organism. The mean time from the onset of symptoms to presentation was 11 d (range 3-30 d). Five cases were undiagnosed by the treating ophthalmologist, before being referred to our center. Of these two were being treated as uveitis, two as conjunctivitis and one as suspected retinoblastoma. There did not seem to be a prediliction for either eye with an almost equal distribution of 5 left and 4 right eyes. Both the eyes were affected in two patients. Five of the 11 vitreous taps showed isolates. The incriminating organisms were fungi in two and bacteria in remaining three (Table 1). Core vitrectomy was done in 10 eyes at a mean of second day after presentation (range 0-20 d).

A positive blood culture was seen only in case 8 which grew pseudomonas in blood, vitreous and also from the hand abscess. An underlying predisposing factor was found in seven patients. Case 1, who developed endophthalmitis secondary to broncho pneumonia and meningitis, the vitreous tap and the cerebrospinal fluid both tested positive for Aspergillus. This child met a fatal end within two weeks of presenting to us due to his systemic condition. Case 5 was referred with a suspected diagnosis of retinoblastoma. Child had multiple small yellowish retinal lesions over posterior pole and periphery in both eyes with a history of septic arthritis. The ocular lesions resolved completely with systemic antibiotics only (Figure 1). Good outcome was seen in 7 eyes of 6 cases (54%), of which final visual acuity of $\geqslant$ 6/9 was seen in 5 eyes and $\leqslant$ 6/36 in 2 eyes. Five eyes of 4 cases ended up with phthisis bulbi and one child died of systemic complications.

DISCUSSION

Detection of endogenous endophthalmitis is based on a through history and a good ocular examination.

Table 1 Baseline characteristics and outcome of all cases

Case	Age (mo)	Sex	Eye	Vitreous growth	Systemic affection		Follow-up (mo)	Final outcome
					Focus	Growth		
1	24	M	LE	Aspergillus flavus	Broncho pneumonia, meningitis with cerebral abscess	Aspergillus flavus	1	Death
2	132	M	LE	Nil	-	-	48	Good
3	48	M	LE	Neisseria meningitides	Fever	-	44	Good
4	36	F	RE	Nil	URI		7	Phthisis bulbi
5	1	F	BE	-	Knee arthritis	-	26	Good
6	7	M	LE	Candida	Pre term		9	Phthisis bulbi
7	48	F	RE	Staphylococci	Fever with cough		24	Good
8	4[1]	M	BE	Pseudomonas aeruginosa	Hand abscess	Pseudomonas aeruginosa	48	Phthisis bulbi
9	108	M	LE	Nil	-	-	9	Good
10	24	F	RE	Nil	-		18	Good
11	48	F	RE	Nil	Fever with URI		3	Phthisis bulbi

[1]In days. LE: Left eye; RE: Right eye; BE: Both eyes; URI: Upper respiratory tract infection; M: Male; F: Female.

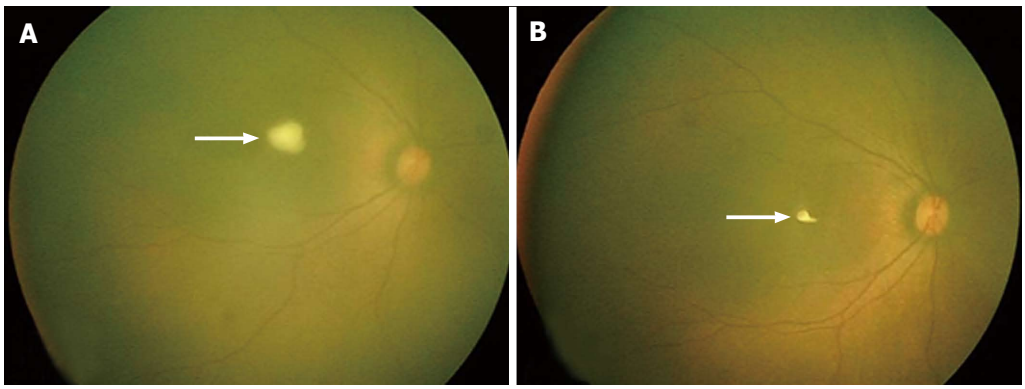

Figure 1 Retcam fundus image showing reduction of retino-choroidal abscess pre and post treatment. A: Fundus picture of right eye showing yellowish lesion over fovea (white arrow) suggestive of active chorio-retinitis; B: Fundus picture of same eye showing dramatic reduction in the size of the lesion (white arrow), 1 wk after systemic antibiotics.

Early detection of endophthalmitis in children is really challenging because they may not be able to identify or express their symptoms. On top of that, it is usually not easy to carry out a thorough ocular examination. Though there have been innumerable studies on adult onset endogenous endophthalmitis there is limited literature in pediatric group. In the study by Basu *et al*[4] six premature infants with extremely low birth weight developed endogenous endophthalmitis. They reported Klebsiella pneumoniae and Pseudomonas aeruginosa in two cases each and Candida albicans and Methicillin resistant *Staphylococcus aureus* in one case each. Three of the 6 cases died in their series and remaining 2 infants retained good vision and one ended up with phthisis bulbi. Our study had two neonates of which one was proven to be pseudomonas. There was one death in our study and 5 (38%) eyes went for phthisis bulbi.

Wrong diagnosis at the time of referral is reportedly seen in 16% to 63% of cases, thus delaying the proper treatment[6,7]. In our study 5/11 cases (45%) were referred to us with a wrong diagnosis, which were, two as uveitis, two as conjunctivitis and one as retinoblastoma. Common sources of infection in endogenous endophthalmitis in children include distal wound infection, meningitis, which was seen in one case each in our study, intravenous catheters, endocarditis and urinary tract infections[8,9]. In United States, the rate of endogenous endophthalmitis from septicemia declined from 8.71 cases in 1998 to only 4.42 cases per 100000 live births in 2006, which is a 6% decrease per year[5]. This may be due to the improvement in neonatal care and the advent of effective broad spectrum antibiotics in the treatement of septicemia. A major review of pediatric infectious endophthalmitis by Khan *et al*[8] found *Streptococcus* and *Staphylococcus* species as the most common cause of post-traumatic and post-operative endophthalmitis and Candida albicans for endogenous endophthalmitis. We had two cases with fungal infection in our study.

In conclusion, endogenous endophthalmitis in children is a diagnostic and therapeutic challenge for ophthalmologists. It can occur at any age, and in either sex. Since there is a usually a septic foci, systemic antibiotics seem to play a much definitive role in treatment. Inspite of early diagnosis and treatment, 1/3rd of patients can still have a dismal outcome.

COMMENTS

Background

Pediatric endogenous endophthalmitis is a devastating infection of the eye

which can lead to permanent blindness.

Research frontiers

Although a blinding condition, early diagnosis and treatment can save the eye and vision.

Innovations and breakthroughs

Finding the source of infection is important as this may lead to a quicker recovery. Apart from systemic antibiotics, core vitrectomy with intravitreal antibiotic injections by a retinal surgeon may improve the prognosis, as seen in the present study.

Applications

The study results suggest that prompt and correct diagnosis and treatment can lead to better outcome.

Terminology

Endogenous endophthalmitis is a severe and serious infection of the eye where the source of infection is from a distal organ. The infective organisms reach the ocular tissues *via* the blood stream.

Peer-review

This study has valuable data that would be of interest if published. It is well written and comprehensive.

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ORIGINAL ARTICLE

Observational Study

Pandemic influenza 2009: Impact of vaccination coverage on critical illness in children, a Canada and France observational study

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Author contributions: Fléchelles O participated to the design, analysis and interpretation of data and drafted the article; Brissaud O participated to the design of the study, acquisition of data, interpretation of data and revised the manuscript critically for important intellectual; Fowler R and Ducruet T participated to the design of the study, interpretation of data and revised the manuscript critically; Jouvet P conceived, participated to the design of the study, analysed the results and draft the manuscript with Flechelles O; all authors gave final approval of the version of the manuscript submitted and agreed to act as guarantor of the work.

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Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: Dataset is available from the corresponding author at philippe.jouvet@umontreal.ca.

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Abstract

AIM

To study the impact of vaccination critical illness due to H1N1pdm09, we compared the incidence and severity of H1N1pdm09 infection in Canada and France.

METHODS
We studied two national cohorts that included children with documented H1N1pdm09 infection, admitted to a pediatric intensive care unit (PICU) in Canada and in France between October 1, 2009 and January 31, 2010.

RESULTS
Vaccination coverage prior to admission to PICUs was higher in Canada than in France (21% *vs* 2% of children respectively, $P < 0.001$), and in both countries, vaccination coverage prior to admission of these critically ill patients was substantially lower than in the general pediatric population ($P < 0.001$). In Canada, 160 children (incidence = 2.6/100000 children) were hospitalized in PICU compared to 125 children (incidence = 1.1/100000) in France ($P < 0.001$). Mortality rates were similar in Canada and France (4.4% *vs* 6.5%, $P = 0.45$, respectively), median invasive mechanical ventilation duration and mean PICU length of stay were shorter in Canada (4 d *vs* 6 d, $P = 0.02$ and 5.7 d *vs* 8.2 d, $P = 0.03$, respectively). H1N1pdm09 vaccination prior to PICU admission was associated with a decreased risk of requiring invasive mechanical ventilation (OR = 0.30, 95%CI: 0.11-0.83, $P = 0.02$).

CONCLUSION
The critical illness due to H1N1pdm09 had a higher incidence in Canada than in France. Critically ill children were less likely to have received vaccination prior to hospitalization in comparison to general population and children vaccinated had lower risk of ventilation.

Key words: Vaccine; Children; Intensive care; Critical care; Influenza; Pandemic

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Core tip: This article is on a two national cohorts study from Canada and France of critically ill children during influenza pandemic and reports that: (1) critically ill French children were much less likely to have received vaccine prior to hospitalization against influenza A(H1N1)pdm09 in comparison to children in the Canadian populations; and (2) in Canada, where vaccination rate was higher, the risk of severe respiratory failure was less among those critically ill children receiving vaccine.

Fléchelles O, Brissaud O, Fowler R, Ducruet T, Jouvet P, the Pediatric Canadian Critical Care Trials Group H1N1 Collaborative and Groupe Francophone de Réanimation et Urgences Pédiatriques. Pandemic influenza 2009: Impact of vaccination coverage on critical illness in children, a Canada and France observational study. *World J Clin Pediatr* 2016; 5(4): 374-382 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/374.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.374

INTRODUCTION

By March 2009, pandemic influenza A(H1N1)pdm09 had begun to spread from Mexico across the globe. The epidemiology of the first pandemic wave in Canada revealed that A(H1N1)pdm09 affected both young healthy patients and patients with underlying conditions. The severity of illness among children was high, predominantly due to severe hypoxic respiratory failure, resulting in prolonged pediatric intensive care unit (PICU) length of stay and mechanical ventilation, in comparison with seasonal influenza[1]. Countries from the Southern Hemisphere also reported early patterns of severity of illness including higher mechanical ventilation rate and higher mortality than previously observed with seasonal influenza[2,3].

To limit the impact of the pandemic influenza A(H1N1)-pdm09 especially on children[4-6], a vaccination campaign was conducted just before the second wave. However, different vaccine coverage across countries was observed, especially between Canada and France[7-10]. In order to study the impact of pandemic influenza H1N1 vaccination prior to hospitalization on critical illness, we conducted a bi-national observational study in 42 centers across Canada and France on pandemic influenza A(H1N1)-associated critically illness in children, the most sensitive population affected by the pandemic. We originally hypothesized that the higher rate of vaccination coverage in children in Canada and previous exposure to influenza A(H1N1)pdm09 would have protected Canadian children from critical illness in the Fall of 2009.

MATERIALS AND METHODS

Ethical considerations

The participating institutions' research ethics boards approved study procedures in the two countries (Sainte-Justine IRB and Bordeaux IRB). The need for informed consent was waived given the non-interventional study design.

Study design

We studied pandemic influenza A(H1N1)pdm09 incidence and severity in children in Canada and France using two multicenter national databases designed for pandemic surveillance. A key difference between the two countries was that 54% of children in Canada and 18% in France had been vaccinated[7-10]. On the other hand, Canada and France are two similar industrialized countries with a gross domestic product par capital ranking, 15th and 23rd rank in the world, respectively - with similar per capita health expenditures[11,12]. Their climates during autumn are similar (average temperatures (low/high) are 0 ℃ to 15 ℃ in Canada and 5 ℃ to 20 ℃ in France). France and Canada have similar health care systems in that they are based on social health insurance to provide near universal coverage to the adult and pediatric populations. Family practitioners provide primary health care in each country and most vaccine delivery does not require out-of-pocket payment. The number of PICU is also similar (2.9 bed/100000 children under 15 years in Canada and 2.5 beds per 100000 children in France)[9,13]. During the pandemic, treatment recommendations were the

same, those of the World Health Organization. Although oseltamivir was not prescribed initially to children under two years of age in Canada, and under one year of age in France, as of October 27, 2009 in Canada and December 10, 2009 in France, these restrictions were abolished[14,15]. Vaccination campaigns were organized in the two countries with the same priority groups and guidelines[16-18]. The campaigns started on October 18, 2009 in Canada and October 20, 2009 in France[19].

Data collection was prospective in all Canadian PICUs (n = 17). In France, data collection was both prospective and retrospective in 25 of 29 French PICUs. Four French PICUs did not participate to the study. All children admitted to a participating PICU in Canada and France, with documented A(H1N1)pdm09 infection between October 1 2009 and January 31 2010, were included. During this second wave of pandemic influenza A(H1N1)pdm09, all children admitted to PICU with clinical symptoms of H1N1 infection or strong epidemiologic link to patients with known H1N1 infection were tested for H1N1, in both countries. Proven A(H1N1)pdm09 corresponded to World Health Organization criteria in both countries: Any specimen yielding influenza A(H1N1)-pdm09 by polymerase chain reaction and/or viral culture[20]. Variables in common between both databases were identified.

Data collection and outcomes

The data collected in both cohorts included demographic characteristics, vaccination history, comorbid conditions, admission severity of illness according to the Pediatric Logistic Organ Dysfunction (PELOD)[21] and Pediatric Index of Mortality 2 (PIM2)[22] scores, and intensive care management conditions. The geographic area of 17 Canadian PICUs corresponded to a pediatric population of almost 6 millions children[23] and the 25 French PICUs cover a pediatric population of almost 11 millions children[24]. We also collected data on infection severity including acute respiratory distress syndrome (ARDS) that is characterized by an acute hypoxemia due to lung inflammation[1] in reaction to viral infection or secondary bacterial infection, nosocomial infection that could result from invasive treatments and seizures.

The study's primary objective was to assess whether vaccination prior to hospitalization protects against critical illness. The secondary outcomes were A(H1N1)pdm09 incidence, the timing of the epidemic peak and the epidemic duration, PICU mortality, the incidence and duration of invasive mechanical ventilation, PICU length of stay between the two countries. Mechanical ventilation was considered invasive if delivered through an endotracheal tube or a tracheostomy. The duration of each episode of mechanical ventilation was defined as the time from intubation to final extubation or death. Mechanical ventilation was considered non-invasive if delivered through a nasal or facemask interface. Total duration of ventilation corresponded to the sum of the periods of both invasive and non-invasive ventilation.

Statistical analysis

Descriptive statistics included counts and proportions, means (and standard deviations), medians (and inter-quartile ranges) as appropriate. Incidence and incidence curves were calculated using as a denominator, the number of susceptible patients in the population in each country from Statistics Canada and the "Institut National de la Statistique et des Etudes Economiques" in France. We compared the two countries using bi-variate analysis including Pearson's χ^2 test or Fisher's exact test for categorical variables. Student's t-test, Wilcoxon rank-sum test or the log-rank test, were used for continuous variables. To assess associations between patient or country factors and outcomes, we performed a multivariate logistic regression for invasive ventilation risk and Cox proportional hazards modeling for time-dependent variables such as length of stay and invasive ventilation duration. Because data came from two different cohorts, there was heterogeneity in data distributions, requiring country-specific analyses for many variables. Variables used in final multivariate models met the following criteria: Factors of clinical interest or possibly associated with the outcomes ($P < 0.1$ in univariate analysis), more than 3 cases per group and per country, and with few (< 5%) missing values in each country. All variables were tested for excessive (> 0.80) co-linearity. For Cox regression modeling, variables respected the proportional hazards assumption. Analyses were considered statistically significant at $\alpha < 0.05$. SPPS version 19 was used for all analyses. The statistical methods of this study were performed by a biomedical statistician (Thierry Ducruet from Sainte-Justine Hospital, co-author).

RESULTS

Epidemiologic data

In total 285 children were included, 160 in Canada and 125 in France. The rate of admission to PICU due to A(H1N1)pdm09, calculated using the estimated population studied (see methods), was 2.63 per 100000 children in Canada and 1.15 per 100000 children in France (Table 1). The incidence curves showed a higher peak (41 *vs* 17 admissions per week, both during week 45) but shorter pandemic period (6 wk *vs* 11 wk) in Canada compared to France (Figure 1).

Baseline characteristics and health status on admission (Table 1)

The sex ratios and age distribution of critically ill children were similar in Canada and in France. After vaccination program start (Figure 1), vaccination coverage prior to hospitalization of children admitted to PICU was higher in Canada than in France (21% *vs* 2% of children respectively, $P < 0.001$), and in both countries, this vaccination coverage was substantially lower than that of the general pediatric population ($P < 0.001$, using conservative estimates of 54% in children in Canada and 18% in

Table 1 Characteristics of critically ill children with influenza A(H1N1)pdm09 virus at admission to the pediatric intensive care unit in two countries

	Canada (*n* = 160)	France (*n* = 125)	OR (95%CI) Canada/France	*P* value
Incidence rate (/100000 children)	2.6	1·1	2.3 (1.8-2.9)	< 0.001
Age, mean (SD), yr	6.6 (0.40)	5.5 (0.48)	NA	0.09
Weight, mean (SD), kg	25.9 (1.62)	20.1 (1.45)	NA	0.01
Female gender, *n* (%)	68 (42)	56 (45)	0.91 (0.57-1.46)	0.70
Vaccination H1N1, *n* (%)	34 (21)	2 (2)	16.6 (3.90-70.6)	< 0.001
Underlying chronic conditions, *n* (%)				
Any underlying conditions	102 (64)	93 (74)	0.60 (0.36-1.01)	0.05
Infant < 1 years old	21 (13)	32 (25)	0.44 (0.24-0.81)	0.007
Lung disease	65 (40)	29 (23)	2.26 (1.34-3.82)	0.002
Asthma	42 (26)	16 (13)	2.40 (1.29-4.56)	0.005
Chronic lung disease	33 (20.6)	14 (11.2)	2.06 (1.05-4.05)	0.03
Cystic fibrosis	0 (0)	2 (2)	NA	NA
BPD	4 (2)	4 (3)	0.78 (0.19-3.16)	0.73[1]
Tracheostomy	5 (3)	1 (1)	4.00 (0.46-33.3)	0.24[1]
Congenital heart disease	24 (15)	3 (2)	7.18 (2.11-24.4)	< 0.001
Neurological disease	31 (19)	19 (15)	1.33 (0.71-2.50)	0.36
Seizure disorder	19 (12)	5 (4)	3.23 (1.18-9.09)	0.02
Immunosuppressive disorder	11 (7)	9 (7)	0.95 (0.38-2.37)	0.91
Diabetes mellitus	6 (3.8)	0 (0)	NA	0.04[1]
Renal insufficiency	7 (4)	1 (1)	5.56 (0.69-50.0)	0.08[1]
Others diseases	32 (20)	28 (22)	0.87 (0.95-1.54)	0.62
PELOD score, mean (SD)[2]	6.67 (0.82)	7.80 (1.47)	NA	0.47
PIM2 score, mean (SD)[3]	8.47 (1.05)	9.74 (2.77)	NA	0.67
Clinical presentation at admission				
Lower respiratory infection, *n* (%)	101 (63)	90 (72)	0.67 (0.40-1.10)	0.11
CNS infection	2 (1)	7 (6)	0.21 (0.04-0.99)	0.04
Shock	13 (8)	6 (5)	1.75 (0.65-4.76)	0.26
Other	48 (30)	35 (29)	1.10 (0.67-1.85)	0.90
Bacterial infection at admission	22 (14)	27 (22)	0.58 (0.31-1.07)	0.08

[1]Fisher's exact test; [2]Missing values PELOD: 42.4% in France, 1.9% in Canada; [3]Missing values PIM2: 37.6% in France, 0% in Canada. Chronic lung disease = chronic restrictive lung syndrome and chronic upper airway disease and tracheo/bronchomalacia and obstructive sleep apnea and recurrent aspiration into lungs and others; Immune deficit = oncologic disorder and HIV and hemoglobinopathy. CI: Confidence interval; NA: Not applicable; BPD: Broncho-pulmonary dysplasia; PELOD: Pediatric logistic organ dysfunction; PIM2: Paediatric index of mortality revised version; OR: Odds ratio; SD: Standard deviation.

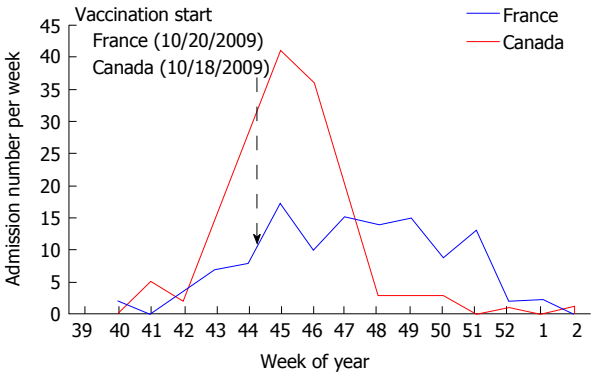

Figure 1 Admission number per week in pediatric intensive care units in Canada (red line) and France (blue line). In Canada, the decrease in incidence starts 2 wk after vaccination campaign start.

France[7-10]). Co-morbid conditions were common in both Canada and France but individual distributions were different.

Clinical presentation and hospital course

The most common reason for PICU admission was lower respiratory infection in both Canada (63%) and France (72%) and clinical presentations at admission were similar between the two countries (Table 1). The mean organ dysfunction score (PELOD score) at day one and mean predicted mortality score (PIM2 score) were similar. During hospitalization, there was a higher rate of severity of illness in France: ARDS, nosocomial infection, nosocomial pulmonary infection, and seizures (Table 2).

Outcomes

Mortality rate (4.4% *vs* 6.5%, *P* = 0.45) and rate of invasive mechanical ventilation (49% *vs* 40%, *P* = 0.14) were similar in Canada and France (Table 2). The duration of invasive mechanical ventilation (median, 4 d *vs* 6 d, *P* = 0.02) and total (invasive and non-invasive) mechanical ventilation (4 d *vs* 5 d, *P* = 0.07) was shorter in Canada than in France (Table 2). The mean PICU length of stay was shorter in Canada (5.7 d *vs* 8.2 d, *P* = 0.03) but median PICU length of stay was not different (3 d *vs* 2.9 d).

Among Canadian patients, independent multivariate analyses showed that H1N1 vaccination and asthma were associated with an almost four-fold decrease risk of invasive ventilation: (OR = 0.3, 95%CI: 0.11-0.83, *P* = 0.02) and (OR = 0.23, 95%CI: 0.09-0.64, *P* = 0.004), respectively (Table 3). This multivariate analysis did not include French patients because there were only 2

Table 2 Hospital course of critically ill children with influenza A(H1N1)pdm09 infection in two countries

	Canada (n = 160)	France (n = 125)	OR (95%CI), difference	P value
Time-dependent variables, median (25th 75th percentile), d				
PICU length of stay	2.9 (2.1-3.6)	3.0 (1.8-4.2)	0.1	0.03
Duration of mechanical ventilation	4.0 (2.8-5.2)	5.0 (3.2-6.8)	1	0.07
Duration of invasive ventilation	4.0 (2.9-5.1)	6.0 (4.6-7.4)	2	0.02
Categorical variables, n (%)				
Mortality	7 (4.4)	8 (6.5)	0.67 (0.24-1.90)	0.45
Respiratory dysfunction				
ARDS	29 (18)	40 (32)	0.48 (0.27-0.81)	0.007
Mechanical ventilation	86 (54)	66 (53)	1.04 (0.67-1.67)	0.87
Invasive ventilation	78 (49)	50 (40)	1.43 (0.91-2.50)	0.14
Pneumothorax	19 (12)	10 (8)	1.17 (0.67-3.33)	0.32
ECMO	3 (2)	8 (6)	0.28 (0.07-1.07)	0.05
Neurologic dysfunction				
Seizures	2 (1)	9 (7)	0.16 (0.03-0.13)	0.01
ADEM	3 (2)	7 (6)	0.32 (0.08-1.26)	0.09
Renal dysfunction				
Dialysis/hemofiltration	10 (6)	4 (3)	2.00 (0.63-6.67)	0.24
Nosocomial infections				
Nosocomial infection	15 (9)	26 (21)	0.39 (0.20-0.78)	0.006
Ventilator-associated pneumonia	9 (6)	21 (17)	0.29 (0.13-0.67)	0.002
Antiviral treatment				
Oseltamivir	148 (93)	111 (89)	1.55 (0.69-3.49)	0.28
Oseltamivir within 48 h	102 (63)	99 (79)	0.46 (0.27-0.79)	0.004

A bivariate analysis compared mortality, organ dysfunction, nosocomial infection and anti-viral treatment between the two countries. OR: Odds ratio; CI: Confidence interval; PICU: Pediatric intensive care unit; ARDS: Acute respiratory distress syndrome: ECMO: Extracorporeal membrane oxygenation; ADEM: Acute demyelinating encephalo-myelitis or demyelinating disorder.

Table 3 Critically ill patient-based factors associated with risk of invasive ventilation in Canada

Included variables	n = 157	OR	95%CI	P value
PIM2 > 7.5	39	6.26	2.43-16.4	< 0.001
Age, years < 1	21	1.88	0.51-6.94	0.35
1-4	52	1.50	0.51-4.35	0.46
5-9	46	2.42	0.45-6.93	0.10
> 10	38	1	(Ref)	
H1N1 vaccine	32	0.30	0.11-0.83	0.02
Asthma	41	0.23	0.09-0.64	0.004
Lung diseases (not asthma)	22	0.99	0.32-3.08	0.99
Neurologic diseases	31	2.51	0.92-6.90	0.07
Cardiologic diseases	28	1.13	0.43-2.97	0.76
Others diseases	47	0.87	0.37-2.05	0.76
Oseltamivir within 48 h	102	1.02	0.47-2.24	0.95

H1N1 vaccine, children vaccinated against H1N1; lung diseases, chronicle lung diseases without asthma; Neurologic disease, neurologic and muscular disorder; Cardiologic diseases, cardiologic diseases before admission; other diseases, all comorbities without lung, cardiologic or neurologic diseases. OR: Odd ratio; CI: Confidence interval; PIM2: Paediatric index of mortality revised version.

children in the vaccine group (Table 1).

DISCUSSION

Key findings

In this bi-national observational study of pandemic influenza A(H1N1)-associated critically illness in children, we found that pandemic influenza A(H1N1) vaccination prior to hospitalization was less common among critically ill children when compared to the general paediatric population, and that history of vaccination was not associated with a clinically relevant difference in PICU length of stay (0.1 d). However, in Canada, with higher vaccine coverage among critically ill patients, the PICU course seems less severe (shorter duration of invasive mechanical ventilation and PICU stay, lesser development of ARDS, and fewer subsequently acquired bacterial infections) (Table 2).

Despite a higher vaccine coverage and potential previous exposure to the virus in Canada during the first pandemic wave in the Spring of 2009[1], the incidence of admission of critically ill children to intensive care due to Influenza A(H1N1)pdm09 during the Fall of 2009 was twice as high in Canada as in France (2.6 per 100000 children *vs* 1.1 per 100000 children). However, the mortality rate for these critically ill children was similar between the two countries.

We originally hypothesized that the higher child vaccination coverage in Canada (> 50% *vs* 18% in France) and previous exposure to influenza A(H1N1)-pdm09 would have protected Canadian children from critical illness in the Fall of 2009. We did not observed such a protection. This hypothesis was based on the following arguments: (1) previous exposure to influenza A(H1N1)pdm09 would have increased herd immunity; (2) adjuvant pandemic vaccine has an efficacy up to 97%[25-27]; (3) an influenza vaccination coverage rate above 45% reduces influenza transmission[28]; and (4) modeling studies suggested that the vaccination campaign was associated with a decrease in mortality and morbidity of 20% and 18% respectively[29]. Other factors previously identified as contributing to outbreak

spread such as proximity to the first infectious focus, human mobility, reproduction number, generation time, population susceptibility, age pyramid, school calendar, and climate[30] were similar between the two countries and the underlying characteristics of the children were similar (Table 1). Given that the difference in incidence of PICU admission was the opposite of what was expected, our study suggests that additional national, geography-specific, and/or further unappreciated factors likely exhibit substantial residual influence on the incidence of pandemic influenza in differing regions of the world.

It has also been shown that the virulence of influenza A(H1N1)pdm09 strains virulence can vary considerably in animals and in humans[31-35]. Some specific strains were associated with severe disease in Canada and France but the proportion of these virulent strains in Canada and France is incompletely reported. Differing virulence could have contributed to the increased incidence of critical illness in Canada, as well as to the higher mortality observed in Argentina and Turkish pediatric cohorts when compared with those in North America, Europe and Australia and New Zealand[36-39].

Despite the higher incidence of critical illness in Canada when compared to France, our study provides some arguments on the positive impact of vaccine on influenza critical illness in children, even when the vaccine is given when pandemic second wave has already started (Figure 1). Our study showed that: (1) the second wave ended earlier than in France, which had a lower vaccine coverage; (2) vaccination coverage was substantially lower in the PICU population than in the general pediatric population; (3) total duration of mechanical ventilation was shorter in Canada; and (4) vaccination was associated with a decreased risk of invasive mechanical ventilation (Table 3). As expected, asthma was also associated with a decreased risk of invasive ventilation. This is consistent with previous findings of a low rate (4.6%) of invasive mechanical ventilation in PICU patients admitted for acute asthma[40]. The significant association between vaccination coverage and reduction in invasive mechanical ventilation is remarkable considering that the rate of invasive mechanical ventilation in children without a diagnosis of asthma diagnosis in this study was > 40%.

Strengths and weaknesses of the study

This study has several strengths: (1) It represents the largest pediatric cohort of critically ill H1N1 infection yet described in Canada and France; (2) the evolution of new H1N1 cases per week in PICUs (Figure 1) was similar to the consultations rates for influenza-like illness in the general population of Canada and France[41,42]; and (3) there was a large difference in vaccine coverage. This difference in coverage may be attributed to differences in perception of risk amongst the population such as awareness of the public health issues, the risk of being infected by the virus, the risk of severe illness if infected, and the risk of harm from a pandemic vaccine[43,44].

Our study has several limitations that should be noted. First, the suspected difference in virulence between the two countries could have created a bias on the analysis of pandemic vaccine impact. However, the analysis of critically ill children in Canada only provided an association between vaccine delivery and reduction in the risk of invasive ventilation (Table 3); second, admission criteria in PICUs are not standardized across countries and this can impact the incidence of PICU admission and inferred critical illness. However, several arguments suggest that admission criteria between Canada and France are similar, including: (1) the similar number of PICU beds per capita; and (2) patients displayed similar organ failure score (PELOD score) and predicted risk of mortality (PIM2) on admission to PICU (Table 1). Interestingly, this difference in ICU admission rate was also observed in adult intensive care units, with a rate of A(H1N1)pdm09-associated admission of 3.5/100000 population in Canada and 2.1/100000 population in France (OR = 1.7)[45,46]. Another limitation is that the two national cohorts used similar but not identical case report forms. Therefore, we needed to compare similar variables that may have been collected in slightly different ways in order to compare the two cohorts. In order to address this point for future outbreaks and pandemics, a number of national critical care research consortia initiated the International Forum of Acute Care Trialists which seeks to improve the care of acutely ill patients around the world by harmonizing case report forms and definitions[47]. This goal has been further advanced by the creation of International Severe Acute Respiratory and Emerging Infection Consortium.

In conclusion, the critical illness due to H1N1pdm09 had a higher incidence in Canada than in France. In both Canada and France, critically ill children were much less likely to have received vaccination against influenza A(H1N1)pdm09 prior to hospitalization when compared with children in the general population. In Canada, with higher vaccine coverage among critically ill patients, the PICU course seems less severe and the risk of invasive mechanical ventilation was lower amongst Canadian critically ill children receiving prior vaccination. There is a need for further studies to confirm our observations as numerous and still uncertain factors influence differences in pandemic influenza incidence and severity in different regions of the world, even in countries with similar population characteristics, access to health care resources and response systems.

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COMMENTS

Background

By March 2009, pandemic influenza A(H1N1)pdm09 had begun to spread from Mexico across the globe. The epidemiology of the first pandemic wave in Canada revealed that A(H1N1)pdm09 affected both young healthy patients and patients with underlying conditions. To limit the impact of the pandemic influenza A (H1N1)pdm0 especially on children, a vaccination campaign started when the second wave occurred. A lot of discussions criticized the vaccination campaign policy.

Research frontiers

Nowadays, Bird flu could combine with human flu to create a virulent kind of super-flu that can spread worldwide. The information gathered from previous pandemic (including the authors' study) are helpful to predict the spread and severity of such a risk.

Innovations and breakthroughs

This study report data on: (1) the incidence of critically ill children with pandemic influenza A (H1N1)pdm09 infection that was not known in Europe and Canada; (2) on mortality rate were higher in South American and Turkish studies; and (3) a positive impact of vaccination, even if started at second wave start, was not previously described in critically ill children.

Applications

According to the results, in case of pandemic, it is recommended to perform the flu vaccination as soon as the vaccine is available to potentially decrease disease severity.

Terminology

H1N1pdm09 infection: Flu pandemic; PICU: Pediatric intensive care units; ARDS: An acute hypoxemia due to lung inflammation.

Peer-review

The study is well designed with detailed methodology to assess the impact of vaccination status on severity of infection and mortality rates.

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SYSTEMATIC REVIEWS

Zinc supplementation as an adjunct to standard therapy in childhood nephrotic syndrome - a systematic review

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Abstract

AIM

To evaluate the role of zinc as add on treatment to the "recommended treatment" of nephrotic syndrome (NS) in children.

METHODS

All the published literature through the major databases including Medline/Pubmed, Embase, and Google Scholar were searched till 31st December 2015. Reference lists from the articles were reviewed to identify additional pertinent articles. Retrieved papers concerning the role of zinc in childhood NS were reviewed by the authors, and the data were extracted using a standardized data collection tool. Randomized trials (RCTs) comparing zinc *vs* placebo was included. Effect of zinc was studied in both steroid sensitive and steroid dependent/frequent relapsing NS. The primary outcome measure was the risk of relapse in 12 mo. The secondary outcome measures were mean relapse rate per patient in 12 mo, mean relapse rate per patient in 6 mo, risk of infection associated relapse in 12 mo, cumulative dose of steroids in two groups, mean length of time to next relapse, adverse effects of therapy, and change in serum zinc levels.

RESULTS

Of 54 citations retrieved, a total of 6 RCTs were included. Zinc was used at a dose of 10-20 mg/d, for the duration that varied from 6-12 mo. Compared to placebo, zinc reduced the frequency of relapses, induced sustained remission/no relapse, reduced the proportion of infection episodes associated with relapse with a mild adverse event in the form of metallic taste. The GRADE evidence generated was of "very low-quality".

CONCLUSION

Zinc may be a useful additive in the treatment of childhood NS. The evidence generated mostly was of "very low-quality". We need more good quality RCTs in

different country setting as well different subgroups of children before any firm recommendation can be made.

Key words: Nephrotic syndrome; Pediatric; Relapse; Zinc; Micronutrient

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Core tip: Relapses in nephrotic syndrome (NS) increase morbidity and mortality. Studies have shown that zinc deficiency is common in NS. Zinc deficiency might lead to down-regulation of T-helper 1 (Th1) cytokines, a relative T-helper 2 (Th2) bias, and an increased risk of infection. The later commonly associated with relapse in NS. Zinc supplementation restores Th1-Th2 imbalance and may decrease relapse. The primary aim of this review is to evaluate the efficacy of zinc in preventing relapses in childhood NS (steroid sensitive and steroid dependent/ frequent relapsing). The secondary aim is to evaluate the safety of zinc supplementation in this regard.

Bhatt GC, Jain S, Das RR. Zinc supplementation as an adjunct to standard therapy in childhood nephrotic syndrome - a systematic review. *World J Clin Pediatr* 2016; 5(4): 383-390 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i4/383.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i4.383

INTRODUCTION

Nephrotic syndrome (NS) is a chronic childhood illness characterized by heavy proteinuria, hypoalbuminemia and oedema. About 80%-85% of the patients with NS shows initial response to corticosteroids and labeled as steroid sensitive nephrotic syndrome (SSNS). Remaining 15%-20% of the patients, who do not respond to steroid therapy are labeled as steroid resistant nephrotic syndrome (SRNS)[1]. About 40%-50% of patients with SSNS have either frequent relapses (FRNS) or steroid dependent (SDNS) courses leading to prolonged course of illness. Relapses are associated with an increased risk of complications such as sepsis, thrombosis, dyslipidemia and malnutrition[2]. Although, relapses can be successfully treated with corticosteroids, repeated usage of high dose corticosteroids lead to significant side-effects like avascular necrosis of hip, hypertension, diabetes and behavioral disorders[3].

Relapses of NS often follow minor infections of the upper respiratory (URI) or gastrointestinal tracts, and the estimated frequency is around 50%-70% among children in developing countries[4,5]. Other infections such as urinary tract infection, diarrhea, peritonitis and skin infections have also been implicated as triggers for relapse[6]. Several theories like cytokine release, immune dysfunction, increased glomerular permeability, and podocytopathy are proposed, but none of them is conclusive[4,7-9].

A number of interventions have been tried to prevent/ decrease relapses in NS. Relapses are significantly reduced when daily corticosteroids are given during onset of viral URIs[10,11] or when the maintenance doses of corticosteroids are increased at the onset of viral URIs[12]. Studies have shown that zinc supplementation reduces relapses in children with SSNS[5,13]. It is proposed that zinc deficiency might lead to down-regulation of T-helper 1 (Th1) cytokines, a relative T-helper 2 (Th2) bias, and an increased risk of infection[14,15]. As a result, zinc supplementation augments the gene expression for IL-2 and IFN-γ, thereby restoring the Th1 immune response[16]. Since, the Th1-Th2 cytokine imbalance is also believed to result in relapses of SSNS, it was proposed that the benefits of supplementation in these patients may be associated with its ability to rectify the immune defect[5]. In the present systematic review, we tried to found the role of zinc supplementation as an adjunct to standard therapy in childhood NS. To evaluate the efficacy and safety of zinc in preventing relapses in childhood NS, steroid sensitive and steroid dependent/ frequent relapsing.

MATERIALS AND METHODS

The review has been registered at the PROSPERO register: CRD42015026456.

Types of studies

Randomized controlled trials (RCTs) and quasi RCT's comparing zinc with placebo or no additional intervention with ⩾ 80% follow-up (to reduce the risk of attrition bias in the included studies in case intention-to-treat analysis has not been done).

Types of participants

Children of 1 to 18 years of age with frequently relapsing or steroid dependent NS were included. Studies including children with first episode NS, secondary NS, impaired renal function, SRNS, congenital NS, serious (peritonitis, Pnumonia, cellulitis) or active infections, leucopenia, thrombocytopenia, and severe anemia were excluded.

Types of intervention

The intervention group received oral zinc supplementation regardless of the dosage and type and the control group received standard therapy alone or an oral supplementation without zinc in adjunct to standard therapy for NS.

Types of outcome measures

Steroid sensitive NS.

Primary outcomes: Frequency of relapses in 12 mo.

Secondary outcomes: Frequency of relapses in 6 mo; risk of relapse per year; risk of infection associated relapse per year; cumulative dose of steroids in two groups; mean length of time to next relapse; adverse

effects of therapy; change in serum zinc levels.

Steroid dependent/frequent relapsing NS
Primary outcomes: Frequency of relapses in 12 mo.

Secondary outcomes: Frequency of relapses in 6 mo; risk of relapse per year; risk of infection associated relapse per year; cumulative dose of steroids in two groups; mean length of time to next relapse; adverse effects of therapy; change in serum zinc levels.

Steroid sensitive: Remission is achieved within 4 wk of steroid therapy.

Relapse: It is defined as urinary protein excretion 3+/4+ on reagent strip or proteinuria > 40 mg/m^2 per hour for 3 consecutive days in patient who had previously been in remission (urine albumin trace or nil or proteinuria < 4 mg/m^2 per hour for 3 consecutive days). Frequent relapse is defined as ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo. For the treatment of relapse, the patient is initially put on daily corticosteroids till remission and then on alternate day steroids.

Steroid dependent: Two consecutive relapses while on alternate steroids or within 14 d of its discontinuation.

Frequent relapse: ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo.

Search methodology
Following major databases were searched systematically: Cochrane Central Register of Controlled Trials, PubMed/MEDLINE, Google Scholar, and EMBASE till 31st December 2015. Following search terms were used: [("zinc"/exp or "zinc" or "zinc phosphate"/exp or "zinc phosphate") and ("child"/exp or "infant"/exp or "school child"/exp or "preschool child"/exp or "toddler"/exp) and ("NS"/exp or "congenital NS"/exp or "kidney disease"/exp)] and ("randomized controlled trial"/exp or "controlled clinical trial"/exp or "clinical trial"/exp).

We also searched the major Pediatric nephrology scientific meetings and contact the authors involved in previous studies for any unpublished work. To identify unpublished trial results, we searched the United Stated National Institutes of Health, Department of Health and Human Services trials registry (http://www.clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform trial registry (http://www.who.int/ictrp/en/). No language restriction was applied. Two reviewers reviewed the search results to identify relevant original human clinical trials.

Data extraction
Data extraction was done using a pilot tested data extraction form. Two authors independently extracted data including author, year, study setting, type of population, exposure/intervention (dose of steroid, duration), results (outcome measures, effect, significance), and sources of funding/support. Any disagreement in the extracted data was resolved through discussion with the third author.

Risk of bias (quality) assessment
Two review authors independently assessed the methodological quality of the selected trials by using Cochrane risk of bias tool[17].

Grade of evidence
For assessment of the quality of evidence we used GRADE Profiler software (version 3.2)[18]. The software uses five parameters for rating the quality of evidence. The parameters used were - limitations to design of randomized controlled trials, inconsistency of results or unexplained heterogeneity, indirectness of evidence, imprecision of results, and publication bias. The rating was done as - no, serious, and very serious limitation.

Statistical analysis
The data from various studies was pooled and expressed as mean difference (MD) with 95%CI in case of continuous data, and odds ratio with 95%CI in case of categorical data. *P*-value < 0.05 was considered significant. Assessment of heterogeneity was done by I^2 statistics. If there is a high level heterogeneity (> 50%), we tried to explore the cause. A fixed effects model was initially conducted, and if significant heterogeneity existed between the trials, potential sources of heterogeneity were considered and where appropriate, a random effects model was used. RevMan (Review Manager) version 5.2 was used for all the analyses.

RESULTS

Description of the studies
Of 56 citations retrieved, full text of 7 articles were assessed for eligibility (Figure 1). Out of these, a total of 6 RCTs were included[5,13,19,20], actually 2 RCTs evaluated both SSNS/FRNS, and SSNS/SDNS[5,19]. Out of these, 2 were conference abstracts[19,20]. We contacted the authors of these abstracts for providing the details but no reply was given, so we included data given in the abstracts only. The detailed characteristics of trials have been described in Table 1. Out of the 4 trials, 2 were conducted in India, 1 in Pakistan, and 1 in Philippines. Five trials included a total of 256 children [SSNS = 2 trials (100 children); SDNS/FRNS = 4 trials (156 children)] of 1 to 18 years age (excluding neonates < 1 mo). The dose of zinc used was 10 mg/d for a period of 12 mo in one trial[5], and 6 mo in another trial[13]. In other 2 trials, one used 20 mg/d zinc for 2 wk starting at the onset of an episode of acute infection[19], and another used zinc at the recommended daily allowance dose[20].

Risk of bias in included studies
Effect of Interventions: (1) steroid sensitive NS: Primary outcome measure: Frequency of relapses in 12 mo: This was reported in 1 out of the 2 trials[5]. The

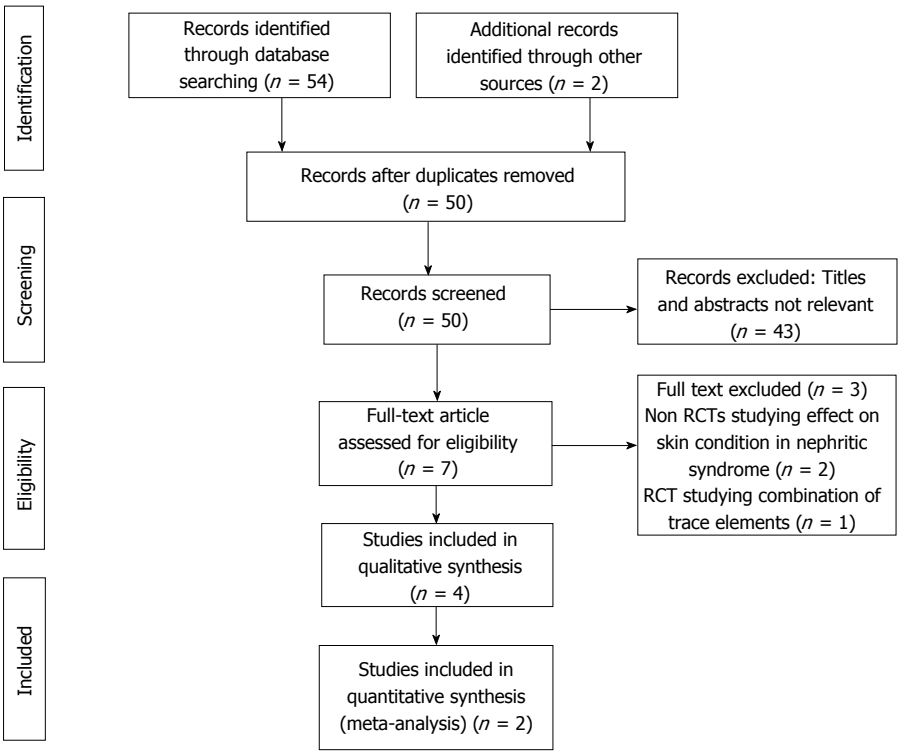

Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram. RCTs: Randomized controlled trials.

mean relapse rate was lower in the zinc group (1.0 ± 1.16) compared to the placebo group (1.2 ± 1.11), the pooled effect size showing 20% reduction that was not significant (MD = 0.2; 95%CI: 0.71-0.31); (2) secondary outcome measure: Frequency of relapses in 6 mo: This was reported in two trials[5,20]. The result could not be pooled as the data was not provided in 1 trial[19]. In one trial, the mean relapse rate was lower in the zinc group (0.49 ± 0.79) compared to the placebo group (0.68 ± 0.92), the pooled effect size showing 19% reduction (MD = 0.19; 95%CI: 0.57-0.19; $P > 0.05$). In another trial, there was significant decrease in the frequency of relapse in the zinc group[20]; risk of relapse per year: This was reported in 1 out of the 2 trials[5]. The zinc group had a 31% lower risk of relapse (RR = 0.69, 95%CI: 0.45-1.07; $P > 0.05$) compared to the placebo group; risk of infection associated relapse in 12 mo: This was reported in one trial, but the data was not provided; cumulative dose of steroids in two groups: This was not reported in any of the trials; mean length of time to next relapse: This was reported in one trial[5]. There was a non-significant decrease in the length of time (mo) to next relapse in the zinc group compared to the placebo group (7.9 *vs* 6.4; $P > 0.05$); adverse effects of therapy: A mild adverse event in the form of metallic taste was reported in three subjects in one trial[5]; change in serum zinc levels: One trial provided this information[5]. At enrollment, 5 children (zinc = 2; placebo = 3) were zinc deficient, but at 12 mo none was zinc deficient.

Steroid dependent/frequent relapsing NS: (1) primary outcome measure: Frequency of relapses in 12 mo: This was reported in 3 trials[5,13,19], however the result could be pooled from 2 trials[5,13]. There was decreased frequency of relapses in the zinc group compared to the placebo group (MD = 0.17; 95%CI: 0.39-0.04; $P = 0.11$) (Figure 2); (2) secondary outcome measure: Frequency of relapses in 6 mo: This was reported in 2 trials[5,19]. The result could not be pooled as the data was not provided in 1 trial[19]. In one trial, the mean relapse rate was lower in the zinc group (0.52 ± 0.0) compared to the placebo group (0.68 ± 0.8), the pooled effect size showing 16% reduction (MD = 0.16; 95%CI: 0.6-0.3; $P > 0.05$). In another trial, there was significant decrease in the frequency of relapse in the zinc group[19]; sustained remission/no relapse: This was reported in 2 trials[5,13]. The zinc group had a higher chance of going into sustained remission/no relapse compared to the compared to the placebo group (RR = 1.42; 95%CI: 0.99-2.05; $P = 0.06$) (Figure 3); proportion of infection episodes associated with relapse: This was reported in one trial[19]. The risk was lower in the zinc group (0.16) compared to the placebo group (0.33) ($P = 0.012$); cumulative dose of steroids in two groups: This was not reported in any of the trials; mean length of time to next relapse: This was not reported in any of the trials; adverse effects of therapy: A mild adverse event in the form of metallic taste was reported in three subjects in one trial[5], and in 10% of children in another trial[13]; change in serum zinc levels: Two trials provided this information[5,19]. None were zinc deficient at 12 mo.

Table 1 Characteristics of included studies

Ref.	Setting, country	Participants	Intervention	Outcomes measured	Comments
Arun *et al*[5]	Hospital (out-patient), India	Number: 81 [Frequent relapse = 52 (zinc = 26; placebo = 26); Infrequent relapse = 29 (zinc = 14; placebo = 15)] Age: 1-16 yr Inclusion: SSNS with infrequent relapses or FRNS with prednisolone requirement ⩽ 0.75 mg/kg on alternate days	Dose: Zinc sulfate 10 mg/d (1 h before or 2 h after meal) Duration: 12 mo	Frequency of relapses, number of relapses (mean), time to first relapse, adverse drug affects, proportion of infection associated relapses, and change in serum zinc level	Double blind placebo-controlled trial. ITT analysis not done. Small sample size (underpowered to show significant differences in the groups). Inclusion of infrequent relapsers may have diluted the significance of the findings. Authors proposed testing of a higher zinc dose along with immunological correlation
Sherali *et al*[12]	Hospital (out-patient), Pakistan	Number: 60 (zinc = 30; placebo = 30) Age: 2-15 yr Inclusion: FRNS	Dose: Zinc sulfate 10 mg/d Duration: 6 mo	Frequency of relapses, number of relapses (mean), episodes of infections, adverse drug affects, and change in serum zinc level	Double blind placebo-controlled trial. ITT analysis not done. Small sample size. Allocation concealment not clear. Post-supplementation zinc level was not measured in all subjects. Authors proposed testing of a higher zinc dose in a larger cohort
Afzal *et al*[18]	Hospital (out-patient), India	Number: 30 (zinc = 16; placebo = 14) Age (mean ± SD): 6.45 ± 2.92 yr Inclusion: FRNS (*n* = 24) and SDNS	Dose: Zinc 20 mg/d Duration: 2 wk starting at the onset of an episode of infection (for 12 mo)	Frequency of relapses, number of relapses (mean), episodes of infections, adverse drug affects, and change in serum and hair zinc level	Open label trial. ITT analysis not clear. Small sample size. Post-supplementation. Authors proposed testing of a higher zinc dose in a larger population
Pardillo *et al*[19]	Hospital (out-patient), Philippines	Number: 34 Age: Not clear (only children included) Inclusion: SSNS (majority) and SDNS	Dose: RDA Duration: 6 mo	Frequency of relapses, number of relapses (mean), episodes of infections, and adverse drug affects	Double blind placebo-controlled trial. ITT analysis not clear. Small sample size. Authors proposed testing of a higher zinc dose in a larger population

SSNS: Steroid sensitive nephrotic syndrome; FRNS: Frequently relapsing nephrotic syndrome; SDNS: Steroid dependent nephrotic syndrome; ITT: Intention-to-treat analysis; SD: Standard deviation; RDA: Recommended daily allowance.

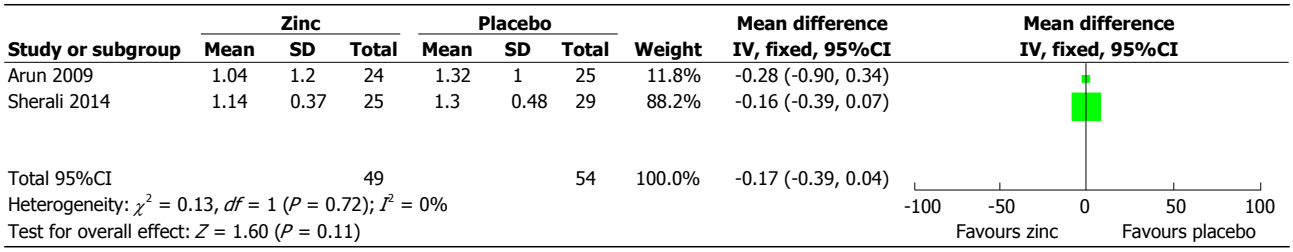

Figure 2 Frequency of relapses in 12 mo in case of frequent relapses/steroid dependent. IV: Inverse variance.

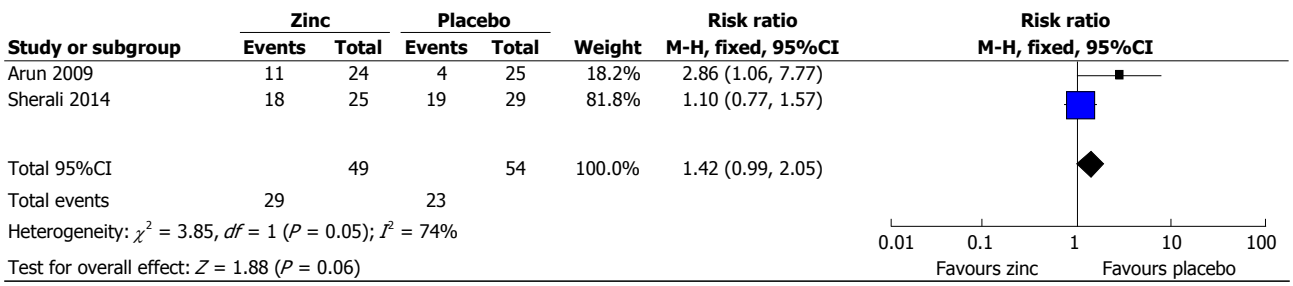

Figure 3 Sustained remission/no relapse in case of frequent relapses/steroid dependent. M-H: Mantel-Haenszel.

Table 2 Zinc for nephrotic syndrome (steroid sensitive nephrotic syndrome)

Patient or population: Patients with nephrotic syndrome Settings: Hospital setting Intervention: Zinc					
Outcomes	Illustrative comparative risks[3] (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Zinc			
Frequency of relapses in 12 mo Follow-up: 12 mo	The mean frequency of relapses in 12 mo in the control groups was 2%	The mean frequency of relapses in 12 mo in the intervention groups was 0.2 lower (0.71 lower to 0.31 higher)		81 (1 study)	Very low[1,2]
Frequency of relapses in 6 mo Follow-up: 12 mo	The mean frequency of relapses in 6 mo in the control groups was 19%	The mean frequency of relapses in 6 mo in the intervention groups was 0.19 lower (0.57 lower to 0.19 higher)		81 (2 studies)	Very low[1,2]
Risk of relapse per year Follow-up: 12 mo	725 per 1000	500 per 1000 (326 to 776)	RR = 0.69 (0.45 to 1.07)	78 (1 study)	Very low[1,2]
Mean length of time to next relapse Follow-up: 12 mo	The mean length of time to next relapse in the control groups was 1.5 mo	The mean length of time to next relapse in the intervention groups was 1.5 higher (0 to 0 higher)		78 (1 study)	Very low[1,2]

[1]Single trial; [2]Small sample size; [3]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI: Confidence interval; RR: Risk ratio; GRADE: Working Group grades of evidence; high quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate.

Publication bias

We could not assess publication bias in the included trials because of fewer numbers.

Grade of evidence

The evidence generated was of "very low quality" for following outcomes under SDNS/FRNS the result of which could be pooled: Frequency of relapses in 12 mo, and sustained remission/no relapse (Tables 2 and 3).

DISCUSSION

Summary of evidence

After an extensive search of the literature we could find 6 trials to be eligible for inclusion. Our result indicates that, for steroid sensitive NS, zinc reduces the frequency of relapses in 12 mo and 6 mo, risk of relapse per year, mean length of time to next relapse with a mild adverse event in the form of metallic taste. For steroid dependent/frequent relapsing NS, zinc reduces the frequency of relapses in 12 mo and 6 mo, induces sustained remission/no relapse, reduces the proportion of infection episodes associated with relapse with a mild adverse event in the form of metallic taste. When we constructed the GRADE of evidence from the available evidence, it was found to be of "very low quality".

The mechanism by which zinc is helpful as an adjunct in the treatment of childhood NS is not clear. The pathogenesis of childhood NS (*e.g.*, SSNS, SDNS, FRNS) and the basis for relapses triggered by various infections are also unclear. There is evidence from the literature that a perturbed immune dysfunction (*e.g.*, elevated levels of IgE and up-regulation of IL-4 and IL-13 suggest a Th2 cytokine bias[14,15]. There have been studies that show a lower blood level of zinc in childhood NS[21]. Moreover, children from developing country setting are more prone for zinc deficiency. Zinc deficiency might lead to down-regulation of Th1 cytokines, a relative Th2 bias, and increased risk of infections[14,15]. Data from various reports suggest that zinc has a therapeutic role in diarrhea and respiratory infections[22,23]. As infections are most common inciting condition leading to relapse in childhood NS, it is believable that that zinc supplementation would reduce the frequency of infections and thereby relapses. The present evidence is also in accordance with this.

Limitations

Most outcomes were reported in single trials, so result could not be pooled except from few. The evidence generated was of "very low quality" (the result could be pooled for only two outcomes, high chance of publication bias, some trial also having moderate to high risk of bias because of the methods of blinding/allocation concealment). As the dose range varied among the trials, we could not determine an optimal therapeutically effective dose of zinc. No trial was conducted in a developed country setting, so it is difficult to make any generalized recommendation to all parts of the world.

Future area of research

More trials including a larger sample of children with FRNS or SDNS are needed in order to strengthen the evidence. A uniform dose of zinc as well different dose should be studied to find any optimal therapeutic benefit. Trials should also report about the cost-benefit ratio. The therapeutic effect of zinc in different subgroups of children should also be studied. The effect of zinc supplementation should be correlated with the immunological markers to strengthen the evidence or recommendation in this regard.

Table 3 Zinc for nephrotic syndrome (frequent relapses/steroid dependent)

Patient or population: Patients with nephrotic syndrome Settings: Hospital setting Intervention: Zinc					
Outcomes	Illustrative comparative risks[4] (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Zinc			
Frequency of relapses in 12 mo Follow-up: 12 mo	The mean frequency of relapses in 12 mo in the control groups was 17%	The mean frequency of relapses in 12 mo in the intervention groups was 0.17 lower (0.39 lower to 0.04 higher)		103 (2 studies)	Very low[1,2,3]
Frequency of relapses in 6 mo	The mean frequency of relapses in 6 mo in the control groups was 16%	The mean frequency of relapses in 6 mo in the intervention groups was 0.16 lower (0.6 lower to 0.3 higher)		50 (2 studies)	Very low[1,2]
Sustained remission/no relapse Follow-up: 12 mo	426 per 1000	605 per 1000 (422 to 873)	RR = 1.42 (0.99 to 2.05)	103 (2 studies)	Very low[1,2,3]
Proportion of infection episodes associated with relapse Follow-up: 12 mo	The mean proportion of infection episodes associated with relapse in the control groups was 17%	The mean proportion of infection episodes associated with relapse in the intervention groups was 0.17 lower (0 to 0 higher)		30 (1 study)	Very low[1,2]

[1]Single trial; [2]Small sample size; [3]Allocation concealment not clear in one study; [4]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI: Confidence interval; RR: Risk ratio; GRADE: Working Group grades of evidence; high quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate.

In conclusion, zinc may be a useful additive in the treatment of childhood NS. The evidence generated mostly was of "very low-quality". We need more good quality RCTs in different country setting as well different subgroups of children and disease subtype before any firm recommendation can be made.

ACKNOWLEDGMENTS

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COMMENTS

Background

Relapses in childhood nephrotic syndrome (NS) increase morbidity and mortality. Studies have shown that zinc supplementation reduces relapses in children with steroid sensitive NS. It is proposed that zinc deficiency might lead to down-regulation of T-helper 1 (Th1) cytokines, a relative T-helper (Th2) bias, and an increased risk of infection. The later commonly leading to relapse in childhood NS. Zinc supplementation restores Th1-Th2 imbalance and may decrease relapse. The primary aim of this review is to evaluate the efficacy of zinc in preventing relapses in childhood NS (steroid sensitive and steroid dependent/frequent relapsing). The second aim is to evaluate the safety of above intervention in the prevention of relapses in childhood NS.

Research frontiers

About 80%-85% of children with NS shows initial response to corticosteroids (SSNS), and remaining 15%-20% who do not steroid resistant NS. About 40%-50% of patients with SSNS have either frequent relapses or steroid dependent courses leading to prolonged course of illness. Relapses often follow infections (*e.g.*, respiratory, gastrointestinal, urinary infections). Several theories like cytokine release, immune dysfunction, increased glomerular permeability, and podocytopathy are proposed, but none of them is conclusive. A number of interventions have been tried to prevent/decrease relapses. Studies have shown that zinc supplementation reduces relapses in childhood NS.

Innovations and breakthroughs

Zinc supplementation has been shown to reduce relapses in childhood NS. It is proposed that zinc deficiency might lead to down-regulation of Th1 cytokines, a relative Th2 bias, and an increased risk of infection. Zinc supplementation probably corrects the underlying immune imbalance and decreases relapse. Retrieved papers (clinical trials) concerning the utility of zinc were reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that zinc may be a useful additive in the treatment of childhood NS. The evidence generated mostly was of "very low-quality". We need more good quality randomized trials in different country setting as well different subgroups of children and disease subtype before any firm recommendation can be made.

Terminology

Steroid sensitive NS: Remission is achieved within 4 wk of steroid therapy. Relapse is defined as urinary protein excretion 3+/4+ on reagent strip or proteinuria > 40 mg/m^2 per hour for 3 consecutive days in patient who had previously been in remission (urine albumin trace or nil or proteinuria < 4 mg/m^2 per hour for 3 consecutive days). Frequent relapse is defined as ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo. For the treatment of relapse, the patient is initially put on daily corticosteroids till remission and then on alternate day steroids. Steroid dependent NS: 2 consecutive relapses while on alternate steroids or within 14 d of its discontinuation. Frequent relapse NS: ⩾ 2 relapses in 6 mo of initial response or > 3 relapses in 12 mo.

Peer-review

In this systematic review, the authors have presented a thorough and critical analysis of the utility of zinc supplementation in prevention/decrease of the frequency of relapses in childhood NS.

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SYSTEMATIC REVIEWS

Middle East respiratory syndrome coronavirus disease is rare in children: An update from Saudi Arabia

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Abstract

AIM

To summarize the reported Middle East respiratory syndrome-coronavirus (MERS-CoV) cases, the associated clinical presentations and the outcomes.

METHODS

We searched the Saudi Ministry of Health website, the World Health Organization website, and the Flutracker website. We also searched MEDLINE and PubMed for the keywords: Middle East respiratory syndrome-coronavirus, MERS-CoV in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in 2012 to 2016. The retrieved articles were also read to further find other articles. Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary.

RESULTS

From June 2012 to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases. Of these cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. Twenty-five (80.6%) of the cases were reported from the Kingdom of Saudi Arabia. The most common source of infection was household contact (10 of 15 with reported source) and 5 patients acquired infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

CONCLUSION

Utilizing serology for MERS-CoV infection in Jordan and

Saudi Arabia did not reveal any positive patients. Thus, the number of the pediatric MERS-CoV is low; the exact reason for the low prevalence of the disease in children is not known.

Key words: Pediatric; Middle East respiratory syndrome-coronavirus; Children; Respiratory tract infection

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Core tip: The number of the pediatric Middle East respiratory syndrome-coronavirus (MERS-CoV) is low and the exact reason for the low prevalence is not known. A total of 31 pediatric MERS-CoV cases were reported since June 2012. Of all the cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. The most common source of infection was household contact followed by infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

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INTRODUCTION

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA)[1]. As more cases were reported, the case fatality rate changed to 40% from 60%[2-5]. In addition, initially there was a predominance of males; later this ratio decreased[2,6]. MERS-CoV is characterized by three different patterns of disease: Sporadic cases, intra-familial transmission[7-9] and health care associated infection[2,3,10-16]. Despite the increased number overtime and the multiple health care associated outbreaks[17], the number of pediatric cases remained low during the study period[18]. The initial description of 47 cases included only a 14-year-old child[4]. The first pediatric case was a 2-year-old child reported from Jeddah, KSA on June 28, 2013[19]. Later an additional three asymptomatic children were reported[4]. The largest report of childhood MERS-CoV cases included eleven, of which two patients were symptomatic and nine were asymptomatic[18]. The exact reason for this low prevalence of the disease in children is not known. In this study, we summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

MATERIALS AND METHODS

We searched the Saudi Ministry of Health website[20], the World Health Organization website[21], the Flutracker website[22], the medical literature and the retrieved published studies for any childhood MERS-CoV infections. We searched MEDLINE and PubMed for the keywords Middle East respiratory syndrome-coronavirus, MERS-CoV, in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in June 2012 until April 19, 2016. The retrieved articles were also read to find other relevant articles.

Statistical analysis

Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary, including mean and standard deviation when applicable and frequency. The statistical review of the study was performed by a biomedical statistician. Statistical review is performed before the submission of the manuscript.

RESULTS

Summary of pediatric cases

From June 2012, to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases as shown in Table 1. Of all the cases, thirteen (13) or 42% were asymptomatic, and there were 17 males, 10 females and 4 unreported (a male to female ratio of 1.7:1). The mean age of patients was 9.8 + 5.4 (0.75-17) years. Twenty-five cases (80.6%) were reported from KSA; the other patients were in Jordan, United Arab Emirates and the Republic of Korea (Table 1). The most common source of the infection was household contact (10 of 15 with reported source), and 5 patients acquired the infection within a health care facility. About one half of the cases were reported in 2014, and 29% were reported in 2013 and 22.6% in 2015 (Table 2).

Screening of pediatric patients for MERS-CoV

Screening of pediatric patients for MERS-CoV infection using real time reverse transcriptase polymerase chain reaction showed that only 9 out of 552 (1.6%) were positive in KSA[23]. However, serologic testing of pediatric patients admitted with lower respiratory tract infection in Jordan and Saudi Arabia revealed no positive tests[24,25] (Table 3).

Pregnancy associated MERS-COV

The effect of MERS-CoV infection on the fetus was described in eight cases[26-29] as summarized in Table 4. The mean age of the mothers was 32.25 + 3.4 years, and the mean gestational age was 28.4 + 6.3 wk. Death of the fetus was observed in 3 (37.5%) of the 8 fetuses.

DISCUSSION

Despite the total number of MERS cases increasing, especially in KSA, the number of pediatric cases remained low during the study period. Initially, the

Table 1 Summary of reported pediatric Middle East respiratory syndrome cases

Age	Gender	Country	Sample source	Year of reporting	Symptoms	Co-morbidity	Signs	Sample type	Viral load ct value	Imaging	Intensive care	Death	Ref.
2	Male	KSA	Hospital inpatient	2013	Fever, respiratory distress	Cystic fibrosis	Chest: Bilateral fine crepitation	NPS	36	Bilateral diffused infiltrate	+	Yes	[18]
14	Female	KSA	Hospital inpatient	2013	Fever	Down's syndrome		NPS	37	Bilateral diffused infiltrate	No	No	[18]
7	Female	KSA	Family contact	2013	Asymptomatic	None	None	N + T	37	ND	No	No	[18]
15	Female	KSA	Family contact	2014	Asymptomatic	None	None	NPS	35	ND	No	No	[18]
14	Male	KSA	Family contact	2014	Asymptomatic	None	None	NPS	34	ND	No	No	[18]
12	Female	KSA	Family contact	2014	Asymptomatic	None	None	NPS	35	ND	No	No	[18]
16	male	KSA	Family contact	2013	Asymptomatic	None	none	NPS	36	ND	No	No	[18]
7	Female	KSA	Family contact	2014	Asymptomatic	None	none	NPS	37	ND	No	No	[18]
3	Female	KSA	Family contact	2013	Asymptomatic	None	none	NPS	38	ND	No	No	[18]
13	Female	KSA	Contact	2014	Asymptomatic	None	none	NPS	34	ND	No	No	[18]
14	Female	KSA	Family contact	2013	Asymptomatic	None	none	NPS	36	ND	No	No	[18]
0.75	Male	KSA	Not known	2014	ICU	Nephrotic syndrome	Respiratory distress	Tracheal aspirate	NA	Diffuse bilateral haziness	Yes	Yes	[35]
4	Male	KSA	NA	2013	Mild respiratory symptoms	None	NA		NA	ND	No	No	[36]
8	Male	KSA	NA	2013	Mild respiratory symptoms	None	NA		NA	ND	NA	No	[37]
17	NA	KSA	Contact	2014	Asymptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
11	NA	KSA	Contact	2014	Asymptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
16	NA	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
13	M	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
10	M	KSA	Hospital contact	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
2	NA	KSA	NA	2014	Symptomatic	Congenital anomalies	NA	NA	NA	NA	NA	NA	[20,22]
11	M	KSA	Hospital contact	2014	Symptomatic	Brain tumor	NA	NA	NA	NA	NA	NA	[20,22]
17	M	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
16	M	South Korea	Hospital contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
2	M	KSA	Hospital contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
16	M	KSA	contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
7	F	Jordan	Contact	2015	Asymptomatic	None	NA	NA	NA	NA	NA	NA	[22]
0.8	F	Jordan	Contact	2015	Symptomatic	None	NA	NA	NA	NA	NA	NA	[22]
14	M	KSA	Contact	2015	Symptomatic	None	NA	NA	NA	NA	NA	NA	[20,22]
4	M	UAE	NA	2014	NA	NA	NA	NA	NA	NA	NA	NA	[22]
8	M	UAE	Family contact	2013	NA	NA	NA	NA	NA	NA	NA	NA	[22]
11	M	UAE	Family contact	2015	Asymptomatic	None	NA	NA	NA	NA	NA	NA	[22]

NPS: Nasopharyngeal swab; N + T: Nasal and tracheal aspirate; ND: Not done; KSA: Kingdom of Saudi Arabia; UAE: United Arab Emirates; ICU: Intensive care unit; NA: Not available.

testing in KSA was directed towards hospitalized patients with severe pneumonia. In 2015, the Saudi Ministry of Health added a specific case definition for MERS-CoV infection in children[30]. The definition includes those $\leqslant$ 14 years, meets the adult case definition and has either a history of exposure to a confirmed or suspected MERS-CoV in the proceeding 14 d or a history of contact with camels or camel products in the proceeding 14 d[30]. The case definition also includes children with unexplained severe pneumonia[30]. The 2015 change in the case definition does not account for the low rate of childhood MERS-CoV infection as 33% of the cases were reported in 2014 before the case definition was changed. One of the reasons for an increased number of cases in 2014 during the Jeddah outbreak was increased testing of asymptomatic and mildly symptomatic patients[11].

Table 2 Summary of the demographic characteristics of pediatric Middle East respiratory syndrome-coronavirus

	No.	%
Male:female	17:10 (1.7:1)	63 *vs* 37
Saudi	20	83.3
City		
Jeddah	7	29.2
Riyadh	7	29.2
Hafr al-Batin	3	12.5
Symptomatic	12	50.0
Death	8	33.3
Year of report		
2013	9	29
2014	15	48.4
2015	7	22.6

Table 3 Summary of different studies examining Middle East respiratory syndrome-coronavirus infection in children

Country	Testing method	Population	Positive *n* (%)	Yr	Ref.
KSA	rRT-PCR	Screening of children	9/552 (1.6)		[23]
KSA	Neutralizing antibodies testing	Serum samples from children hospitalized for lower respiratory tract infections	0/158 (0)	May 2010-May 2011	[25]
Jordan	rRT-PCR	Hospitalized children < 2 yr of age	0/2427 (0)		[24]

rRT-PCR: Real time reverse transcriptase polymerase chain reaction; KSA: Kingdom of Saudi Arabia.

Table 4 Summary of pregnancy associated Middle East respiratory syndrome-coronavirus infection

Age of the patient (yr)	Gestational age	Fetal outcome	Diagnostic test	Country	Ref.
39	5 mo	Still birth	Antibody by EIA	Jordan	[26]
33	32 wk	Healthy infant	PCR	Saudi Arabia	[27]
32	32 wk	Healthy	PCR	United Arab Emirates	[28]
34	34 wk	Died	PCR	Saudi Arabia	[29]
32	38 wk	Survived	PCR	Saudi Arabia	[29]
31	24 wk	Died	PCR	Saudi Arabia	[29]
27	22 wk	Survived	PCR	Saudi Arabia	[29]
30	23 wk	Survived	PCR	Saudi Arabia	[29]

PCR: Polymerase chain reaction; EIA: Enzyme immunoassay.

The pattern of MERS-CoV pediatric cases was similar to the 2003 SARS outbreak. Children were less affected than adults and children less than 2 years of age had milder disease[31]. In the largest screening of contacts, the rate of MERS-CoV positive children (1.6%, 9/616) compared to 2.2% (99/4440) in adults (P = 0.23)[23]. Thus, in this study utilizing MERS-CoV PCR the positivity rate did not differ in children and adults.

In adults with MERS-CoV infections, three patterns of transmissions were observed: Sporadic (primary) cases presumed to be due to animal exposure (mainly camels), household contacts or health care associated infections[32]. In KSA, the majority (45%) of cases were health care-associated infections, 38% were primary cases, and 13% were household contacts[32]. In contrast, in the majority of pediatric cases that reported source of acquisition (66.7% of the 15 with reported source), the disease was acquired through household contact. This pattern indicates a low exposure of children to animals and a higher rate of health care associated infections in adult wards. The male to female ratio (2.8:1 and 3.3:1) was initially high[3,4]. This apparent male predominance could be explained by the nature of hospital outbreaks[2]. Eventually the male to female ratio was reduced to 1.3:1 to 1.8:1[5,6]. Consistent with these studies, the male to female ratio in children with MERS-CoV was 1.7:1 and may indicate similar exposure of children to index cases in the household settings and differential host factors.

Possible explanations for the lower number of pediatric cases compared to adults include differential testing of adult patients and milder diseases in children; although, serologic testing of pediatric patients in KSA and Jordan did not reveal any positive cases[24,25]. In the largest sero-epidemiologic survey in KSA, the study did not include children and thus it is difficult to establish the rate of sero-positivity in children[31].

The MERS-CoV infection rate in children remains low and possible explanations include: A milder disease in children, asymptomatic infection, or the presence of yet to be identified factors. The development of a shorter duration of MERS in children is another possible explanation. If this is the case, it may limit the development of a positive serology. In one study, delayed antibody responses as measured with the neutralization test was associated with severe diseases[33]. The longevity of antibodies in MERS-CoV cases might be limited as was the case with SARS[33,34]. The only study of serology among children was done among hospitalized pediatric cases who presented with lower respiratory tract infections[25]. There is no systematic screening of exposed children using serologic testing; this limited the interpretation of available serologic studies.

Little data also exist regarding the effect and the likelihood of MERS-CoV in pregnancy. Eight cases were reported[26,27,29]. The outcome was favorable in the majority of cases. The exact prevalence of MERS-CoV antibodies and exposure of pregnant women to MERS-CoV is not known.

In conclusion, the number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add

to the understanding of the low prevalence in this age group.

COMMENTS

Background

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA). Despite the increased number of MERS-CoV cases overtime, the number of pediatric cases remained low. The exact reason for this low prevalence of the disease in children is not known. The aim of this study is to summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

Research frontiers

The first pediatric case was a two-year-old child reported from Jeddah, KSA on June 28, 2013. Later an additional three asymptomatic children were reported. The largest report of childhood MERS-CoV cases included eleven, including nine asymptomatic cases.

Innovations and breakthroughs

The number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add to the understanding of the low prevalence in this age group.

Applications

Despite the low number of pediatric MERS-CoV cases, it is important to continue to monitor the development of this disease in this age group and to understand the risk factors.

Terminology

MERS-CoV is a new emerging virus that was first isolated in 2012.

Peer-review

This complication of all known pediatric cases is a useful contribution to the medical literature, and knowing it is possible but rare is important.

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Can language acquisition be facilitated in cochlear implanted children? Comparison of cognitive and behavioral psychologists' viewpoints

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Abstract

AIM

To study how language acquisition can be facilitated for cochlear implanted children based on cognitive and behavioral psychology viewpoints?

METHODS

To accomplish this objective, literature related to behaviorist and cognitive psychology prospects about language acquisition were studied and some relevant books as well as Medline, Cochrane Library, Google scholar, ISI web of knowledge and Scopus databases were searched. Among 25 articles that were selected, only 11 met the inclusion criteria and were included in the study. Based on the inclusion criteria, review articles, expert opinion studies, non-experimental and experimental studies that clearly focused on behavioral and cognitive factors affecting language acquisition in children were selected. Finally, the selected articles were appraised according to guidelines of appraisal of medical studies.

RESULTS

Due to the importance of the cochlear implanted child's language performance, the comparison of behaviorist and cognitive psychology points of view in child language acquisition was done. Since each theoretical basis, has its own positive effects on language, and since the two are not in opposition to one another, it can

be said that a set of behavioral and cognitive factors might facilitate the process of language acquisition in children. Behavioral psychologists believe that repetition, as well as immediate reinforcement of child's language behavior help him easily acquire the language during a language intervention program, while cognitive psychologists emphasize on the relationship between information processing, memory improvement through repetitively using words along with "associated" pictures and objects, motor development and language acquisition.

CONCLUSION

It is recommended to use a combined approach based on both theoretical frameworks while planning a language intervention program.

Key words: Language; Cochlear implantation; Behavior; Child; Cognition

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Core tip: Cognitive and behavioral theoretical frameworks are not in opposition to one another, at least when translated to practice. So, an intelligent practitioner in the field of speech therapy may make practical benefit of both theories simultaneously in a combined approach, by planning to promote the child's cognitive and motor development and his ability for information processing, accompanied by appropriate reinforcement for his correctly imitated or spontaneous responses. This of course needs experimental research for verification of enhanced effectiveness.

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INTRODUCTION

Communication is an important way by which information and idea is transferred between people. Getting in touch with others through language is the well-known method of communication all over the world[1]. Although language is the best means of communication, it cannot be totally acquired in hearing impaired children. Hearing impaired children usually suffer from different kinds of language disorders which include disabilities in comprehension, speech processing and writing. They usually experience one or more of the phonological, syntactic, semantic and pragmatic types of disorders that cause them to be highly in need of systematic rehabilitation programs for language acquisition[2].

Before cochlear implants innovation about 35 years ago, children with profound hearing impairment could only rely on hearing aids for receiving the slightest degrees of auditory stimuli. However, nowadays cochlear implants have effectively replaced older means of speech and language acquisition in children who suffer from sensorineural hearing loss. Based on the evolution from use of hearing aids to cochlear implantation, it is also expectable to see significant changes in language treatment procedures of hearing impaired children. Also, these days' researches on cochlear implants are taking new path and direction. More and more research is focusing on pre-linguistically cochlear implanted children, that is, those who have noticeably gained benefit in language acquisition post-cochlear implantation[3]. Due to the importance of the cochlear implanted child's language performance, the authors have turned their efforts to respond to a rather basic question: How can language acquisition programs be facilitated and their effects maximized for cochlear implanted children. Different studies up to now have indicated that the cochlear implanted child's success in language acquisition is significantly related to certain factors including the age at which deafness occurred, length of hearing loss and the age at which the child underwent cochlear implantation[4,5]. However, if the above-mentioned demographic variables were kept controlled, would the outcome of cochlear implantation be influenced by any other variables? In other words, is there any other remaining factor affecting language acquisition and performance in this group of children? The authors speculate that language acquisition is highly correlated with some cognitive and behavioral factors which have been mostly ignored over the years, especially regarding hearing impaired children, and specifically in the case of those who have underwent cochlear implantation.

Evidently, hearing impaired children encounter significant delay and disorders of speech and language development[6,7]. Such children have much difficulty in communication and social adjustment. These problems will still be prevalent among hearing impaired children after cochlear implantation. It is now well-known that cochlear implantation with no language intervention following it cannot be much helpful to the acquisition of language by the child[8-10].

There are different language treatment protocols all over the world, most of which have indicated the importance of timely language intervention for language disordered children or those at risk of it. However, they differ in terms of the theories, concepts and principles underpinning their intervention strategies. Each of these different treatment protocols may have proven effective for different target groups but to our knowledge, no study has proposed the best treatment strategy for hearing impaired children who have undergone cochlear implantation. With the growing number of these children and the usually limited period of golden time remaining for their language training, it seems quite necessary and urgent that we figure out the best strategies fitting

Table 1 Levels of evidence in medical research

Level of evidence	Study design
Level Ⅰ	Systematic review (with homogeneity) of RCTs
	RCT with statistically significant difference or narrow confidence intervals
Level Ⅱ	Low quality RCT (*e.g.*, < 80% follow-up)
	Cohort study or other Prospective comparative study
	Systematic review of cohort studies
Level Ⅲ	Case-control study or other Retrospective comparative study
	Systematic review of case-control studies
Level Ⅳ	Case series
	Poor quality case-control studies
Level Ⅴ	Expert opinion
	Narrative reviews

Adopted from URL: http://www.cebm.net. RCT: Randomized control trial.

their specific state of health.

As a small step towards this goal, in this article we plan to explain behavioral psychologists' and cognitive psychologists' theories and viewpoints, mainly based on expert-opinion type literature relevant to language acquisition and to compare and discuss them in order to find clues for facilitating language acquisition in cochlear implanted children.

MATERIALS AND METHODS

In order to study literature related to behaviorist and cognitive psychology prospects about language acquisition, some relevant books as well as Medline, Cochrane Library, Google scholar, ISI web of knowledge and Scopus databases were searched. While screening titles and abstracts, the authors excluded any duplicates, case reports and articles written in languages other than English. Studies accessed only in abstract form were also excluded.

At first 25 articles were selected, but only 11 met the inclusion criteria and were included in the study. The inclusion criteria consisted of review articles, expert opinion studies, non-experimental and experimental studies that clearly focused on behavioral and cognitive factors affecting language acquisition in children.

After collecting relevant articles, they were appraised according to guidelines of appraisal of medical studies (Table 1)[11].

RESULTS

The 11 studies that met the inclusion criteria are described below in Table 2.

Behavioral psychologists' point of view regarding language acquisition

A number of single subject studies which have specifically focused on the language responses of language impaired children have demonstrated diverse language behaviors in this group of children[12,20].

Behavioral psychologists usually emphasize on a noticeable relationship between child's encouragement and language acquisition. They believe that as well as any other behavior, language acquisition might happen through operant conditioning. In addition, they suggest that immediate reinforcement of child's language behavior causes him to acquire the language as fast as he can. So, learning language has a positive relationship with visual and auditory reinforcements that the child receives when making improvements. Based on this theory, language acquisition is not dependent on complex mental development but the most critical variable in language acquisition is functional feedback[12]. Hence, teaching a new behavior with step by step reinforcements is the effective way of acquiring that behavior.

Also, in behavioral psychology, repetition and modeling a word or a verb are recommended to facilitate language acquisition. Therefore, the clinician is asked to model an appropriate response to help the child imitate it.

The behavioral theory is the basis of most conventional language treatment programs for various language disordered children, including those with hearing impairment who have undergone cochlear implantation[18]. Actually, the first step in auditory verbal training of cochlear implanted children is to help them be aware of the verbal and non-verbal sounds by conditional responses. The normal process in such programs is that first, every correctly imitated response is encouraged. After 4-5 times of encouragement, the reinforcements are reduced to once for every 2-3 correct responses in a fixed rate. Finally, the child cannot predict the exact time of receiving prizes because of the variant rate of reinforcements. By this method the number of child's correct responses will increase dramatically[8,18].

Cognitive psychologist's point of view in language acquisition

Cognitive psychologists emphasize that the complexity of language structures in a child indicates his level of cognitive development and *vice versa*[8,15]. Although it seems that young language learners acquire language simply by exposure to their mother's tongue in a natural trend[9], the process is actually more complex than it appears. In fact, a young child's language acquisition is based on a series of perceptual and cognitive skills. Language in humans is acquired in unique ways that require information processing. As a result, early sensory deprivation, especially hearing loss will cause impairments in language acquisition that may last a life time[5].

Information processing generally refers to a complex set of mental processes that include perception, cognition and thought. It is concerned with many functions that are themselves based on cognition, such as object recognition, perceptual learning, memory development, and language processing skills like speech perception and production. In fact, different aspects of information processing such as sensation, perception, memory, thought, language processing and problem-solving are

Table 2 Study characteristics and outcomes

Ref.	Yr	Study design	Evidence level	Sample	Result
Hegde *et al*[12]	1979	Case-control	Ⅲ	Normal children Language disorder children	Behaviorist Language learning is limited to what is trained especially in language disordered children Reinstatement and generalization are very rare
Elger *et al*[13]	1997	Low quality RCT	Ⅱ	Temporal lob impaired patients	Cognitive based There is a relationship between temporal lobe structures for memory and language acquisition
Kutas *et al*[14]	2000	Systematic review of case-control studies	Ⅲ	Normal children	Cognitive based The organization of semantic memory has an effect on word processing
Pisoni[15]	2000	Expert opinion	V	Cochlear implanted children	Cognitive based Promotion of cognitive development, information processing and language acquisition are the most important results of early cochlear implantation
Bloom[8]	2000	Narrative review	V	Normal children	Cognitive based Acquiring language is the result of cognitive abilities that include the abilities to acquire concepts and understanding of the mental status of other people
Iverson *et al*[16]	2004	Low quality RCT	Ⅱ	Normal children	Cognitive based There is an age related increase in frequency of vocal motor coordination in children A temporal pattern similar to that is seen in adult gestures and speech coordination
Clark[9]	2004	Narrative review	V	Normal children	Cognitive based Conceptual and linguistic representations for talking about experience provide the starting point for language from the age of 12 mo
Pulvermüller[17]	2005	Expert opinion	V	Normal children	Cognitive based Motor development prompts cognitive development The neuronal connection between systems for action and language perception is seen
Yu *et al*[18]	2007	Single subject studies	V	Normal children	Cognitive based and behaviorist Child's social cognitive capacities like joint attention, prosody and intention reading help him acquire the meaning of words. In other word, a combination of cognitive and behavioral development play important role in language development
Behrens *et al*[19]	2011	Systematic review of case-control studies	Ⅲ	Normal children Language disorder children	Cognitive based and behaviorist There is a relationship between motor and language development
Hegde *et al*[20]	2013	Prospective study	Ⅱ	Learning disabled children	Behaviorist Reinforcement, imitation and modeling facilitate language acquisition Reinstatement and generalization are very rare

RCT: Randomized control trial.

all part of a spectrum and are all related to cognitive processing and cannot be considered independently and separately[15]. Appreciation of one requires understanding and consideration of the others[21]. Also, the more complex aspects of information processing that appear at older age are hierarchically dependent on the more simple aspects that have occurred earlier[13,15,22].

The information processing approach helps better understand the cognitive and language development in language impaired children[15].

Based on the cognitive psychologists' point of view, one of the preconditions of language acquisition is memory and memory improvement. In fact, it is said that separation of the process that supports language perception from that which supports memory is impossible. When a word is produced, the meaning is derived from a life-long storage of knowledge, experience and memory in the brain. Evidence has shown that this storage of knowledge is organized in different dimensions and can be used flexibly[14].

For young children to understand the meaning of a new word among the various word-referent pairs in their environment, it is commonly presumed that this needs the repeated accompanying of auditory stimuli in the form of a word with a simultaneous extra-linguistic stimulus such as seeing and experiencing an object or an action[18]. This mechanism of word learning is called "associationism" and usually starts with the most familiar objects and actions in a child's environment[5,8,9]. "Association" improves memory and helps the child keep

visual and auditory stimulations in his mind.

As with any other young language learner, perception and production of intelligible speech in a cochlear implanted child needs to have a structured system for symbolizing and coding sounds in the brain[9,21-23]. According to cognitive psychologists' point of view, this is actually what happens among cochlear implanted children during the process of language acquisition[18]. So, cognitive psychologists suggest that one of the best methods of language treatment in cochlear implanted children is to strengthen memory *via* repetitively using words along with "associated" pictures and objects[24].

In addition, one other precondition for language acquisition that is often overlooked and thus requires additional attention is the child's motor development. The impact of this developmental domain on the child's language acquisition is an issue that requires further attention.

In human beings, movement and thought have always been correlated. Nowadays, research has shown that movement in human life occurs with other intentions than movement itself[19]. The main reason that causes the psychologists to believe in interrelationship between motor and language development is derived from the idea that infant's motor development encourages him to explore his surrounding as much as he can[16]. The children's locomotion ability enable them to achieve new experiences by investigation of the environment and object manipulation. These new experiences provide an opportunity to develop communication skills. According to these finding, psychologists and other scientists need to explore the link between motor development and language acquisition furthermore[17,19].

Locomotion and object-manipulation are two important components of motor movement that facilitate language acquisition in children, especially those with language impairment. This finding has resulted from research on monkeys' brains which have shown connections between their motor cortex and that part of their cortex which is similar to the human language cortex. So, it can be assumed that faster information processing is the consequence of correlating language and action[17,19].

DISCUSSION

The review of literature regarding theoretical frameworks of behaviorists' and cognitive psychologists' prospects in language acquisition, indicates some key points which might facilitate language acquisition in language impaired children, especially those with hearing loss who have undergone cochlear implantation.

In behavioral methods of language training, expansion and generalization of the trained element is reached by repetition of the items that are being taught. Accordingly, a gradual increase of training trails will similarly cause enhancement of generalization. However, it should be noted that generalization occurs with different number of newly trained items in the case of a pronoun for example, than in the case of a verb. So, training in each modality is not influenced by training in other modalities[20].

Furthermore, according to behavioral theories the parents' response to a child by smiling, hugging or imitation of what they have heard when the child makes a sound or produces a word or a phrase, are the best means of communication and encouragement for language acquisition. Such environmental reinforcements are the basic of behavioral treatment protocols in language impaired children[12,20].

On the other hand, according to cognitive theories there are a number of cognitive factors that are necessary to be taken into consideration, while planning a language training program[8,9,13-17,19].

The two main cognitive principles of language acquisition are memory development and motor movement training. As a result, cognitive psychologists believe that it is necessary to focus on a child's cognitive improvement and his understanding of the association between words and meaning while planning a language intervention program. Also, including motor movement training in a language intervention program may facilitate language acquisition in a child by promoting investigation of his surroundings[16,17]. Since movement allows the child to find and focus attention on new objects of interest, he is more likely to learn new words associated with the new objects.

Given that the two theoretical frameworks are not in opposition to one another, at least when translated to practice, the authors speculate that a practitioner in the field of speech therapy can intelligently make benefit of both theories simultaneously and in a combined approach. For example, in order to help cochlear implanted children develop language, based on their cognitive as well as their behavioral development, it can be proposed that a combination of visual and auditory stimuli accompanied by memory exercises using pictures, objects and asking the child to repeat and imitate the words that are being heard, be utilized[13-15]. This of course should be followed by positive response and reinforcement from the therapist and the family. Also, making use of language exercises that somehow include actions related to different parts of the body in semantic terms, can be eventually added to the training process to facilitate the process of language acquisition through previously mentioned mechanisms activated by movement. Once the child's attention is directed towards a newly discovered object, the caregiver can then provide input. This input may be words referring to certain characteristics of the new object, along with positive reinforcements (*e.g.*, "Yes dear, that's a cup!").

Finally, the authors suggest that this combined approach for children, especially those with hearing impairment who have undergone cochlear implantation, be put to trial by researchers and compared with training interventions based on each of the theoretical frameworks independently.

In conclusion, given that the two theoretical frameworks are not in opposition to one another, at least when translated to practice, the authors speculate that a practitioner in the field of speech therapy can

intelligently make benefit of both theories simultaneously and in a combined approach by planning to promote the child's cognitive and motor development and his ability for information processing, accompanied by appropriate reinforcement for his correctly imitated or spontaneous responses. This of course needs experimental research for verification of enhanced effectiveness.

COMMENTS

Background

Hearing impaired children usually suffer from one or more of the phonological, syntactic, semantic and pragmatic types of disorders that cause them to be highly in need of systematic rehabilitation programs for language acquisition. Although cochlear implantation is now considered to be one of the most effective interventions for children with sensori-neural deafness in terms of language acquisition, cochlear implantation with no language intervention following it cannot be much helpful to the acquisition of language by the child. There are different language treatment protocols all over the world. However, no study has proposed the best treatment strategy for hearing impaired children who have undergone cochlear implantation.

Research frontiers

Due to the importance of the cochlear implanted child's language performance, one of the current research hotspots in the field of cochlear implantation, is to figure out the best strategies for language acquisition in this group of children.

Innovations and breakthroughs

There are different language treatment protocols all over the world, most of which have indicated the importance of timely language intervention for language disordered children or those at risk of it. Each of these different treatment protocols may have proven effective for different target groups but to our knowledge, no study has proposed the best treatment strategy for hearing impaired children who have undergone cochlear implantation. According to this study, in a language intervention program for cochlear implanted children, the two theoretical frameworks can be used in a combined approach by planning to promote the child's cognitive and motor development and his ability for information processing, accompanied by appropriate reinforcement for his correctly imitated or spontaneous responses.

Applications

Since the two theoretical frameworks are not in opposition to one another at least when translated to practice, the authors suggest that practitioners in the field of speech therapy intelligently make benefit of both theories simultaneously by planning to promote the child's cognitive and motor development and his ability for information processing, as well as by providing appropriate reinforcement for his correct responses.

Terminology

A cochlear implant is an electronic device which functions similar to how the inner ear functions and is used to transfer sound signals to the brain in patients who suffer from hearing loss because of damaged inner ear. Rehabilitation is a word most commonly used to facilitate language acquisition following cochlear implantation.

Peer-review

The authors are writing down a well written narrative review related to behaviorist and cognitive psychology prospects about language acquisition for cochlear-implanted children.

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