What's New in Childhood Infections?

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Source: Dierikx TH, van Kaam AHLC, de Meij TGJ, de Vries R, Onland W, Visser DH. Umbilical cord blood culture in neonatal early-onset sepsis: a systematic review and meta-analysis. Pediatr Res 2021. DOI: 10.1038/s41390-021-01792-0

The authors in this systematic review and meta-analysis assess the diagnostic test accuracy of umbilical cord blood culture (UCBC) for earlyonset sepsis (EOS). The gold standard for diagnosis of neonatal earlyonset sepsis is peripheral blood culture, but uncertainty remains concerning its value for this specific diagnosis. UCBC has higher sensitivity and comparable specificity for clinical EOS and might be considered as a diagnostic test for EOS. For diagnosis of neonatal earlyonset sepsis, umbilical cord blood culture vs peripheral blood culture had higher sensitivity and comparable specificity, which avoided the risk for iatrogenic anemia and consequently might be employed as a diagnostic tool for earlyonset sepsis. Due to imperfect diagnostic methods of neonatal earlyonset sepsis, low quality of evidence was generated in this work.

Source: O'Reilly D, Murphy CA, Drew R, El-Khuffash A, Maguire PB, Ainle FN, Mc Callion N. Platelets in pediatric and neonatal sepsis: novel mediators of the inflammatory cascade. Pediatr Res 2021. DOI: 10.1038/s41390-021-01715-z

Pediatric sepsis has been challenging to accurately define, and, this review tries to place into context the role of pediatric platelets in the development of fulminant sepsis. Additionally, how platelet transfusions could interfere with the complex links between immune cells in infection was also examined. Growing recognition of platelets as important "first responders" to immune threats is becoming more obvious. The clinical postulation that pediatric platelets and transfused adult platelets have a similar phenotype is likely faulty. In pediatric and neonatal sepsis, thrombocytopenia development is common, with trial data indicating worse outcomes in neonates in relation to increased platelet transfusions. This is assumed to happen because of a "developmental hemostatic mismatch risk", where adult platelets compromise the delicate homeostasis of neonatal bleeding. A "developmental immunological mismatch risk" may also be conferred by platelet transfusions with relatively hyperactive platelets and immunologically active extracellular vesicles (EVs). Such risk may inadvertently impair outcomes in the presence of an inflammatory stimulus like sepsis. EVs are demonstrably different between neonates and adults.

Source: Denti P, Wasmann RE, van Rie A, Winckler J, Bekker A, Rabie H, Hesseling AC, van der Laan LE, Gonzalez-Martinez C, Zar HJ, Davies G, Wiesner L, Svensson EM, McIlleron HM. Optimizing dosing and fixed-dose combinations of rifampicin, isoniazid, and pyrazinamide in pediatric patients with tuberculosis: a prospective population pharmacokinetic study. Clin Infect Dis 2021:ciab908. DOI: 10.1093/cid/ciab908

In 2010, dosing guidelines for the treatment of childhood tuberculosis were revised by the WHO. In this study, first-line anti-tuberculosis drug exposures were investigated under these guidelines, dose optimization was explored using the current dispersible fixed-dose combination (FDC) tablet of rifampicin/isoniazid/pyrazinamide; 75/50/150 mg and a new FDC with revised weight-bands was suggested. Pharmacokinetic sampling was performed in children with drug-susceptible tuberculosis while receiving first-line tuberculosis drugs as single formulations according to 2010 WHO-recommended doses. 1, 2, 3, or 4 FDC tablets (rifampicin/isoniazid/pyrazinamide 75/50/150 mg) were administered daily for 4–8, 8–12, 12–16, and 16–25 kg weight-bands, respectively, to 180 children. Low rifampicin exposures were recorded with the current pediatric FDC doses. The current FDCs did not result in the achievement of optimal dosing of all drugs. Exposures to all three drugs improved with providing 1, 2, 3, or 4 optimized FDC tablets (rifampicin/isoniazid/pyrazinamide 120/35/130 mg) to children <6, 6–13, 13–20, and 20–25 kg, and 0.5 tablet in <3-month-olds with immature metabolism.

Source: Cook A, Hsia Y, Russell N, Sharland M, Cheung K, Grimwood K, Cross J, Cotrim da Cunha D, Magalhães GR, Renk H, Hindocha A, McMaster P, Okomo U, Darboe S, Alvarez-Uria G, Jinka DR, Murki S, Kandraju H, Dharmapalan D, Esposito S, Bianchini S, Fukuoka K, Aizawa Y, Jimenez-Juarez RN, Ojeda-Diezbarroso K, Pirš M, Rožič M, Anugulruengkitt S, Jantarabenjakul W, Cheng CL, Jian BX, Spyridakis E, Zaoutis T, Bielicki J. Association of empiric antibiotic regimen discordance with 30-day mortality in neonatal and pediatric bloodstream infection - a global retrospective cohort study. Pediatr Infect Dis J 2021;40(2):137–143. DOI: 10.1097/INF.0000000000002910

While there have been studies in adults reporting discordant empiric antibiotic treatment associated with poor outcomes, this area is relatively unexplored in children and neonates despite evidence of increasing resistance to recommended first-line treatment regimens. The authors compared the relationship between concordance of empiric regimen and 30-day mortality using multivariable regression. Four hundred fifty-two children with blood-culture-positive BSI receiving early empiric antibiotics were reported by 25 hospitals in 19 countries. Adjusting for age, sex, presence of comorbidity, unit type, hospital-acquired infections, and gram stain, the odds of 30-day mortality were 2.9 (95% confidence interval: 1.2–7.0; $p = 0.015$) for patients receiving discordant early empiric antibiotics. In simple language, the odds of mortality in confirmed pediatric BSI are nearly threefold higher for patients receiving a discordant early empiric antibiotic regimen.

Source: Garegnani L, Styrmisdóttir L, Roson Rodriguez P, Escobar Liquitay CM, Esteban I, Franco JV. Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children. Cochrane Database Syst Rev 2021;11:CD013757. DOI: 10.1002/14651858.CD013757

According to this Cochrane review, the available evidence suggests that prophylaxis with palivizumab reduces hospitalization due to RSV infection and results in little to no difference in mortality or adverse events. Moreover, palivizumab results in a slight reduction in hospitalization due to respiratory-related illness and may result in a large reduction in RSV infections. Palivizumab also reduces the number of wheezing days. These results may apply to children with a high risk of RSV infection due to comorbidities. Further research is needed to establish the effect of palivizumab on children with other comorbidities known as risk factors for severe RSV disease (e.g., immune deficiencies) and other social determinants of the disease, including children living in low- and middle-income countries, tropical regions, children lacking breastfeeding, living in poverty, or members of families in overcrowded situations.

Source: Yue J, Zheng R, Wei H, Li J, Wu J, Wang P, Zhao H. Childhood mortality after fluid bolus with septic or severe infection shock: a systematic review and meta-analysis. Shock 2021;56(2):158–166. DOI: 10.1097/SHK.0000000000001657

A considerable debate on whether fluid bolus could decrease childhood mortality in pediatric patients with septic or severe infection shock is still unresolved. The authors conduct a systematic review and meta-analysis to investigate the mortality rates after fluid bolus among children with septic or severe infection shock. A total of 19 studies with 9,321 severe sepsis or septic shock pediatric patients were included and exhibited acceptable quality. Of the 17 studies that reported mortality at 48 hours, no bolus group decreased the mortality rate when compared with bolus group with a risk ratio (RR) of 0.74 [95% confidence interval (CI) = 0.62–0.88, $p < 0.01$], and showed no heterogeneity ($I^2 = 0\%$). Similar results were observed on colloids and crystalloids solution in malaria shock cases with a RR of 0.79 (95% CI = 0.62–1.02). For the subgroup of general shock patients, no significant difference was shown with an RR of 0.79 (95% CI = 0.62–1.02, $p = 0.07$) and no significant heterogeneity ($I^2 = 0\%$). In plain simple language, for the mortality at 48 hours, the no bolus group showed decreased mortality when compared with the bolus group, especially in the malaria group. Similar results were found in the colloids and crystalloids solution in patients with malaria shock.

Source: Ssentongo P, Hehnly C, Birungi P, Roach MA, Spady J, Fronterre C, Wang M, Murray-Kolb LE, Al-Shaar L, Chinchilli VM, Broach JR, Ericson JE, Schiff SJ. Congenital cytomegalovirus infection burden and epidemiologic risk factors in countries with universal screening: a systematic review and meta-analysis. JAMA Netw Open 2021;4(8):e2120736. DOI: 10.1001/jamanetworkopen.2021.20736

Congenital cytomegalovirus (cCMV) infection is probably the most common congenital infection and one of the leading acquired causes of developmental disabilities and sensorineural deafness, yet a reliable assessment of the infection burden is lacking. Seventy-seven studies comprising 515,646 infants met the inclusion criteria from countries representative of each World Bank income level. The estimated pooled overall prevalence of cCMV was 0.67%. The pooled birth prevalence of cCMV was threefold greater in LMICs than in HICs. Screening methods with blood samples demonstrated lower rates of cCMV than urine or saliva samples. Higher maternal CMV seroprevalence, higher population-level HIV prevalence, lower socioeconomic status, and younger mean maternal age, were associated with higher rates of cCMV. In this meta-analysis, LMICs appeared to incur the most significant infection burden. Lower rates of cCMV were reported by studies using only blood or serum as a screening method.

Source: Kato H, Hagihara M, Asai N, Koizumi Y, Yamagishi Y, Mikamo H. A systematic review and meta-analysis of myelosuppression in pediatric patients treated with linezolid for gram-positive bacterial infections. J Infect Chemother 2021;27(8):1143–1150. DOI: 10.1016/j.jiac.2021.03.003

The authors performed a systematic review and meta-analysis to reveal the incidence of linezolid-induced thrombocytopenia and anemia, and the impact of the administration period of linezolid on myelosuppression based on individual data analysis of pediatric patients. Thirteen studies with 969 pediatric patients were identified. The pooled incidences of thrombocytopenia and anemia were 9 and 4%, respectively. The meta-analysis showed the extension of the linezolid administration period (>14 days) resulted in a higher incidence of thrombocytopenia and anemia. This meta-analysis revealed linezolid administration period for >14 days was one of the risk factors associated with linezolid-induced myelosuppression. Therefore, especially for pediatric patients treated with linezolid for >14 days, careful monitoring of myelosuppression is required.

Vikram S Kumar
Professor
Department of Pediatrics,
Subbaiah Institute of Medical Sciences,
Shivamogga, Karnataka, India
e-mail: vikramskumar@yahoo.co.in