Renal dysfunction in hospitalised children with COVID-19

Children and adolescents with COVID-19 fare considerably better than adults, with mortality rates in paediatric patients (age <18 years) of less than 1% reported in early studies.[1,2] The most common clinical features in children described in the literature are fever, dry cough, and pneumonia.[2] However, multisystem involvement is increasingly being recognised, including the development of hyperinflammatory shock.

Acute kidney injury has been reported in adult patients with COVID-19, with a high prevalence across inpatient admissions (≤7%) and admissions to adult intensive care units (ICUs; ≤23%), as first reported in Wuhan, China.[3] In adult patients with COVID-19, acute kidney injury is related to an increased mortality risk, even after adjustment for age, sex, and comorbidities.[4] In addition, a large proportion of adults have proteinuria (44%) and haematuria (27%) at presentation, despite an elevated serum creatinine prevalence of only 16%.[4]

Qui and colleagues[2] described the characteristics of 36 hospitalised paediatric patients (age 0–16 years) with COVID-19 in China and none were reported to have renal dysfunction, as defined by serum creatinine greater than 110 µmol/L or serum urea greater than 7 mmol/L.

Here, we present the findings of 52 paediatric patients (age 0–16 years) admitted to Great Ormond Street Hospital for Children NHS Foundation Trust (London, UK) since March 25, 2020, with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, diagnosed by either a positive PCR result or seropositivity (appendix p 1). We looked specifically at the prevalence of acute kidney injury within this cohort. Diagnosing acute kidney injury in children is challenging as serum creatinine varies with age and is dependent on muscle mass. Furthermore, the Kidney Disease Improving Global Outcomes (KDIGO) 2012 diagnostic system for acute kidney injury uses baseline serum creatinine to define staging. As most of our cohort were previously healthy and presented acutely, a baseline creatinine measurement was often unavailable. We therefore referenced serum creatinine values for our cohort against age-specific upper limit of reference interval (ULRI) values according to published guidance from the British Association of Paediatric Nephrology (BAPN).[5] Acute kidney injury was then defined as a serum creatinine 1·5 times greater than the ULRI.

Of 52 inpatients, 24 (46%) had a serum creatinine greater than the ULRI, and 15 (29%) met the BAPN diagnostic criteria for acute kidney injury. Urine output was not used to define acute kidney injury as fluid balance was often inaccurately recorded at the time of transfer to our hospital. Most cases of acute kidney injury occurred in those admitted to the paediatric ICU (14 [93%] patients), and in those with paediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS; 11 [73%] patients). Unsurprisingly, patients with acute kidney injury were more likely to have diarrhoea and vomiting at presentation (appendix p 1), thereby suggesting prerenal involvement. Tullie and colleagues[6] reported on eight children with severe gastrointestinal manifestations of COVID-19 referred to our hospital. Two patients in their cohort were included in our cohort, who had acute kidney injury with PIMS-TS. These same two patients were included in a study of PIMS-TS by Whittaker and colleagues.[7] Among our 52 paediatric patients, a minority (22 [42%]) were screened for proteinuria by either urinalysis or urine albumin to creatinine ratio. Haematuria was more likely to be detected as urine was often sent for microscopy as part of a septic work-up (for 40 [77%] patients; appendix p 1). Of the acute kidney injury cohort, five (33%) had abnormal renal ultrasound findings that showed enlarged kidneys greater than the 95th percentile for age in bipolar length. We found no evidence of reduced cortico-medullary differentiation or increased echogenicity in any of the ultrasound imaging. Even when accounting for different acute kidney injury diagnostic criteria, we are seeing higher rates of acute kidney injury in the hospitalised paediatric population in the UK than in China, where rates of hyperinflammatory syndrome also appear to be lower. None of our patients with acute kidney injury required kidney biopsy or continuous renal replacement therapy, and only one case did not show a decrease in serum creatinine to lower than the ULRI value during admission. This patient has previously had recurrent episodes of acute kidney injury associated with an underlying metabolic disorder. Median serum creatinine and estimated glomerular filtration rate values for the acute kidney injury cohort during admission are shown in the appendix (p 2).

Specific mechanisms for kidney injury secondary to COVID-19 have been proposed. The virus spike (S) protein binds to angiotensin-converting enzyme 2 (ACE2), attached to the outer surface of cells in the lungs, vascular endothelium, kidneys, heart, and intestines. In doing so, it activates angiotensin II. Transmembrane protease serine 2 (TMPRSS2) cleaves and primes the S protein, allowing the release of viral fusion peptides, thus facilitating membrane fusion. Co-expression of ACE2 and TMPRSS2 is therefore believed to have an important role in allowing SARS-CoV-2 to enter host cells.[8] Transcriptome analysis has shown high co-expression of ACE2 and TMPRSS2 in podocytes

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and straight tubular cells. By viral invasion, SARS-CoV-2 might have a direct cytopathic effect on these kidney cell types.[8] Quantification of SARS-CoV-2 viral load in autopsy tissue of patients who have died from COVID-19 shows tropism for renal tissue, particularly in those with more than two organ systems involved, and this is unrelated to underling chronic kidney disease.[8] Viral load is detectable in all renal compartments with an apparent affinity for the glomeruli.[8]

Our study is the first to show that, at least in the UK, approximately half of hospitalised paediatric cases of COVID-19 show evidence of renal dysfunction, and more than a quarter meet acute kidney injury diagnostic criteria. Of those with acute kidney injury, six (40%) were in the most severe category 3 (ie, serum creatinine 3 times greater than the ULRI). During the COVID-19 pandemic, our hospital has acted as a large regional referral centre, managing most hospitalised paediatric patients with suspected or confirmed SARS-CoV-2 infection in north London. As such, we have admitted patients with a wide spectrum of disease severity, not all of whom have required tertiary level care. However, we appreciate that many of our patients were admitted directly to the paediatric ICU, where rates of acute kidney injury are higher than for non-ICU admissions and are often associated with multiorgan dysfunction. An interplay of hypovolaemic and hyperinflammatory shock appears to have contributed to the large number of acute kidney injury cases that we observed. However, the manifestations of this interaction are not necessarily unique to COVID-19 compared with other infectious aetiologies. In general, renal function improved following fluid resuscitation and the commencement of inotropic support. Additional therapies, such as corticosteroids, intravenous immunoglobulin, and anakinra, were used in cases of PIMS-TS. In our acute kidney injury cohort, median serum creatinine value at presentation was 133 µmol/L and this more than halved, to 63 µmol/L, by day 4 of admission (appendix p 2). Only four (27%) patients with acute kidney injury had underlying comorbidities and none were immunosuppressed (appendix p 1). Unfortunately, only a small number of patients were screened for the presence of both proteinuria and haematuria. Evidence suggests that these markers of nephritis might be useful in predicting the risk of capillary leak syndrome and subsequent respiratory decompensation, but this association requires further exploration in children.[9]

Our data highlight the importance of renal function surveillance in all hospitalised paediatric cases of COVID-19, while simultaneously avoiding factors that exacerbate kidney injury, such as hypovolaemia and the use of nephrotoxic drugs. Standard care should involve screening for nephritis and follow-up for long-term sequelae of acute kidney injury, such as hypertension and proteinuria. A collaborative multicentre approach should be sought to quantify rates of renal dysfunction in paediatric cases of COVID-19. Further research should seek to compare SARS-CoV-2-positive paediatric patients against controls with other infectious causes of hypovolaemic or hyperinflammatory shock to evaluate whether COVID-19 predisposes children and adolescents to a disproportionately higher risk of acute kidney injury.

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1 Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020; **20:** 669–77.
2 Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis* 2020; **20:** 689–96.
3 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395:** 497–506.
4 Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; **97:** 829–38.
5 Think Kidneys. Guidance for clinicians managing children at risk of, or with acute kidney injury. December, 2019. https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2019/12/AKI-Guidance-paediatric-patients-Dec2019.pdf (accessed May 21, 2020).
6 Tullie L, Ford K, Bisharat M, et al. Gastrointestinal features in children with COVID-19: an observation of varied presentation in eight children. *Lancet Child Adolesc Health* 2020; published online May 19. https://doi.org/10.1016/S2352-4642(20)30165-6.
7 Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020; published online June 8. DOI:10.1001/jama.2020.10369.
8 Puelles VG, Lütgehetmann M, Lindenmeyer MT. Multiorgan and renal tropism of SARS-CoV-2. *N Eng J Med* 2020; published online May 13. DOI:10.1056/NEJMc2011400.
9 Gross O, Moerer O, Weber M, Huber TB, Scheithauer S. COVID-19-associated nephritis: early warning for disease severity and complications? *Lancet* 2020; **395:** e87–88.