Yu *et al.* reported that the PHD inhibitor L-mimosine exerted dual action on CKD progression in a rat model of subtotal nephrectomy. Midterm administration of L-mimosine inhibited renal fibrosis, and macrophage infiltration and CKD progression; however, the long-term administration of L-mimosine worsened all these parameters.[7] Therefore, the protective effect of HIF activation against CKD progression might depend on the timing of HIF-PHI administration. In contrast, a recent study reported that in patients with CKD at stage 3 to 5 receiving either roxadustat or placebo, there was no significant between-group difference in progression of CKD, as measured by the rate of change in estimated glomerular filtration rate over time.[8]

FGF23 is mainly produced in osteocytes to regulate phosphate homeostasis. Plasma levels of FGF23 are elevated in patients with CKD, which is an independent risk factor for end-stage renal disease and cardiovascular mortality. HIF activation, as well as EPO and iron deficiency, can increase FGF23 mRNA transcription with increased posttranscriptional cleavage.[9] Vadadustat increased plasma total and intact FGF23 levels in non-CKD mice. In contrast, in CKD mice, vadadustat diminished the elevated plasma levels of total and intact FGF23, which is inconsistent with previous findings. According to the authors, vadadustat reduced plasma FGF23 levels in the CKD model owing to the amelioration of kidney function and impaired iron utilization. However, the mechanism by which HIF-PHIs affect FGF23 regulation in CKD still needs to be clarified.

Overall, the study by Hanudel *et al.* provides new information on the effects of HIF-PHIs in improving the anemia of CKD, which could be useful in current clinical practice. Furthermore, despite its experimental nature, the study provides future directions for research on the action of HIF-PHIs in patients with CKD (Figure 1).

DISCLOSURE

The author declared no competing interests.

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COVID-19 and the multisystem inflammatory syndrome in children: how vulnerable are the kidneys?

Vimal Chadha[1,2,3] and Bradley A. Warady[1,3]

When affected by coronavirus disease 2019 (COVID-19), most children have milder disease than what is experienced by adults. However, a subset of these children develops a multisystem inflammatory syndrome that can lead to shock and multiorgan failure. In the current issue, Basalely *et al.* characterize acute kidney injury in pediatric patients with acute COVID-19 and multisystem inflammatory syndrome. Despite the associated morbidity, this cohort provides evidence of kidney recovery in most affected children.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as the cause of coronavirus disease 2019 (COVID-19) in Hubei province, China, in December 2019 and was declared a pandemic in March 2020. Although the adult case fatality rate of 3.4% for SARS-CoV-2 is lower than those reported for SARS-CoV-1 in 2003 (9.6%) and Middle East respiratory syndrome coronavirus (35%), the former is much more contagious and as a result has become a pandemic of historic proportions. COVID-19 and its 2 predecessors share many important features in their clinical presentations and in their propensity for

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Table 1 | Centers for Disease Control and Prevention case definition for MIS-C

- Aged <21 yr
- Fever ≥38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h
- Laboratory evidence of inflammation, including but not limited to ≥1 of the following:
  - An elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, interleukin 6, elevated neutrophils, reduced lymphocytes, and hypoalbuminemia
- Clinically severe illness requiring hospitalization with multisystem (≥2) organ involvement:
  - Cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic
- No alternative plausible diagnoses
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antibody, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before the onset of symptoms

COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcription–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

progression to severe disease involving multiple organs with high rates of morbidity. Although predominantly a respiratory infection, COVID-19 often progresses to a multisystem disorder, with kidney involvement common in adult patients who experience moderate to severe disease.

Early reports from China described high rates of hematuria and proteinuria, but relatively low rates of acute kidney injury (AKI), associated with COVID-19. Highly variable rates of AKI in adults have since been reported from Europe and the United States, with a lack of uniformity in the cohort being described (e.g., hospitalized vs. intensive care) believed to be an important factor resulting in the variability of reported rates, and a factor further impacted by the evolution of hospitalization patterns that has occurred over the course of the pandemic. For example, although AKI occurred in 56.9% of 3345 hospitalized adults with COVID-19 in the Montefiore Health System (Bronx, NY), a much higher rate (87.2%) was seen in the subset of patients who required intensive care unit (ICU) admission.[1] This rate of ICU-related AKI is greater than the rate of 57.3% reported by the Acute Kidney Injury–Epidemiologic Prospective Investigation study (international cross-sectional study performed in 97 ICUs) that found similar risk-adjusted rates of AKI and mortality worldwide.[2] Studies comparing the risk of AKI in COVID-19 patients with retrospective cohorts of patients hospitalized with severe influenza have found that although the overall risk of AKI was similar in the 2 groups of patients, stage 3 AKI, as defined by Kidney Disease: Improving Global Outcomes (KDIGO), was almost 3 times more common in patients with COVID-19.[3] A substantial percentage (up to 28.5%) of adult COVID-19 patients with AKI have, in turn, been reported to require renal replacement therapy, a development that has been associated with mortality rates as high as 75% to 90%.[1,2,4] In addition, up to one-third of those who have survived following renal replacement therapy did not achieve full recovery of kidney function at the time of discharge.[4]

For reasons that are still speculative, children and adolescents make up a small proportion of COVID-19 cases. National statistics from countries in Asia, Europe, and North America have revealed that pediatric cases account for 2.1% to 7.8% of confirmed COVID-19 cases; however, the actual incidence is likely much higher as COVID-19 disease in most children and adolescents is associated with mild symptoms (if any symptoms at all) and may not prompt confirmatory testing. The mild symptoms of the disease in children, with particular reference to kidney function, were initially borne out in a retrospective observational study of 238 children admitted to Wuhan Children's Hospital with COVID-19, in which the reported incidence of AKI was only 1.2%. Subsequent pediatric studies from Saudi Arabia and the United Kingdom did report much higher AKI rates of between 21% and 29% in children hospitalized with COVID-19, highlighting the importance of further investigation of this complication in children. In this issue of *Kidney International*, Basalely *et al.* do just that by providing additional data on the incidence, clinical characteristics, and outcomes of COVID-19 in a cohort of 152 children (aged <18 years) who were admitted to 4 New York hospitals during the height of the COVID-19 pandemic.[5] AKI developed in 11.8% (18 patients) of this cohort (combined acute COVID-19 and multisystem inflammatory syndrome in children [MIS-C]) and completely resolved in 83% of them. These findings are in contrast to a cross-sectional point prevalence study of AKI in COVID-19 patients that reported the development of AKI in nearly half (44%) of 106 children admitted to ICUs in 41 centers, 32 of which were United States based.[6] It is noteworthy that the AKI rate in the cohort reported by Basalely *et al.* increases to 28% if only the 60 patients who required intensive care are considered. Of interest, this AKI rate is similar to the rate of 26.9% seen in a review of 4683 patients reported by the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) study, a multinational, prospective study designed to describe AKI epidemiology in critically ill children.[7] In addition, the percentage of ICU patients with severe AKI (KDIGO AKI stage 2–3) reported by Basalely *et al.* (13.3%) also approximates the incidence of severe AKI (11.6%) seen in the AWARE study. The length of hospitalization was significantly impacted by the presence of AKI, and one patient with AKI (representing 5% of all AKI patients and 12.5% of those with severe AKI) died, with the latter rate being similar to that reported by AWARE (11% mortality with severe AKI), but significantly less than the adult COVID-19 experience.

Unique to the pediatric population of COVID-19 patients has been the development of a constellation of clinical findings coined the MIS-C. In mid-May 2020, the Centers for Disease Control and Prevention published a case definition for this syndrome, characterized by fever and inflammation (Table 1), a presentation similar to Kawasaki disease. It was detected in children and adolescents, aged <21 years, and was found to be temporally associated with SARS-CoV-2 infection.

Table 2 | AKI rates in patients with SARS-CoV-2 disease (COVID-19 and MIS-C)

First author, journal	Region, country	Single center vs. multicenter	SARS-Cov-2 disease category	No. of patients	AKI rate, %
Qiu *et al.*[S1] *Lancet Infect Dis.*	Zhejiang, China	Multicenter	COVID-19	36	0
Wang *et al.*[S2] *Pediatr Nephrol.*	Wuhan, China	Single center	COVID-19	238	1.3
Kari *et al.*[S3] *Res Sq.*	Kingdom of Saudi Arabia	Multicenter	COVID-19	89	21
Stewart *et al.*[S4] *Lancet Child Adolesc Health.*	London,UK	Single center	COVID-19 and MIS-C	52	29
Bjornstad *et al.*[6] *Clin J Am Soc Nephrol.*	International	Multicenter	Did not differentiate	106	44
Basalely *et al.*[5] *Kidney Int.*	NY, USA	Multicenter	COVID-19	97	8
			MIS-C	55	18
Whittaker *et al.*[S5] *JAMA.*	UK	Multicenter	MIS-C	58	22
Dufort *et al.*[S6] *N Engl J Med.*	NY, USA	Multicenter	MIS-C	99	10
Feldstein *et al.*[9] *N Engl J Med.*	USA	Multicenter	MIS-C	186	6
Lipton *et al.*[S7] *Kidney360.*	NY, USA	Single center	MIS-C	57	46
Grimaud *et al.*[S8] *Ann Intensive Care.*	Paris, France	Multicenter	MIS-C	20	70
Capone *et al.*[S9] *J Pediatr.*	New York, USA	Single center	MIS-C	33	70
Lee *et al.*[S10] *J Clin Invest.*	Boston, MA, USA	Single center	MIS-C	28	21
Miller *et al.*[S11] *Gastroenterology.*	NY, USA	Single center	MIS-C	44	16
Moraleda *et al.*[S12] *Clin Infect Dis.*	Spain	Multicenter	MIS-C	31	13
Pouletty *et al.*[S13] *Ann Rheum Dis.*	Paris, France	Multicenter	MIS-C	16	56
Toubiana *et al.*[S14] *BMJ.*	Paris, France	Single center	MIS-C	21	52

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Limited to reports with n > 10.

MIS-C is hypothesized to be primarily postinfectious in nature and distinct from COVID-19 as it occurs 2 to 4 weeks after infection with SARS-CoV-2. Although this COVID-19–associated disorder is uncommon (2 in 100,000 persons aged <21 years) when compared with COVID-19 cases (322 in 100,000), it can lead to serious and life-threatening complications. The disorder is distinct from Kawasaki disease as patients with MIS-C are older (average age, >7 years), have intense inflammation, and have greater myocardial injury than patients with Kawasaki disease, and are more likely to be non-Hispanic Blacks. Because of the multisystem involvement that is characteristic of MIS-C, there have been concerns regarding the possible frequent development of AKI in this group of patients as a higher percentage (80%) of them receive intensive care, 20% receive mechanical ventilation, and 48% receive vasoactive support, all of which are associated with a higher risk of AKI.[8]

Fortunately, in a report of 186 patients with MIS-C from 26 states in the United States, AKI was diagnosed in <10%, while the most commonly involved organ systems were gastrointestinal (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%).[9] In addition, in a recent report comparing the course of 577 children and adolescents with acute COVID-19 and 539 with MIS-C, the presence or absence of AKI was not even commented on. However, there has been a spectrum of AKI rates reported from pediatric centers globally, with most cases being mild and transient in nature (Table 2). In the publication by Basalely *et al.*, 55 of the 152 hospitalized patients (36.2%) were, in fact, diagnosed with MIS-C. The greater severity of illness associated with MIS-C compared with acute COVID-19 disease in the remaining 97 patients was reflected by the greater percentage of children with MIS-C who developed AKI (18.2% vs. 8.2%), who had stage 3 AKI (40% vs. 25%), and who required intensive care (61.8% vs. 27%). Most of the patients (80% with MIS-C and 50% with COVID-19) who developed AKI were found to have decreased kidney function at the time of hospital admission, often with gastrointestinal symptoms, suggesting a possible prerenal

etiology. Echocardiographic evidence of systolic dysfunction was more common in patients with MIS-C who had AKI compared with those who did not, a finding that has also been seen by others and that suggests the possible contribution of renal hypoperfusion to the impaired kidney function. Nevertheless, none of the patients with MIS-C required renal replacement therapy, and 9 of 10 patients had resolution of AKI before hospital discharge. With 6 of the 8 acute COVID-19 patients also demonstrating resolution of AKI, these data further suggest that the kidney injury in pediatric patients with COVID-19 and MIS-C is not severe in most instances.

At present, children aged <16 years are not eligible for vaccination against SARS-CoV-2 and thus we are likely to continue to see children with COVID-19 and MIS-C in the foreseeable future. Although the information presented by Basalely *et al.* is informative and optimistic in terms of the generally favorable AKI-related outcome, the limited experience presented precludes any definitive statement regarding the epidemiology of COVID-19–related AKI in children and highlights the importance of ongoing multicenter/national surveillance of the affected pediatric population with sharing of those experiences as a means to ideally optimize care until universal prevention can be achieved.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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APOL1-associated kidney disease in northern Nigerians with treated HIV infection

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Apolipoprotein L1 (*APOL1*) high-risk genotypes strongly associate with HIV-associated nephropathy, and antiretroviral therapy reduces the incidence of HIV-associated nephropathy and progression to end-stage kidney disease. Wudil *et al.* report cross-sectional *APOL1* associations with proteinuria and estimated glomerular filtration rate in a northern Nigerian sample with HIV infection on antiretroviral therapy. Multiple ethnic groups with different *APOL1* risk variant frequencies were included. Overall, *APOL1* was associated with proteinuric chronic kidney disease; however, relationships with underlying causes of nephropathy and progression rates require further study.

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Association between the acquired immunodeficiency syndrome (AIDS) and an aggressive form of focal segmental glomerulosclerosis in African American individuals from Brooklyn was reported by Dr. T.K. Sreepada Rao and colleagues in 1984.[1] At the time, the causative HIV was unknown and employees at Kings County Hospital wore protective gowns, masks, and gloves because of the fear of contracting AIDS. In fact, the scene was eerily similar to the rapidly spreading severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in early 2020. Patients who presented with normal kidney function and proteinuria rapidly progressed to full-blown nephrotic syndrome and end-stage kidney disease (ESKD) and died within 3 months. Nephrologists debated whether chronic dialysis was of

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