MIS-C and More

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Abstract

This PID journal watch provides valuable insights into various aspects of infectious diseases and antibiotic resistance. It highlights the need for continued research, improved diagnostic strategies, and targeted interventions to effectively combat these national and global health challenges. The findings from these journal articles contribute to the growing body of knowledge in the field and can inform clinical practice and public health policies.

Keywords: Extended-spectrum beta-lactamase-producing Enterobacteriaceae, Multisystem inflammatory syndrome in children, Neonatal infections, Tuberculosis preventative therapy, Viral-only diarrhea.

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Source: Jackson HR, Miglietta L, Habgood-Coote D, et al. Diagnosis of multisystem inflammatory syndrome in children by a whole-blood transcriptional signature. J Pediatr Infect Dis Soc 2023;12(6):322–331. DOI: 10.1093/jpids/piad035.

This study aimed to find a set of genes that could be used as a diagnostic blood test to distinguish multisystem inflammatory syndrome in children (MIS-C) from other similar diseases. The researchers recruited children with MIS-C from hospitals in the United Kingdom and the European Union and analyzed their blood samples using ribonucleic acid (RNA) sequencing.

By comparing the gene expression profiles of MIS-C patients with those of children diagnosed with Kawasaki disease (KD), bacterial infections, and viral infections, the researchers identified a group of genes that showed significant differences in expression. They found a total of 5,696 genes that were significantly differentially expressed between MIS-C and the combined comparator disease groups.

To narrow down the list of genes and identify the most promising ones, the researchers used feature selection techniques. They selected five genes, namely *HSPBAP1*, *VPS37C*, *TGFB1*, *MX2*, and *TRBV11-2*, which they believed could effectively distinguish MIS-C from the other diseases.

To validate the diagnostic potential of these genes, the researchers developed a diagnostic test using reverse transcription quantitative polymerase chain reaction (RT-qPCR) assays. They evaluated the performance of this five-gene signature in an independent validation set, which included cases of MIS-C, KD, bacterial infections, viral infections, and coronavirus disease 2019 (COVID-19).

The results were promising, as the five-gene signature achieved high accuracy in distinguishing MIS-C from KD, bacterial infections, and viral infections in both the discovery and validation sets. The researchers reported an impressive area under the curve (AUC) of 96.8% in the discovery set and an AUC of 93.2% in the independent validation set.

These findings suggest that the five-gene blood RNA expression signature has the potential to be developed into a diagnostic test for MIS-C. Such a test would be valuable in accurately diagnosing MIS-C and differentiating it from other similar diseases, allowing for timely and appropriate treatment.

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However, further research and validation are necessary to refine and optimize the diagnostic test before it can be implemented in clinical practice. Nonetheless, this study represents a significant step forward in improving the diagnosis and management of MIS-C, offering hope for more effective and targeted interventions for this condition.

Source: Bock M, Theut AM, van Hasselt JGC, et al. Attainment of target antibiotic levels by oral treatment of left-sided infective endocarditis: a POET substudy. Clinical Infect Dis 2023;77(2):242–251. DOI: 10.1093/cid/ciad168

Infective endocarditis is a serious infection of the heart valves, often caused by bacteria such as streptococci, staphylococci, or enterococci. Traditionally, intravenous antibiotics have been the standard treatment for this condition. However, the POET (Partial Oral Endocarditis Treatment) trial challenged this practice by demonstrating that oral step-down therapy was noninferior to full-length intravenous antibiotic administration. To further investigate the efficacy of oral treatments, this study aimed to perform pharmacokinetic/pharmacodynamic analyses for oral antibiotics used in the treatment of infective endocarditis.

The study enrolled 236 patients as part of the POET sub-study. Plasma concentrations of oral antibiotics, including amoxicillin, dicloxacillin, linezolid, moxifloxacin, and rifampicin, were measured on days 1 and 5. Minimal inhibitory concentrations (MICs) were determined for the bacteria causing infective endocarditis. Pharmacokinetic/pharmacodynamic targets were predefined based on existing literature, using parameters such as time above MIC or the ratio of AUC to MIC. Population pharmacokinetic

modeling and pharmacokinetic/pharmacodynamic analyses were conducted to assess the probabilities of target attainment (PTAs) for each antibiotic.

The study found that the majority of patients reached the target levels for amoxicillin and linezolid, with PTAs ranging from 88 to 100%. For moxifloxacin and rifampicin, the PTAs were slightly lower, ranging from 71 to 100%. However, the PTAs for dicloxacillin, when using a clinical breakpoint for staphylococci, were significantly lower, ranging from 9 to 17%. Among the patients who had available pharmacokinetic and MIC data for two oral antibiotics, a small number did not reach the target for either antibiotic.

The findings of this study support the efficacy of oral step-down antibiotic treatment for infective endocarditis. The high PTAs observed for amoxicillin and linezolid indicate that these antibiotics are effective in achieving the desired pharmacokinetic/pharmacodynamic targets. However, the low PTAs for dicloxacillin suggest that this antibiotic may not be as effective against staphylococci, which are commonly implicated in infective endocarditis. It is also worth noting that some patients did not reach the target levels for both antibiotics, indicating a potential need for alternative treatment strategies in these few cases. However, the study also demonstrated that patients with sub-target levels for one antibiotic were compensated by the administration of a second antibiotic, ensuring that the overall treatment goals were met.

The use of population pharmacokinetic modeling allowed for a comprehensive analysis of the pharmacokinetic/pharmacodynamic profiles of the oral antibiotics studied. This approach provides valuable insights into the probability of achieving therapeutic levels of antibiotics in patients with infective endocarditis.

In conclusion, this study provides evidence supporting the efficacy of oral step-down antibiotic treatment for infective endocarditis. The majority of patients achieved the target levels for the individual orally administered antibiotics, with any sub-target levels being compensated by the administration of two different antibiotics. These findings have important implications for the management of infective endocarditis, as oral step-down therapy offers a convenient and effective alternative to full-length intravenous antibiotic treatment. Further research, especially in children, is warranted to explore the optimal combination and dosing strategies for oral antibiotics in the treatment of this condition.

Source: Melnychuk L, Perlman-Arrow S, Lisboa Bastos M, et al. A systematic review and meta-analysis of tuberculous preventative therapy adverse events. Clinical Infect Dis 2023;77(2):287–294. DOI: 10.1093/cid/ciad246

Tuberculosis preventative therapy (TPT) is an important component of the World Health Organization's strategy to combat tuberculosis (TB). However, the occurrence of adverse events (AE) is a concern with TPT regimens. To provide insights for clinical decision-making, a systematic review and meta-analysis were conducted to estimate the incidence of AE and hepatotoxicity associated with different TPT regimens.

The researchers searched multiple databases for studies reporting AE related to TPT. They included studies that provided information on AE stratified by regimen and the number of participants receiving each regimen. A random-effects model was used to analyze the cumulative incidence of AE.

The analysis included 175 publications describing TPT-related AE in 277 cohorts. Among adults, the incidence of any AE was 3.7%, and hepatotoxicity leading to drug discontinuation was 1.1%. In comparison, the incidence of any AE in children was 0.4%, and hepatotoxicity leading to drug discontinuation was 0.02%. The TPT regimen with the highest incidence of any AE and AE leading to drug discontinuation was 3 months of isoniazid and rifapentine (3HP), while the lowest incidence was observed with 4 months of rifampin (4R). 4R also had the lowest incidence of hepatotoxic AE and drug discontinuation due to hepatotoxic AE. 3HP also had a low incidence of hepatotoxic AE.

The study concluded that although there were limitations in the methods and quality of AE reporting in the reviewed studies, pediatric populations had a very low incidence of AE with all TPT regimens. In adults, rifamycin-based regimens were generally safer compared to mono-H regimens, with 4R having the lowest incidence of TPT-related AE and hepatotoxicity.

This study provides valuable information on the incidence of AEs and hepatotoxicity associated with different TPT regimens. It highlights the lower incidence of AE in pediatric populations and the relative safety of rifamycin-based regimens, particularly 4R, in adults. However, the study acknowledges the limitations of the reviewed studies and emphasizes the need for further research and standardized reporting of AEs in TPT studies.

Source: Readman JB, Acman M, Hamawandi A, et al. Cefotaxime/sulbactam plus gentamicin as a potential carbapenem- and amikacin-sparing first-line combination for neonatal sepsis in high ESBL prevalence settings. J Antimicrob Chemother 2023;78(8):1882–1890. DOI: 10.1093/jac/dkad177

In neonatal intensive care units (NICUs), infections caused by extended-spectrum beta-lactamase (ESBL)—producing Enterobacteriaceae are widespread, and the increasing levels of antibiotic resistance are a major concern. Distinguishing between bacterial and viral sepsis in neonates can be difficult, leading to the use of empirical antibiotics without a definitive diagnosis. Empirical therapy often relies on broad-spectrum antibiotics, which contributes to the development of further antibiotic resistance.

To address this issue, the researchers conducted a study to evaluate the effectiveness of different antibiotic combinations against ESBL-producing Enterobacteriaceae isolates that caused neonatal sepsis and meningitis. They performed various *in vitro* tests, including susceptibility testing, chequerboard combination analysis, and dynamic analyses using a hollow-fiber infection model. The antibiotics tested were cefotaxime, ampicillin, gentamicin, and β-lactamase inhibitors.

The results showed that all antibiotic combinations exhibited either additive or synergistic effects against the clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae*. Specifically, the combination of cefotaxime or ampicillin with sulbactam, along with gentamicin, consistently inhibited the growth of ESBL-producing isolates at typical neonatal doses. Furthermore, this combination was able to clear the hollow-fiber infection model system of organisms that were resistant to each individual agent. They also found that the combination of cefotaxime/sulbactam and gentamicin was consistently bactericidal at clinically achievable concentrations. The concentrations used in the study were within the range that can be achieved in clinical practice.

The inclusion of sulbactam in the standard ampicillin/gentamicin or cefotaxime/gentamicin regimen, using standard doses, shows promise as a combination therapy for neonatal settings with a high prevalence of ESBL-producing bacteria, especially in cases where sulbactam is not already being used.

The study found that viable bacteria were eradicated within 7 days using standard doses, indicating that the commercially available ratio of ampicillin/sulbactam and cefotaxime/sulbactam (2:1) is likely sufficient. These findings suggest that the combination of cefotaxime/sulbactam/gentamicin could be an effective strategy against Enterobacteriaceae infections that cause sepsis, using concentrations that can be achieved in clinical practice. Using combinations of cefotaxime/sulbactam/gentamicin to combat multidrug-resistant bacterial infections may serve as a potential alternative to using "Watch" agents like amikacin and meropenem.

Source: Strasser S, Relly C, Berger C, et al. Structured immune workup in healthy children with a first episode of severe bacterial infection: a 7-year single-center study. J Infect Dis 2023;228(1):8–17. DOI: 10.1093/infdis/jiad098

This retrospective analysis examined routine immunological testing in previously healthy children with bacterial pneumonia, meningitis, and/or sepsis. The study found that 6% of cases had significantly impaired immune function, while an additional 11% showed milder abnormalities or delayed immune maturation. These findings support the importance of routinely investigating children with serious bacterial infections to identify potential immunological disorders. Most of the detected abnormalities affected the humoral immune system and were transient, suggesting a B-cell maturation disorder without a known genetic cause. The study emphasizes the need for standardized investigations of immune disorders in seemingly healthy children with invasive bacterial infections.

The overall mortality rate in the study cohort was low, but the fatality rate for sepsis alone was higher. Four children (2%) were diagnosed with innate immunity disorders, similar to previous studies. However, the study did not test for certain immune deficiencies, potentially missing some cases. The proportion of patients with immunological abnormalities varied depending on the clinical phenotype, with sepsis or septic meningitis and younger age being associated with a higher risk. Children with pneumonia without sepsis had the lowest rates of relevant immunological abnormalities, possibly due to prior antimicrobial treatment or nonbacterial infections.

The study found a high rate of isolated immunoglobulin A (IgA) and/or IgM deficiency in children with bacterial infections compared to the general population. Although the clinical significance of these findings remains unclear, they highlight the need for further investigation. The authors suggest routinely performing immunological investigations in children after recovery from invasive bacterial infections, such as pneumonia, meningitis, or sepsis. This can help identify children who may benefit from additional vaccines, antibiotic prophylaxis, and parental and primary care physician awareness.

Genetic testing was not routinely conducted in this study, but the authors suggest that combining immunological investigations with genetic testing may provide a more comprehensive approach. Monogenic conditions may be more common than previously thought, but functional confirmation of genetic variants remains challenging. The study acknowledges its limitations, including its retrospective nature and potential biases. However, it emphasizes the clinical relevance of routine immunological investigations in children with serious bacterial infections to optimize preventive measures and avoid future episodes.

In conclusion, this study highlights the importance of routine immunological investigations in previously healthy children with serious bacterial infections. It identifies a significant proportion of cases with impaired immune function or abnormalities, particularly in those with sepsis or meningitis. These findings support targeted counseling, preventive measures, and further research in this population.

Source: Balodhi A, Jain K, Gupta P, et al. A meta-analysis on the prevalence of Taenia solium and Taenia saginata infections in India. Trans R Soc Trop Med Hyg 2023;117(8):539–545. DOI: 10.1093/trstmh/trad022

Tapeworm infections caused by *Taenia solium (T. solium)* and *Taenia saginata (T. saginata)* pose a significant public health threat. However, the existing data on these infections is fragmented and underutilized. To address this gap, the present study conducted a systematic review of the scientific literature following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The aim was to assess the overall burden and distribution of taeniasis and cysticercosis caused by *T. solium* and *T. saginata* in India.

Nineteen eligible articles were included in the analysis. The findings revealed that the prevalence of *T. solium*-associated taeniasis/cysticercosis in India was estimated to be 11.06% [95% confidence interval (CI) 6.856–16.119]. Additionally, the prevalence of *T. saginata*-associated taeniasis was found to be 4.7% (95% CI 3.301–6.301).

These results highlight the substantial burden of tapeworm infections in India and emphasize the need for active surveillance and targeted public health interventions. The identification of areas with high prevalence rates can guide the implementation of preventive measures and control strategies. By synthesizing the available evidence, this study provides valuable insights into the epidemiology of taeniasis and cysticercosis in India, contributing to the understanding of the public health impact of these infections.

It is important to note that this study relied on existing literature, which may have limitations in terms of data quality and representativeness. However, despite these limitations, the findings underscore the urgency of addressing tapeworm infections as a public health priority in India. Further research and data collection efforts are needed to enhance our understanding of the burden, distribution, and risk factors associated with these infections, ultimately informing evidence-based interventions and control measures.

Source: Garbern SC, Islam MT, Islam K, et al. Derivation and external validation of a clinical prediction model for viral diarrhea etiology in Bangladesh. Open Forum Infect Dis 2023;10(7):ofad295. DOI: 10.1093/ofid/ofad295

This study aimed to develop and validate clinical prediction models that could effectively distinguish viral-only diarrhea from other causes, utilizing a few easily measurable clinical factors routinely collected in healthcare settings. Data from extensive surveillance systems in Bangladesh were employed to enhance our understanding of viral-only diarrhea predictors across all age groups. These insights could potentially lead to more prudent antibiotic use.

Research has shown that a significant portion of children under 5 years of age receive inappropriate antibiotics for diarrhea, primarily caused by viruses. Antibiotic use remains high due to a lack of tools for assessing viral diarrhea risk, influencing antibiotic prescription decisions. This study created prediction models to aid clinicians in identifying viral-only diarrhea cases, potentially

reducing unnecessary antibiotic prescriptions. A recent trial using a similar model found that for every 10% increase in predicted viral-only probability, the odds of antibiotic prescription decreased by 14%.

The research revealed that age significantly predicted viral-only diarrhea, with the probability dropping after early childhood. However, viral diarrhea still affects adults, challenging the presumption that it is limited to children. Notably, nearly one in five adults aged 18–55 years had viral pathogens detected, underlining the need for heightened awareness in this group. Clinical features such as bloody stool and abdominal pain were predictive of nonviral causes, aligning with previous findings.

A simplified model involving age, abdominal pain, and bloody stool performed comparably well, suggesting its practicality in resource-constrained settings. The model accounting for diarrhea severity and vomiting did not significantly improve performance, indicating their limited predictive value. Seasonal variations also influenced viral-only etiology, consistent with known diarrhea patterns.

This study had limitations, including potential bias from data collected exclusively in hospitals and its limited generalizability to outpatient settings. Other predictor variables might have enhanced model performance, and the lack of a gold standard for attributing diarrhea etiology to TaqMan Array Cards (TACs) necessitated the use of an arbitrary cycle threshold (Ct) value. Furthermore, the study concentrated on predicting viral etiology, considering clinical utility.

In conclusion, this study constructed and validated clinical prediction models to differentiate viral-only diarrhea, aiding clinicians in more accurately identifying cases and reducing unnecessary antibiotic prescriptions. The research underscores the significance of age, clinical symptoms, and seasonal patterns in predicting viral etiology. By offering evidence-based tools, this study contributes to better management of pediatric diarrhea and supports antibiotic stewardship efforts.

Source: Varma A, Thysen SM, Martins JSD, et al. Overall effect of a campaign with measles vaccine on the composite outcome mortality or hospital admission: a cluster-randomized trial among children aged 9-59 months in rural Guinea-Bissau. International J Infect Dis 2023;134:23–30. DOI: 10.1016/j.ijid.2023.05.011

This cluster-randomized trial aimed to assess the nonspecific effects (NSEs) of a campaign-modeled measles vaccination (C-MV) in comparison to routine MV. Surprisingly, no beneficial NSEs of C-MV were found, in contrast to previous studies that indicated positive NSEs of measles vaccination. While exploratory analysis hinted at a potential reduction in mortality/hospital admissions before oral polio vaccine (OPV) and vitamin A supplementation (VAS) campaigns during follow-up, this reduction was modest (14%) and limited to girls, falling short of the anticipated effect (30%).

The contrast between the main result and prior studies, which highlighted the mortality-reducing effects of MV/C-MV, could be attributed to several factors. Changes in disease burden over time might influence NSEs. The pretrial mortality rate was much higher than among enrolled children, potentially affecting outcomes. Cluster randomization may have created intervention groups with different health profiles. Moreover, differences in outcomes and exposures in previous studies could contribute to the varying results. It was observed that exposure to OPV + VAS campaigns during follow-up might have interfered with the hypothesized NSEs of C-MV. This was supported by the fact that C-MV seemed to have potential beneficial NSEs on unrelated outpatient consultations in a subgroup unexposed to OPV + VAS campaigns. The findings indicate a need to investigate the interaction between C-MV and other campaigns further.

Strengths of the study include its sample size, cluster randomization, and no loss to follow-up. However, pretrial mortality was higher in the intervention group, potentially impacting the ability to detect a positive effect. Being a nonblinded trial, self-selection and healthcare-seeking behaviors could have influenced outcomes. The study also relied on parental reports, which might introduce imprecision in event details. Additionally, concurrent events and health campaigns during follow-up could confound the results.

In conclusion, contrary to expectations, this study did not find beneficial NSEs of C-MV on mortality/hospital admissions. In fact, C-MV seemed to have a negative overall impact in the rural Guinea-Bissau setting. The interaction between C-MV and OPV + VAS campaigns requires further investigation. While the results provide valuable insights, other factors might also contribute to the unexpected findings.

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