INTRODUCTION
Worldwide, children make up a minority of confirmed cases of coronavirus disease 2019 (COVID-19), usually contributing to between 1% and 5% of total case numbers. Where adults typically present with acute respiratory distress syndrome in the second week of illness, the paediatric clinical presentation seems to be milder and atypical, including gastrointestinal symptoms and fever, with few respiratory symptoms. This disparity in clinical presentation between adults and children remains inexplicable. Hypotheses include differences in receptors in the renin-angiotensin system and altered inflammatory responses to pathogens. Recently, reports from Europe and North America have described clusters of children and adolescents requiring admission to intensive care units with a multisystem inflammatory condition with some features similar to those of Kawasaki disease (KD) and toxic shock syndrome (TSS). This syndrome seems to be related to COVID-19, based on positive serology in a majority of patients, and is known as paediatric multisystem inflammatory syndrome – temporally associated with SARS CoV-2 (PIMS-TS) in Europe and multisystem inflammatory syndrome in children (MIS-C) in the United States. Fortunately, critical illness in paediatric COVID-19 remains rare (~1%), with most cases recovering quickly after treatment; but deaths have been reported. Similarly to data from other countries, the burden of COVID-19 disease in South Africa is lower in young children compared to adults. Children made up 3.3% of COVID-related admissions, despite constituting approximately one-third of the South African population. Of the children aged ≤18 years admitted, 7% were admitted to an intensive care unit, 2% had to be ventilated and 1% died. We present the case of a South African child, infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presenting with reactive urticaria and thrombocytosis, further broadening the clinical spectrum of COVID-19 in children.

CASE DESCRIPTION
A two-year-old South African girl of African descent, previously healthy and HIV-unexposed, was admitted to a private hospital with a first episode of wheezing. A nasopharyngeal swab sent for polymerase chain reaction (PCR) testing was positive for SARS-CoV-2. Haematological testing was within normal limits. A chest radiograph revealed bronchial wall thickening and left upper-lobe infiltrates (see Figure 1). She was treated with intravenous antibiotics and bronchodilator therapy and never needed oxygen therapy. She was discharged after five days and asked to quarantine at home for 14 days.

The day after her discharge from the private hospital, the child developed a new onset fever, anorexia and an itchy migrating
CASE REPORT

rash. Given her COVID-positive status, the mother struggled to re-access the private healthcare institution and she was requested to contact our hospital, a tertiary academic centre and a current referral centre for COVID-19 in the region.

On arrival at our hospital, the child appeared generally well and her vital signs were stable, except for a mild tachycardia (152 heartbeats/min). She was pyrexial, with documented fever up to 39.6°C. There was a clear urticarial rash on the trunk and the legs (see Figure 2). The rash was itchy but not painful, and migratory in nature. No respiratory signs were present, neither was there lymphadenopathy nor hepatosplenomegaly, and her mucous membranes and conjunctivae were normal in appearance.

Haematological testing revealed a normal haemoglobin, normal white cell count with mild lymphopenia (3.17 \( \times \) 10^9/L), elevated C-reactive protein (CRP) (5.4 mg/dL) and markedly elevated platelets (936 \( \times \) 10^9/L). Liver-function tests and albumin were within normal limits. The patient was prescribed antihistamines and was discharged home on the same day.

Given reports on the association between COVID-19 and KD, it was decided to review the child 48 hours later during a short 24-hour admission. During this assessment, the skin rash had disappeared, she was afebrile and clinical examination was completely normal. Repeat haematological testing demonstrated a drop in CRP to 2.1 mg/dL, but persistent thrombocytosis (901 \( \times \) 10^9/L) and new onset anaemia (haemoglobin 9.9 g/dL). Her cardiac sonar was normal. A repeat test for SARS-CoV-2 on nasopharyngeal aspirate was negative. Serology for Epstein–Barr-virus (EBV) and cytomegalovirus (CMV) were negative as well as a multiplex PCR-respiratory virus panel done by obtaining a nasopharyngeal aspirate. No cytokine studies were done. A follow-up date was arranged with the mother for two weeks later.

On follow-up two weeks later, the child was well, her clinical examination was still unremarkable and her blood results had normalised (haemoglobin 11.6 g/dL and platelet count 558 \( \times \) 10^9/µL).

DISCUSSION

We present the case of a two-year-old girl who presents in the second week of COVID-19 illness with reactive urticaria and severe reactive thrombocytosis. The patient did not fulfil the diagnostic criteria for KD, since there was no associated mucous membrane or lymph-node involvement (see Table I). The World Health Organization (WHO) case definition for multi-inflammatory syndrome in children was equally not met since there was no multi-system involvement (see Table II). The inflammatory response to SARS-CoV-2 is probably a continuum, with our patient having a milder presentation.

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If ≥4 of the above criteria are present, a diagnosis of KD can be made on day four of illness.

<table>
<thead>
<tr>
<th>TABLE I: DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE (KD)</th>
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<tr>
<td>The diagnosis of KD requires the presence of fever lasting at least five days* without any other explanation combined with at least four of the following criteria:</td>
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<tr>
<td>1. Bilateral bulbar conjunctival injection</td>
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<td>2. Oral mucous membrane changes, including injected or fissured lips, injected pharynx or strawberry tongue</td>
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<tr>
<td>3. Peripheral extremity changes, including erythema of palms or soles, oedema of hands or feet (acute phase) and periungual desquamation (convalescent phase)</td>
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<tr>
<td>4. Polymorphous rash</td>
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<tr>
<td>5. Cervical lymphadenopathy (at least one lymph node &gt;1.5 cm in diameter)</td>
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Urticaria wheals are raised, erythematous and usually intensely pruritic. Individual lesions normally last less than 24 hours. They are migratory in nature and do not leave skin changes after resolution. This distinguishes urticaria (alone) from urticarial vasculitis. The most common cause of acute urticaria in children is a viral infection (approximately 60% of children). Dermal mast cells can be activated through the interaction of immunoglobulin (Ig)G and IgE receptor on mast cells. Degranulation of the mast cell results in the release of histamine, serotonin, proteases and tumour necrosis factor alpha. Activated mast cells also release cytokines such as interleukin (IL)-1, with an escalation in human inflammation against the culprit antigen. These pathways lead to the formation of urticaria (wheals).10

Urticaria in SARS-CoV-2 infection has been reported in adults, both in Europe and in China,11 but to our knowledge this is the first paediatric case report. Although the exact pathogenesis of the urticarial reaction is unknown, it is not surprising that SARS-CoV-2 can cause acute urticaria and COVID-19 should from now be considered as a differential in these patients.
REFERENCES


TABLE II: WHO CASE DEFINITION FOR MULTI-INFLAMMATORY SYNDROME IN CHILDREN7

All 6 criteria must be met:

1. Age 0–19 years

2. Fever for ≥3 days

3. Clinical signs of multisystem involvement (at least two of the following):
   - rash; bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral/hands/feet)
   - hypotension or shock
   - features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities
   - evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
   - acute gastrointestinal symptoms (diarrhoea, vomiting or abdominal pain)

4. Elevated markers of inflammation (eg ESR, CRP or PCT).

5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal TSS.

6. Evidence of SARS-CoV-2 infection, any of the following:
   - positive SARS-CoV-2 RT-PCR
   - positive serology
   - positive antigen test
   - contact with an individual with COVID-19


It should be remembered that children with acute infections often have penicillin prescribed to them by healthcare practitioners. In practice, it is impossible to dissociate between these two distinct causal factors. Urticarial skin reactions can occur if penicillin (eg amoxicillin and ampicillin) is prescribed to children in the presence of a penicillin allergy. It is possible that the virus–drug association acting against the SARS-CoV-2 are merely assumptions and clearly more data and research are needed to better describe the inflammatory response in children infected with this novel virus, possibly trying to explain the skin and haematological manifestations of this disease.

LEARNING POINTS

- Children, as with adults, can experience clinical worsening in the second week of illness caused by SARS-CoV-2, in keeping with the proposed pro-inflammatory pathophysiology.
- Symptoms after discharge for COVID-19 warrant further investigation; in addition, systems need to be in place to receive these children in an appropriate isolation room and to transport them safely to and from home.
- Urticaria and thrombocytosis are inflammatory responses to SARS-CoV-2 and are further broadening the clinical and biochemical characteristics of COVID-19 in children.
- In paediatrics, testing for SARS-CoV-2 should be considered widely in a range of clinical scenarios, including skin rashes.

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DECLARATION OF CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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