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Forum

Children and SARS-CoV-2

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A previously immune-naïve world population is experiencing natural infection with SARS-CoV-2. Severe COVID-19 predominantly impacts adults, yet multisystem inflammatory disorder primarily impacts children. Herein, we discuss known clinical and biological features of SARS-CoV-2 in children and reflect on currently identified immune features and discuss what remains unknown.

Acute SARS-CoV-2 infection in children**Known**

Similar to other viral infections such as the influenza virus, the risk of hospitalization in patients with acute COVID-19 significantly increases with age, with the exception of the first months of life (Docherty et al., 2020). Children are susceptible to SARS-CoV-2 infection, but most often have no or mild disease manifestations and account for less than 1.5% of all COVID-19-related hospitalizations (Castagnoli et al., 2020). It is estimated that between 29% to 68% of children who are hospitalized have a known preexisting condition such as immunosuppression, cancer, chronic pulmonary or heart disease, neurological diseases, known immunodeficiency, or chronic heart condition (Göttinger et al., 2020; Preston et al., 2021). This means that about half of hospitalized children do not have a clear yet identified risk factor.

Children mount effective B and T cell responses against SARS-CoV-2 (Cotugno et al., 2021). The quality of antibodies against SARS-CoV-2 was not compromised in children in comparison to convalescent adults in our series (Gruber et al., 2020). Children also appeared to mount productive CD4⁺ T cells and CD8⁺ T cell responses (Cotugno et al., 2021). In the Mount Sinai series that monitored the outcome of hundreds of adult hospitalized patients with COVID-19, less than 10% of hospitalized patients failed to develop SARS-CoV-2 antibody response

and these patients did very poorly (data not shown). Most adult patients that developed severe disease or died of COVID-19, however, mounted a productive immune response against SARS-CoV-2 (data not shown). These results suggest that while immunity against SARS-CoV-2 is required to control disease outcome, disease continued to progress in many patients despite developing strong immunity against SARS-CoV-2. These results are consistent with the finding that at the time of death, lungs of most patients were devoid of virus (Schaefer et al., 2020), suggesting that while the virus certainly triggers the disease, it was not directly responsible for the organ damage. Thus, the ability of children to mount a productive immune response without associated tissue damage likely reflects their ability to parse beneficial from pathogenic inflammation in response to a novel virus or that they are better able to repair tissue damages caused by the inflammatory response.

While most children are protected from severe COVID-19 disease, earlier studies have suggested that they may represent an important virus reservoir that contributes to spreading SARS-CoV-2 in schools. However, a meta-analysis of more than 30 studies suggests that while children can transmit the virus, they play only a limited role in overall transmission of SARS-CoV-2 in schools. This might be partly due to the fact that asymptomatic carriers are less likely to contaminate others.

Importantly, children—unlike adults—appear to control SARS-CoV-2 infection remarkably well, suggesting that their immune response is adequate and that they are less at risk of triggering the main drivers of severe disease. While this statement is true comparatively to adults, in the US alone there were more than 2,600 COVID-19-related hospitalizations of children over the last year (COVID-NET). This leads to an estimate of more than 50,000 COVID-19-related hospitalizations of children worldwide. Thus, there is no room for complacency in regard to COVID-19 in our youngest.

Unknown

While the factors that put adult patients at risk for developing severe diseases have been described extensively (Vabret et al., 2020), the majority of hospitalized children do not have a known underlying risk factor for severe disease (Göttinger et al., 2020). One avenue that needs to be scrutinized are inborn errors of immunity which could predispose children to severe viral infections, such as those described in type I IFN pathway (Zhang et al., 2020). It has been often suggested that the ability of children to contain SARS-CoV-2 infection is unusual in comparison to adult population. We argue the opposite, as in fact children are known to control viral infection better than adults as in the cases for mumps and measles. Maybe the best comparison to SARS-CoV-2 is influenza, where although there is no naïveté on a population level, seasonal viral mutations often mimic such a



scenario to an extent. During seasonal viral antigenic drifts and shifts, the age susceptibility and risk of hospitalization significantly increases with age, with the exception of the very young (Lafond et al., 2016), suggesting that immune-naive children, as for SARS-CoV-2, are likely to produce a strong immune response to a majority of viruses. These results may also suggest that children are able to handle strong immune responses triggered upon the first exposure to microbes.

It is interesting indeed that the main risk factor for severe COVID-19 is old age. Age is known to lead to chronic inflammation and to vascular damage that may contribute to excessive inflammatory responses and defects in the resolution of inflammation and tissue repair triggered upon primary viral infections. In contrast, children are more likely to have an enhanced ability to resolve inflammatory responses and to repair tissue damage, which may partly explain their reduced susceptibility to severe COVID-19. Thus, a deeper mapping and molecular investigation of the immune system of our youngest in health and disease is warranted. A greater understanding of the levels of inflammation induced, viral replication, innate immune activation, diversity and quality of both humoral and cellular immunity following SARS-CoV-2 and other childhood viruses is not only going to benefit our approach to treating and protecting children, but also unravel novel pathways that promote tissue repair.

Multisystem inflammatory disorder in children (MIS-C)

Known

About a month after the SARS-CoV-2 epidemic started, while data were suggesting that children were relatively spared from severe acute infections with SARS-CoV-2, a 30-fold increase in Kawasaki disease (KD)-like clinical presentation in children were described first in Europe and then in North America. Similar to KD, children presented to the emergency room with a multisystem hyper-inflammatory syndrome (MIS), with fever, abdominal pain, and/or rash or myocarditis (Whittaker et al., 2020). However, some distinct features such as gastrointestinal (GI) involvement, shock, and lymphopenia led to the naming of MIS-C (MIS in children) or pediatric inflammatory multi-

system syndrome temporally associated with SARS-CoV-2 (PIMS) (Sancho-Shimizu et al., 2021). Incidence is estimated to be at about 1 in 100,000. Most children had usually asymptomatic SARS-CoV-2 infection 3–6 weeks prior to MIS-C presentation and were SARS-CoV-2 antibody positive at the time of admission. Currently children are treated with intravenous immunoglobulin (IVIG) and/or prednisone and usually do well within days of admission.

A few studies of the past year have documented in detail the immunological parameters associated with MIS-C. Children presenting with MIS-C develop relatively normal antibody responses to SARS-CoV-2, but have systemic inflammation present at the time of hospital admission with levels of c-reactive protein, erythrocyte sedimentation rate, IL-6, and dozens of other cytokines elevated (Gruber et al., 2020; Vella et al., 2021). They also have mild lymphopenia, normal distribution of naive, effector, and memory T cells, both in the CD4⁺ and CD8⁺ compartments (unlike acute COVID-19 patients), and a slight reduction in non-classical monocytes and CD56^{lo} NK cells suggestive of leukocyte egress to peripheral tissues (Consiglio et al., 2020; Gruber et al., 2020; Vella et al., 2021). While the pathophysiology of MIS-C and KD are still elusive and mostly reflect the consequences of systemic inflammation, three important patterns are emerging. (1) There is a racial/ethnic bias in incidence of MIS-C, where Black and Hispanic children are disproportionately affected (Sancho-Shimizu et al., 2021). (2) There appears to be an expansion of a unique TCR repertoire (TRBV11) consistent with a super antigen selection process in patients with MIS-C (Porritt et al., 2021; Ramaswamy et al., 2021). (3) A few groups have documented the presence of increased levels of antibodies targeting autoantigens expressed by target organs of MIS-C pathology (Consiglio et al., 2020; Gruber et al., 2020; Ramaswamy et al., 2021).

Unknown

Despite remarkable efforts and depths of studies published, we still cannot predict who will develop MIS-C, or KD, highlighting the need to continue to investigate the pathophysiology of MIS-C and KD. Although there are some relatively mild genetic associations associated

with KD, we need to continue to decipher the genetic risks that predispose to MIS-C (Sancho-Shimizu et al., 2021). As more groups are discovering an association between MIS-C and TCR β variable gene 11 (TRBV11) expansion, it appears that the concept of super antigens may also contribute to the MIS-C pathology, although the relative frequency of TRBV11 in the population alone cannot explain the incidence of MIS-C. Importantly, to establish the causal contribution of autoantibodies to MIS-C disease pathophysiology, we will need to map post-viral disease autoantibody profiles in healthy children as compared to those who develop MIS-C or KD. Those autoantibodies that appear consistently associated with disease should be rigorously tested for their ability to lead to tissue damage and disease pathophysiology.

We propose a unified germline-environmental theory as the dominant determinant of MIS-C. Given the incidence of MIS-C in about 1 in 100,000 children and only few reports of MIS in adults (although it is likely underreported), genetic susceptibility alone is likely to play a dominant role in a minority of cases. KD is more prevalent in Asian children, although that association is significantly weaker in Asian children who grow up in the US, suggesting that undefined environmental factors also influence KD development. Similarly, while the increased rate of MIS-C in Black and Hispanic children may to an extent be linked to their genetics, environmental factors may also play an underappreciated role in disease, beyond the exposure rate to SARS-CoV-2 alone. Given that MIS-C develops 3–6 weeks following usually asymptomatic SARS-CoV-2 infection, it is likely that a combination of genetic and environmental triggers contribute to breaking of tolerance leading to the development of auto-antibody formation and super antigen-specific T cell response resulting in a delayed post-infectious systemic inflammatory syndrome.

Vaccinating the children

Remarkable vaccination efforts are underway worldwide. Unfortunately, there is a delay in clinical trials involving children and there has been reluctance among parents to vaccinate children. Although this is understandable since many children are spared from severe disease,

vaccination can prevent tens of thousands of COVID-19 hospitalizations in children and will help achieve herd immunity as children represent 24% of the US population. It is also possible that more virulent variants may arise and ensuring that children develop some immunity to the wild-type virus will help protect them from new variants.

In conclusion, despite intense investigation of the disease, COVID-19 remains a difficult-to-treat disease. Understanding the viral replication levels, quality of the immune response, and the dynamics and nature of the inflammatory response that develop in children with and without symptoms are critical. These results will help further our understanding of the disease pathophysiology and teach us how to best protect our youngest and oldest populations.

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