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Karnataka Paediatric Journal

Journal Review

Journal watch

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Received: 14 June 2022
Accepted: 26 June 2022
EPub Ahead of Print: 12 August 2022
Published: 16 November 2022

DOI
10.25259/KPJ_16_2022

Quick Response Code:

Source: Mattila *et al*. Effect of point-of-care testing for respiratory pathogens on antibiotic use in children: A randomised clinical trial. *JAMA Netw Open. 2022 Jun* 1;5(6):e2216162. doi: 10.1001/jamanetworkopen.2022.16162. PMID: 35679047.

There is limited data available on the clinical impact of multiplex polymerase chain reaction (PCR) point-of-care testing for respiratory pathogens in acutely ill children.

This unblended and randomised clinical trial study tries to evaluate the effect of multiplex PCR point-of-care testing for respiratory pathogens on antibiotic use in acutely ill children. The participants were followed up until hospitalisation or discharge from the emergency department (ED) for the primary outcome. The participants were randomly assigned in a 2:1 ratio either to undergo multiplex PCR point-of-care testing (18 respiratory viruses and three bacteria with results ready within 70 min) on arrival at the ED or to receive routine care. The primary outcome was the proportion of children receiving antibiotic therapy. The secondary outcomes were the number of diagnostic tests and radiographic imaging procedures performed and costs.

After exclusions, 1243 children (692 boys [56%]) were randomly allocated to either the intervention (829 children) or control (414 children) group. Multiplex PCR point-of-care testing for respiratory pathogens did not reduce the overall prescribing of antibiotics in the ED (226 children [27.3%] in the intervention group vs. 118 children [28.5%] in the control group; risk ratio, 0.96; 95% CI, 0.79–1.16). Targeted antibiotic therapy was started in 12 children (1.4%) tested with point-of-care multiplex PCR and two children (0.5%) in the control group (risk ratio, 3.0; 95% CI, 0.76–11.9). The number of diagnostic tests did not differ between the groups, nor did the costs.

Therefore, testing for respiratory pathogens appears to have a limited impact on clinical decision-making for acutely ill children.

Source: Edlow *et al*. Neurodevelopmental outcomes at 1 year in infants of mothers who tested positive for SARS-CoV-2 during pregnancy. *JAMA Netw Open. 2022 Jun* 1;5(6):e2215787. doi: 10.1001/jamanetworkopen.2022.15787. PMID: 35679048.

The authors have published the findings of a study evaluating the association between exposure to SARS-CoV-2 *in utero* and neurodevelopmental disorders within the first 12 months of life. They included 7772 live births across six hospital sites with 222 births to mothers who tested positive for SARS-CoV-2 and found an association between SARS-CoV-2 and a diagnostic code for a neurodevelopmental disorder after adjusting for preterm birth. Although the prevalence of neurodevelopmental disorder diagnoses cannot be calculated exactly due to suppressed counts, it was estimated to be approximately 3% in the unexposed group and 6% in the exposed group within the first 12 months.

Given that we are only 2 years into the pandemic, much of the effect of *in utero* exposure to maternal SARS-CoV-2 infection remains poorly understood. As noted by the authors, the inflammatory environment that is observed with infection is concerning for long-term adverse health consequences for the offspring and has been demonstrated with other infections. Yet, we wonder whether it is the virus itself or the societal changes and stresses of the pandemic that is adversely affecting childhood outcomes.

The authors appropriately note two critical limitations of their work: (1) It is difficult to fully adjust for all the baseline differences between groups with and without a positive SARS-CoV-2 test in pregnancy and (2) there is potential for ascertainment bias. Although the authors performed a series of sensitivity analyses to ensure that their data are robust and performed multivariable modeling to adjust for confounding, there may still be residual confounding from differences in the home environment or other exposures during pregnancy. The earlier timing of diagnosis of neurodevelopmental disorders in the exposed group suggests that they may have been evaluated earlier or more frequently for neurodevelopmental disorders when compared with the unexposed group. Ideally, all offspring in the cohort would have been evaluated using a standardised methodology, which will be important moving forward as prospective studies are designed rather than needing to rely on diagnostic codes.

These preliminary data are critically important, yet, many questions remain. Essentially, all of what we know now about the effects of *in utero* exposure to maternal SARS-CoV-2 infection is from children who were exposed to the early and alpha variants of SARS-CoV-2 as those are the only children now old enough to undergo rigorous neurodevelopmental assessments. Knowledge about the effects of other variants is lacking. We know that the delta variant substantially damaged the placenta and was associated with a much higher risk of stillbirth compared with other variants. This placental damage in conjunction with inflammation and cytokine release has the potential for substantial ramifications for the offspring. Thus, outcomes may be different by a variant of maternal SARS-CoV-2 infection. Importantly, we also have no data on whether prior vaccination will have a protective effect against adverse neurodevelopmental outcomes for the offspring of mothers with SARS-CoV-2 beyond the direct benefit of persistent antibodies in the cord blood and through infancy.

Ultimately, it is not surprising that the pandemic and *in utero* exposure to maternal SARS-CoV-2 infection may adversely affect neurodevelopmental outcomes in young children. As a retrospective cohort study, this publication can only demonstrate associations and causality cannot be determined. This type of work is intended to be hypothesis-generating and that goal has been accomplished as these preliminary findings generate numerous additional research questions to explore. Are there genetic predispositions to adverse outcomes? Will we observe differential effects by SARS-CoV-2 variant, by the severity of infection and by trimester of infection? Is it the virus itself or all of the societal changes that occurred during this period including differences in how those changes were experienced among those with and without SARS-CoV-2?

Perhaps, the most important question is how do we intervene to help mitigate the adverse effects of the pandemic on young children? Prospective studies to validate these findings, tease out some of the nuances and identify those at highest risk will help health care practitioners appropriately dedicate resources to improve outcomes as we follow the life course of this generation of children born during the COVID-19 pandemic.

Source: Ogundele MO, Yemula C. Management of sleep disorders among children and adolescents with neurodevelopmental disorders: A practical guide for clinicians. *World J Clin Pediatr. 2022 Mar* 15;11(3):239-252. doi: 10.5409/wjcp.v11.i3.239. PMID: 35663001; PMCID: PMC9134149.

There is a complex relationship between sleep disorders and childhood neurodevelopmental, emotional, behavioural and intellectual disorders (NDEBIDs). NDEBID includes several conditions such as attention-deficit/hyperactivity disorder, autism spectrum disorder, cerebral palsy, epilepsy and learning (intellectual) disorders. Up to 75% of children and young people (CYP) with NDEBID are known to experience different types of insomnia, compared to 3% to 36% in normally developing population. Sleep disorders affect 15%–19% of adolescents with no disability, in comparison with 26% to 36% among CYP with moderate learning disability (LD) and 44% among those with severe LD. Chronic sleep deprivation is associated with significant risks of behavioural problems, impaired cognitive development and learning abilities, poor memory, mood disorders and school problems. It also increases the risk of other health outcomes, such as obesity and metabolic consequences, significantly impacting the well-being of other family members.

This narrative review of the extant literature provides a brief overview of sleep physiology, aetiology, classification and prevalence of sleep disorders among CYP with NDEBIDs. It outlines various strategies for management, including parenting training/psychoeducation, use of cognitive-behavioural strategies and pharmacotherapy. Practical management, including assessment, investigations, care plan formulation and follow-up, is outlined in a flow chart.

Source: Lelak K, Vohra V, Neuman MI, Toce MS, Sethuraman U. Paediatric melatonin ingestions — united states, 2012–2021. *MMWR Morb Mortal Wkly Rep 2022*;71:725–729. DOI: http://dx.doi.org/10.15585/mmwr.mm7122a1external icon

It is known that Melatonin is regulated by the Food and Drug Administration as a dietary supplement and is a widely available over-the-counter sleep aid for adults and children. Melatonin is widely available in tablet, capsule, liquid and gummy formulations. However, during 2012–2021, the annual number of paediatric ingestions of melatonin increased by 530% with a total of 260,435 ingestions reported. Most hospitalised patients were teenagers with intentional ingestions, whereas the largest increase in hospitalisation occurred among children aged ≤5 years with unintentional ingestions. Paediatric hospitalisations and more serious outcomes also increased, primarily due to an increase in unintentional melatonin ingestions in children aged ≤5 years.

This report shows that increased use of over-the-counter melatonin might place children at risk for potential adverse events. Public health initiatives, especially in our country, should focus on raising awareness of increasing melatonin ingestion among children and on preventive measures to eliminate this risk.

Source: de Sonnaville ESV, Königs M, van Leijden O, Knoester H, van Woensel JBM, Oosterlaan J. Intelligence outcome of paediatric intensive care unit survivors: A systematic meta-analysis and meta-regression. *BMC Med. 2022 Jun* 1;20(1):198. doi: 10.1186/s12916-022-02390-5. PMID: 35642037; PMCID: PMC9158152.

Long-term morbidity after paediatric intensive care unit (PICU) admission is a growing concern. Both critical illness and accompanying PICU treatments may impact neurocognitive development as assessed by its gold standard measure; intelligence. This meta-analysis and meta-regression quantify intelligence outcomes after PICU admission and explore risk factors for poor intelligence outcomes.

Using random-effects meta-analysis, the authors calculated the standardised mean difference in full-scale intelligence quotient (FSIQ) between PICU survivors and controls across all included studies and, additionally, distinguished between PICU subgroups based on indications for admission. The relation between demographic and clinical risk factors and the study's FSIQ effect sizes was investigated using random-effects meta-regression analysis.

A total of 8119 PICU survivors and 1757 controls could be studied. They found 0.47 SD (7.1 IQ points) lower FSIQ scores in PICU survivors compared to controls. All studied PICU subgroups had lower FSIQ compared to controls. Later years of PICU admission (range 1972–2016) and longer PICU stay were related to greater FSIQ impairment, whereas male sex and a higher rate of survivors were related to smaller FSIQ impairment. Meta-regression in PICU subgroups showed that later year of PICU admission was related to greater FSIQ impairment in children admitted after cardiac surgery and heart- or heart-lung transplantation. Male sex was related to smaller FSIQ impairment in children admitted after cardiac surgery. Older age at PICU admission and older age at follow-up were related to smaller FSIQ impairment in children admitted after heart- or heart-lung transplantation.

PICU survivors, distinguished in a wide range of subgroups, are at risk of intellectual impairment. Length of PICU stay, female sex and a lower rate of survivors were related to greater intelligence impairment. Intelligence outcome has worsened over the years, potentially reflecting the increasing percentage of children surviving PICU admission.

Source: Bhandari AP, Nnate DA, Vasanthan L, Konstantinidis M, Thompson J. Positioning for acute respiratory distress in hospitalised infants and children. ***Cochrane*** *Database Syst Rev. 2022 Jun* 6;6(6):CD003645. doi: 10.1002/14651858.CD003645.pub4. PMID: 35661343; PMCID: PMC9169533.

This Cochrane review compares the effects of different body positions in hospitalised infants and children with acute respiratory distress syndrome aged between 4 weeks and 16 years. This is an update of a review published in 2005, 2009 and 2012.

Positioning and mechanical ventilation have been regularly used to reduce respiratory distress and improve oxygenation in hospitalised patients with Acute Respiratory Distress Syndrome. Due to the association of prone positioning (lying on the abdomen) with sudden infant death syndrome (SIDS) within the first 6 months, it is recommended that young infants be placed on their back (supine). However, prone positioning may be a non-invasive way of increasing oxygenation in individuals with acute respiratory distress and offers a more significant survival advantage in those who are mechanically ventilated. There are substantial differences in respiratory mechanics between adults and infants. While the respiratory tract undergoes significant development within the first two years of life, differences in airway physiology between adults and children become less prominent by 6–8 years old. However, there is a reduced risk of SIDS during artificial ventilation in hospitalised infants. Thus, an updated review focusing on positioning for infants and young children with ARDS is warranted.

The authors could include six trials: Four cross-over trials and two parallel randomised trials, with 198 participants aged between 4 weeks and 16 years, all but 15 of whom were mechanically ventilated. Four trials compared prone to supine positions. One trial compared the prone position to good-lung dependent (where the person lies on the side of the healthy lung, e.g., if the right lung was healthy, they were made to lie on the right side) and independent (or non-good-lung independent, where the person lies on the opposite side to the healthy lung, e.g., if the right lung was healthy, they were made to lie on the left side) position. One trial compared good-lung independent to good-lung

dependent positions. When the prone (with ventilators) and supine positions were compared, there was no information on episodes of apnoea or mortality due to respiratory events. There was no conclusive result in oxygen saturation; blood gases, PCO_2, PO_2, or lung function. However, there was an improvement in oxygenation index with prone positioning in both the parallel trials and the cross-over study.

Derived indices of respiratory mechanics, such as tidal volume, respiratory rate and positive end-expiratory pressure (PEEP) were reported. There was an apparent decrease in tidal volume between prone and supine groups in parallel. When prone and supine positions were compared in a cross-over study, there were no conclusive results in respiratory compliance; changes in PEEP, or resistance. One study reported adverse events. There were no conclusive results for potential harm between groups in extubation; obstructions of the endotracheal tube; pressure ulcers; and Hypercapnia. One study (50 participants) compared supine positions to good-lung dependent and independent positions. There was no conclusive evidence that PaO_2 was different between supine and good-lung dependent positioning. There was also no conclusive evidence for supine position and good-lung independent positioning; or between good-lung dependent and independent positioning.

As most trials did not describe how possible biases were addressed, the potential for bias in these findings is unclear.

In conclusion, although included studies suggest that prone positioning may offer some advantage, there was little evidence to make definitive recommendations. There appears to be low certainty evidence that positioning improves oxygenation in mechanically ventilated children with ARDS. Due to the increased risk of SIDS with prone positioning and lung injury with artificial ventilation, it is recommended that hospitalised infants and children should only be placed in this position while under continuous cardiorespiratory monitoring.

Source: Stick SM, Foti A, Ware RS, Tiddens HAWM, Clements BS, Armstrong DS, Selvadurai H, Tai A, Cooper PJ, Byrnes CA, Belessis Y, Wainwright C, Jaffe A, Robinson P, Saiman L, Sly PD; COMBAT CF Study Group. The effect of azithromycin on structural lung disease in infants with cystic fibrosis (COMBAT CF): A phase 3, randomised, double-blind and placebo-controlled clinical trial. *Lancet Respir Med. 2022 Jun* 2:S2213-2600(22)00165-5. doi: 10.1016/S2213-2600(22)00165-5. Epub ahead of print. PMID: 35662406.

It is known that structural lung disease and neutrophil-dominated airway inflammation are present from 3 months of age in children diagnosed with cystic fibrosis after newborn screening. The authors hypothesised that azithromycin, given 3 times weekly to infants with cystic fibrosis from diagnosis until age 36 months, would reduce the extent of structural lung disease as captured on chest CT scans.

A phase 3, randomised, double-blind and placebo-controlled trial was done. Infants (aged 3–6 months) diagnosed with cystic fibrosis following newborn screening were included; while children with prolonged mechanical ventilation in the first 3 months of life, clinically significant medical disease or comorbidities other than cystic fibrosis or macrolide hypersensitivity were excluded.

The two primary outcomes were the proportion of children with radiologically defined bronchiectasis and the percentage of total lung volume affected by the disease. The secondary outcomes included clinical outcomes and exploratory outcomes were inflammatory markers.

A total of 281 patients were screened, of whom 130 were enrolled, randomly assigned and received the first study dose. Sixty-eight participants received azithromycin and 62 received a placebo. At 36 months, 88% (n = 50) of the azithromycin group and 94% (n = 44) of the placebo group had bronchiectasis and total airways disease and did not differ between groups. The secondary outcome results included fewer days in the hospital for pulmonary exacerbations and fewer courses of inhaled or oral antibiotics for those in the azithromycin group. For the pre-planned and exploratory analysis, concentrations of airway inflammation were lower for participants receiving azithromycin, including interleukin-8 and neutrophil elastase activity at age 36 months, although no difference was noted between the groups for interleukin-8 or neutrophil elastase activity at 12 months. There was no effect of azithromycin on the body-mass index at age 36 months, nor any evidence of pathogen emergence with the use of azithromycin. There were few adverse outcomes with no differences between the treatment groups.

Hence, azithromycin treatment from diagnosis of cystic fibrosis did not reduce the extent of structural lung disease at 36 months of age; however, it did reduce airway inflammation, morbidity including pulmonary exacerbations in the 1st year of life and hospitalisations and improved some clinical outcomes associated with cystic fibrosis lung disease.

Source: Vogt MR, Wright PF, Hickey WF, De Buysscher T, Boyd KL, Crowe JE Jr. Enterovirus D68 in the anterior horn cells of a child with acute flaccid myelitis. ***N*** *Engl J Med. 2022 May* 26;386(21):2059-2060. doi: 10.1056/NEJMc2118155. PMID: 35613028.

This research has found evidence that a viral infection followed by a 'robust' immune response is the cause of a polio-like paralysing illness in children called acute flaccid myelitis (AFM). AFM is a serious neurologic condition that causes muscle weakness, sometimes leading to permanent paralysis. Of the 682 AFM cases confirmed in the United States since 2014, only two deaths have been reported, but patients rarely recover full strength.

The suspect virus, enterovirus D68 (EV-D68), can cause mild-to-severe symptoms including runny nose, wheezing, cough, bodyaches and muscle aches. EV-D68 has been detected in respiratory specimens from AFM patients, but firm evidence of direct causation was lacking – until now.

By examining autopsy specimens from a 5-year-old boy who died from AFM in 2008, the researchers discovered the virus, EV-D68, had directly infected neurons in the spinal cord. They also noted the presence of cytolytic CD8+ T-cells and immune cells that normally kill infected cells during a viral infection. The research highlights the importance of autopsies and biobanking tissues for future study. The decision by the family of the 5-year-old boy to have an autopsy performed 'could, in turn, be lifesaving for future children diagnosed with AFM'.

Source: Olm MR, Dahan D, Carter MM, Merrill BD, Yu FB, Jain S, Meng X, Tripathi S, Wastyk H, Neff N, Holmes S, Sonnenburg ED, Jha AR, Sonnenburg JL. Robust variation in infant gut microbiome assembly across a spectrum of lifestyles. *Science. 2022 Jun 10*;376(6598):1220-1223. doi: 10.1126/science.abj2972. Epub 2022 Jun 9. PMID: 35679413.

A team of researchers has found that the gut microbiome of infants living in a hunter-gatherer society in Tanzania is markedly different from the gut microbiome of infants living in modern urban areas. Noting that most biome gut sequencing research has been conducted on people living in urban areas, the researchers wondered about the gut biomes of people living in remote, non-urban settings. Noting also that some prior research has shown that people living in such areas tend to have a more diverse gut biome than people living in urban areas, they wondered about the gut biomes of infants in such places.

The team collected stool samples from dozens of Hadza infants living in Tanzania, along with stool samples collected from 23 of the infant's mothers. They, then, conducted ribosomal RNA sequencing on all of the samples to determine the kinds of bacteria in their guts that make up the biome. They compared the diversity of the gut microbiomes in the infants in Tanzania with those in the guts of infants living in modern urban areas around the world. They found that the Hadza infants had more diversity in their guts after approximately 6 months than did infants living in urban areas. They also found that approximately 20% of the bacteria types found in the Hadza infants' microbiomes had not been previously documented.

The researchers also found that the differences in the gut microbiome could be traced back to their mothers along with some influences from the local environment. They also suggest the main reason for the differences in the gut microbiome appeared to be related to lifestyle rather than geography. Moreover, they also speculate on the possibility of a link between a less diverse gut microbiome in urban areas and diseases that are more common in the industrialised world – such as those related to inflammation.

Source: Kimberly P. Newton *et al*. Incidence of type 2 diabetes in children with non-alcoholic fatty liver disease, *Clinical Gastroenterology and Hepatology (2022)*. DOI: 10.1016/j.cgh.2022.05.028

Non-alcoholic fatty liver disease (NAFLD) is the most common paediatric liver disease, affecting 5–8 million children in the United States. In NAFLD, the cells of the liver store large fat droplets, which can affect the function of the liver. Physicians have long observed a relationship between NAFLD and type 2 diabetes (T2D) in adults, but much less is known about a similar connection in children.

Rates of T2D have doubled in children over the past 20 years. Children with NAFLD have features of insulin resistance, a key characteristic of T2D and so may be at risk for developing the disease.

This study included 892 children with NAFLD and with a mean age of 12.8 (2.7) years followed by 3.8 (2.3) years with a total 3234 person-years at risk. The incidence rate of T2D was 3000 new cases per 100,000 person-years at risk. At baseline, 63 children had T2D and during follow-up, an additional 97 children developed incident T2D, resulting in a period prevalence of 16.8%. Incident T2D was significantly higher in females versus males and had more severe liver histology including steatosis grade and fibrosis stage.

The authors conclude that children with NAFLD are at high risk for existing and incident T2D. In addition to known risk factors for T2D (females and BMI z-score), the severity of liver histology at the time of NAFLD diagnosis was independently associated with T2D development. Targeted strategies to prevent T2D in children with NAFLD are needed.

Declaration of patient consent

Patients' consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

Author Vikram Sakleshpur Kumar is one of the State Advisory Members of the Journal.

How to cite this article: Kumar VS. Journal watch. Karnataka Paediatr J 2022;37:65-9.