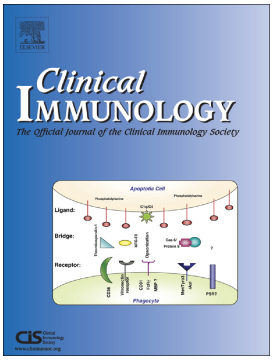

COVID-19 – Considerations for the paediatric rheumatologist

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COVID-19 – Considerations for the Paediatric Rheumatologist

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Key words

COVID, SARS, SARS-CoV2, paediatric, inflammation, ARDS, cytokine storm, rheumatology

Abstract

The novel coronavirus SARS-CoV2 is a threat to the health and well-being of millions of lifes across the globe. A significant proportion of adult patients require hospitalisation and may develop severe life-threatening complications. Children, on the other hand, can carry and transmit the virus, but usually do not develop severe disease. Mortality in the paediatric age-group is relatively low. Differences in virus containment and clearance, as well as reduced inflammation-related tissue and organ damage may be caused by age-specific environmental and host factors. Since severe complications in adults are frequently caused by uncontrolled immune responses and a resulting "cytokine storm" that may be controlled by targeted blockade of cytokines, previously established treatment with immunosuppressive treatments may indeed protect children from complications.

Mini Review

SARS-CoV2 is the pathogen causing COVID-19, a pandemic threatening millions of lifes globally. While in most individuals SARS-CoV2 infections are unapparent or associated with mild to moderate symptoms, as many as 10-20% develop severe or life-threatening disease[1].

Surprisingly for an air-borne viral infection, the number for children diagnosed with COVID-19 is relatively small (2.1% of 42.672 confirmed COVID-19 cases in China were children and young people (<19 years)), and disease-associated mortality among children is low[2,3] (table 1).

Molecular studies targeting the pathophysiology of COVID-19 are sparse, but clinical and molecular parallels with related coronaviruses (SARS-, MERS-CoV) may be extrapolated.

Infection and immune evasion **--** Both SARS-CoV and SARS-Cov2 use ACE2 as entry receptor facilitating infection. Reflecting common organ involvement, ACE2 is expressed on pulmonary and intestinal epithelial cells[1,4]. As ACE2 is only expressed on a small subset of immune cells, other receptors and/or phagocytosis of virus-containing immune complexes may be involved in their infection[1,5,6].

SARS-CoV and SARS-CoV2 share the potential to escape the host's immune response [6]. Usually, RNAs viruses, including coronaviruses, are detected by endosomal TLR-3 and 7 and/or cytoplasmic RNA sensors RIG-I and MDA5. TLR-3 and 7 promote nuclear shuttling of transcription factors NFκB and IRF3, while RIG-1/MDA5 ligation results in activation of IRF3. This triggers increased expression of type 1 interferons (T1IFN) (through IRF3) and other innate pro-inflammatory cytokines (IL-1, IL-6, TNF-α through NFκB)[6,7]. These induce an "anti-viral state" and innate and adaptive immune cell responses which contribute to pathogen containment and clearance. Novel coronaviruses can escape these mechanisms by altering ubiquitination and degradation of the RIG-I/MDA5 adaptor molecule mitochondrial antiviral-signalling protein (MAVS), and inhibition of the nuclear translocation of IRF3 and TNF receptor-associated factors (TRAF)3 and 6 which induce NFκB signalling[8]. Furthermore, SARS-CoV and SARS-CoV-2 can counteract T1IFN through inhibition of STAT transcription factor phosphorylation[7].

COVID-19 associated cytokine storm **--** Several clinical and laboratory features of COVID-19 are associated with poor outcomes. Early studies from China linked cytopenias (leukopenia, lymphopenia, anaemia, thrombocytopenia) and elevated inflammatory parameters (IL-6, CRP, ESR) with unfavourable outcomes, suggesting cytokine storm syndrome in these patients[9]. ICU dependency in particular was associated with increased plasma levels of innate chemokines IP-10, MCP-1, MIP-1A, and the pro-inflammatory cytokine TNF-α[10].

Though seemingly contradictory to aforementioned immune evasion through reduced cytokine expression, enhanced innate immune activation promotes morbidity and mortality in COVID-19. However, possible contributors to uncontrolled inflammation are cell damage and death as a result of viral replication[11]. In SARS-CoV infected mice, innate immune cells are recruited to the site of infection, where they induce strong inflammatory responses that further promote tissue damage and systemic inflammation[12].

Another mechanism contributing to poor outcomes may be antibody-dependent enhancement which is caused by early antibody production. Resulting virus-containing immune complexes promote cellular uptake of virus particles through Fcγ receptors. This may result in persistent viral replication in cells (including antigen-presenting cells), and immune complex mediated inflammation and damage[13-15]. Indeed, blood vessel occlusion

and infarctions have been reported in COVID, and show histopathologic features associated with immune complex vasculitis[12].

Why do children not get sicker? **--** Currently, it is not known why children usually develop mild/moderate disease and only rarely develop cytokine storm syndrome (table 1). Several contributors may alter risk in children:

i) Children are not travelling for business, reducing exposure to people. This may have played a role at the beginning of the pandemic.
ii) While pathogen clearance may be reduced in adults, particularly in individuals at risk (elderly patients, diabetics, etc.)[6,10], children have fewer comorbidities, including obesity.
iii) Different immune response compared to adults, including strong innate and weaker adaptive immune responses. This may contribute to effective virus containment/clearance and/or reduced secondary lymphocyte-mediated inflammation[16].
iv) Local microbiomes, co-infections (and co-clearance) with other viruses, and/or immune priming to coronavirus infections as a result of frequent/constant exposure may help children to overcome SARS-CoV2 more effectively.
v) As ACE2 is essential for epithelial cell infection, but also controls pulmonary inflammation and repair, variable ACE2 expression patterns may affect disease susceptibility and progression[17,18].

Risk for patients receiving immunosuppressive treatment **--** Coronaviruses, including SARS-CoV2 are "masters" of immune evasion, which contributes to uncontrolled virus replication and delayed but significant pro-inflammatory cytokine responses. While most children and young people effectively control infections and less frequently develop severe disease, patients receiving immune modulating treatments may have reduced ability to do so. Reassuringly, in a cohort of 200 liver transplant patients on immune suppressive treatment, only three tested positive for SARS-CoV2 and none developed relevant disease[19].

There are no evidence-based, approved treatments for COVID-19 and/or associated cytokine storm syndromes. Though children receiving immunosuppressive treatment may be at an increased risk for SARS-CoV2 infections, immunosuppression may protect from complications. Antimalarial treatments (chloroquine/hydroxychloroquine) may prevent infection through endocytosis. Classical and/or biologic DMARDs (particularly IL-6 and IL-1 blockers) may control pro-inflammatory cytokine expression and limit tissue/organ damage. Delayed activation of adaptive immune responses may be of benefit, as early antibody production may promote infection of immune cells and/or cause immune complex mediated pathology[15].

Conclusions **–** While data on COVID-19 is limited, children appear to be protected from severe disease. Paediatric Rheumatology Societies, including the Paediatric Rheumatology European Society (https://www.pres.eu/news/newsstory.html?id=29), recognize that discontinuation of immune modulating treatment may result in disease flares. In the absence of symptoms, immune modulating treatment should therefore be continued and

changes should only be made under close monitoring by the responsible clinical service. International collaboration is needed to safely assess individual risk in vulnerable patient groups. Until reliable data is available, close clinical monitoring and social distancing should be prioritized, but the collection of prospective data is required to improve the evidence base.

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Table 1: Disease severity and laboratory findings in children with COVID-19.

Source	Cai *et a.*	Cai *et al.*	Chen *et al.*	Feng *et al.*	Wang *et al.*	Zeng et al.	Zhang *et al.*	Liu *et al.*	Kam *et al.*	Chan *et al.*	Zhang *et al.*	Zhao *et al.*	Sun *et al.* [20]	Li *et al.* [21]	Su *et al.* [22]	Qiu *et al.* [23]	Lin *et al.* [24]	Zheng *et al.* [25]	Dong *et al.* [3]
	Summarised in Henry et al. [2]																		CDC data
No of cases	10	1	1	15	31	1	1	1	1	1	2	1	8	2	9	36	1	25	2143
Age (median; range)	6yr (3mo - 11yr)	7yr	13mo	12yr	7yr (6mo - 17yr)	2wk	3mo	7yr	6mo	10yr	14mo (twins)	13yr	5yr (2mo - 15yr)	4yr (4yr)	3.6yr (11mo-9yr)	8.3 (1-16yr)	7yr	3yr (2-9yr)	7yr (2-13yyr)
Region	China	China	China	China	China	China	China	China	Singapore	China	China	China	China	China	China	China	China	China	China
Males	4 (40%)	1 (100%)	1 (100%)	5 (33%)	15 (48%)	1 (100%)	0	1 (100%)	1 (100%)	1 (100%)	0	1 (100%)	6 (75%)	1 (500%)	3 (33%)	23 (64%)	0	14 (56%)	1213 (56.6%)
Symptoms	10 (100%), mild	1 (100%), mild	1 (100%), mild	3 (20%), mild	27 (87%), mild	1 (100%), mild	1 (100%), mild	1 (100%), mild	0	0	2 (100%), mild	1 (100%), mild	***8 (100%), severe or critical***	2 (100%), moderate	3 (33%), mild to moderate	36 (100%), 17 (47.2%) mild, 19 (52.8%) moderate	1 (100%), mild	25 (100%), 8 (32) mild, 15 (60%) moderate, 2 (8%) severe	2047 (94.9%), 1091 (50.9%) mild, 831 (38.8%) moderate, ***112 (5.2%) severe, 13 (0.6% critical)***
Chest radiographic changes	4 (40%)	1 (100%)	1 (100%)	9 (60%)	14 (45%)	1 (100%)	1 (100%)	1 (100%)	0	1 (100%)	1 (50%)	1 (100%)	8 (100%)	2 (100%)	5 (55.5%)	19 (53%), all in moderate disease	0	17 (68%)	N/A
WBC ↑	3 (30%)	1 (100%)	1 (100%)	0	3 (9.7%)	0	0	0	0	0	2 (100%)	0	2 (25%)	0	0	0	0	0	N/A
WBC ↓	1 (10%)	0	0	7 (15%)	2 (6.5%)	0	0	0	1 (100%)	0	0	0	1 (12.5%)	0	3 (33%)	7 (19.4%)	0	0	N/A
Lymphocytes ↑	1 (10%)↑	N/A	1 (100%)	N/A	4 (12.9%)	N/A	N/A	0	0	0	N/A	0	0	0	0	11 (30.5%)↓	0	0	N/A
Lymphocytes ↓	0	N/A	0	N/A	2 (6.5%)	N/A	N/A	0	1 (100%)	0		0	1 (12.5%)	0	0		0	0	N/A
HB↓	0	N/A	1 (100	N/A	N/A	0	0	N/A	N/A	0	0	0	3 (37.5	N/A	5 (55%	N/A	0	N/A	N/A

			%)										%)		)				
PLT ↑	2 (20%)	0	0	N/A	2 (6.5 %)	1 (100 %)	1 (100 %)	0	0	0	2 (100 %)	0	2 (25%)	N/A	0	N/A	0	N/A	N/A
PLT ↓	1(10 %)	1 (100 %)	0	N/A	0	0	0	0	1 (100 %)	0	0	0	1 (12.5 %)	N/A	1 (11%)		0		
CRP ↑	3 (30%)	1 (100 %)	1 (100 %)	N/A	3 (9.7 %), N/A for 1 (3.2 %)	0	0	0	N/A	0	1 (50%)	0	5 (62.5 %)	1 (50%)	0	1 (2.0 %)	0	N/A, median 14.5 mg/L 0.91-25.04) (Normal: <10 ml/L)	N/A
ESR ↑	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	N/A	N/A	0	0	N/A	N/A	N/A
LFT ↑	2 (20%)	0	N/A	N/A	7 (22%)	N/A	N/A	0	N/A	0	2 (100 %)	0	3 (37.5 %)	0	0	3 (8.3 %	0	0	N/A

Currently available datasets are from Chinese cohorts. Most children experienced mild or moderate disease, while 133 of 2290 children summarised in table 1 were severely or critically ill (***bold italics***) (5.8%), and 2 died (0.09%). Few children who developed severe COVID-19 did not consistently exhibit clinical and/or laboratory signs of cytokine storm syndromes, such as cytopenias, or altered liver function. While data are very limited, this appears to be in contrast to adult cohorts, where significant proportions of severely ill patients show signs of cytokine storm syndrome, which is associated with poor outcomes [1,9]. **Abbreviations:** WBC: white blood counts, HB: haemoglobin, PLT: Platelet counts, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, LFT: liver function tests (AST and/or ALT elevation), N/A: not available.

Highlights

- The novel coronavirus SARS-CoV2 causes COVID-19, a pandemic threatening millions of lifes globally
- Children with COVID-19 rarely develop severe symptoms and mortality is relatively low
- Co-infections (and co-clearance) with other viruses may help children to overcome SARS-CoV2
- Fewer comorbidities and age-specific host factors may protect children
- Limited experience suggests that pre-existing anti-inflammatory treatment may not increase risk significantly