

# Fifteen-minute consultation: Does this child have COVID-19 (and does it matter)?

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## ABSTRACT

SARS-CoV-2 was identified as a new virus in January 2020 following reports of pneumonia of unknown aetiology from China. Since then, the virus has spread rapidly throughout the world. While evidence accumulates on the collateral damage to children as a result of system changes, SARS-CoV-2 appears to rarely cause serious illness in younger age groups. However, the emergence of an inflammatory condition associated with COVID-19 has complicated initial assessment. We present a summary of how the virus has affected children with a synopsis of testing and treatment to help acute paediatricians make informed decisions.

## INTRODUCTION

When the WHO declared a global pandemic on 12 March 2020, acute and emergency paediatricians prepared for an influx of cases similar to adult services which had the potential to be overwhelmed by seriously ill patients. The picture that evolved was different with a dramatic reduction in paediatric emergency department (ED) attendances in the UK (similar to that seen in Italy<sup>1</sup>) with low admission rates and very few deaths, even in those with comorbidities.<sup>2,3</sup> While adults presented with severe respiratory illness,<sup>4</sup> children were mainly identified following universal screening of admitted patients and presented innocuously with a febrile illness, cough and tonsillitis or lethargy with poor feeding in neonates. These children needed either symptomatic treatment or a short period of admission, usually less than 48 hours and had an uncomplicated clinical course. A systematic review of a case series of children affected with SARS-CoV-2 reported fever occurring in 59% of the patients, cough in 46% and gastrointestinal symptoms in 12%.<sup>5</sup>

At the beginning of May 2020, case reports emerged of an inflammatory condition temporally related to COVID-19 which caused concern as symptoms were heterogeneous on presentation.

## COVID-19 IN CONTEXT

*A three year old presents to ED with a 2-day history of fever and sore throat. She appears well and has no concerning clinical features, apart from being mildly tachycardic for her age. She has a temperature of 38.9°C. The parents wanted her to be tested for COVID-19, but testing of non-admitted children is not recommended by the hospital. The clinician is aware that examining the throat of children is not recommended<sup>6</sup> but on the basis of her history diagnoses tonsillitis. Her clinical condition improved after anti-pyretics, antibiotics are prescribed and she is sent home with safety netting.*

*She reattends 2 days later with a continued history of fever and now reported reduced eating and drinking. Parents repeat their request for the COVID-19 test. She is observed in the department and is able to tolerate fluids enough to pass urine (which is dipstick negative for glucose, nitrates and leucocytes and has 1+ of ketones). After a long consultation with a senior clinician, the parents take her home with a clear plan regarding fluid intake.*

*She reattends a further 48 hours later with report she has not passed urine in the last 12 hours, is complaining of abdominal pain and is refusing anything to drink. She is admitted and given intravenous fluids and antibiotics, and a reverse transcriptase-PCR nasopharyngeal aspirate samples (NPA-RT PCR) was done as a part of the universal screening for admitted children. Her C reactive protein is 42, all other blood tests were unremarkable. The child improved after 24 hours and was*



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discharged home. The results of the NPA RT-PCR are reported a day later, the test was positive, and the child had made an uneventful recovery by this time.

This case raises a number of questions including, but not limited to, whether testing for SARS-CoV-2 changes management and should a diagnosis of paediatric inflammatory multisystem syndrome temporally related to COVID-19 (PIMS-TS) be considered in every febrile child who presents to an ED?

This is the clinical decision-making dilemma that will present itself often during this winter. Through this paper we explore COVID-19's varied and heterogeneous manifestations in children ranging from the asymptomatic to a potential severe end of the spectrum, the paediatric inflammatory multisystem syndrome. The aim to aid general and acute paediatricians in initial investigation and management of children with potential SARS-CoV-2 infection.

### WHAT IS SARS- COV-2?

SARS-CoV-2 has been classified as a novel beta-coronavirus within the subgenus Sarbecovirus. Six coronaviruses are known to cause human disease, four cause a mild respiratory disease like a common cold. Two of the coronaviruses are zoonotic, SARS coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus. There have been previous outbreaks, SARS in 2002 and MERS in 2012, resulting in severe illness and deaths. The 2020 pandemic is caused by SARS-CoV-2.

### HOW DOES IT AFFECT CHILDREN?

A large case series from China initially reported that clinical manifestations in children were generally less severe than those of adults; however, young children, particularly infants were vulnerable to infection.<sup>7</sup> Studies from Europe<sup>8</sup> then reported that clinical features in symptomatic children were different from adults and children tended to have a milder illness. The most common presenting features were cough and fever followed by upper respiratory tract symptoms such as rhinorrhoea and sore throat. Most children can be managed at home with isolation and supportive care, with good safety netting advice. Recently, the International Severe Acute Respiratory and emerging Infection Consortium WHO Clinical Characterisation Protocol UK cohort has been published for children.<sup>9</sup> This observational prospective cohort study of 651 admitted patients under 19 years found the most common presenting symptoms were fever (70%; 431/617), cough (39%; 233/599), nausea/vomiting (32%; 179/564) and shortness of breath (30%; 173/570). As the age of the patients increased, fever and rhinorrhoea became less common but nausea and vomiting, abdominal pain, headache and sore throat increased with age. From the start of the pandemic there have been concerns that children with existing comorbidities or underlying conditions would be

disproportionately affected. In this cohort, the most common comorbidities were neurological (11%; 65/614), haematological, oncological or immunological (8%; 48/615) and asthma (7%; 45/615). Only 6 (1%) of 627 patients died in hospital, all of whom the authors stated as having 'profound comorbidity'.

Because of the heterogeneity and poor specificity of symptoms with SAR-CoV-2 positivity predicting a positive swab is very challenging. A preprint paper of 1530 children presenting to EDs found the WHO pneumonia algorithm<sup>10</sup> and the Paediatric Observation Priority Score<sup>11 12</sup> had higher point estimates for c-statistics (area under receiver operating characteristic curve) than other tools for predicting adverse outcome in children with suspected SARS-CoV-2.<sup>13</sup> However, there were only 19 cases of COVID-19 and 26 adverse outcomes in this cohort so the authors concluded there was 'little to be gained from treating children with suspected COVID-19 any differently from those presenting with other febrile illnesses (other than for infection control purposes)'. Reassuringly for children who are asymptomatic, a study from the USA of children testing for SARS-CoV-2 before surgery, clinic visits or hospital admissions found only 250 positives from 33 041 children (age range, 0–18 years) without symptoms tested across 28 hospitals.<sup>14</sup>

### WHAT IS THE ROLE OF CHILDREN IN CATCHING AND TRANSMITTING THE DISEASE?

The reason why children are less affected includes: limited risk of exposure, fewer comorbidities and differing immune response with stronger innate and weaker adaptive response in comparison to adults (immature immune competence due to lower 'priming' with other coronaviruses may explain the very low frequency of abnormal immune response against SARS-CoV-2 in childhood.<sup>15</sup> Human ACE 2 is proposed to be the key factor with ACE2 thought to be the primary entry receptor for coronaviruses, and its differential expression between children and adults is the cause for the different impact.

The role of children in passing the disease to others is debated with examples of outbreaks<sup>16</sup> and low to no transmissions in school.<sup>17</sup> Studies from Guangzhou, China, report that children were unlikely to be the index case with a lower likelihood of acquiring infection, and lower rates of children bringing infections into households.<sup>18</sup>

### HOW AND WHO TO TEST?

The definitive test for diagnosis of COVID-19 is detection of SARS-CoV-2 RNA by real-time reverse transcription-PCR (RT-PCR). NPA RT-PCR is sensitive (reported as low as 71% and as high as 95%–97%).<sup>19</sup> The diagnostic testing window is perhaps one of the most important factors impacting test sensitivity. False negatives may be caused by low viral loads in the early and late stages of infection.<sup>20</sup> The sensitivity of NPA

RT-PCR is also dependent on the person doing the swab, which may be technically more challenging in children. Every test result is only as good as the sample from the patient. NPA samples are difficult to obtain and often momentarily painful for the patient.<sup>20</sup> Most patients, even with superb instruction, will not acquire adequate samples and thus the rate of false negatives for such testing will potentially be high. One study from China reports that by combining the modified RNA extraction method and real-time quantitative PCR technology, 80% of samples were positive for SARS-CoV in the real-time RT-PCR assay.<sup>21</sup> Their results also indicated that the viral load increases as the disease progresses.

After consideration of the above factors, and noting that there is no change in the clinical outcome based on test results, it was thought that there was no added benefit in testing children with mild symptoms. Many countries, including the UK, have focused on testing the most unwell children.

Other tests include serology—IgG and IgM antibody to SARS-CoV-2 which does not have a role in acute illness but will show past exposure to COVID-19. Serology could be of help in confirming suspected cases, especially in patients with either mild to moderate illness or tested in the late phase of COVID-19, not detected with molecular assays.<sup>20</sup>

Live virus was detected in faeces, implying that SARS-CoV-2 may be transmitted by the faecal route.<sup>22</sup> A study from China showed that faecal PCR testing was as accurate as respiratory specimen PCR detection, and faecal excretion persisted after sputum excretion in 23% patients for 1 to 11 days.<sup>23</sup>

A number of testing strategies have been suggested (box 1). Currently UK guidance would recommend any child and family who is tested for COVID-19 should be isolated until results are available.

### A NEW DISEASE?

In mid-April 2020, reports emerged of children presenting to ED with a febrile illness and shock or partial Kawasaki features. The first case series to describe these children was published in May by Ripenhagen.<sup>24</sup> They reported a cluster of children with hyperinflammatory shock, showing features

similar to atypical Kawasaki disease (KD), KD shock syndrome or toxic shock syndrome. A clinical picture ranging from the benign to the life-threatening made this a challenging clinical condition for Emergency and Paediatric staff. The Royal College of Paediatrics and Child Health (RCPCH) defined the new condition as PIMS-TS on the first of May 2020. It is hypothesised that PIMS-TS is a dysregulation of the immune response to a pathogen which may occur as a late reaction to SARS-CoV-2 infection.<sup>25</sup>

An example of the range of clinical features is highlighted in a case series (table 1) of children presenting to one ED.

PIMS-TS is an artful masquerader. Prompt diagnosis is not easy due to the heterogeneity of the disease presentation. Children can present with fluid refractory shock (patients 3 and 4), cardiac dysfunction (patient 2) or partial Kawasaki features of rash and conjunctivitis (patients 2 and 4). It can mimic an acute abdomen associated with appendicitis (patient 6). Children can also appear to be well while having abnormal observations. Patient 3 was noted to look alert and well and had a tonsillar focus. She was eating and drinking but hypotensive at presentation. She went on to develop fluid refractory shock within 6 hours and was transferred to paediatric intensive care unit (PICU) but ultimately had a good outcome.

The first four children with PIMS-TS illustrated in this series presented to ED in April 2020 before the RCPCH defined the condition. Three children were admitted based on the clinical acumen of the receiving paediatric clinician. Good clinical examination, review of observations, treating unwell children according to National Institute for Health and Care Excellence and Advanced Paediatric Life Support guidelines, early escalation and discussion with tertiary centres resulted in identification of these children. For the emergency paediatrician, the mainstay of management remains considering the diagnosis and instigating supportive measures for children with PIMS-TS with early involvement of specialist teams.

A fourth child, an Afro-Caribbean girl aged 10 years (patient A), presented to ED twice in a period of 10 days with fever and sore throat. She had exudative tonsillitis, was started on oral antibiotics and discharged home. Her discharge observations were within normal limits and she was noted to appear well. She presented for the third time, 48 hours after the second attendance, with fluid-resistant shock needing inotropes. At this time, she was additionally noted to have conjunctival injection and a polymorphic rash. She was diagnosed to have PIMS-TS and was transferred to PICU. Her RT-PCR and serology were positive for COVID-19 and she had a good clinical outcome.

This patient highlights a significant clinical conundrum for those managing children acutely during the COVID-19 pandemic. Are there any features that would have helped make a diagnosis at an early stage?

#### Box 1 Who to test?

- ▶ Universal testing of all admitted children.
- ▶ Universal testing of all children presurgery.
- ▶ Children with fever and respiratory distress presenting to emergency department.
- ▶ Children with comorbidities—oncological conditions, respiratory and cardiac conditions.
- ▶ Persistent fever for more than 5 days with no identifiable cause, there is no definitive requirement for this and the decision should be made by a senior clinician.

Table 1 Case series of children with PIMS-TS

No	Age	Sex	Ethnicity	Presenting features	COVID-19 tests	Bloods (CRP;mg/L & Trop; ng/L)	Treatment	Outcome
Patient 1	12	M	Caucasian	Fever 4/7, vomiting, abdominal pain, diarrhoea, rash	RT-PCR positive	CRP 74 Trop 576	Intravenous antibiotics IVIG	Discharged home
Patient 2	9	M	Afro-Caribbean	Fever 3/7, pain abdomen, rash, conjunctival injection	Serology positive	CRP 127, Trop 171	Intravenous antibiotics IVIG	Referred to ID
Patient 3	15	F	Afro-Caribbean	Fever 5/7, sore throat, hypotensive	Serology positive	CRP 183	Intravenous antibiotics, intravenous fluids, epinephrine infusion, IVIG	Referred to PICU
Patient 4	10	F	Afro-Caribbean	Fever 10/7, sore throat, abdominal pain, loose stools, rash, in shock, conjunctival injection, 2 ED visits in 10 days	Serology positive RT-PCR positive	Leucocytes 22, CRP 314	Intravenous antibiotics, fluids, epinephrine infusion, IVIG, methylprednisolone	Referred to PICU
Patient 5	12	M	Afro-Caribbean	Fever 4/7, headache vomiting, neck pain, conjunctival injection	Serology positive	CRP 287	Intravenous antibiotics, IVIG, intravenous methylprednisolone	Discharged home
Patient 6	11	M	Afro-Caribbean	Fever 3/7, severe abdominal pain Suspected appendicitis MRI abdomen mesenteric adenitis	Serology positive	CRP 208	Intravenous antibiotics IVIG, Intravenous methylprednisolone	Discharged home

CRP, C reactive protein; ED, emergency department; F, female; ID, infectious diseases; IVIG, intravenous immunoglobulin; M, male; PICU, paediatric intensive care unit; PIMS-TS, paediatric inflammatory multisystem syndrome temporally related to COVID-19; RT-PCR, reverse transcription PCR; Trop, troponin.

Patient 4 was an Afro-Caribbean with no comorbidities. The presence of a focus, the non-compliance with antibiotics and the child looking relatively well appear to be the confounding factors in the late diagnosis. She also developed features of KD (bilateral conjunctival injection and rash) at a later stage. It is unlikely, especially on her first presentation, whether anything would, or should have, prompted consideration of PIMS-TS. Bloods would not have been indicated based on current local or national guidance.<sup>26</sup> It is also important that KD and PIMS-TS are not viewed as interchangeable diseases as this may result in under-treatment of either conditions.

The proportion of febrile children without serious pathology presenting to ED remains considerably higher than those with PIMS-TS. Even in centres with a high proportion of children with PIMS-TS, there will remain a pragmatic balance between early identification of PIMS-TS balanced against a need to avoid overinvestigating children. Striking this balance so that every febrile child is not overinvestigated and treated as PIMS-TS will be difficult, especially this winter when a second wave of the infection may well combine with seasonal respiratory syncytial virus and influenza.

#### OTHER INVESTIGATIONS AND MANAGEMENT OF PIMS-TS

Investigations such as ferritin, d-dimer and troponins should be done after discussion with tertiary centres.

These are not investigations that ED clinicians or general paediatricians may be familiar with in the febrile child leading to difficulties in interpretation and subsequent repeat investigations which may be not be required.

This is an emerging condition and there is uncertainty regarding best treatment. Patients are being treated with a range of immunomodulatory medications. In a case series, 71% were treated with intravenous immunoglobulin and 64% with corticosteroids.<sup>27</sup> Three patients received anakinra and eight infliximab. 22% of the patients recovered with supportive care alone. The study did not provide evidence on effectiveness of treatment of PIMS-TS.

Observational studies, clinical trials and controlled research studies will be key to creating an evidence base for the best treatment. A timeline of individual patients with plotting of intervention and subsequent change in clinical condition, observations and inflammatory markers may give us further corroborative evidence.

#### DECISION-MAKING IN COVID-19

National guidance suggests cohorting patients on the basis of their symptomology; however, this approach while useful to avoid unnecessary spread of the disease does not help in the identification of cases (a number of children are asymptomatic) nor in management (as the majority of children will be very well). It is difficult



to work out the pretest probability of SARS-CoV-2 in children presenting to EDs and assessment units as observational studies have not taken swabs on both admitted and discharged patients. In one observational study there were only 22 positive patients in 10 777 presentations [29]; however, only admitted patients were swabbed, so this is likely to be an underestimate of point prevalence. Unlike previous influenza pandemics where case identification may aid management, focusing large amounts of resource on finding patients with COVID-19 is probably not worthwhile. In an opportunistic study in Turin, Italy, two groups of children were compared.<sup>28</sup> One of all those admitted to the ED with COVID-19-related symptoms and another composed of patients without any COVID-19-associated symptoms (who were swabbed as a screening test before hospital admission). Cough was the only symptom associated with SARS-CoV-2 infection with fever only significantly related to COVID-19 if paired with another symptom. The key challenge then to paediatricians is identifying those with COVID-19 complications; however, it could be argued this itself should not significantly change practice as taking blood tests specifically looking for raised inflammatory markers will still have a high false positive rate. Ultimately, the same poorly defined concept of gestalt will need to be applied to children with potential COVID-19 as it does for any child with a fever who may have sepsis or children with a headache who may have a brain tumour.

## CONCLUSION

SARS-CoV-2 infection appears to affect children less often, and with less severity including frequent asymptomatic or subclinical infection. The majority of children with COVID-19 have a mild illness which is indistinguishable from other common endemic viral illnesses. PIMS-TS is thought to be rare and the risk of children getting this is low; however, there may be cases of PIMS-TS which go under the radar mimicking other childhood illness and getting better with supportive management. The proportion of febrile children without serious pathology presenting to ED remains considerably higher than those with PIMS-TS so there needs to be a careful balance between early identification of PIMS-TS and overinvestigating children. As in all of paediatrics safety netting for patients and families is vital when discharging these children home.

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