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REVIEW

Kidney implications of SARS-CoV2 infection in children

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Abstract
Research indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection can impact every organ, and the effects can range from asymptomatic to severe disease. Since it was first discovered in December 2019, our understanding has grown about its impact on kidney disease. In general, children have less severe disease than adults, and this tendency appears to extend to special pediatric kidney populations (e.g., chronic kidney disease and immunosuppressed patients with solid organ transplants or nephrotic syndrome). However, in a fraction of infected children, SARS-CoV2 causes an array of kidney manifestations, ranging from acute kidney injury to thrombotic microangiopathy, with potential implications for increased risk of morbidity and mortality. Additional considerations surround the propensity for clotting extracorporeal circuits in children with SARS-CoV2 infection that are receiving kidney replacement therapy. This review provides an update on our current understanding of SARS-CoV2 for pediatric nephrologists and highlights knowledge gaps to be addressed by future research during this ongoing pandemic, particularly the social disparities magnified during this period.

Keywords SARS-CoV2 · COVID-19 · Pediatric nephrology · Acute kidney injury · Transplant · Glomerular diseases · Chronic kidney disease · Dialysis · Epidemiology

Introduction

In recent decades, there have been coronavirus-related outbreaks across the world, but none have changed the course of so many lives as the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic that first emerged in December 2019. The first coronavirus-related outbreak in the past few decades was severe acute respiratory syndrome (SARS) caused by the first SARS-CoV strain identified in late 2002. The strain was highly infectious and led to a global epidemic with a peak in March–April of 2003, but by the end of 2003, it was contained. A major reason for its containment was that SARS-CoV rarely caused mild disease and therefore severe disease was easy to detect and isolate [1]. The second outbreak began in 2012 due to the Middle East respiratory syndrome coronavirus (MERS-CoV), but this strain has very limited human-to-human transmission. The current outbreak due to SARS-CoV2, first identified in Wuhan, China in December 2019, has led to the largest and most destructive global pandemic in over a century. The World Health Organization (WHO) officially declared SARS-CoV2 a pandemic on 11 March 2020, due to its infectious potential and high human-to-human transmission. Current global key milestones of SARS-CoV2 are presented in Fig. 1. The mortality, health disparities, and economic devastation attributable to SARS-CoV2 have not been seen since World War II or the 1918 influenza pandemic.

In addition to only causing moderate to severe disease, the initial SARS-CoV strain primarily impacted the respiratory system [1]. The MERS-CoV strain started to diverge and impacted the kidney and liver in addition to the lungs [1]. Initial descriptions of SARS-CoV2 infections that led to coronavirus-associated disease 2019 (COVID-19) focused on severe respiratory illnesses. However, as the pandemic has progressed, it has become clear that COVID-19 also impacts the brain, heart, liver, vascular system, endocrine system, and the kidneys [2, 3]. In addition, a large proportion of infected individuals are contagious yet remain asymptomatic. Even mild disease not requiring hospitalization is associated with increased long-term morbidity and mortality

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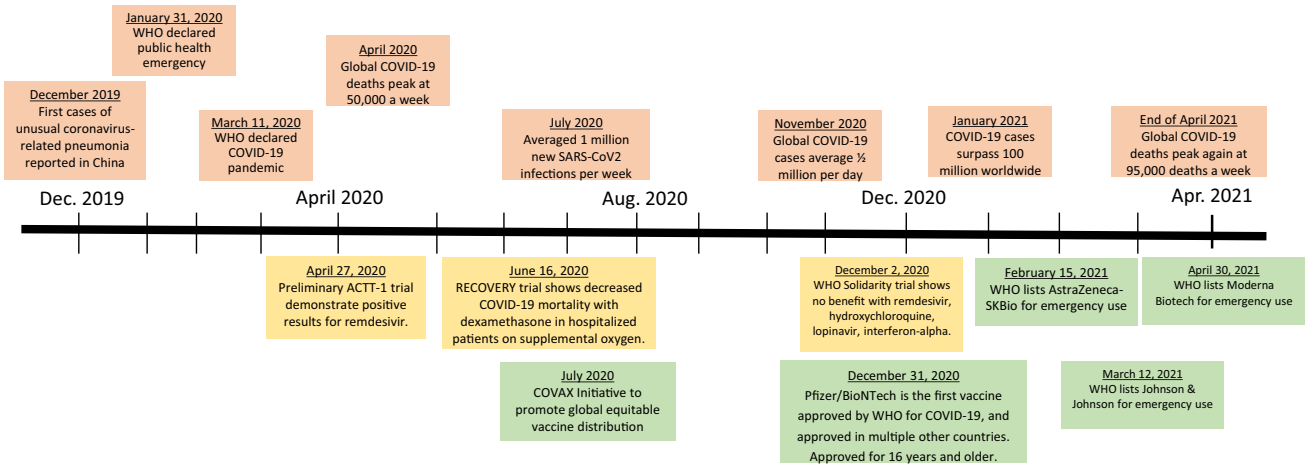


Fig. 1 Timeline of key developments in the coronavirus-associated disease 2019 (COVID-19) pandemic, December 2019–May 2021. Top of timeline demonstrates key milestones of the COVID-19 pandemic cases and deaths worldwide as of May 2021. Bottom of timeline demonstrates key milestones in therapeutics for COVID-19 (yellow) and vaccine development based on emergency use authorization by the World Health Organization (WHO) (green). Emergency listing by the WHO is key to facilitating vaccine approval and uptake particularly in low- and middle-income countries and a requirement for vaccines to be included in the COVAX initiative [91–93]

[4]. This review is meant to provide a summary of current knowledge about SARS-CoV2 and its implications for pediatric nephrology as of May 2021.

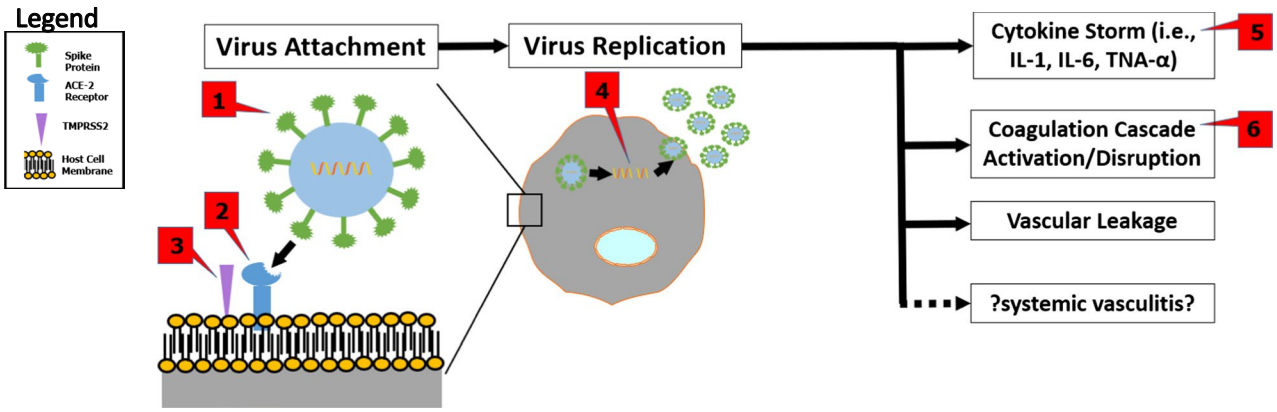
Pathophysiology of SARS-CoV2 infection

SARS-CoV2 virus is primarily transmitted by human-to-human interaction and inhalation of viral particles [2]. One of the reasons that SARS-CoV2 is thought to be more pathogenic than previous coronaviruses and generate persistent symptoms in milder cases is its 10- to 20-fold higher binding affinity to its entry receptor, the angiotensin-converting enzyme 2 (ACE2) receptor [5]. SARS-CoV2 is made up of multiple structural proteins, the spike (S) protein being the protruding protein that is most important for host cell attachment and interaction [1, 5]. SARS-CoV2 enters through the respiratory tract, and its S protein binds to the ACE2 receptor on host cell surfaces [2]. The receptor transmembrane protease serine 2 (TMPRSS2) on host cells is activated by the SARS-CoV2 S protein to cleave the ACE2 receptor [2]. This promotes viral entry into the cell by endocytosis where its RNA is unpackaged and facilitates rapid replication of additional virions that are released for further cellular infection [2]. This early stage is followed by an inflammatory response and cytokine release of signaling molecules that lead to invasion of T lymphocytes, monocytes, and neutrophils. SARS-CoV2-mediated pulmonary vascular injury leads to increased blood vessel permeability and subsequent pulmonary edema [2]. In addition, the vascular injury triggers the coagulation cascade and microthrombi form throughout the lungs, and the activation can lead to systemic thrombotic microangiopathy [2]. See Fig. 2 for a simplified pictogram with key therapeutic targets.

SARS-CoV2 affects other organ systems in addition to the lungs. ACE2 is primarily a transmembrane receptor bound to cell surfaces, but a small portion is found freely soluble in the blood [6]. ACE2 receptors are ubiquitously found throughout the body, including the heart, blood vessels, kidney, gut, lungs, testis, and brain. Specifically, in the kidney, ACE2 receptors with TMPRSS2 protease receptors are found in the proximal tubules, epithelial and endothelial cells, as well as podocytes [6, 7]. However, the kidney manifestations of SARS-CoV2 are multifactorial, stemming not only from direct toxicity of the virus but also from the viral trigger of cytokine release, lung-kidney cross-talk, kidney hypoperfusion and ischemia, and often iatrogenic nephrotoxin exposures. Of interest, elderly patients have the least abundance of ACE2 receptors yet have the most severe disease, indicating that other pathways and mechanisms of injury are involved [6]. One hypothesis is that SARS-CoV2 interacts with the classical arm of the renin-angiotensin system (RAAS) cascade, rather than the alternative RAAS pathway that relies on ACE2 signaling [8]. In addition to variable ACE2 expression, other factors involved in the heterogeneity of disease across the lifespan may include overall RAAS balance, immune system maturity, and exposure level to SARS-CoV2 virions.

General SARS-CoV2-related clinical manifestations

SARS-CoV2 causes a spectrum of illnesses ranging from asymptomatic disease to acute infection with COVID-19 as well as a post-inflammatory response. While this post-inflammatory response primarily impacts children, it has been documented in young adults. A global consensus definition of the



	Therapeutic target	Examples
1	Antibody against spike protein	Vaccines, bamlanivimab plus etesevimab, casirivimab plus imdevimab, convalescent plasma
2	ACE2 receptor blockade	Enalapril, lisinopril, losartan, etc. Recombinant ACE2 receptor-like enzymes.
3	TMPRSS2 inhibition	Experimental agents camostat and nafamostat
4	Interrupt RNA-dependent RNA replication	Remdesivir
5	Immunomodulatory agents/therapies	Dexamethasone, tocilizumab, anakinra, baricitinib; procedures such as plasmapheresis, hemoperfusion
6	Anti-coagulation and anti-platelet therapies	Unfractionated heparin for prophylaxis, experimental trials on treatment dosing for abnormal coagulation markers

Fig. 2 Mechanism of SARS-CoV2 infection and potential therapeutic targets. SAR-CoV2 virion enters cells expressing the angiotensin-converting enzyme 2 (ACE2) receptor. The viral spike protein bears significant homology to ACE2, and the interaction with the receptor initiates a process, facilitated by the host transmembrane-bound serine protease 2 (TMPRSS2), resulting in virus to cell membrane fusion, endocytosis, and release of viral RNA-capsid into the cytoplasm. The RNA undergoes RNA-dependent RNA replication followed by translation, virion assembly, and virion release. Potential therapeutic targets are listed with example agents/therapies [2, 94]

syndrome has not been reached (see Table 1). The US Centers for Disease Control and Prevention defines it as a multisystem inflammatory syndrome in children (MIS-C) or adults (MIS-A) [9, 10]. The UK defines it as pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) [11]. The WHO has given no specific name to the inflammatory syndrome but provides a relatively clear symptom- and laboratory-based case definition (see Table 1) [12]. Though children made up a fraction of the initial waves of the pandemic and generally have milder disease than adults, children can suffer severe and fatal complications from SARS-CoV2 [13, 14]. Distinguishing signs and symptoms of acute COVID-19 and its inflammatory sequelae are presented in Table 1.

Kidney-specific SARS-CoV2 clinical manifestations

SARS-CoV2 and acute kidney injury

In both hospitalized adults and children, SARS-CoV2 infections are associated with high rates of acute kidney injury (AKI) [3, 15, 16]. Despite initial reports of limited kidney involvement, now there is a plethora of literature describing adult patients with AKI as an important complication in those hospitalized with SARS-CoV2 infection [15, 16]. In addition, a large multicenter study of pediatric critical care units found that 37% of critically ill children with SARS-CoV2 developed AKI, rates that are comparable to those in children with sepsis [3]. Similarly, a recent study from the UK found that critically ill children with SARS-CoV2 and clinical characteristics of MIS-C were most at risk for AKI [17]. However, another report from New York indicates that all hospitalized children with SARS-CoV2 are at high risk of AKI, not just the critically ill or those with MIS-C [18]. An adult comparison study of hospitalized patients with and without COVID-19, suggests that COVID-19 is an independent risk factor for AKI that is higher than other diseases leading to intensive care hospitalizations [19].

There is emerging evidence that acute kidney dysfunction in SARS-CoV2 is also associated with worse outcomes. A prospective report from China in May 2020 revealed an increasing risk of mortality for each increase in AKI stage [20]. In New York, a retrospective comparison of adult patients with and without COVID-19 found that SARS-CoV2-positive patients who also had AKI had a 2.6-fold higher mortality risk than those with AKI and not infected with SARS-CoV2 [19]. Similarly, among COVID-19-hospitalized adult patients, the risk of death with AKI was 3.4 times higher than those without AKI, and the risk of death doubled (adjusted hazard ratio 6.4) in those who required

Table 1 Signs and symptoms of acute SARS-CoV2 infection and multisystem inflammatory syndrome associated with SARS-CoV2

	Acute SARS-CoV2 infection [2, 14, 95]	Multisystem inflammatory syndrome associated with SARS-CoV2 [9–12, 95, 96]
		Primarily affecting children and young adults
Signs/Symptoms	Fever	Fever
	Cough	Abdominal pain
	Shortness of breath	Vomiting
	Respiratory distress	Diarrhea
	Fatigue	Skin rash
	Myalgias	Mucocutaneous lesions
	Headache	Hypotension/shock
	Nausea	
	Vomiting	
	Diarrhea	
	Anosmia	
	Aguesia	
Laboratory/imaging findings	Elevated inflammatory markers	Elevated inflammatory markers
	Coagulopathy, thrombocytopenia	Cardiac dysfunction (high troponins, elevated BNP)
	Liver/kidney function abnormalities	Kidney function abnormalities
	Bilateral chest disease with lower lobe infiltrates and ground glass opacities	Pleural effusions
Multisystem inflammatory syndrome definitions		
MIS-C (similar for MIS-A)—US Centers for Disease Control [9, 10]	PIMS-TS—UK RCPCH [11]	Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19—World Health Organization [12]
< 21 years	Child	0–19 years
Fever ≥ 38 °C for ≥ 24 h, or subjective fever ≥ 24 h	Persistent fever ≥ 38.5 °C	Fever for ≥ 3 days
Laboratory evidence of inflammation (e.g., elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, and neutrophils or decreased lymphocytes and albumin)	Inflammation (neutrophilia, elevated CRP, lymphopenia, abnormal fibrinogen, high d-dimer, high ferritin, and low albumin)	Elevated markers of inflammation such as CRP, ESR, and procalcitonin
Clinically severe multisystem organ involvement (≥ 2 systems: cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological	Evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, and neurological disorder	2 of the following: -Hypotension or shock -Heart dysfunction (myocarditis, pericarditis, valvitis, coronary abnormalities by echo or elevated troponin or NT-proBNP) -Signs of coagulopathy (elevated PT, PTT, or d-dimer) -Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, feet) -Acute GI problems (vomiting, diarrhea, abdominal pain)
No alternative plausible explanation	Exclusion of other causes	No other obvious microbial cause of inflammation
Positive for current or past infection with PCR, serology, or antigen testing	SARS-CoV2 PCR testing may be positive or negative	Evidence of COVID-19 by PCR, serology, or antigen testing or likely exposure to someone with COVID-19

Abbreviations: *BNP* or *NT-proBNP*, B-type natriuretic peptide; *COVID-19*, coronavirus-associated disease of 2019; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *GI*, gastrointestinal; *LDH*, lactic acid dehydrogenase; *IL-6*, interleukin-6; *MIS-A*, multisystem inflammatory syndrome in adults; *MIS-C*, multisystem inflammatory syndrome in children; *PCR*, polymerase chain reaction; *PIMS-TS*, pediatric inflammatory multisystem syndrome temporally associated with COVID-19; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *RCPCH*, Royal College of Paediatric and Child Health

dialysis compared to no AKI [21]. Yet, there remains limited data in children with SARS-CoV2-related AKI and its associated outcomes. A retrospective report from four centers in New York during the first part of the pandemic (March to May 2020) found that children presenting with AKI were more likely to require intensive care [18].

The Acute Disease Quality Initiative (ADQI) has released management guidelines for AKI in COVID-19 [22]. Additional AKI guidelines have been developed by the COVID-LMIC (low- and middle-income countries) Task Force and Mahidol-Oxford Research Unit [23]. Pediatric-specific AKI guidelines have been released by the Critical Care Nephrology Section of the European Society of Paediatric and Neonatal Intensive Care and the Canadian Association of Paediatric Nephrologists (summarized in Table 2) [24, 25].

During the initial waves of COVID-19, adult centers saw drastic surges in demand for kidney replacement therapy. Some centers had to rapidly develop and deploy urgent peritoneal dialysis programs, and others developed resource-sharing strategies for the limited number of continuous kidney replacement therapy machines [26]. Though pediatric centers have not seen this rapid surge in demand, ingenious solutions were still required as adult and pediatric centers often share some of the same resources (e.g., machines, solutions, staff) [27]. Also, at times many pediatric hospitals cared for adult patients to offload the overwhelming hospitalization rates in adults, and pediatric nephrologists were often called on to care for acute dialysis needs in these adult patients [28]. There is clinical consensus that patients with SARS-CoV2 infection are more difficult to dialyze due to their coagulopathy and propensity to clot an extracorporeal circuit. This led to several organizations recommending increased or supra-therapeutic (heparin and citrate) anti-coagulation dosing compared to the usual prescription for kidney replacement therapy [22, 24, 28]. Trials have been proposed to evaluate the efficacy and safety of double anticoagulation for patients on continuous kidney replacement therapy. To date, there have not been randomized trials or strong observational studies on the optimal management of dialysis in COVID-19-related AKI. However, there are small and ongoing studies to evaluate alternative methods of hemoperfusion and cytokine clearance such as with CytoSorb® filter, Seraph® 100 filter, or therapeutic plasma exchange (TPE), given the data around an imbalanced immune response and cytokine storming in severe COVID-19 or MIS-C/PIMS-TS [29–31]. One study has assessed the role of TPE in critically ill children with COVID-19 and MIS-C ($n=27$); those who received TPE had a rapid improvement in left ventricular ejection fraction and decrease in pediatric logistic organ dysfunction (PELOD) scores [31]. Additional guidelines have considered the effect of extracorporeal clearance of newer therapies against COVID-19, such as remdesivir [32].

Other forms of kidney damage in SARS-CoV2

Since SARS-CoV2 enters cells primarily via ACE2 receptors that are abundant in the kidney, there may be more direct viral damage to kidneys contributing to the high rates of AKI and kidney dysfunction in patients with SARS-CoV2 [3, 4, 16]. An adult multicenter study found that high AKI rates in hospitalized patients with COVID-19 were not completely explained by the severity of illness or other known risk factors for hospital-acquired AKI, suggesting that there may be unexplored risk factors or even direct viral toxicity in the kidney from SARS-CoV2 [16].

Given the preponderance of evidence of SARS-CoV2 causing microthrombi and coagulation cascade abnormalities, there is growing evidence that adults infected with SARS-CoV2 can have thrombotic microangiopathy (TMA)-related changes in the kidney [33, 34]. A propensity score-matched cohort analysis found anti-coagulation directed therapy to lower d-dimer levels had both lower mortality and AKI rates compared to standard of care [35]. This may reflect the role of systemic microthrombi as an important driver in COVID-19 complications and mortality [35]. There have been additional reports of children with TMA-like presentations with kidney involvement [36]. In an evaluation of 50 hospitalized children with minimal COVID-19, severe COVID-19, or MIS-C, there was a high prevalence of TMA (48% among the entire cohort and 86% among cohort with complete clinical data) [36]. Interestingly, the authors evaluated soluble C5b9 membrane attack complex (sC5b9) as a biomarker of complement activation and TMA, and they found significantly increased levels across the spectrum of COVID-19 (minimal and severe disease as well as MIS-C), suggesting that compared to healthy controls robust complement activation (and TMA) may have both acute and potentially long-term implications not yet understood in all children infected with SARS-CoV2 [36]. This is important for potential kidney implications as well because they also found high sC5b9 levels correlated with AKI rates in this cohort [36].

Adults infected with SARS-CoV2 have seen a variety of kidney manifestations in addition to acute tubular necrosis (ATN) and TMA [37]. The most common presentation after ATN is focal segmental glomerulosclerosis (FSGS), particularly the collapsing variant. In a small biopsy series ($n=17$) of adult patients with COVID-19 and either AKI or proteinuria, 41% had evidence of FSGS on biopsy [37]. Importantly, only 3 of the 17 patients had severe COVID-19. The presence of FSGS is a potentially pivotal finding that deserves further exploration as it has common activation pathways and scarring patterns, which could have implications for understanding the long-term sequelae (e.g., chronic kidney disease (CKD) and hypertension) of SARS-CoV2 infections. In children, case series and reports suggest SARS-CoV2

Table 2 Summary of guidelines on AKI prevention and management of COVID-19 in hospitalized children and adolescents [24, 25]

Monitoring	-Daily volume status and fluid balance assessments by clinical examination and non-invasive hemodynamic measurements (consider invasive measurements if critically ill) -Minimize iatrogenic nephrotoxic medication exposures as much as feasible -Measure serum creatinine, urea, and electrolytes on admission and then daily or at a minimum every 2 days while hospitalized
Diagnostic considerations	*If AKI detected:* -Conduct thorough history and clinical examination to determine etiology -At a minimum obtain urinalysis to evaluate for hypoperfusion, hematuria, proteinuria -Depending on resources, consider kidney ultrasound with Doppler -If no plausible explanation can be found, or significant proteinuria, consider kidney biopsy
Unique therapeutic considerations with COVID-19	-Optimize COVID-19 or post-inflammatory therapies when indicated (e.g., steroids, remdesivir, anakinra, etc.) -Optimize AKI medical management (e.g., remove nephrotoxins, fluid balance, blood pressure control, electrolyte imbalances). Of note, patients with COVID-19 can present severely volume depleted so it is important to replete sufficiently and get to euvolemia before considering KRT
If KRT is needed (staff, resource, facility considerations)	-Full PPE is needed for all staff in contact with infected patients -Consider risk–benefit balance of prolonging filter life and thus decreasing staff exposure versus shortening filter life and perhaps increasing effective clearance for patient -In units where the bedside staff (i.e., ICU nurse/clinician/physician) do not directly manage the dialysis, hemodialysis machines can be set up outside of the room to minimize staff exposure -If unit has limited CKRT machines, consider switching to prolonged intermittent therapies with double the usual clearance so multiple patients can benefit from the same machine (with proper cleaning in between) or intermittent modalities (if patient's hemodynamics will tolerate it). However, minimal clearance may be required if dialysate solutions are also in low supply -In severely constrained scenarios such as surge scenarios, limited resources, etc., consider acute peritoneal dialysis and/or consider mixing your own consumables of dialysate fluid -In prolonged or acutely severe constraint scenarios for units that share chronic and acute dialysis patients, consider decreasing the frequency of outpatient hemodialysis sessions to the minimum required for safety and/or transitioning chronic patients to home peritoneal dialysis modalities when possible. This can free up staff and resources to be reallocated to acute inpatient needs
If KRT is needed (patient considerations)	-For hemodialysis access, the internal jugular is preferred, particularly as many severely ill COVID-19 patients may benefit from prone positioning -Propensity for hypercoagulability and clotting are common. If frequent clotting occurring, balance risk-benefits of increasing usual anticoagulation: –Consider increasing goals with systemic unfractionated heparin (10–20% above normal) –Consider dual therapy with systemic unfractionated heparin at usual goals with regional citrate or prostacyclin anticoagulation. Close monitoring of calcium is required as severe COVID-19 infections can result in liver damage and subsequent increase risk of citrate toxicity/lock -One study showed no difference in timing of KRT initiation when urgent indications not present, so if resources are constrained delaying therapy may be advisable -Higher than usual prescriptions may be needed if resources are limited and unable to perform usual therapy of choice. For example, if patient would benefit from CKRT, but insufficient machines, use higher dose of clearance in prolonged intermittent therapies or use higher fill volumes with higher dextrose in acute peritoneal dialysis therapies

Abbreviations: *AKI*, acute kidney injury; *COVID-19*, coronavirus associated disease 2019; *CKRT*, continuous kidney replacement therapy; *KRT*, kidney replacement therapy; *PPE*, personal protective equipment

may induce additional kidney presentations such as minimal change disease and other glomerular syndromes [38, 39].

With the immune dysregulation seen to accompany SARS-CoV2-related infections, there is also a growing amount of literature that suggests it may be a trigger for new autoimmune manifestations (i.e., systemic lupus erythematosus (SLE), ANCA) in at-risk individuals. This hypothesis is extensively explored in a comprehensive systematic review of the early pandemic waves by Novelli and colleagues [40]. A review in *Clinical Rheumatology* evaluates the evidence for theories supporting these concerns: endotheliitis has been demonstrated in SARS-CoV2 infections and autoantibodies, including anti-Ro/SSA, and antiphospholipid antibodies can arise de novo in the serum of patients infected with SARS-CoV2 who previously did not have known autoimmune diseases [41]. The report suggests up to 30% of COVID-19 patients develop antibodies to anti-nuclear antigens [41]. There are important implications for pediatric nephrologists if the COVID-19 pandemic is associated with a surge in autoimmune diseases with kidney involvement, such as SLE.

SARS-CoV2 infection in special pediatric nephrology populations

SARS-CoV2 infection in pediatric kidney transplantation

There was a drastic decrease in solid organ transplant rates in the early months of the COVID-19 pandemic, in part due to fears of more severe disease in immunosuppressed patients [42, 43]. As the COVID-19 pandemic progressed, guidelines were developed around non-pharmaceutical prevention efforts for this high-risk population. As transplants resumed, there were reports of high morbidity and mortality in adult kidney transplant recipients who contracted SARS-CoV2 [44]; however, these have also been balanced with high rates of morbidity and mortality in patients with chronic kidney failure who contracted SARS-CoV2 as well [42, 45]. A systematic review from January to July 2020 found that among 420 adult kidney transplant recipients with confirmed COVID-19, 93% required hospitalization, 30% were admitted to the ICU, and 22% died [45].

Specific data on pediatric kidney transplant rates and outcomes with COVID-19 are limited, though outcomes are somewhat less worrisome among those who are transplanted. An analysis of US pediatric kidney transplant centers showed early in the pandemic that there were significant decreases in living donor transplantations, decreases in new waitlist activations, yet increases in deaths among those on transplant waitlists [43]. However, the trends appeared to be dissipating by the summer of 2020 [43]. The Improving Renal Outcomes Collaborative (IROC) learning health system reported on 281 patients who had been tested for SARS-CoV2 among 2732 pediatric kidney transplant recipients (~ 10% tested); only 24 tested positive (8.5% of those tested, 0.9% of cohort), suggesting a low incidence of disease in pediatric kidney transplant recipients despite the presence of both CKD and immunosuppression [46]. Outcomes in this population were favorable with only a third requiring hospitalization and no reported episodes of respiratory failure, allograft loss, or deaths [46].

Over the past year, additional kidney transplant-specific guidance has emerged and programs have mostly adapted to continuing kidney transplantation with modified COVID-19 protocols, consent processes, and procedures [47]. The majority of the literature surrounds clinical characteristics and outcomes of SARS-CoV2 infection in kidney transplant recipients. Overall, there is a tendency to reduce or withdraw immunosuppression if a recipient contracts COVID-19 [47, 48]. Observational or clinical trial data as to optimal care in these complex patients (pediatric or adult) is lacking at the time of writing.

Emerging data regarding organ donation after SARS-CoV2 infection are somewhat reassuring. There are case reports and series that suggest this could be a valid possibility if alternatives are not available or in difficult-to-transplant patients (such as with high PRAs). Successful transplantation has occurred in adult recipients without evidence of SARS-CoV2 transmission [49]. Similarly, successful transplantation of adult kidney recipients who have recently recovered from SARS-CoV2 have been reported [50]. These areas all continue to deserve further investigations.

Additional emerging questions surround the antibody and protective responses to COVID-19 vaccinations among kidney transplant recipients. One pediatric transplant study showed good antibody response up to 75 days after SARS-CoV2 infection, suggesting promise for prolonged humoral responses after vaccination in this at-risk population [51]. However, a systematic review of mostly adult (only one pediatric study included) maintenance dialysis patients and kidney transplant recipients found that cellular and humoral responses to SARS-CoV2 are blunted in kidney transplant patients compared to dialysis patients [52]. This has potentially important implications for the timing of COVID-19 vaccination in the peri-transplant period. As most COVID-19 vaccines with approval are limited to adult and adolescent populations, there is a lack of data on vaccine responses in pediatric kidney transplant recipients at this time.

SARS-CoV2 implications for children on chronic immunosuppression for non-transplant kidney conditions

Limited data exist on SARS-CoV2 implications in children with other kidney diseases requiring chronic

immunosuppression, such as nephrotic syndrome or glomerulonephritis. One retrospective study across 30 countries from the early waves of March to July 2020 included only 113 children with SARS-CoV2 positivity and chronic immunosuppression for kidney diseases, approximately half of whom were transplant patients [53]. The study was limited by the self-reporting nature of participating nephrologists but demonstrated that those impacted with SARS-CoV2 had similar reassuring rates of hospitalization, need for respiratory support, and mortality as children not treated with chronic immunosuppression [53]. Surveys have been done of adult patients with SLE that suggest similar infection rates and severity levels as those without SLE, but as yet there are no pediatric reports [54]. All of these studies are limited by enrollment bias, reporter bias, and the cross-sectional nature of the reports, not to mention that they are reports from the earlier waves which do not include newer virus variants that seem to have disproportionate effects in children. The limited evidence to date does not suggest the need to systematically alter usual immune suppression protocols in the time of the pandemic. However, the American College of Rheumatology (ACR) has issued guidance on the timing of COVID-19 vaccination in patients on common immunosuppressive regimens used in pediatric nephrology, such as steroids, rituximab, and cyclophosphamide [55]. In general, the ACR supports COVID-19 vaccination regardless of disease and immunosuppression status; specific details can be found in the reference document [55]. The interim ACR guidelines in general suggest no change to oral immunosuppression regimens and those with prednisone-equivalent doses < 20 mg/day except they suggest holding mycophenolate for 1 week after vaccine administration if the patient's condition is stable and low risk to hold [55]. For most intravenous infusions (including cyclophosphamide, rituximab, abatacept), the timing of COVID-19 vaccination and infusion should be altered for optimal response/reduction in side effects, typically 1–4 weeks [55].

SARS-CoV2 considerations in children with chronic kidney disease/failure

The majority of the literature on SARS-CoV2 in patients with CKD and chronic kidney failure is from adult cohorts and single-center case series detailing resource management, non-pharmaceutical interventions, and screening protocols [56]. Adults with CKD and chronic kidney failure have been shown to have a higher risk of severe disease in SARS-CoV2 infection. A large systematic review and meta-analysis found adult hemodialysis patients to have a high mortality of 22% after contracting SARS-CoV2 infection, though it should be viewed with caution given the high heterogeneity and reporting bias of publications [57]. In contrast, one study from Italy reports on the milder outcomes of SARS-CoV2 infection in children with CKD [58]. This report is similar to other pediatric reports in that the data are from the early months of the pandemic in April 2020, yet perhaps more importantly the report highlights that 83% of the 1572 children were quarantined at home during the study period [58]. Far more data are needed from subsequent waves when children have been less sheltered and new variants of SARS-CoV2 have emerged that may impact pediatric populations differently.

There are reports of nosocomial transmission of SARS-CoV2 in both adult and pediatric dialysis units [59]. Several leading health authorities have compiled guidelines on adjustments in care, routines, and screening for chronic dialysis patients during the COVID-19 pandemic to optimize resources and minimize potential exposures [60–62]. Similar guidelines have evolved to discuss considerations in children receiving dialysis as well [63]. See Table 3 for a summary of pediatric-specific guidance.

One of the greatest unresolved concerns is the risk for long-term sequelae following COVID-19 infection. A comprehensive evaluation of long-term COVID-19 sequelae in adults indicates that acute infection leads to a higher risk of CKD, chronic kidney failure, and hypertension among a myriad of other chronic conditions [4]. Unfortunately, there is a paucity of literature on COVID-19 long-term implications in children with pre-existing CKD or on the incidence of CKD after COVID-19 that has been shown in adults.

Only limited data exist on COVID-19 vaccination response in CKD and chronic kidney failure, even less in children. Early immunologic studies revealed that seropositivity of IgG to SARS-CoV2 may last up to 6 months in patients on chronic dialysis [64]. These results seem to be consistent with post-vaccination data [52]. However, a new study comparing chronic dialysis patients with healthcare workers found that immune response to the Pfizer-BioNTech BNT 162b2 vaccination was less among dialysis patients than the healthcare workers after controlling for multiple potential confounding factors [65]. Emerging data in the near future will be critical to formulating recommendations regarding timing of and potential boosters for optimal vaccination of chronic kidney failure patients as the impact of a blunted immune response on infection rates and outcomes with COVID-19 is unclear, particularly in children.

SARS-CoV2 and medication implications

ACEi/ARBs

When it was discovered that ACE2 served as the primary cellular entry point for SARS-CoV2, researchers rushed to determine the implications for patients with hypertension and particularly those who routinely take ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs). There

remain mixed results with some studies suggesting a protective effect for those taking ACEi/ARBs as they may competitively inhibit the receptors, while others showing a deleterious effect from higher rates of AKI and admissions to critical care units and electrolyte derangements [66, 67]. A meta-analysis among adult patients with hypertension and COVID-19 revealed lower mortality among those who were on ACEi/ARBs compared to those not on the medications [68]. A recent large observational study of almost 2 million hypertensive adults found that those treated with ACEi or ARBs were less likely to be hospitalized and less likely to be intubated or die from COVID-19 compared to those treated with calcium channel blockers [69]. Though the RAAS/ACE2 relationship in SARS-CoV2 infection has remaining questions yet to be answered, especially in children for whom no studies of this pathway have emerged at this time, the prevalent data do not suggest a need to discontinue RAAS blockade as has been suggested in the lay press.

Remdesivir

When remdesivir was initially explored as a potential therapy for acute SARS-CoV2 infection, there were theoretical concerns of its nephrotoxic potential. Remdesivir was initially investigated as a treatment for Ebola. It is relatively insoluble and requires a carrier that has a theoretical risk of nephrotoxicity, sulfobutylether-b-cyclodextrin (SBECD) [70]. Animal studies showed kidney injury associated with remdesivir, but at doses of 5–20 mg/kg for 7 days, which is much higher and has longer duration than most currently recommended therapies (maximum 5 mg/kg for one dose then 2.5 mg/kg daily for 5–10 days) [70]. Similarly, animal studies of the carrier fluid component SBECD have shown kidney tubular obstruction but at doses 50–100 times larger than recommended clinical doses of remdesivir [70]. Initial trials on remdesivir for COVID-19 excluded patients with low eGFR either from AKI or CKD, making it hard to draw conclusions. However, one randomized clinical trial for remdesivir reported essentially no adverse kidney complications with its use compared to placebo [71]. Since then, an observational cohort of patients treated with remdesivir for COVID-19 ($n = 103$), found that 21 would have met original exclusion criteria for the clinical trials (eGFR < 50 ml/min/1.73 m^2) [72]. No patient was found to have severe nephrotoxicity, 10% in the low eGFR group experienced a decrease in eGFR more than 10 ml/min/1.73 m^2, and no patient had remdesivir stopped due to toxicity concerns [72]. A recent meta-analysis was conducted to evaluate the incidence of AKI in COVID-19 patients treated with remdesivir and found essentially no increased risk (remdesivir group's AKI incidence 7% versus non-remdesivir group's AKI incidence 10%) [73]. One pediatric study on AKI in COVID-19 and MIS-C patients found no difference in AKI development for those that received remdesivir, though this should be viewed with caution as only 7 patients in the cohort were treated with remdesivir [74]. Further data on the potential or lack of nephrotoxicity in children with COVID-19 is lacking, but the emerging evidence suggests its potential benefits may outweigh its theoretical risks.

SARS-CoV2 infection and pediatric racial/ethnic disparities

Early in the COVID-19 pandemic differences quickly appeared in the racial and ethnic distribution of case detection and death across the globe [75–78]. Initial studies indicated that minority populations were at higher risk of severe disease and mortality from COVID-19. However, further research indicated that the relationship between COVID-19 disease severity and race may be more related to higher rates of comorbidities in minority populations and the complex structural disparities among immigrant and minority populations. More specific proposed theories include disparities in access to diagnostics, unbiased health care, safe housing, and essential frontline employment which disproportionately affect minority communities [76, 77]. A large urban medical center in the USA found that of more than 9000 screened adults, Hispanic (65.3%) and non-Hispanic Black (68.5%) adults were more likely than non-Hispanic white (53.0%) adults to test positive for SARS-CoV2 (p value < 0.001) [78]. However, after controlling for comorbidities, socioeconomic status, and other confounders, racial and ethnic minority populations did not experience worse clinical outcomes compared to non-Hispanic white adults with SARS-CoV2 [78]. Minorities did however have more chronic conditions, suggesting evidence that disproportionate burden of chronic conditions and exposure levels related to social determinants of health are driving factors in the inequalities experienced with SARS-CoV2 in minority populations. Additional large US and European studies have found that after accessing hospital care, there is no consistent difference in SARS-CoV2-related mortality in minority populations after adjusting for comorbidities and sociodemographic factors [13, 79]. These studies suggest that there is not a biological difference in outcomes from COVID-19, but rather there are persistent and pervasive disparities in overall health and socioeconomic determinants of health in minority populations [80]. Compounding these inequalities may be the recent discovery of higher rates of new chronic conditions in those contracting SARS-CoV2, regardless of severity [4].

To date, an in-depth evaluation of outcome differences among pediatric minority groups with SARS-CoV2-related infections, which also accounts for comorbidities and sociodemographic factors, has not been completed. However, data in children suggests similar trends as adults of higher infections and hospitalization rates among racial and ethnic

Table 3 Recommendations for mitigation of COVID-19 in pediatric dialysis units by roles [60, 61, 63]

	Healthcare staff	Patients	Caregivers
Continuous/Ongoing			
Education—signs/symptoms of COVID-19 and MIS-C/PIMS-TS; COVID-19 vaccination and prevention measures	X	X	X
Education—donning/doffing PPE, COVID-19 guidelines (local, state, national, international), epidemiological trends in COVID-19 locally and hot spots where patients may frequent	X		
Education—obtaining SARS-CoV2 samples for testing (may be limited to those who would do the testing at your facility)	X		
Contingency plans in place and updated regularly for shortages of staff, PPE, machines, and other consumables	X		
Prior to arrival			
Screening questionnaire for symptoms, signs, exposures	X	X[+]	X
Temperature checks	X	X	X
Encouraged to stay home if unwell	X[++]		X
Limit patient to 1 caregiver to accompany inside the unit to minimize exposures			X
SARS-CoV2 testing should occur prior to non-Emergent surgical procedures (i.e., dialysis access)		X	
Arrival/during therapy			
The facility should have triage procedures in place for when a patient, caregiver, or staff member become symptomatic at the Dialysis Unit	X		
Separate isolation room with negative pressure ventilation (if available) for those that are suspected or confirmed SARS-CoV2 positive. *Consider cohorting patients/rooms with staff if multiple patients are suspected or confirmed for SARS-CoV2*		X	
Surgical masks*	X	X	X
When caring for a patient suspected or confirmed for SARS-CoV2, minimum guidance recommends use of N-95 respirator or higher, face shield/eye protection, gloves, gown, *cap, shoe covers***	X		
Consider adopting universal testing and/or PPE of N-95 masks, eye protection, gloves, gowns, etc. *as supplies allow if multiple cases identified in a center or an outbreak of COVID-19 is suspected*	X	X	X
Promote hand hygiene frequently, especially on arrival	X	X	X
When feasible, patients should be designated a single machine for long-term use		X	
Considerations for home therapy patients (peritoneal dialysis, home hemodialysis)			
Whenever feasible, remote monitoring should be offered	X	X	X
Facility considerations			
In addition to standard facility protocols for cleaning and disinfecting dialysis units, additional care should be taken with hospital-grade cleaning solutions against COVID-19 for the isolation rooms or any other equipment or surfaces that are used by those suspected or confirmed to have SARS-CoV2	X		
When possible, the air should be decontaminated with ultraviolet light for 30 min between dialysis shifts	X		
Patient chairs/beds should be spaced a minimum of 1 m apart and/or curtains should be used to provide additional separation	X		

[+]If household member is suspected of SARS-CoV2 and your area has sufficient testing, patient can continue per usual safety measures while awaiting household test result; otherwise, consider isolating per safety measures of suspected SARS-CoV2. If household member is confirmed positive for SARS-CoV2, patient should be isolated in accordance with suspected cases until confirmatory testing can occur per local testing protocols and guidance

[++]This requires that the facility/region has sufficient staff for coverage and that staff are provided job security and sufficient paid time off

*Ideal is for all ≥ 2 years of age with no breathing difficulties to wear surgical masks, but this is not feasible or available in all settings. Next, best facial covering is double masking or double/triple-layer cloth masks, and a minimum facial covering is a single-layer cloth face mask. As some children have developmental delays and may not be able to tolerate mask, at a minimum provide curtain coverage or other ways to minimize airflow between patients

**Caps and shoe covers not listed by all guidelines

Abbreviations: *COVID-19*, coronavirus-associated disease 2019; *MIS-C*, multisystem inflammatory syndrome in children; *PIMS-TS*, pediatric inflammatory multisystem syndrome temporally associated with COVID-19; *PPE*, personal protective equipment

minority groups. In a report of almost 1000 children hospitalized with COVID-19 or MIS-C in New York from March to June 2020, Black and Hispanic children were 2–3 times more likely to be hospitalized than white children [81]. An evaluation from March to July 2020 among three academic centers found with universal screening for pre-surgical

cases that Black and Hispanic children were more likely than white children to test positive for SARS-CoV2 [82]. A US report from 2020 found that racial disparities of SARS-CoV2 infection in children have been dominant throughout the pandemic, though fluctuations have occurred across different time points [83].

Complicating the evaluations of these disparities is the reliance on medical record reporting of race/ethnicity. A recent epidemiological analysis estimates that due to inherent biases of medical record documentation and missing data, complete case analyses are likely underestimating the magnitude of the racial and ethnic disparities seen in most reporting thus far, and at a minimum suggest using quantitative bias analysis methods that account for unequal and non-random missingness [84].

Kidney diseases, in general, have a disproportionate impact among racial and ethnic minorities, and these have been exacerbated among adults with kidney diseases during the COVID-19 pandemic as well [85]. A handful of pediatric studies on AKI have addressed race as a secondary objective and have seen differences in racial distribution of AKI rates [3, 74], but specifically evaluating the multifaceted and complex interplay of race and social structures of society have not been evaluated in children with kidney diseases. Given the long-term implications of pediatric kidney disease and its impact on outcomes in adulthood (i.e., health, social and behavioral adjustments, education success, employment security) and perpetuated disparities, this gap in knowledge deserves immediate attention. If children of minority races/ethnicities are at higher risk of infection, and there is the possibility (as seen in adults) of higher rates of chronic conditions after infection (such as CKD and hypertension), then this will have lifelong ramifications in children that must be addressed.

Similar racial and ethnic disparities are emerging surrounding access and acceptance of available COVID-19 vaccines. A large US and UK population-based cohort assessed vaccine hesitancy and actual vaccine receipt across a diverse population from December 2020 to February 2021, and it was found that racial and ethnic minorities had a significantly higher level of vaccine hesitancy for COVID-19 compared to non-Hispanic white counterparts [86]. However, among participants who desired a vaccine, only the US participants who were also Black had less receipt of the vaccine, suggesting there are both disparities in vaccine hesitancy and disparities in vaccine access that need to be addressed [86]. A focus group of key stakeholders and community advocates from New York found similar concerns that barriers for COVID-19 vaccine access center around healthcare access, transportation, scheduling difficulties with employment and caregiving responsibilities, Internet access for scheduling, and language barriers [87]. Though vaccine hesitancy should be acknowledged, these social determinants of health also contribute to the ongoing disparities in vaccine uptake among minority populations. A US national survey of 1643 Black and white adults found that perceived racial fairness in the health care setting increased trust in influenza vaccines and vaccine uptake, whereas experiences of discrimination in the health care setting decreased trust, increased perceived risk of side effects, and reduced uptake [88]. Beyond large public health initiatives to address these barriers, we as pediatric nephrology providers should help both caregivers and patients navigate these complex systems to access vaccines, understand their importance, and help remove barriers to COVID-19 vaccination. Best individual-level practices for clinicians to support vaccine uptake include verbal acknowledgement of historical context which might contribute to vaccine concerns (e.g., US Public Health Service Syphilis Study at Tuskegee), positive support of autonomy, and providing children and caregivers with evidence for rigorous testing and safety of the vaccine [89].

COVID-19 has highlighted minority disparities within nations, but the vaccine race has magnified the ever-present income (and subsequent health) disparities between nations. Published research on this topic is minimal yet lay press reporting suggests that deep disparities in vaccine availability exist with > 85% of administered vaccines occurring in high- and upper-middle-income countries, while low-income countries have seen less than 0.3% of all administered vaccines [90]. Both national and global inequities perpetuate and exacerbate existing health disparities, promote development of more pathogenic variants of SARS-CoV2, and threaten to erode progress against this devastating pandemic for all of us.

Key summary points

- SARS-CoV2 causes a wide spectrum of illness and affects almost every organ, including the kidney.
- SARS-CoV2 leads to high rates of AKI among hospitalized children. Though common risk factors for sick children exist, there may be a portion of kidney dysfunction caused by microthrombi, TMA, and other unique direct kidney toxicities from the SARS-CoV2 virions.
- Worse outcomes among adults with SARS-CoV2 and kidney disease (transplants, immunosuppression, CKD, chronic kidney failure, hypertension) have been documented, but for the most part children continue to have a mild disease when evaluated as a whole. However, given the lower rates of hospitalization in children, it may be a sample size issue that chronic kidney-specific conditions may also confer higher risks of severe disease once children are hospitalized that needs further evaluation.

- Further research is needed into the timing of COVID-19 vaccination among CKD/transplant recipients and immunological responses among all children with kidney disease, particularly those on chronic immunosuppressive medications.
- Data suggests that infection with SARS-CoV2 is not a contraindication in and of itself for certain medications, such as ACEi/ARBs or remdesivir, but should be taken into usual considerations for electrolyte derangements and kidney function monitoring.
- COVID-19 has highlighted and exacerbated health disparities worldwide, particularly racial, ethnic, and immigrant disparities. This has also included those with kidney diseases, though specific attention is needed to explore this in-depth in children with kidney diseases, as these may add additional burdens on children already facing many barriers.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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