Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Steroids or intravenous immunoglobulin as first line in MIS-C in LMICs

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SARS-CoV-2 infection in children is associated with lower morbidity and mortality than in adults, with many children experiencing mild symptoms or entirely asymptomatic disease. In April, 2020, a novel condition emerged; this rare, presumed post-COVID-19, immune-mediated hyperinflammatory response was termed paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by the Royal College Of Paediatrics and Child Health, and multisystem inflammatory syndrome in children (MIS-C) by the US Centers for Disease Control and Prevention and WHO. MIS-C has been associated with variable phenotype and severity, but common features include persistent fever, multiorgan dysfunction, and raised inflammatory markers 2–6 weeks after SARS-CoV-2 infection.

As is the case for acute SARS-CoV-2 infection, health disparities between racial and social groups are also apparent for MIS-C. The condition appears to disproportionately affect children who are from Black, Asian, and other racial and ethnic groups compared with children who are from White racial groups, and children from socially deprived areas.[1,2] As COVID-19 continues to spread across the globe, it is vital that affordable treatment options and protocols suitable for low-income and middle-income countries (LMICs) are made available.

The novelty and heterogeneity of MIS-C presents a considerable challenge in establishing the best treatment strategies. Early in the pandemic, in the absence of available evidence, a consensus of expert opinion was necessary to guide clinicians. As such, a three-phase Delphi process and virtual consensus meeting in the UK summarised recommended pathways for the investigation and management of children with MIS-C.[3] This guideline is applicable in high-income countries, with access to all suggested treatment options and levels of paediatric high dependency and intensive care. In children who require treatment, but are not enrolled in a clinical trial, intravenous immunoglobulin is considered first line, with second doses considered for suboptimal response. High-dose methylprednisolone is recommended as second-line therapy, followed by biologics.[3]

There are several areas of equipoise in the management of MIS-C, including the role of intravenous immunoglobulin and methylprednisolone. A French retrospective cohort study[4] suggested treatment with intravenous immunoglobulin and methylprednisolone was favourable to intravenous immunoglobulin alone, in terms of fever course, left ventricular dysfunction, requirement for haemodynamic support, and duration of paediatric intensive care unit stay. Addition of methylprednisolone to intravenous immunoglobulin was associated with faster recovery of left ventricular ejection fraction in a further single-centre study.[5] A retrospective multicentre US study[6] showed that intravenous immunoglobulin and methylprednisolone was associated with reduced risk of cardiovascular dysfunction and reduced requirement for adjunctive immunomodulatory treatment. The BATS observational cohort study[7] reviewed 614 children from 32 countries, and found no difference in primary

outcomes (ie, inotropic support, mechanical ventilation, or death) in children who had received intravenous immunoglobulin and glucocorticoids together, or either drug in isolation. Combination of glucocorticoids and intravenous immunoglobulin was associated with reduced frequency of escalation to immunomodulatory treatment. At present, data from randomised studies with direct comparison between intravenous immunoglobulin and methylprednisolone is insufficient.

Given the novelty of MIS-C, insights from similar conditions might be able to guide treatment strategies. MIS-C has many features of a vasculitis, and corticosteroids form the foundation for treatment of almost all forms of vasculitis. The similarities of MIS-C to Kawasaki disease in many patients lead to intravenous immunoglobulin being adopted as a primary treatment, but evidence is mounting in support of the use of primary adjunctive corticosteroids in Kawasaki disease, strengthening the case for steroids in MIS-C.[8]

No official data are available on the burden of MIS-C in the paediatric population of India, although the available evidence suggests that symptomatology and severity of paediatric COVID-19 is comparable to the global picture.[9] It is, nevertheless, important to consider the impact of cost and access to treatment options. A study[10] estimated the incidence of MIS-C in the USA to be 316 per million SARS-CoV-2 infections. If these figures are extrapolated based on SARS-CoV-2 infections in India until July, 2021, a conservative estimate of intravenous immunoglobulin requirement could be in the order of 55 000 g, costing in excess of 100 million rupees (£1 million). The under-recording of infections and higher incidence of MIS-C among Asian people makes the likely cost even higher.

Steroids are a low-cost therapy that are easy to access, store, and transport, and understanding their potential benefits as a primary treatment for MIS-C is vital from a global health perspective. Methylprednisolone (1–2 mg/kg) has been recommended as first-line treatment of MIS-C in India, with intravenous immunoglobulin added if there is no improvement, in Kawasaki-disease phenotype, or in the case of severe illness.[9] The cost difference between methylprednisolone and intravenous immunoglobulin is substantial—for a 50 kg child in India, 10 mg/kg methylprednisolone costs around 500 rupees (£5), whereas 2 g/kg intravenous immunoglobulin costs around 200 000 rupees (£2000). As a blood product, intravenous immunoglobulin poses additional challenges in terms of availability, storage, and acceptability. The side-effects of corticosteroids are well understood to be generally mild and transient in children. Intravenous immunoglobulin can induce rare, but serious hypersensitivity reactions and consideration must be given to the risk of fluid overload, particularly in cardiac compromise.

The RECOVERY randomised controlled trial (ISRCTN50189673) has been trying to address the areas of equipoise in MIS-C treatment. While we await results, it is important for paediatricians in LMICs to understand that it is reasonable to consider treating children with steroids as first line, particularly in settings where intravenous immunoglobulin is expensive and difficult to access.

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