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Journal Review

Journal watch: ROP, HOCM, vitiligo and more

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Source: Aggarwal V, Bhatia R, Tan K. (2023). Oxygen saturation levels and retinopathy of prematurity in extremely preterm infants – a case-control study. *BMC Paediatrics*, 23(1), 449. https://doi.org/10.1186/s12887-023-04278-6

A retrospective case-control study was carried out to compare the oxygen saturation levels in extremely preterm infants, with and without retinopathy of prematurity (ROP). The data from oxygen saturation (SpO_2) readings indicated that infants without ROP experienced longer periods of hyperoxia compared to those with ROP. In addition, the ROP group displayed greater variability in oxygen saturation levels, suggesting more frequent oxygen desaturation events.

When infants in both the ROP and non-ROP groups were administered supplemental oxygen (fraction of inspired oxygen >21%), their SpO_2 levels showed similar distributions. This suggests that there is no strong evidence to support the idea that supplemental oxygen had a significant impact on the development of ROP in the infants studied. However, it is important to note that the SpO_2 data were only collected at hourly intervals, potentially missing brief episodes of both low and high oxygen levels.

Further analysis of additional clinical factors revealed that neonatal surgery was associated with an increased likelihood of developing ROP in the studied cohort.

To enhance the quality of care in neonatal intensive care units and reduce unnecessary oxygen exposure in preterm infants, it is imperative to implement quality improvement processes aimed at auditing oxygen delivery. These processes will help identify and address any shortcomings in oxygen management, ensuring better outcomes for these vulnerable infants.

Source: Mukhtar G, Sasidharan B, Krishnamoorthy KM, Kurup HK, Gopalakrishnan A, SasiKumar D, *et al.* (2023). Clinical profile and outcomes of paediatric hypertrophic cardiomyopathy in a South Indian tertiary care cardiac centre: a three-decade experience. *BMC Paediatrics*, 23(1), 446. https://doi.org/10.1186/s12887-023-04255-z

This study is the most extensive investigation of paediatric cardiomyopathy in South Asia to date. The researchers examined the clinical characteristics and outcomes of cardiomyopathy in children under 18 years old. Out of the 233 cases identified, 63 cases were diagnosed with hypertrophic cardiomyopathy (HCM), with a significant number presenting in infancy. The median age of presentation for HCM patients was 7 years. The study also found that LV outflow obstruction was present in 47% of patients, similar to previous paediatric studies.

The study identified several interesting cases, including one patient with infantile-onset obstructive HCM who developed infective endocarditis of the mitral valve at 8 years old. Fortunately, the patient responded well to medical treatment. In addition, 14% of HCM patients

in the study had Noonan syndrome, with a higher percentage presenting in infancy. The outcomes for these patients were generally positive, with all patients alive over a mean follow-up period of 7 years.

The study reported a 5-year survival rate of 82% and a 10-year survival rate of 78%, which is comparable to other studies. However, the study had a high attrition rate, with 33% of patients lost to follow-up. Among the patients whose outcomes were known, 26% died, with sudden cardiac death being the most common cause. The study also noted a trend toward higher rates of death or ventricular arrhythmias in patients with consanguinity, possibly indicating underlying inborn errors of metabolism.

The study had limitations, including the high attrition rate and limited availability of genetic and metabolic testing throughout the study period. Despite being a single-centre study, it provided valuable insights into paediatric cardiomyopathy in the region. The smaller number of HCM patients compared to other studies may be attributed to a lack of systematic family screening in the early years of the study.

In conclusion, this study sheds light on the clinical profile and outcomes of paediatric cardiomyopathy in South Asia. It highlights the importance of early detection and management of HCM, particularly in infants, and emphasises the need for further research and comprehensive testing to better understand the underlying causes and improves patient outcomes.

Source: Milani GP, Edefonti V, De Cosmi V, Bettocchi S, Mazzocchi A, Silano M, *et al*. (2023). Protein and growth during the 1st year of life: a systematic review and meta-analysis. *Pediatric Research*, 94 (3), 878–891. https://doi.org/10.1038/s41390-023-02531-3

The current study aims to explore the impact of varying protein intake on the growth of healthy full-term infants during their 1st year of life. This investigation is carried out through two main methods: First, a systematic review of existing literature encompassing interventions with different protein content, such as infant formulas, follow-on formulas, or complementary feeding; and second, a quantitative synthesis of the data through a meta-analysis, which assesses the effects of various formula-based interventions on growth outcomes consistently measured at different time points in similarly designed studies.

The systematic review was conducted to examine the growth effects of interventions involving different protein levels in infant formula composition within the 1st year of life for healthy term infants. In the absence of other comparable information during the research period, a meta-analysis was performed to specifically compare weight or length gain at 120 days between high-protein (>2.0 g/100 kcal) and low-protein (≤2.0 g/100 kcal) formula groups. A total of 12 papers, involving 2275 infants, were included in the study, with five of them, totalling 677 infants, contributing to the meta-analysis. Most of the studies compared high-protein formula, low-protein formula and breastfeeding. However, due to the diversity in study design and treatments, the evidence from the systematic review could not provide clear conclusions.

The meta-analysis, despite its limitations in scope and statistical power, did not find substantial support for the idea that high-protein formulas, as compared to low-protein formulas, have a significant impact on growth outcomes during the initial months of exclusive milk-feeding. This suggests that the debate regarding the optimal amount of dietary protein for healthy full-term infants in the early stages of life remains unresolved. Overall, the findings challenge the previous assumption that high-protein formulas lead to different growth outcomes in the first 4 months of life during exclusive milk-feeding.

Source: Farajzadeh S, Khalili M, Mirmohammadkhani M, Paknazar F, Rastegarnasab F, Abtahi-Naeini B. (2023). Global clinicoepidemiological pattern of childhood vitiligo: a systematic review and meta-analysis. *BMJ Paediatrics Open*, 7(1), e001839. https://doi.org/10.1136/bmjpo-2022-001839

In this study, the most common presentation of vitiligo in children was observed in school-aged girls with vitiligo vulgaris, primarily starting on the head and neck. A positive family history was noted in approximately 17% of cases. There was a potential link between vitiligo and conditions such as anaemia, thyroid disorders and halo nevus. The findings of this meta-analysis indicated a higher prevalence of vitiligo in females compared to males, with a female-to-male ratio of 1.3–1. However, some studies reported different gender ratios, with near-equal incidence or an opposite trend. This higher incidence among girls may be attributed to the increased prevalence of autoimmune conditions in females and the associated social stigma related to the cosmetic appearance of vitiligo. As vitiligo is often seen as a cosmetic concern, medical attention may be sought earlier for female children. Furthermore, the meta-regression analysis revealed a significant association between the predominance of vitiligo in females and geographical location, with a lower ratio in Asia and Europe compared to Africa. This difference could be due to variations in ethnicity and a greater awareness of childhood vitiligo in more developed countries. Approximately 50% of initial vitiligo lesions were found on the head and neck, possibly linked to increased sun exposure during outdoor activities, which can elevate the risk in genetically susceptible individuals. In addition, this area is more noticeable and easily evaluated. Extensive sun exposure can lead to the production of harmful oxygen free radicals, which can damage melanocytes in vitiligo. Genital involvement in children with vitiligo was less common, potentially due to fewer active melanocytes

in children, reduced vulnerability and less friction or melanocyte loss associated with sexual activity in older children. Stress and trauma were identified as common precipitating factors for vitiligo. However, a higher incidence of trauma as a precipitating factor might bias the correlation between vitiligo and the previous childhood trauma. Halo nevus was the most prevalent cutaneous association with childhood vitiligo, followed by atopic and allergic diastasis and premature canities. Genetic factors were noted as playing a significant role in vitiligo pathogenesis, resulting in positive family histories unrelated to ethnicity but more closely linked to an individual's genetic background in children with vitiligo.

The study faced limitations due to the heterogeneity of included studies, which was partially addressed through strict inclusion criteria and quality assessment. Only English-language papers were included, which might introduce bias.

Despite these limitations, the study's strength lies in its use of established systematic review methods, thorough searching and comprehensive quality assessment of included studies.

Overall, this review helps identify the clinical and epidemiological patterns of childhood vitiligo and suggests that vitiligo is more prevalent in female children. However, patterns such as the age of onset, lesion locations and family history of vitiligo were similar across American, Asian, European and African children. Understanding these patterns in different regions can aid in the clinical identification and management of the disease. Further research in diverse geographic regions and community settings is recommended for more reliable data in the future.

Source: Yu A, Alder N, Lain SJ, Wiley V, Nassar N, Jack, M. (2023). Outcomes of lowered newborn screening thresholds for congenital hypothyroidism. *J Paediatr Child Health*, 59: 955–961. https://doi.org/10.1111/jpc.16425

This study examined the impact of lowering the initial newborn screening (NBS) blood thyroid-stimulating hormone (b-TSH) threshold for detecting congenital hypothyroidism (CH). Lowering the threshold from 15 mIU/L to 8 mIU/L resulted in identifying more infants with preliminary CH diagnoses, but at the cost of reduced positive predictive value (PPV). This change led to an eight-fold increase in recall rates. The study also noted that pre-term infants were more frequently identified with CH using the lower threshold and the clinical relevance of identifying transient or mild CH in these infants remains uncertain.

Furthermore, a subset of infants diagnosed with CH through the lower threshold had clinically relevant CH, including permanent CH. This finding aligned with similar studies conducted in Italy and Greece, which observed increased CH detection with lowered thresholds. Geographical variations in NBS b-TSH levels were also noted, partly influenced by sampling timing and maternal iodine levels.

The study reported a lower percentage of newborns with elevated b-TSH levels compared to earlier years, likely due to iodine fortification of bread and increased iodine supplementation for pregnant women. However, monitoring the iodine status based on the World Health Organisation thresholds was challenging due to differences in sampling times.

The study emphasised the need for further research to assess the long-term outcomes of infants with transient or mild CH detected through lower thresholds and to evaluate potential psychological harm from false-positive NBS CH results. In addition, the increase in recall rates poses workload implications for NBS programs.

In conclusion, lowering the b-TSH threshold for CH detection increased the identification of clinically relevant CH cases but came with higher recall rates, higher workload for NBS staff and decreased PPV. The study highlighted the need for a balanced consideration of benefits and harms when determining optimal NBS thresholds, taking into account long-term outcomes and potential psychological impact.

Source: Li Q, Chen Z, Wang J, Xu K, Fan X, Gong C, *et al*. (2023). Molecular diagnostic yield of exome sequencing and chromosomal microarray in short stature: A systematic review and meta-analysis. *JAMA Pediatrics*, e233566. Advance online publication. https://doi.org/10.1001/jamapediatrics.2023.3566

At present, the effectiveness of exome sequencing (ES) and chromosomal microarray analysis (CMA) in diagnosing short stature cases remains uncertain. Despite previous studies noting the widespread use of ES and CMA, a definitive diagnostic rate has not been established. The primary goal of this study was to investigate how effective ES and CMA are in diagnosing short stature. For inclusion in the meta-analysis, eligible studies needed to have at least 10 participants with short stature diagnosed using either ES or CMA, with the reported number of diagnosed patients. Out of 5222 initially identified studies, only 20 met the criteria for inclusion. Relevant information from each study was extracted by two independent researchers and a proportional meta-analysis was performed to determine the overall diagnostic rate of ES and CMA. A subgroup meta-analysis was also conducted to assess whether the diagnostic rate varied depending on whether ES was used as the first-tier or last-resort test. In addition, a meta-regression analysis was carried out to examine how the diagnostic rate changed over time.

The study included 20 studies involving 1350 patients who underwent ES and 1070 patients who underwent CMA for short stature. The overall diagnostic rate for ES was 27.1% (95% confidence interval [CI], 18.1–37.2%), while for CMA, it was 13.6% (95% CI, 9.2–18.7%). There was no statistically significant difference observed between the first-tier (27.8%;

95% CI, 15.7–41.8%) and last-resort groups (25.6%; 95% CI, 13.6–39.6%) (P = 0.83), nor in the percentage of positively diagnosed patients over time.

In conclusion, this systematic review and meta-analysis provide substantial evidence supporting the diagnostic effectiveness of ES and CMA in individuals with short stature. These findings offer valuable guidance to clinicians in their decisions regarding the recommendation of these genetic tests.

Source: Farias JS, Villarreal EG, Savorgnan F, Acosta S, Flores S, Loomba RS. (2023). The use of neutrophil-lymphocyte ratio for the prediction of refractory disease and coronary artery lesions in patients with Kawasaki disease. Cardiology in the Young, 33(8), 1409–1417. https://doi.org/10.1017/S1047951123000653

Several scoring systems have been developed to assess the risk of non-responsiveness to standard intravenous immunoglobulin treatment or the development of coronary artery issues in Kawasaki disease patients. This study aimed to evaluate whether the neutrophil-lymphocyte ratio could serve as an indicator for predicting refractory disease and coronary artery problems in Kawasaki disease patients.

A systematic review of 12 studies involving 5,593 patients was conducted. The results showed that the neutrophil-lymphocyte ratio was higher in patients with refractory disease both before and after therapy, indicating a potential association. In addition, the neutrophil-lymphocyte ratio was also higher in patients with coronary artery lesions before therapy. These findings suggest that the neutrophil-lymphocyte ratio could be a useful tool for identifying patients at risk of refractory disease and coronary artery lesions in Kawasaki disease.

Source: Ilves N, Pajusalu S, Kahre T, Laugesaar R, Šamarina U, Loorits D, *et al*. (2023). High prevalence of collagenopathies in preterm- and term-born children with periventricular venous haemorrhagic Infarction. Journal of Child Neurology, 38 (6-7), 373–388. https://doi.org/10.1177/08830738231186233

The main finding of the study is the high prevalence of collagenopathies, specifically pathogenic/likely pathogenic variants in COL4A1/2 and COL5A1 genes, in children with periventricular haemorrhagic infarction/periventricular venous infarction. These variants are found in both term-born and preterm-born children with different severities of periventricular venous infarction. The study also identified previously unassociated genetic variants in collagen genes. The presence of these variants suggests a shared pathogenesis of microangiopathy, as indicated by the high occurrence of microbleeds, cerebral white matter abnormalities and lacunar infarcts in children with collagenopathies. Children with pathogenic variants in collagen genes were more likely to develop severe motor deficits and epilepsy compared to those without genetic variants. In addition, the study found variants in other genes, such as MT-TL1 and NOTCH3, which are connected with microangiopathy and stroke-like episodes. The study highlights the importance of genetic testing in children with periventricular haemorrhagic infarction/periventricular venous infarction to guide counselling for recurrence risks and identify potential complications later in life. However, the study's limitations include the small sample size and the lack of genetic testing in children with the worst outcomes.

Source: Thangaraj A, Anbazhagan J, Chandrasekaran V, Philomenadin FS, Dhodapkar R. (2023). Clinical profile of influenza virus-related hospitalisations in children aged 1–59 months: A five-year retrospective study from South India. Pediatric Pulmonology, 58(9), 2520–2526. https://doi.org/10.1002/ppul.26539

This study aimed to examine the clinical manifestations, morbidity and mortality patterns associated with different strains of influenza virus. The study also aimed to identify the predominant strains responsible for hospitalisations and to determine the seasonal trends in hospitalisation. In addition, the study aimed to identify risk factors for mortality in children aged 1–59 months who were hospitalised with influenza.

The researchers retrospectively analysed the medical records of children hospitalised with influenza between June 2013 and June 2018. Out of the 693 children tested for influenza, 91 were found to be positive and 68 of them (74.7%) required hospitalisation. Influenza infections were observed during both summer and winter months. The predominant strain identified was A (H1N1) pdm09, accounting for 63.2% of the cases. Other strains detected included A (H3N2) and influenza B. Pneumonia was the most common diagnosis among hospitalised children. The need for mechanical ventilation was more common in cases of influenza B infection (P = 0.035). No significant risk factors for mortality were identified in the study.

Influenza infections did not exhibit a clear seasonal pattern, with A (H1N1) pdm09 being the most prevalent strain and Influenza B emerging as an important contributor to disease severity.

Source: Kourti M, Papakonstantinou E, Papagianni A, Arsos G, Ioannidou M, Pantoleon A, *et al*. (2023). Hodgkin lymphoma in children and adolescents of Northern Greece: 25-Year Results and Long-term Follow-up. Journal of Pediatric Hematology/Oncology, 45(6), 322–326. https://doi.org/10.1097/MPH.0000000000002625

The aim of this study was to assess the long-term treatment outcomes and complications associated with Hodgkin's disease. The researchers conducted a review of medical records for 93 patients who were diagnosed with classic

Hodgkin lymphoma, treated and followed up over the past 25 years. This cohort consisted of 49 males and 44 females, with a median age of 11.8 years (ranging from 3.95 to 17.42 years). The most common subtype was nodular sclerosis, observed in 47 out of 93 patients (50.5%). B symptoms were present in 15 out of 93 patients (16.1%). Between January 2009 and December 2020, 55 patients (59%) diagnosed with Hodgkin lymphoma received treatment based on the European Network for Paediatric Hodgkin Lymphoma-C1 protocol.

In terms of outcomes, a total of 89 out of 93 patients are currently alive. Relapse occurred in 7 out of 93 patients. Second malignancies were reported in five patients, including three cases of solid tumours (thyroid cancer, breast cancer and osteosarcoma) and two cases of acute myeloid leukaemia. The overall survival rate and event-free survival rate for the entire cohort were 95.7% and 83.9%, respectively. The disease-free survival rate was 92.5%.

While a significant proportion of Hodgkin's disease patients can achieve continuous complete remission, they remain at a heightened risk of experiencing long-term complications related to their treatment. Implementing personalised treatment strategies and innovative therapies can help achieve high cure rates and reduce the occurrence of late effects.

Source: Herthelius M. (2023). Antenatally detected urinary tract dilatation: long-term outcome. *Paediatric nephrology (Berlin, Germany)*, 38(10), 3221–3227. https://doi.org/10.1007/s00467-023-05907-z

This review provides updated information on the long-term outcomes of children with antenatally diagnosed urinary tract dilatation (UTD), previously known as antenatal hydronephrosis. The definition of UTD varies, making it challenging to compare studies and draw generalised conclusions.

Approximately one-third of antenatally diagnosed UTD cases, defined as a certain measurement of renal pelvis diameter during pregnancy, will resolve before birth. Another third will resolve within the first few years of life, while the remaining cases will either persist or be diagnosed with a congenital abnormality of the kidney and urinary tract (CAKUT) after birth. The risk of a postnatal CAKUT diagnosis increases with the degree of prenatal and postnatal dilatation, except for vesicoureteral reflux (VUR), which cannot be predicted based on the degree of UTD.

Urinary tract infections (UTIs) occur in 7–14% of children with UTD during early childhood. The risk of UTI is higher in children with traditional risk factors such as dilated VUR, hydroureteronephrosis, female gender and intact foreskin. In selected cases, continuous antibiotic prophylaxis may be considered during the 1st year of life.

In long-term follow-ups, it is uncommon for children with moderate or severe UTD to develop hypertension, proteinuria, or reduced estimated glomerular filtration rate (0–5%). On the other hand, children with mild UTD have an excellent long-term outcome and do not require unnecessary examinations or follow-up.

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