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Journal Summary

Current advances in paediatric healthcare

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1. Immunological markers in kids with recurrent respiratory infections

Source: Machura E, Krakowczyk H, Kleszyk M, Swiętochowska E, Grzywna-Rozenek E, Rusek M, Góra A, Chrobak E, Pukas-Bochenek A, & Szczepanska M. (2024). Serum levels of selected cytokines and chemokines and immunoglobulin G4 in children with recurrent respiratory tract infections. *J Immunol Res,* 5170588. doi: 10.1155/2024/5170588.

The study provides valuable insights into the immunological profile of children with recurrent respiratory infections (RRIs), particularly with a focus on pro-inflammatory cytokines such as regulated upon activation, normal T cell expressed and secreted (RANTES), interleukin (IL)-18 and IL-23 as potential biomarkers. There are several strengths to highlight, but also areas where some further clarity or context could enhance the overall interpretation.

First, the finding that RANTES shows such high sensitivity and specificity as a biomarker for RRI is notable and adds a solid clinical implication to the study. However, while the significance of this result is clear, some additional discussion on how this could be applied in practice would be beneficial. For instance, could RANTES levels be used in routine clinical settings to predict RRIs? Exploring any potential limitations of using it as a diagnostic tool would add depth to the conclusion.

The study's focus on pro-inflammatory cytokines is relevant to understanding the pathophysiology of RRIs, but the authors do mention the limitation of not looking at anti-inflammatory markers. Since a balance between pro- and anti-inflammatory responses is critical in regulating immune function, considering both sides of the inflammatory spectrum would provide a more comprehensive view. A brief mention of future work that could explore this could help acknowledge this gap without detracting from the current findings.

The elevated immunoglobulin G4 (IgG4) levels observed are intriguing, and while this is noted as possibly reflecting chronic antigen exposure, the implications could be explored more fully. Does this suggest a specific immune adaptation in these children? In addition, IgG4's role in non-allergic immune responses is touched on, but some more elaboration on its function in recurrent infections would help round out this aspect of the study.

The correlation between IL-18 and other cytokines is well presented, but some further explanation of its clinical significance in the context of RRI would strengthen the discussion. For example, IL-18's involvement in Th1/Th2 responses and its role in respiratory infections is important, but understanding how this influences disease progression or outcomes in children with RRIs would be helpful.

In summary, the study presents solid data on the immune profiles of children with RRIs and highlights important biomarkers that could have diagnostic value. Some additional context

regarding the clinical applications of these findings, particularly for RANTES and IgG4, and acknowledgement of the broader immune balance could add to the depth of the analysis. While the immunological insights from this study are highly relevant to understanding RRIs in children globally, including in India, local epidemiological, environmental and socioeconomic factors would need to be considered. Further research in the Indian context would help validate and adapt these findings to the local population and healthcare system.

However, overall, the research adds to the understanding of immune responses in paediatric RRIs and opens avenues for future work to build on these findings.

2. Acquired demyelination syndromes in Indian paediatric cohorts

Source: Chakrabarty B, Gulati S, Madaan P, Kumar A, Sondhi V, Dubey R, Gupta J, & Pandey RM. (2024). Acquired demyelination syndrome in children and adolescents: 10 years experience from a tertiary care centre in North India. *Neurol India,* 72(5):997-1002. doi: 10.4103/neurol-india.NI_1141_20. Epub 2024 Oct 19.

This study provides valuable insights into paediatric acquired demyelination syndrome (ADS) in India, emphasising the unique challenges faced in resource-constrained settings. The study offers a comprehensive analysis of demographic, clinical, radiological and immunological features, comparing monophasic and recurrent cases. Such an exploration is critical for identifying predictors of recurrence, particularly in a paediatric cohort, and is relevant for clinical practice in similar low-resource environments.

The study provides a detailed characterisation of paediatric ADS subtypes: Clinically isolated syndrome (CIS) (48.4%), acute disseminated encephalomyelitis (ADEM) (23.2%), multiple sclerosis (MS) (18.9%) and neuromyelitis optica spectrum disorder (9.5%), emphasising regional variations and the influence of genetic and environmental factors.

The gender distribution, showing male predilection, contrasts with findings from Western cohorts, where female preponderance is more common, especially in MS. This variation, however, aligns with some studies from East Asia, indicating possible regional or ethnic influences. The study's comparison of various cohorts from France, Italy and Japan strengthens the discussion on how age, gender and genetic/environmental factors shape ADS manifestations. The observation that MS is common in the first decade, contrary to some literature, adds to the growing body of evidence that early-onset MS needs greater attention in paediatric populations.

The detailed radiological findings are consistent with established literature on ADS, but the study's focus on polyfocal presentations in CIS is particularly notable, given the younger age group. The subtle but important observation that ADEM-like initial presentations do not rule out MS is crucial for early and accurate diagnosis, which can be challenging in young children.

The findings on cerebrospinal fluid inflammation and the role of pleocytosis and raised protein levels in predicting recurrence are significant, especially given that these are easily accessible bedside tests. While interferon-β, glatiramer acetate and fingolimod are the Food and Drug Administration-approved first-line therapies for paediatric MS, their high cost and the need for repeated injections limit their feasibility in this setting. The study offers compelling evidence that azathioprine and rituximab could serve as practical long-term therapies in resource-poor settings where traditional first-line agents may not be feasible. The use of azathioprine as a long-term immunomodulatory treatment due to its affordability and tolerability is practical in low-resource settings. However, it would be beneficial to explore the long-term efficacy and potential side effects of such treatment in larger cohorts alongside more expensive options like rituximab.

A notable strength of this study is its attempt to delineate early predictors of recurrence in a paediatric population, which can guide early therapeutic interventions. However, the study's retrospective design and limited sample size are constraints. Prospective studies with larger cohorts are essential to validate these findings.

In conclusion, the study highlights the importance of recognising paediatric ADS in resource-poor settings, where diagnostic and therapeutic options may be limited. Early immunotherapy is critical, and studies like this provide a foundation for optimising treatment protocols. The exploration of cost-effective treatments like azathioprine is particularly relevant for countries like India, where healthcare resources are limited. However, further research, particularly prospective studies, is needed to fine-tune the management of paediatric ADS and ensure better outcomes for these patients.

3. Exploring the global burden and mechanisms of vaccine-associated Guillain-Barré syndrome

Source: Jeong YD, Park S, Lee S, Jang W, Park J, Lee K, Lee J, Kang J, Udeh R, Rahmati M, Yeo SG, Smith L, Lee H, & Yon DK. (2024). Global burden of vaccine-associated Guillain-Barré syndrome over 170 countries from 1967 to 2023. *Sci Rep*, 14(1):24561. doi: 10.1038/s41598-024-74729-2. PMID: 39427003; PMCID: PMC11490553.

This study addresses a critical gap in the literature concerning Guillain-Barré syndrome (GBS) as a potential adverse neurological effect of vaccines, particularly during the COVID-19 pandemic. While the investigation utilises data from the World Health Organization pharmacovigilance

database, its conclusions about the association between vaccines and GBS warrant cautious interpretation.

The study identifies a notable increase in GBS reports associated with COVID-19 vaccines during the pandemic, emphasising the need for comprehensive data on vaccine-related adverse events globally. Specifically, the analysis reveals a 5.47-day mean time to onset of GBS symptoms post-vaccination, indicating that most cases manifest within 1 week of receiving the vaccine.

Reports associated with COVID-19 vaccines showed a marked increase, particularly with Ad5-vectored vaccines, compared to mRNA vaccines, which had the highest incidence of GBS. Some studies suggest that vaccination against varicella zoster might reduce the risk of GBS compared to natural infection. While GBS has been associated with vaccines like the tetanus-diphtheria-pertussis and rotavirus vaccines, the overall incidence remains low.

Notably, despite the surge in reports, the relative risk of GBS from COVID-19 vaccines appears low compared to the incidence associated with infections. The analysis reveals age-related risks, with a more significant association in older populations. Interestingly, a gender imbalance was noted in the 45–64 age group, contrasting with traditional GBS epidemiology, which typically shows a male predominance.

The study discusses the plausible mechanisms for vaccine-associated GBS, notably the molecular mimicry hypothesis. However, it also points out that the patterns observed with the Ad5-vectored COVID-19 vaccine differ from those seen with traditional vaccines, highlighting a need for further research into specific antigens responsible for this association.

The authors stress the importance of considering vaccination history in GBS cases, particularly in older patients, and the potential for delayed treatment in low-income countries to affect patient outcomes adversely.

The findings align with the natural epidemiological patterns of GBS, wherein incidence rises with age. This context enriches our understanding of the interplay between vaccines and GBS and emphasises the necessity for continued surveillance. Before the COVID-19 pandemic, three mechanisms contributing to immune system activation were implicated in explaining vaccine-associated GBS. The molecular mimicry hypothesis has garnered significant attention.

The study's strengths lie in its comprehensive approach, and the extensive database utilised, allowing for an analysis that transcends geographical boundaries. However, limitations include potential underreporting from lower-income countries, biases in reporting and challenges in establishing causation due to the nature of GBS onset following infections and vaccinations. The lack of detailed age stratification may further obscure the relationship between age and GBS risk.

In conclusion, while this study provides valuable insights into the relationship between vaccines and GBS, it underscores the necessity for ongoing research and vigilant monitoring of vaccine safety, especially in high-risk groups. The findings can guide future vaccination protocols, contributing to improved public health strategies and patient safety.

4. Parental arsenic exposure and their infants born with spina bifida

Source: Tindula G, Mukherjee SK, Ekramullah SM, Arman DM, Islam J, Biswas SK, Warf BC, Christiani DC, Lemos B, Liang L, Cardenas A, & Mazumdar M. (2024) Parental arsenic exposure and tissue-specific DNA methylation in Bangladeshi infants with spina bifida. *Epigenetics*, 19(1):2416345. doi: 10.1080/15592294.2024.2416345. Epub 2024 Oct 19. PMID: 39425535; PMCID: PMC11492674

The hypothesis connecting arsenic toxicity to disrupted epigenetic mechanisms, particularly DNA methylation, is gaining traction. This study explores the correlation between parental arsenic exposure and DNA methylation patterns in tissue samples (in infant dural tissue collected during spina bifida surgery) from 28 infants diagnosed with spina bifida in Bangladesh. This approach may provide valuable insights into the potential epigenetic impacts of arsenic exposure.

A significant link was identified between arsenic levels in fathers' toenails and DNA methylation at the CpG site methylation (CpG) site cg24039697 (located on chromosome 10 within the gene body of *FLJ45983)* in dural tissue ($P = 7.6 \times 10^{-9}$), even after adjusting for multiple hypotheses and relevant covariates. Gene ontology analysis revealed biological pathways connected to neural tube defects, particularly Wnt signalling pathways linked to paternal arsenic exposure and infant whole blood. Furthermore, regional analyses identified 3–19 differentially methylated regions (DMRs) associated with parental arsenic exposure and infant DNA methylation, covering diverse metabolic pathways. These findings highlight the critical relationship between parental arsenic exposure – a pressing public health issue – and tissue-specific DNA methylation in infants, including in the underexplored nervous system tissue.

In the regional analysis, significant associations were observed between parental arsenic exposure and infant DNA methylation in dural tissue, with fathers linked to three DMRs and mothers to nine. Gene ontology analysis highlighted various biological pathways, with 'Wnt' signalling pathways being particularly relevant. These pathways are crucial for embryonic development processes, including neurulation and neural tube closure, with this study revealing connections to regulation and cell signalling within the 'Wnt' pathway.

The current study's limitations include a small sample size, which restricted the power to detect significant associations

between parental arsenic exposure and infant DNA methylation, leading to predominantly null findings in individual CpG analyses. Furthermore, tissue collection was confined to infants undergoing surgery for neural tube defect closure, and as controls were not included, it was impossible to compare epigenetic differences between affected and unaffected individuals.

Conversely, the study's strengths lie in the thorough characterisation of arsenic exposure through toenail samples from both parents, which reflect exposures over the past 3–18 months. Given the pervasive arsenic contamination in Bangladesh's water supply, exposure levels are presumed to be relatively stable over time. By including paternal exposure data, this study contributes to the existing literature linking parental exposure to child DNA methylation outcomes. Findings indicated associations at both CpG and regional levels related to parental arsenic exposure, underscoring the relevance of this understudied tissue in understanding epigenetic impacts.

In summary, this study assessed arsenic levels, a chemical prevalent due to contaminated drinking water, in toenail samples from parents of infants with spina bifida, a significant congenital disability associated with long-term health challenges. This research is particularly relevant to India, where similar issues of arsenic contamination in water sources pose substantial public health risks. The findings highlight the urgent need for addressing environmental health factors linked to developmental disorders in vulnerable populations.

5. Endoscopic injection versus ureteral reimplantation in high-grade vesicoureteral reflux

Source: Nascimben F, Molinaro F, Maffi M, Nino F, Lachkar A, Zislin M, Ogunleye M, Becmeur F, Messina M, Cobellis G, Lima M, Angotti R, & Talon I. (2024). Endoscopic injection versus anti-reflux surgery for moderate- and high-grade vesicoureteral reflux in children: A cost-effectiveness international study. *J Robot Surg*, 18(1):371. doi: 10.1007/s11701-024-02103-5.

This study offers a comparative analysis of endoscopic injection (EI) and ureteral reimplantation (UR) for treating vesicoureteral reflux (VUR) in paediatric patients, specifically those with grades III, IV and V of the condition. VUR, though common, lacks standardised treatment guidelines, especially for moderate-to-severe cases. The findings emphasise the strengths and limitations of both procedures, with EI emerging as a promising option for grade III VUR due to its lower complication rate, shorter hospital stays, reduced pain and lower overall costs. On the other hand, for higher-grade VUR (IV and V), UR – whether performed open, laparoscopically or robotically – offers better long-term outcomes and fewer redo surgeries, although it involves higher costs and longer recovery times.

Despite the general advantages of EI, such as reduced post-operative pain and quicker recovery, the higher risk of recurrences and redo surgeries limits its efficacy in more severe cases. The study also highlights that while minimally invasive surgeries such as laparoscopic and robotic-assisted approaches provide better cosmetic outcomes and post-operative comfort, they come with a higher financial burden, especially in contexts with limited resources and robotic expertise. In particular, robotic-assisted ureteral reimplantation should be cautiously implemented, especially in centres with limited paediatric robotic experience, as the higher costs may not be offset by significant benefits in terms of success rate or reduced complication rates compared to open or laparoscopic UR.

This study's retrospective nature and the inclusion of patients from three different institutions introduce some variability in the results, which could affect the reliability of the findings. The lack of multivariable adjustment for factors such as age, gender, comorbidities and hospital differences adds another layer of complexity to the data interpretation.

The study also touches on an important concern regarding radiation exposure in paediatric urology, specifically from procedures like voiding cystourethrogram, which may increase the long-term risk of gonadal tumours, leukaemia and other malignancies. Non-ionising technologies, such as colour-flow Doppler ultrasonography, are proposed as safer alternatives for monitoring VUR, especially in India, where large-scale population screening is often essential and the risks associated with radiation need to be minimised.

In the Indian context, the findings of this study are particularly relevant. Given the country's resource constraints, the cost-effectiveness of treatments is a key consideration. EI, with its lower cost and reduced hospital stay, may be a viable option for treating low-to-moderate grades of VUR in resource-limited settings. However, the higher rates of recurrence and redo surgeries suggest that a more cautious approach is required for severe cases, where UR may offer better long-term outcomes despite its higher initial costs. Robotic-assisted surgery, although gaining popularity globally, may still be out of reach for most Indian paediatric centres due to financial and technical limitations.

In summary, while EI proves to be an excellent first-line treatment for lower grades of VUR, particularly in terms of cost-effectiveness, UR remains superior for managing higher-grade cases. Future prospective studies and standardised treatment protocols will be essential in determining whether minimally invasive techniques can become the gold standard for managing severe VUR. The study's limitations underscore the need for more controlled, multivariable analyses to account for various patient and institutional factors.

6. Non-invasive neurally adjusted ventilatory assist in preterm infants

Source: Minamitani Y, Miyahara N, Saito K, Kanai M, Namba F, & Ota E. (2024). Non-invasive neurally-adjusted ventilatory assist in preterm infants: A systematic review and meta-analysis. *J Matern Fetal Neonatal Med*, 37(1):2415373. doi: 10.1080/14767058.2024.2415373. Epub 2024 Oct 15. PMID: 39406682.

This study systematically reviews and analyses the effects of non-invasive neurally adjusted ventilatory assist (NIV-NAVA) compared to conventional non-invasive respiratory support (nasal continuous positive airway pressure [NCPAP]/ nasal intermittent positive pressure ventilation [NIPPV]) in preterm infants with respiratory distress. The evidence gathered from five randomised controlled trials (RCTs) involving 279 preterm infants suggests that NIV-NAVA may improve patient-ventilator synchrony and reduce the incidence of extubation failure in post-extubation respiratory support.

The primary finding, indicating a significant reduction in treatment failure with NIV-NAVA in comparison to NCPAP/ NIPPV, holds potential clinical relevance, particularly in reducing reintubation rates, which are associated with severe complications like bronchopulmonary dysplasia (BPD). This improved synchrony, specific to NIV-NAVA, helps preterm infants match their respiratory efforts more effectively with the ventilatory support, reducing work of breathing and fatigue and potentially minimising apnoea-related reintubation.

However, the evidence is tempered by several limitations. The included RCTs were small, with high risks of performance, detection and attrition biases, largely due to the challenge of blinding in ventilation studies. The limited sample sizes and broad confidence intervals also reduce the certainty of the findings. Importantly, while NIV-NAVA showed benefits in preventing extubation failure, it did not significantly impact secondary outcomes such as BPD, severe BPD or mortality. This discrepancy suggests that while NIV-NAVA may provide short-term benefits in preventing immediate extubation failure, its influence on long-term respiratory outcomes remains unclear.

One notable limitation of the review is the heterogeneity in study protocols, including differences in patient populations, ventilation settings and outcome definitions. The lack of gestational age subgroup analyses, as well as non-uniform criteria for diagnosing outcomes like BPD, further complicates the interpretation. While the systematic review demonstrates promising short-term results for NIV-NAVA, further research, particularly large, well-designed trials, is required to confirm these findings and explore the potential for broader clinical impact.

In the Indian context, where neonatal care units face significant resource constraints and high preterm birth rates, the findings suggest that adopting NIV-NAVA could reduce the need for more invasive interventions like reintubation, which is associated with longer hospital stays and higher healthcare costs. However, the applicability of these findings in Indian neonatal intensive care units, where access to advanced ventilatory support technologies like NIV-NAVA may be limited, warrants further exploration. Future research should consider cost-effectiveness, resource availability and the practicalities of integrating such technologies into lower-resource settings.

7. Waning immunity of single-dose typhoid conjugate vaccine

Source: Qadri F, Khanam F, Zhang Y, Biswas PK, Voysey M, Mujadidi YF, Kelly S, Bhuiyan AI, Rajib NH, Hossen I, Rahman N, Islam S, Pitzer VE, Kim YC, Clemens JD, Pollard AJ, & Liu X. (2024). 5-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Bangladeshi children (TyVOID): A cluster randomised trial. *Lancet,* 404(10461):1419-1429. doi: 10.1016/S0140-6736(24)01494-6.

The study follows an important trajectory in typhoid prevention, particularly in high-burden regions such as Bangladesh and India. It extends the findings of the original TyVAC trial to assess the long-term protection offered by a single-dose typhoid conjugate vaccine (TCV), tracking its effectiveness up to 5 years post-vaccination. A notable decline in vaccine efficacy between the 3rd and 5th years raises significant questions about the durability of TCV-induced immunity, particularly in younger children. This age group (<7 years at fever visits) exhibited a sharp reduction in vaccine protection, from 85% to 24%, hinting at a worrying vulnerability in the years most critical for maintaining immunity.

The age-related waning observed adds to the complexity of TCV administration. It is unclear why younger children experience this more pronounced decline in immunity. Some possible explanations are that younger children may have underdeveloped bone marrow, impairing their ability to sustain long-lived plasma cells or that older children may have had more exposure to *Salmonella typhi*, which could boost their immune response over time. This leaves a gap in protection at school entry age (around 4–5 years), which the study hints may be a period of increased vulnerability to typhoid fever. The discussion around waning protection, tied to the decay of anti-Vi immunoglobulin G concentrations, urges us to rethink the current single-dose regimen, especially for younger children in high-burden settings.

The findings diverge from those of the Malawi trial, which reported no significant waning of immunity up to 4.3-year

post-vaccination. The difference might stem from the higher natural exposure to *S. typhi* in Bangladesh, which is about 3 times that of Malawi. This higher exposure could mean that Bangladeshi children require a stronger or more sustained immune response to achieve the same level of protection. Essentially, the study argues that regions with higher bacterial exposure, like Bangladesh (and, by extension, India), may require more robust vaccination strategies than those with lower exposure, suggesting that a single dose may not be enough in these contexts.

Despite the methodological limitations, particularly the lack of blinding and the differences in follow-up durations amongst groups, the study remains robust in its primary finding of waning immunity. The use of test-negative design and sensitivity analyses strengthens the argument for a decline in vaccine effectiveness, especially when compared to unvaccinated children. While these limitations do not seem to induce significant bias, they do call for more rigorous research, particularly large-scale RCTs, that can capture the full extent of TCV's medium- and long-term efficacy.

In terms of relevance to India, the implications are clear. India, like Bangladesh, has a high typhoid burden, and the introduction of TCV in routine immunisation programmes is underway. The findings suggest that a booster dose around school entry age may be necessary to maintain immunity, especially for children vaccinated at younger ages. This could have a substantial public health impact, as maintaining high levels of immunity during the school years – when exposure risk is highest – might prevent a resurgence of typhoid cases.

Policywise, the World Health Organization's current recommendation of a single dose might need to be revisited. If the data from Bangladesh hold true in other high-burden regions like India, a booster dose strategy would be essential to sustaining immunity. While this presents logistical challenges, especially in resource-limited settings where routine preschool visits may not be standard, there is growing momentum for introducing such a visit globally. The idea of using TCV as a catalyst to push for broader preschool vaccination could be a game-changer in countries like India.

Ultimately, this study highlights the need for ongoing vigilance in typhoid vaccine programmes. While the short-term protection offered by TCV is substantial, the medium-term decline suggests that without adjustments to the current vaccine schedule, we risk leaving a large cohort of children vulnerable just as they enter their peak exposure years. This calls for more research, better data and, perhaps most urgently, a policy shift towards booster doses for sustained protection.

8. Non-invasive continuous positive airway pressure and extubation failure in preterm infants

Source: Ho JJ, Kidman AM, Chua B, Chang G, Fiander M, & Davis PG. (2024). Nasal continuous positive airway pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev*, 10(10): CD000143. doi: 10.1002/14651858.CD000143.pub2.

This updated Cochrane (this is an update of a review first published in 1997 and last updated in 2003) review addresses the ongoing challenge of respiratory failure in preterm infants following extubation from invasive mechanical ventilation. Historically, interventions such as head box oxygen or low-flow nasal cannulae were used, but non-invasive pressure support, specifically non-invasive continuous positive airway pressure (NCPAP), has emerged as a potentially more effective method in stabilising the upper airway, reducing apnoea and improving lung function post-extubation. The review includes data from nine trials with a total of 726 infants, with most studies conducted in high-income countries and one from Chile, classified as upper-middle income at the time.

The key outcomes of the review suggest that NCPAP may reduce the risk of extubation failure (relative risk [RR]: 0.62, 95% confidence interval [CI] 0.51–0.76) and subsequent endotracheal reintubation (RR: 0.79, 95% CI 0.64–0.98), although the evidence supporting the latter is highly uncertain due to heterogeneity across studies and variability in results. A notable strength of the review is its low risk of detection bias in most trials, as objective criteria were used to define primary outcomes. However, there remains a high risk of performance bias, as the nature of the intervention precluded the blinding of clinical staff. This is a crucial limitation to acknowledge.

The review also touches on the potential impact of NCPAP on bronchopulmonary dysplasia, although the evidence here is equally uncertain, with little difference observed between intervention and control groups (RR: 0.89, 95% CI: 0.47–1.68). Neurodevelopmental outcomes were not assessed in any of the included trials, representing a significant gap in the evidence base.

In the Indian context, where neonatal intensive care units often face constraints in resources and staff, the findings of this review are particularly relevant. While NCPAP has become standard practice in many high-resource settings, its application in resource-constrained environments like India needs careful consideration. India has a large burden of preterm births, and ensuring access to and the correct application of NCPAP could significantly impact outcomes in these vulnerable infants. Given the low-certainty evidence but widespread adoption of the intervention, there may be less need for further large-scale studies on its efficacy. However, more research on long-term neurodevelopmental outcomes, especially in lower-income countries, would be of considerable value.

Important points:

- NCPAP may significantly reduce extubation failure post-invasive ventilation in preterm infants

- Evidence supporting reduced reintubation and its impact on bronchopulmonary dysplasia is highly uncertain
- The absence of neurodevelopmental outcome data highlights a key gap in the research
- High risk of performance bias in all trials due to a lack of blinding
- Relevance to India includes the potential for NCPAP to improve outcomes in resource-limited neonatal units, but long-term outcome studies are needed.

While NCPAP is a promising intervention for immediate respiratory support post-extubation, the long-term impact, especially in low- and middle-income settings like India, remains to be fully understood. The study underscores the need for further research focusing on the specific challenges and resource limitations in these environments, particularly regarding long-term developmental outcomes.

9. Pharmacological Interventions in paediatric migraine prophylaxis

Source: Kohandel Gargari O, Aghajanian S, Togha M, Mohammadifard F, Abyaneh R, Mobader Sani S, Samiee R, Kermanpour A, Seighali N, & Haghdoost F. (2024). Preventive Medications in Paediatric Migraine: A Network Meta-Analysis. *JAMA Netw Open*, 7(10):e2438666. doi: 10.1001/jamanetworkopen.2024.38666.

This comprehensive review attempts to address a critical gap in the management of paediatric migraine – effective prophylactic pharmacological interventions. Paediatric migraine, which significantly impacts quality of life and academic performance, demands a focused approach, particularly in developing safe and effective preventive treatments. This NMA, the largest conducted to date, evaluated a variety of pharmacological agents across a substantial number of paediatric patients. While the findings affirm the effectiveness of certain drugs in reducing migraine frequency, they also expose limitations in the current therapeutic strategies, particularly in terms of improving quality of life and reducing migraine duration.

Several key points emerge from the review. First, migraine frequency, a central metric in assessing treatment efficacy, was significantly reduced with agents such as pregabalin, topiramate (with and without vitamin D3), flunarizine, levetiracetam, cinnarizine and amitriptyline compared to placebo. Interestingly, combinations such as cinnarizine and propranolol showed a synergistic effect, further amplifying cinnarizine's efficacy in reducing headache intensity by up to 55%. However, propranolol alone failed to show significant impact, challenging earlier findings.

Second, while these drugs reduced both migraine frequency and intensity, no treatment improved quality of life (measured by PedMIDAS) or headache duration. This points to an essential but overlooked aspect of paediatric migraine care: Even if medications reduce the burden of attacks, their failure to improve daily functioning calls for a broader therapeutic perspective. Clinically, this is significant, as parents and clinicians often measure treatment success by improvements in life quality, not just attack reduction.

This study acknowledges several limitations that warrant attention. Heterogeneity in dosing, treatment formats and reporting methods across trials may influence both statistical outcomes and their real-world applicability. In addition, a substantial proportion of participants were from Iran (44.8%), potentially skewing the generalisability of the results. Moreover, some of the included medications, such as levetiracetam, cinnarizine and flunarizine, were tested in fewer than 100 patients, raising concerns about small-study effects and the robustness of the findings.

A major confounder in paediatric migraine research is the high placebo effect, a well-documented challenge in this population. Many included studies showed a placebo response that diminished the apparent effectiveness of active treatments. This effect was particularly evident with propranolol, where despite showing some efficacy, it was not statistically significant when compared to placebo, highlighting the need for more nuanced clinical trials.

In terms of methodology, this NMA stands out for its sophisticated approach. Unlike prior reviews that merged categorical and continuous variables into singular metrics, this analysis provided discrete evaluations for each outcome – migraine frequency, intensity, quality of life and duration – offering a more granular understanding of drug efficacy. The meta-regression analysis further solidifies the findings by showing that baseline characteristics had minimal influence on the treatment outcomes, enhancing the study's reliability.

In the Indian context, where paediatric migraine is often underdiagnosed and undertreated, these findings have significant clinical relevance. First-line treatments such as topiramate, pregabalin and flunarizine, particularly when combined with vitamin supplements, may be more effective in reducing migraine frequency than previously thought. The idea of combination therapies, especially with cost-effective supplements such as vitamin D3 and riboflavin, could be particularly valuable in India, where access to expensive treatments may be limited. However, caution is necessary when interpreting these results, given the high placebo response in paediatric populations and the potential for over-reliance on pharmacological interventions without corresponding improvements in quality of life.

This review rightly calls for more randomised, placebo-controlled trials on under-researched drugs such as levetiracetam, cinnarizine and flunarizine, with an emphasis on combination therapies and real-world efficacy beyond

placebo effects. Given the lack of improvement in quality of life and duration outcomes, future research should also explore non-pharmacological interventions, behavioural therapies and comprehensive care models that may better address the multifaceted needs of paediatric migraine patients.

To conclude, while this study strengthens the evidence base for several pharmacological agents in reducing migraine frequency and intensity, it underscores the persistent gap in improving life quality and functional outcomes in paediatric patients. This calls for a broader, more integrated approach to migraine management that goes beyond mere attack frequency and focuses on long-term well-being. As paediatric migraine becomes an increasingly recognised burden, especially in under-resourced settings such as India, there is a clear imperative for targeted research that addresses both the biological and social dimensions of this condition.

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