COVID-19
LITERATURE REPOSITORY

Current Evidence for the management of severe COVID-19 in children

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Discussion

As the global impact of COVID-19 on the adult population continues to rise, fortunately the impact on the paediatric population has been less severe. Early epidemiological studies from China found that children are less likely to acquire SARS-CoV-2, as well as being less likely to develop severe or critical disease (1). Similar conclusions have been obtained from studies in Iceland (2) and the United States (US) (3). In addition, critical illness appears very rare with the studies from the US and China showing 1-2% of children infected developing severe illness. As a result, there are few guidelines for the acute management of Paediatric COVID-19. The published recommendations have extrapolated from the literature on the management of adult patients with severe COVID-19, encompassing acute respiratory distress syndrome (ARDS), refractory hypoxemia and multi-organ dysfunction syndrome (MODS).

In summary, acute management has the following considerations:

1) Early application of appropriate supportive care, depending on symptom severity;
2) Trials of potential targeted therapies, with close monitoring due to the potential risk of harm.

Respiratory management will be discussed separately, and this review will focus on other aspects of care from the Surviving Sepsis Guideline (4), including fluid management, use of vasoactive agents, steroids, empiric antibiotics, plasma transfusion and anti-viral therapy.

<u>Supportive management:</u>

The mainstay of therapy for paediatric COVID-19 is supportive, including antipyretics, physical cooling if required (5), careful attention to fluid management and nutrition (6), as well as oxygen supplementation as required; in the context of close observation of vital signs. Conservative fluid management in mechanically ventilated adults has been adopted, based on previous studies of ARDS, however there is limited evidence regarding fluid management in the specific context of ARDS following SARS-CoV2 in children. For fluid resuscitation in shock, evidence suggests that crystalloids i.e. normal saline, should be used over colloids (4), however fluid management in children with severe infection remains controversial (7).

In patients with septic shock, noradrenaline, adrenaline or vasopressin may all be considered, as all of these agents have benefits and risks and none have strong evidence of superiority (4, 8). Choice of agent should be

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based on the patient and close monitoring (including both clinical and objective parameters) should be undertaken so dosage can be titrated and adverse effects avoided.

There is limited data on bacterial co-infection in COVID-19 patients however it was found that 18% of critically ill patients with Middle Eastern Respiratory Syndrome (MERS) also had bacterial infections, and *S. aureus* is common in patients with influenza pneumonia (9). Using these as precedent, it is recommended that mechanically ventilated patients with refractory hypoxemia should also receive empiric antibiotic coverage.

Corticosteroids:

The use of corticosteroids has been controversial, and there is no conclusive evidence for the use or avoidance of steroids in COVID-19. Early studies recommended the avoidance of steroid therapy in COVID-19, for fear of unchecked viral replication (10). This week, early results have been released from the ongoing RECOVERY trial showing a 30% reduction in 28-day mortality amongst ventilated adults with severe COVID-19, lesser benefit in those requiring oxygen therapy alone and no benefit amongst those with mild or moderate COVID infection. While these promising results suggest dexamethasone as the first therapy to reduce mortality, they are extrapolated from adults and may not reflect the underlying causes of paediatric COVID-associated mortality (11) and have also been released prior to peer review and full data scrutiny. The use of steroids should be reserved for severely unwell COVID-19 patients with refractory shock in the context of ARDS.

Convalescent plasma

The use of convalescent plasma from recovered COVID-19 patients is controversial, with unknown efficacy and safety. It was trialled in China with no published reports on success or lack thereof, and many studies are ongoing (12). There have been previous attempts to use convalescent plasma in viral illness, including influenza, SARS-CoV (13) and Ebola however the trials were small, and no discernible positive effects were reported.

Antiviral therapy

There is no current effective antiviral therapy, despite early hopeful studies showing *in vitro* inhibition of SARS-CoV-2 viral replication with Lopinavir/ritonavir and Remdesivir (10, 14). As a result, treatment guidelines are cautious about recommending antiviral therapy for children (15), and recommend that any trials be guided by stringent human research ethics principles and evaluate drugs already available and licensed for paediatric populations, reflecting the difference in pharmacokinetics between paediatric and adult populations. Multiple RCTs which are currently running in adult ICUs around the world, demonstrating minimal evidence of clinical benefit of antiviral therapy for patients with COVID-19, and as such, cannot be routinely recommended for use. Similarly, the burden of disease amongst children seems to be immune-mediated, including multisystem inflammatory syndromes (PIMS-TS/MIS-C, discussed separately) rather than overwhelming viral infection, highlighting antiviral therapy is likely unnecessary in paediatric patients (16). Trials are ongoing for Remdesivir after initial results suggested possible shorter recovery time (with no significant change in mortality) following therapy, in adults (17).

Other therapeutic agents

Despite promising *in vitro* effects of hydroxychloroquine on SARS-CoV-2, studies of *in vivo* efficacy were terminated early for demonstrated lack of efficacy (18). In addition, prior studies looking at its use for influenza, dengue virus and chikungunya virus also showed no clinical benefit. Early trials in adults using immunomodulatory drugs (19) and monoclonal antibodies including IL-1 receptor antagonists (Anakinra) (20) and IL-6 receptor antagonist (Tocilizumab) (21) in adults, are promising results although there are currently no data on efficacy or safety for SARS-CoV2 in children.

Conclusions

The overwhelming majority of children with COVID-19 experience a mild, self-limited illness for which supportive management is sufficient. For more severe disease, the search for effective target therapies continue; however this should not deter our focus from the mainstays of good intensive care therapy which already have a strong evidence base. As such, the focus should be on early initiation of appropriate supportive care, maintaining target haemodynamics, oxygenation, organ perfusion and proven management strategies to optimise lung recovery in ARDS.

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