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COVID-19 in Children and Altered Inflammatory Responses

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Background

The COVID-19 pandemic while affecting all age-groups appears to be less severe in children. In this journal we have international contributions relaying experiences from paediatricians across the world. Patients under 18 years only account for 2% of severely affected patients. However children can still be vectors if they are asymptomatic and shedding the virus. Dong et al described a cohort of 2143 children with suspected infection. In 34% infection was confirmed but there was little critical illness and one death. There appeared to be proportionally more severe illness in infants, a result that could have be confounded by concomitant bronchiolitis(1). Chen H et al and others have also shown there is no evidence of vertical transmission in pregnant women (2-6), although this possibility may still exist. Possible reason for this disparity in severity between adults and children may related to differences in receptors in the Renin-angiotensin system (RAS) and altered inflammatory responses to pathogens.

Angiotensin-converting enzyme 2 receptor(ACE2)

In this issue off the journal Zhu et al. et al have looked for reasons that children have relatively milder illness (7). Alterations in immune function and crucial receptors in the renin-angiotensin system (RAS) are implicated. The virus uses the angiotensin-converting enzyme (ACE)2 receptor to invade cells which is the same receptor as that for SARS-CoV, and mainly spreads through the respiratory tract. These receptors are present on many cell types in the body including immune cell such as monocytes, neutrophils and lymphocytes. The RAS system is associated with inflammation via angiotensin II and ACE2 alters RAS activity from pro- to anti-inflammatory responses (8). Specific inhibitors such as angiotensin II type 1 receptor (AT1R) antagonist, losartan, have been shown to be effective in animal models of septic shock (9). Patients with either very high ACE2 levels (such as in Diabetes or cardiovascular disease) or very low levels (animal models of hypertension) can have an abnormal immune response and pulmonary inflammation (10). Decreasing ACE2 is notable in animal models of ageing (11). Sodhi C et al demonstrated that neutrophil inflammation following bacterial pneumonia was altered by pulmonary ACE2 activity. Alterations in ACE2 are critical for neutrophil influx and lung inflammation(10). In Respiratory Syncitial Virus (RSV) ACE2 protected against severe lung injury both in children and an experimental mouse model. RSV disease pathogenesis was worsened via activation of angiotensin II type 1

receptor (AT1R) and a recombinant ACE2 decreased the severity of RSV-associated lung injury (Guo et al 2015, scientific reports)(9). However Schouten et al found that in contrast to preclinical models there are no significant differences in ACE and ACE2 in different age groups from newborns to old age(12).

Inflammation

Inflammatory responses in adults and children differ and vary throughout the lifespan (13). Schouten et al (2019) found that increasing proinflammatory cytokines associated with neutrophil function with age also correlated with severity of Acute Respiratory Distress Syndrome (ARDS) and may partially explain age-dependent difference(12). Levels of myeloperoxidase, interleukin (IL)-6, IL-10, and p-selectin were higher with increasing age, whereas intercellular adhesion molecule-1 was higher in neonates in bronchoaveolar lavage samples. Wong et al found that 2360 genes in neutrophils, 965 in monocytes and 109 genes in lymphocytes were up or downregulated in paediatric septic shock, reinforcing the data that circulating lymphocytes are not the main leukocyte population with altered gene profiles during septic shock(14). Wynn et al found dramatic differences in the transcriptomic response related to age in paediatric septic shock (15).Jeljeli et al (2019) studied the ontogeny of cytokines production in response to PHA from neonates to adults and noted the change from increased IL-10 as neonates to balanced IL-10/Th1/Th2/Th17 cytokine levels early in life. This allows protection from pathogens but ameliorates the cytokine storm(16).

Severe COVID-19 infection is characterised by a massive proinflammatory response or cytokine storm that results in ARDS and Multiorgan dysfunction (MODS). This result suggests that the etiology may be hemophagocytosis or macrophage activation syndrome. It is suggested that patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends (eg, increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate) to identify the subgroup of patients for whom anti-inflammatory treatment could improve mortality (17).

Therapeutic options include steroids, intravenous immunoglobulin, selective cytokine blockade (eg, anakinra or tocilizumab), Remdesivir, hydoxyxhrolquine and JAK inhibition (18). Remdesivir (GS-5734), blocks RNA dependent polymerase and is a nucleotide analog prodrug currently in clinical trials for treating Ebola virus infections. It has a broad spectrum of antiviral activities against RNA viruses, including SARS-CoV and Middle East respiratory syndrome (MERS-CoV)(19). Chloroquine blocks viral entry into endosomes. Hydroxychloroquine in combination with azithromycin showed promise in an open label non-randomized clinical trial of treatment in COVID-19 (20). Chloroquine appeared to limit the replication of SARS-CoV-2 (virus causing COVID-19) in vitro in a systematic review of 6 studies (21).

There is an ongoing clinical trial in China including severely affected patients with elevated IL-6 that have been treated with tocilizumab. This study has had positive results and shown improvement in symptoms in 20 patients enrolled to date. (ref-COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765))(22). Tocilizumab targets the IL-6 receptor and is a monoclonal antibody. It is approved for use in giant cell arteritis and rheumatoid arthritis. However in disorders such as juvenile immune arthritis it appears that IL-6 blockade alone is insufficient to control the inflammatory cascade, especially in patients who are afebrile with lower cell counts and ferritin levels, and higher liver enzymes (23). Corticosteroids block inflammation but the current interim WHO guidance advised against their use due to the lack of evidence for benefit and the risks of harm due to immunosuppression and secondary bacterial or fungal infection.(24)

Sepsis has been described as two different phases as the body responds to systemic infection. First there is a profound initial proinflammatory phase or cytokine storm. This is then followed by a period of potentially prolonged immunosuppression(25). This dysregulated immunosuppression phase is the major cause of sepsis related fatalities. The immune suppression and dysregulation associated with sepsis is undeniably the major cause of sepsis related fatalities (26).Therefore anti-inflammatory therapies administered in this phase would be deleterious. This suggests that further information on the individualised immune response would be useful to initiate therapies such as anti-IL6 and monitoring of pro and anti-inflammatory responses throughout the treatment course would be valuable (27). In addition sepsis definitions and responses are known to be different in children and

neonates(28). Thus, there are several reasons why children may fare better if infected with COVID-19 . In addition further understanding the differences in immune responses in difference ages groups is valuable for targeted immunotherapies.

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