



Effect of adult COVID-19 surge on the provision of kidney replacement therapy in children

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Introduction

The current novel coronavirus pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) caused an unprecedented demand on global adult critical care services [1]. It was recognized that without increased health care capacity, demand for critical care beds would outstrip supply, leading to increased mortality. One of the several strategies developed to increase capacity for adult critical care was to utilize some of the pediatric intensive care unit (PICU) beds across various units.

Children are managed either in children's standalone hospitals or in institutions where children's services are colocated within established adult hospitals. Depending upon local needs and arrangements, capacity for managing children in children's standalone hospitals can be increased so that PICU beds can be utilized to provide critical care to adults in the colocated hospitals. Different hospitals, based on their local arrangements, either converted their PICUs completely into adult COVID-19 ICUs or accommodated both children and adults on the same PICU managed by the PICU medical and nursing staff creating a hybrid model of critical care. Each model has its unique pros and cons. Being based within an adult-based hospital, equipment, consumables, and staffing have a shared pool, and redeployment and diversion of resources become easier [2]. The mantra is flexible and collaborative working.

A lot of importance has been given to the need for ventilators, and all institutes were asked to arrange for much higher numbers of ventilators in anticipation of the surge, but it was

soon realized that a significant proportion of adult patients with severe COVID-19 were developing acute kidney injury (AKI) with requirement for kidney replacement therapy (KRT) [3]. Though children with COVID-19 are less frequently and less severely affected and the initial rates of AKI in these children have been found to be low, due to increased demand for KRT in adult patients and diversion of KRT resources to the adult COVID-19 surge, a strategy needs to be developed for children in the setting of limited resources. In addition, AKI occurs with higher frequency in the newly diagnosed hyperinflammatory condition in children, which mimics atypical Kawasaki disease or toxic shock syndrome—pediatric inflammatory multisystem syndrome—temporally associated with SARS-CoV2 (PIMS-TS) [4]. Cytokine storm, hyperinflammatory state, hypercoagulability, dehydration, and vasculitis are some of the postulated explanations for multisystem involvement including AKI.

This commentary will focus on special adaptations (in the setting of hypercoagulability and increased filter clotting) or deviations from the “norm” to be made during the delivery of KRT to patients with COVID-19-induced AKI. This is also important for the future with more COVID-19 surges predicted and pediatricians having to manage either adult patients on PICU or being redeployed to the adult ICUs to take care of adult patients. Importantly, if pediatric patients required KRT during the pandemic state, the same principles will apply as most of the resources (coming from the same common pool) would have been diverted to the adult surge. These are not evidence-based recommendations but based on experience of different centers worldwide.

Study by Lipton et al.

The study published by Lipton et al. [5] from New York very elegantly describes the experience of a children's hospital that adopted a hybrid model of critical care and managed both

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children and critically ill adult patients with COVID-19 on their PICU. Taking up the challenge, the largest pediatric service in the New York Presbyterian (NYP) hospital system—Columbia Irving Medical Centre (NYP/CUIMC)—started to treat adult patients on their site. The main trigger for the children’s hospital to start accepting adult patients in their PICU was the increased KRT demands on the adult ICUs. Both adult and pediatric services used different continuous kidney replacement therapy (CKRT) machines (Prismaflex in pediatrics and Nx Stage in adults). They chose to treat COVID-19 positive patients on their PICU, and by retaining their staff and machines for CKRT, it was relatively easy for the staff to work in their usual place of work with the same machines rather than working in an unfamiliar environment with CKRT machines they were not used to. When NxStage CKRT dialysis fluid was in short supply, the team used fluids from Baxter (PrismaSol). They optimized their anticoagulation regimens to deal with the increased frequency of filter-clotting. In addition, pediatric nephrology staffs were redeployed to work in the adult ICU to take care of adults with AKI and KRT. Therefore, the team’s response evolved according to the evolving needs during this pandemic—taking care of adults in their PICU as well as redeploying their pediatric staff to the adult ICUs. The team in New York very aptly demonstrates that with tactical planning, flexibility, collaboration, and team work, it is possible to deal with the worst clinical situation which a pandemic can bring.

Role of pediatric specialists in managing adult surge in London

In London, different models were utilized during this surge—intensive care capacity was increased in children’s standalone hospitals (Great Ormond Street Hospital and Evelina Children’s Hospital, London), whereas the co-located hospitals adopted two different models based on local requirements. King’s College Hospital admitted both children and adult patients on to their PICU, whereas other co-located PICUs completely converted into adult COVID-19 critical care units. Similar to the experience from the New York group, it was realized that a substantial number of adults admitted to the COVID-19 ICUs were developing AKI and needed KRT. After medical management with fluids, diuretics, and meticulous use of nephrotoxic drugs, where resources were available, we resorted to using CKRT as the default modality of choice. However, the number of patients with AKI fulfilling the criteria for initiation of KRT started to rise exponentially. Soon, the CKRT machines and consumables used by adult colleagues were exhausted, which meant KRT resources from pediatrics had to be diverted to deal with this crisis. The problem was compounded by the fact that adult and pediatric CKRT teams used two different types of CKRT machines—

Prismaflex (Baxter) by the adult team and Aquarius (Nikkisso) by the pediatric team. PICU nurses trained adult ICU nurses on the use of Aquarius machines. CKRT machinery and consumables (fluids, filters, and anticoagulants) were being arranged from all possible sources to meet the COVID-19 adult demand (standalone pediatric hospitals as pediatric work load had decreased considerably, private sector, KRT industry loaning extra CKRT machines (being shipped from overseas)). In addition, we started to use alternative modes of KRT (intermittent hemodialysis (IHD) in hemodynamically stable patients and peritoneal dialysis) to lessen the dependency on CKRT machines and consumables. At this point, PICU diverted all CKRT machines except two to our adult services; which meant that if we had to initiate CKRT for our pediatric patients, had the surge hit us, we would face the same resource crunch as our adult colleagues, hence anticipation of the scale of resource crunch is vital.

Special considerations in the delivery of KRT during the COVID-19 surge

Rather than physiology, indications and timing of initiation of KRT in a pandemic state are dictated by the availability of resources and safety of health care workers minimizing exposure. Currently, there is no data to support the early initiation of KRT, with the recently published STARRT-AKI trial not showing any mortality benefit at 90 days between accelerated and standard treatment strategies of KRT [6]. In fact, during the pandemic, one might have to make stricter KRT initiating criteria than in the non-pandemic state. Table 1 summarizes the differences between what should be ideally offered and what is offered in reality to patients requiring CKRT in a pandemic state. Irrespective of the availability of resources, provision of KRT in COVID-19 positive patients is based on three main principles: keeping yourself and your team safe by appropriate use of personnel protective equipment (PPE), limiting exposure to health care personnel to an absolute minimum, disinfection of all dialysis equipment to be done as per hospital guidelines.

Choosing KRT modality

The various KRT modalities available in any institution are CKRT, IHD, prolonged intermittent KRT (PIKRT) or sustained low efficiency dialysis (SLED), and peritoneal dialysis (PD). The first decision is to choose between intermittent and continuous KRT—this depends on the hemodynamic status of the patient and available resources. The advantages of CKRT include better tolerance in hemodynamically unstable children, accuracy in fluid removal, and familiarity of the ICU

Table 1 Provision of continuous kidney replacement therapy (CKRT) in an “ideal” versus pandemic state

Ideal situation	Reality
CKRT	Limited resources—equipment and consumables
Initiation of CKRT before onset of life threatening complications	Need to apply stricter criteria—availability of resources determine the timing and indications for initiation of CKRT
Prescription of dose follows the standard local CKRT guideline and compensates for unplanned ‘downtime’	Limited fluids
Fluids from the same company as the CKRT machine	Fluids and CKRT machines can be from different companies—need to know the fluid composition
Optimal anticoagulation to maintain filter patency	High risk of filter clogging/clotting
Highly qualified staff	Less qualified staff/surge staff
ICU environment	Noncritical care area
Provision according to high standards and benchmarks	Need to accept standards which might not be gold standard

staff in using this modality. Depending on expertise, staffing and resources, CKRT would remain the preferred dialytic modality among critically ill patients with AKI in this pandemic. This is also true from the logistics point of view, as not every ICU has facilities to deliver IHD (reverse osmosis—RO system). Intermittent hemodialysis requires 1:1 nursing, use of PPE for each nurse and constant exposure, while 1 nurse can manage > 1 patient on CKRT, thereby limiting the use of PPE and exposure to the frontline nursing staff. Therefore, even among patients who are hemodynamically stable and could tolerate IHD, CKRT, or PIKRT, it may be the preferred modality, provided resources are available. Peritoneal dialysis (PD) is not very often used in PICUs especially in the developed world—in fact, in most reports from across the globe, use of PD resulted in much less dependence on CKRT especially when resources—both equipment and consumables were in short supply.

Though a number of guidelines have been proposed by various organizations/societies, while managing patients with COVID-19 AKI, one should continue using the established KRT modality and equipment which the institution is comfortable with. Any last-minute changes in the existing CKRT guidelines during the COVID-19 pandemic might create more chaos and confusion. Training of medical and nursing staff with any new modality at this time is not recommended, and it can increase the chances of medical errors and compromise the treatment of critically sick patients with COVID-19 [7].

Where resources are available

In this scenario, the management of KRT in children with COVID-19 is based on the same principles as KRT in non-COVID patients. Indications for starting KRT remain the same as in non-COVID patients in resource appropriate conditions—azotemia, fluid overload, electrolyte, and acid-base

abnormalities and the cytokine storm which is implicated in the multisystem disease [8]. A good sized functioning vascular access located in the internal jugular vein (easily accessible and does not easily bend or kink when the patient is nursed in the prone position for severe respiratory failure) is the most important pre-requisite. In experienced hands, this site can be accessed in the prone position under ultrasound guidance. Though cytokines can theoretically be better removed with convection-based modalities, there is no evidence to suggest that convection is better than dialysis [9]. Therefore, we recommend using the unit’s established CKRT practices which the staff are used to in a non-pandemic state.

Increased need for anticoagulation

It has been seen that SARS-CoV2 frequently induces hypercoagulability, with both microangiopathy and local thrombus formation and a systemic coagulation defect that leads to large vessel thrombosis and major thromboembolic complications [10–12]. Therefore, filters clot more frequently due to this prothrombotic condition. It is the downtime for treatment which has the most deleterious effect on the efficacy of CKRT as it has been convincingly shown that the more the downtime, the less the prescribed dose delivered. If filters clot more frequently, there will be increased frequency of alarms and increased exposure of healthcare professionals to attend to alarms and troubleshoot, leading to inadvertent increased use of PPE. Additionally, changing filters and circuits frequently in the wake of an already depleted pool of resources will put additional strain on resources.

Circuit and filter factors need to be optimized to prevent frequent filter clotting—an appropriate-sized well-functioning vascular catheter is the best anticoagulant [13]. Therefore, select large catheters and address all catheter-related issues, such as kinking, leakage, and bending; this is especially

important when patients are nursed in the prone position in severe acute respiratory distress syndrome (ARDS). Reduction of the ultrafiltration rate to decrease the viscosity of blood, increasing blood flow rates using filters with relatively large surface area to reduce the transmembrane pressure, and keeping the filtration fraction <20% while using the CVVHD mode are some of the recommendations to prevent frequent filter clotting.

After optimizing circuit factors, use of an appropriate and safe anticoagulant which maintains the fluidity of blood in the circuit with minimal effects on systemic circulation is essential. All staff involved should be well trained in the use and recognition of side effects of the chosen anticoagulant. The route of administration of anticoagulant can be systemic (intravenous or subcutaneously) or regional into the circuit, or a combination of the two.

Unfractionated heparin

Heparin remains the most commonly used anticoagulant in these patients as a number of these patients develop pulmonary emboli or deep vein thrombosis and are started on systemic infusion of unfractionated heparin. If patients are not on a systemic heparin infusion, a prefilter bolus of unfractionated heparin (20 units per kg) followed by an infusion of heparin at the dose of 20–30 units per kg per hour (higher than the usual dose of 10–20 units per kg per hour) should be started. Activated clotting time (ACT) is regularly monitored; we recommend a target ACT of 180–220 s. If the ACT is low and the filter clots, increasing the dose of unfractionated heparin by 10–20% of the previous dose is recommended. Side-effects related to unfractionated heparin need to be borne in mind especially the increased risk of bleeding, heparin resistance, and heparin-induced thrombocytopenia (HIT).

Regional citrate anticoagulation

Regional citrate anticoagulation (RCA) prolongs the circuit life and reduces the hemorrhagic complications of heparin. Adding citrate to blood will bind free calcium and inhibit clotting. Previous studies have demonstrated the feasibility of using RCA in children [14–17]. The usual dose of citrate is 1.5 times the blood flow rate, and calcium infusion is returned to the patient to maintain normocalcemia. In non-COVID-19 patients on CKRT, we maintain circuit ionized calcium levels between 0.35 and 0.5 mmol/l. If frequent circuit clotting is observed with a standard RCA protocol, lower ionized calcium levels (0.2–0.25 mmol/L) in the CKRT circuit can be targeted. Since many adult patients with COVID-19 have deranged liver function tests, citrate accumulation can occur in these patients, leading to severe hypocalcemia or citrate lock. Therefore, strict monitoring of calcium is required while using citrate as an anticoagulant.

Combination of unfractionated heparin and regional citrate anticoagulation

In the event of frequent filter clotting despite optimal doses of unfractionated heparin (UFH) or RCA used independently, experienced centers can try a combination of RCA (in the usual recommended dose as for non-COVID patient) alongside systemic UFH infusion. Systemic UFH at 10 U/kg/h plus RCA at the dose of 1.5 times the blood flow rate can be used.

Prostacyclin/combination of regional prostacyclin and unfractionated heparin

Prostacyclin is another anticoagulant which helps to reduce the chances of filter clotting due to its antiplatelet and heparin sparing activity. The recommended dosage is between 4 and 8 ng/kg/min [18]. In order to minimize the dose of heparin used for anticoagulation and heparin-induced side effects, a combination of heparin and prostacyclin can be used (both administered prefilter). In this setting, heparin at 10 units per kg per hour is combined with prostacyclin given at the rate of 4–8 ng/kg/min [19].

Low molecular weight heparin (LMWH)

In case of shortage of infusion pumps to deliver infusions of regional or systemic anticoagulants (UFH, RCA, or prostacyclin), low molecular weight heparin may be used in the treatment dose.

There might be instances where the availability of infusion pumps to deliver heparin infusion might be inadequate. In these circumstances, low molecular weight heparin (dalteparin, enoxaparin) administered subcutaneously in the treatment dose might be an option. Anti-Xa levels are strictly monitored and kept between 0.35 and 0.45. Some centers administer enoxaparin intravenously in children in order to reduce the discomfort of subcutaneous administration.

If filters still clot on LMWH, RCA may be added to optimize filter half-life. Therefore, the main difference in the provision of CKRT to the COVID-19 positive patient is the use of anticoagulant measures to prevent excessive filter clotting, thus decreasing the downtimes for the treatment, optimizing resources and minimizing exposure to the healthcare professionals.

Shortage of equipment: machines, filters, circuits, and infusion pumps

In case of shortages of CKRT machines, more than 1 patient could be treated by 1 CKRT machine in 24 h using higher than recommended exchange rates to gain metabolic control—50–60 mL/kg/h instead of the recommended dose of 35–45 mL/kg/h or 2 l/1.73 m² [20–22]. Therefore, one machine can deliver CKRT to 2–3 patients in 24 h. In case of shortage of both

equipment and consumables, alternative methods of KRT can be considered.

Acute peritoneal dialysis

Acute peritoneal dialysis is another useful KRT modality which can be used in this scenario. Unlike adults, there is a lot of experience in the use of PD in the cardiac ICU in children. However, maintaining PD in patients who have been prone ventilated is a challenge. PD catheters are inserted in

the supine position before the patient is nursed in the prone position. The usual dose of PD can be increased to optimize fluid and solute removal. Dwell times can be increased to optimize solute removal. However, this can carry the potential risk of fluid retention and worsening respiratory failure. Common problems associated with PD catheters in critically sick children are pericatheter leaks, peritonitis, blockage of catheter, and unpredictable fluid removal [23].

Intermittent hemodialysis can be judiciously used in hemodynamically stable patients after adequate facilities are set up on the ICU—like setting up a reverse osmosis unit. Training

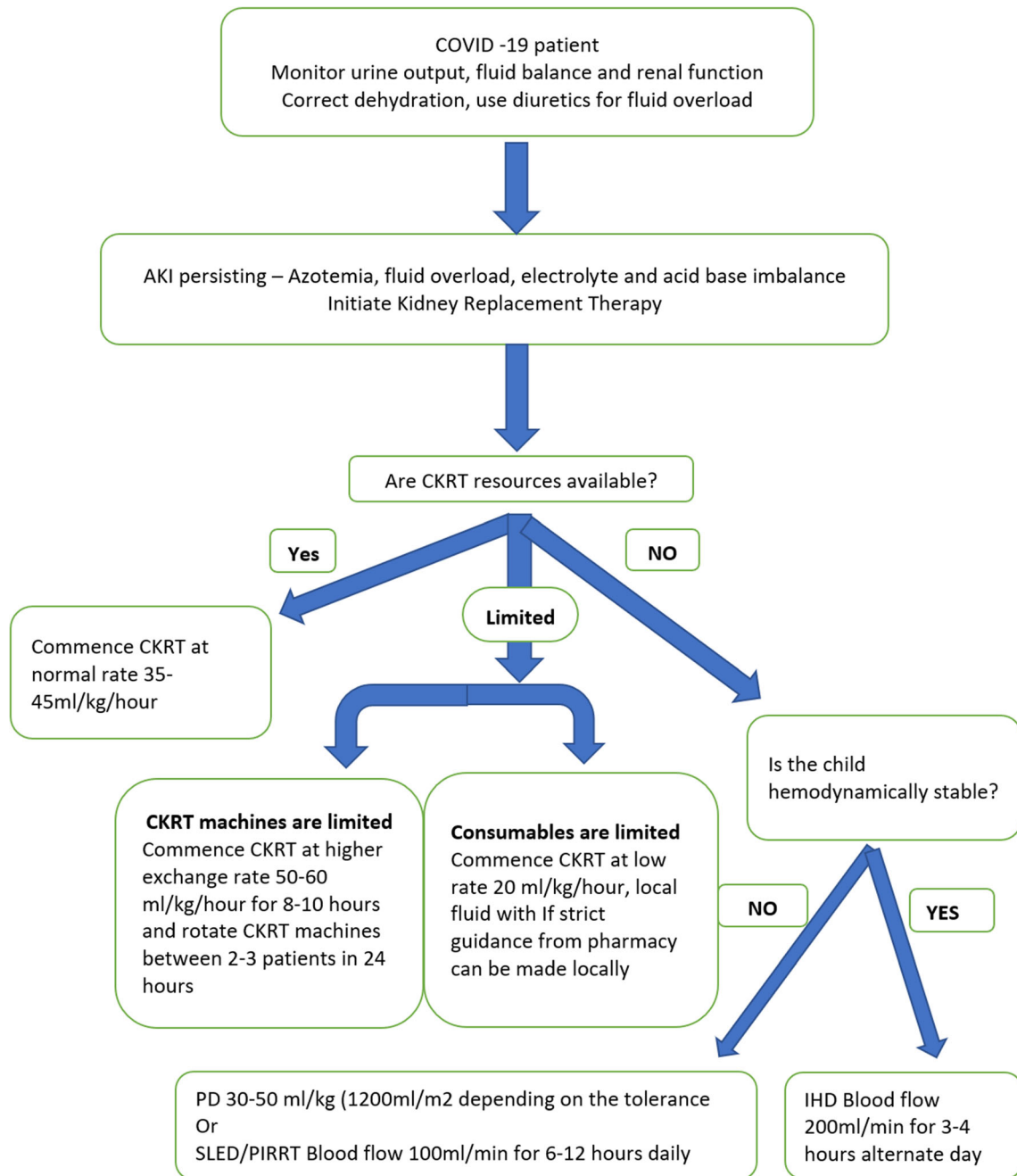


Fig. 1 Suggested flow diagram describing management of kidney replacement therapy (KRT) in COVID-19

of staff and collaboration with other specialities like nephrology and interventional radiology is vital.

Shortage of consumables: (replacement and dialysate fluid, anticoagulant)

When the replacement fluid is in short supply, a less than usual dose of CKRT (as low as 15–20 ml/kg/h) for 24 h can be used as long as metabolic control is achieved. Though not ideal, replacement fluid manufactured by one company can be used interchangeably in the CKRT machine from another company. Some centers manufacture their own replacement and dialysate fluid. Figure 1 summarizes the approach to the delivery of KRT in a pandemic state depending on the availability of resources.

Therefore, provision of KRT in a pandemic state is full of challenges which are summarized in Table 2 along with the potential solutions. Collaboration with other teams and being able to identify and utilize staff in unfamiliar circumstances is the key to tackling these challenges.

Other extracorporeal kidney support in COVID-19 (total plasma exchange and hemoperfusion)

The host response to infection in COVID-19 involves a complex interaction of cytokine storm, inflammation, endothelial dysfunction, and abnormal pathways of coagulation leading to

multisystem involvement. Awaiting the definitive treatment of the virus, modifying the systemic response to the infection should be aggressively sought. Extracorporeal therapies such as hemoperfusion can be beneficial in COVID-19 patients with AKI as these remove the cytokines and other inflammatory mediators from the blood via macroporous sorbent, offering hemodynamic, and multiorgan support [24]. Cytosorb can be integrated into the CKRT circuit pre- or postfilter or as a bypass in ECMO circuit. This process is technically easy and does not interrupt an ongoing treatment. Cartridges have to be changed every 24 h. However, there is currently no evidence of the use of this modality in children except in research or rescue/compassionate grounds.

Therapeutic plasma exchange and plasmapheresis

Plasmapheresis can potentially remove excessive cytokines and reduce the free radical damage. This can ameliorate the cytokine storm thereby reducing the multiorgan damage in patients severely affected by SARS-CoV2. SARS and MERS were treated with plasmapheresis therapy [25, 26]. Therapeutic plasma exchange can be potentially beneficial in critically ill children with COVID-19 who develop thrombocytopenia-associated multiple organ failure (TAMOF: with two or more failing organs), and acquired ADAMTS-13 deficiency indicating a thrombotic microangiopathic process [27].

Table 2 Various challenges in the delivery of continuous kidney replacement therapy (CKRT) during the setting of a pandemic and potential solutions

Challenge faced	Potential solutions
Many more patients than ICUs are used to caring for	Novel use of ICU spaces as per local arrangements – recovery, operating theaters, certain wards with oxygen supplies and facility for reverse osmosis
High proportion of ICU patients develop AKI and require KRT	<ul style="list-style-type: none"> • Rationalize use of KRT • Stricter criteria for initiation of KRT than we might otherwise use.
Lack of enough CKRT machines to provide every patient who needs one	<ul style="list-style-type: none"> • Borrow machines where possible from other areas within the hospital • When there are adequate consumables but a critical shortage of machines, rotate machines between patients. • Alternative methods of KRT (acute PD/IHD) • Collaboration with other teams – nephrology, interventional radiology, vascular
Frequent filter clotting CKRT consumables are being used more quickly than usual or shortage of consumables	<ul style="list-style-type: none"> • Adjust dialysate and replacement fluid ratios • Ensure lowest possible exchange rate used. • Full anticoagulation to prevent filter clotting with regular liaison with hematology team
Increased level of stress at the bedside (physical, emotional, moral, use of PPE)	<ul style="list-style-type: none"> • Support from the senior staff and management • Well-being hubs looking after the mental health of all staff
Similar problems experienced globally at exactly the same time (limiting the possibility of outside help).	Effective communication (what are others doing?) within the network and supporting the healthcare community instead of being institution based

IHD, intermittent hemodialysis; ICU, intensive care unit; PICU, pediatric intensive care unit; PD, peritoneal dialysis; PPE, personal protective equipment

Conclusion

In the setting of a pandemic, circumstances change quickly. With increasing demands in adult surge, staffing, equipment, and consumables will be in short supply for children as well. Increased level of “stress” at the bedside (physical, emotional, moral, PPE, less experienced staff), preparedness to change plans at short notice, and urgent need for rapid education, audit and research during busy times, are some of the challenges faced by clinicians during these unanticipated times. The most important weapons are collaborative team work, timely dissemination of knowledge by education and training, developing resilience in the system and being innovative and flexible in the best interests of the patient. These are unprecedented times; the spectrum of clinical presentation of children affected by COVID-19 is evolving, and we, as clinicians, will need to adapt to this new “unknown”.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Code availability (software application or custom code) Not applicable.

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