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Augmented Renal Clearance: An Under-Recognized Phenomenon Associated With COVID-19

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ABSTRACT: Augmented renal clearance (ARC) is a phenomenon that has been described mainly in critically ill patients and is characterized by increased creatinine clearance and elimination of renally cleared medications that could place patients at risk of therapeutic failure. The COVID-19 pandemic has led to an overwhelming number of ICU admissions with many reports of the impact of COVID-19 on the kidney. This report aims to increase clinician awareness of, and risk factors for ARC in patients with COVID-19, especially in comparison to other critical illnesses.

KEY WORDS: augmented renal clearance; COVID-19; creatinine clearance; critical care

To the Editor:

WHAT IS AUGMENTED RENAL CLEARANCE?

Augmented renal clearance (ARC) is a phenomenon that has been described mainly in critically ill patients and is characterized by increased creatinine clearance (CrCl) and elimination of renally elimination solutes including medications (1). While there have been several definitions used, there is currently no consensus definition for ARC; however, the most commonly used definition is a urine or measured CrCl of greater than 130 mL/min/1.73 m^2 (1). The true prevalence of ARC is poorly described but has been reported in 20–65% of patients in ICUs (2). The prevalence variability may be linked to the inconsistent methods for determining CrCl, ranging from calculated or estimated methods using Cockcroft-Gault and other equations to measured 8- or 24-hour urine CrCl (3).

ARC has been reported in several critical care populations including neurologic injury, burn injuries, sepsis, and trauma (1). More recently, it has also been described in febrile neutropenia and pediatric patients (4). The most consistent risk factor for ARC is age less than 50 years (3). Other risk factors include: male gender, a low severity score on scoring systems like Acute Physiology and Chronic Health Evaluation II or Sequential Organ Failure Assessment score, and/or high blood pressure (3, 5). There is not an optimal surrogate marker of ARC, making it very challenging clinically to identify and monitor for this phenomenon. The Augmented Renal Clearance in Trauma Intensive Care scoring system was developed as a tool to identify trauma patients at high risk for developing ARC, although the specificity of this tool is low at below 70%. The categories of this tool include these previously identified risk factors and include age categories (< 56 yr and between 56 and 75 yr), serum creatinine (< 0.7 mg/dL), and male sex (6).

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The time course of ARC is also not well defined. Although measured urine CrCl is a more accurate determination method, the measurements are usually limited to the first few days of ICU admission. Thus, a true picture of the onset and duration of ARC is largely unknown. Given the diverse nature of the ebb and flow of critical illness in the many different populations that may experience ARC, this time course for ARC is likely variable as well. This presents further challenges for clinicians caring for these patients.

The clinical implications of ARC are related to potential underexposure to renally eliminated medications and risk for clinical failure. Most reports have been associated with antimicrobial agents where shorter half-life, lower peak and trough drug concentration, and lower area under the concentration curve have been reported (3). The association with these pharmacokinetic alterations is hypothesized to lead to worse outcomes including an increased risk for antimicrobial resistance (3); however, while this has been reported in some studies, not all studies confirm this hypothesis (7). There is an urgent need for research to understand adequate drug dosing for all drugs that are renally eliminated and administered to critically ill patients that are linked to meaningful clinical outcomes.

Since December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), described as COVID-19, has caused an international outbreak and has led to an overwhelming number of ICU admissions, primarily as a result of a respiratory illness (8, 9). Initially, very little attention was focused on the renal manifestations; however, there is growing evidence that the virus invades the kidneys. Recently, there has been a proliferation of articles describing acute kidney injury (AKI) (9–11), and thus, all attention has been focused on reduced renal function. However, the question is, could COVID-19 patients also experience ARC? Given the linkage between ARC and sepsis in non-COVID-19 patients and the presence of sepsis in COVID-19, we sought to conduct a rapid review to collate and summarize published evidence of ARC in COVID-19 and compare it to other critically ill patients with sepsis and/or in a mixed ICU. It is critical that clinicians appreciate the full spectrum of impact of COVID-19 on the kidney to improve patient care through appropriate drug selection and dosing interventions. In conducting the review, PubMed, Embase, and Web of Science were searched using keywords focusing on ARC and COVID-19. Reviews and non-English and non-human items were excluded. COVID-19 studies were compared with publications whose primary objective was to describe the epidemiology in a mixed population of critically ill patients and/or sepsis or septic in the title or abstract.

HOW DOES COVID-19 AFFECT THE KIDNEY?

The pathophysiology of both COVID-19 on the kidney and ARC are poorly described and mainly hypothesized (1, 8, 12, 13). While the bulk of the data in both critical illness and COVID-19 focus on the risk of AKI, it is critical to evaluate the hypothesized relationship of COVID-19 illness on the kidney and compare these effects to the proposed mechanisms of ARC in non-COVID-19 to identify commonalities in mechanisms that might suggest ARC could also manifest in COVID-19 patients (**Fig. 1**).

Since the first cases of COVID-19 in late 2019, severe cases of acute respiratory distress syndrome with multisystem organ system failure and death have been reported (14). As the disease progressed, it was clear other organ systems were directly impacted by this COVID as a result of the widespread clinical manifestations reported. The kidney was one of these organ systems where there appeared to be both direct and indirect effects of COVID-19. To date, the majority of reports describe AKI, with a reported prevalance of 28–36.4% of critical care COVID-19 cases, an average day of onset of 5 to 9 days after hospital admission, and an associated high-mortality rate (9). Some of the reports of AKI described not only increases in serum creatinine but also abnormalities in the urinary sediment, including proteinuria and hematuria, and direct evidence of urinary SARS-CoV-2 excretion (8). A small cohort study of severe disease patients also reported hypokalemia with kaliuresis, suggesting renin-angiotensin-aldosterone system (RAAS) activation (8). Figure 1 outlines some of the proposed direct and indirect effects of SARS-CoV-2 on the kidney (left side of Fig. 1). Direct effects that have been hypothesized include direct cellular injury on the podocytes and proximal tubular cells due to viral entry via the angiotensin-converting enzyme 2 receptor, an imbalanced RAAS system, pro-inflammatory cytokines because of the virus, and thrombosis within the kidney. Nonspecific effects include factors related to the ICU stay (fluid loading, hemodynamic alterations, and

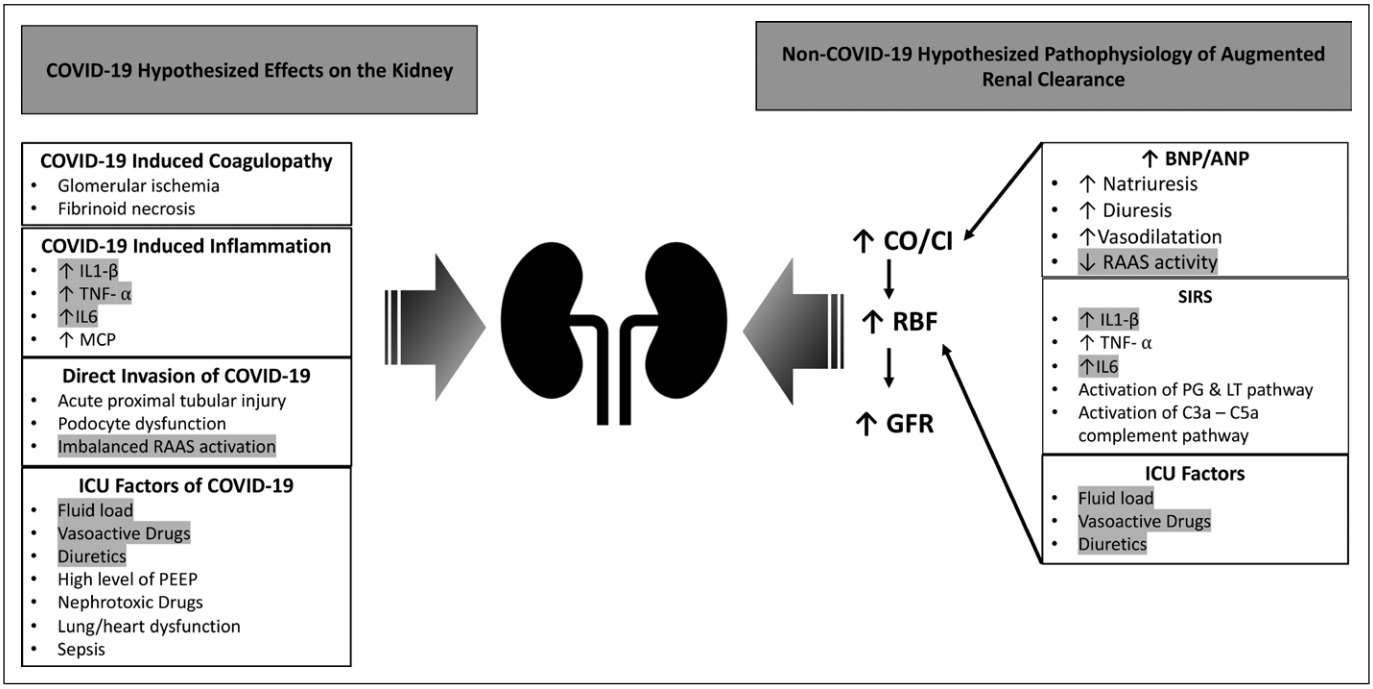

Figure 1. Comparison of COVID-19 hypothesized effects on the kidney with the hypothesized pathophysiology of augmented renal clearance (ARC) (1, 2, 5, 8, 13, 14). The *right side* of the figure outlines the hypothesized pathophysiology of ARC, while the *left side* of the figure provides the hypothesized effects of COVID-19 on the kidney that could result in either acute kidney injury or ARC. The *gray* highlights depict the commonalities between COVID-19 effects on the kidney and the pathophysiology of ARC. ANP = atrial natriuretic peptide, BNP = NT-proB-type natriuretic peptide, CI = cardiac index, CO = cardiac output, GFR = glomerular filtration rate, IL = interleukin, LT = leukotriene, MCP = monocyte chemoattractant protein, PEEP = positive end-expiratory pressure, PG = prostaglandin, RAAS = renin-angiotensin-aldosterone system, RBF = renal blood flow, TNF-α = tumor necrosis factor-α.

administration of vasoactive agents), administration of nephrotoxic agents, use of diuretics, heart/lung dysfunction (particularly right ventricular failure), sepsis, and high levels of positive expiratory end pressures (8, 13). For more detailed information, please refer to comprehensive reviews that describe the COVID-19 effects on the kidney (8, 13).

While these effects are thought to be the primary mechanisms related to the development of AKI, many of the renal effects of COVID-19 on the kidney are similar to the hypothesized pathophysiology of non-COVID-19 ARC in ICU patients (right side of Fig. 1). This might suggest that not only AKI but ARC may be seen in ICU patients with COVID-19 and thus should be explored.

WHAT IS THE PROPOSED PATHOPHYSIOLOGY OF AUGMENTED RENAL CLEARANCE?

Our current understanding of the mechanisms underlying ARC is poorly understood, although most hypothesize it is related to many components of the nephron physiology from renal tubular reabsorption, renal tubular secretions, and increased glomerular filtration rate (3). The common factor is related to a hyperdynamic state either directly related to underlying diseases and/or various ICU interventions. So, ARC may also have both direct and indirect mechanisms that may overlap with those described in COVID-19 patients (gray shaded areas of Fig. 1). The heart of the direct pathophysiological mechanisms is related to the systemic inflammatory response syndrome (SIRS). Potential causes of SIRS related to ARC include: trauma, burn, autoimmune disorders, pancreatitis, sepsis, and surgical procedures. SIRS is driven by the release of endogenous cytokines and inflammatory mediators, in addition to the relative cellular dysoxia. Renal blood flow has been reported to follow cardiac output such that high cardiac output states are associated with increased renal blood flow. There are also indirect factors related to ICU care that are associated with ARC including administration of vasoactive agents, especially those that alter cardiac output, fluid loading, and use of diuretics (12). For brain injury patients, other mechanisms related to cerebrovascular

pressure reactivity, altered pituitary signaling, and brain natriuretic peptide and atrial natriuretic peptide have been described (1).

The mechanisms of ARC associated with COVID-19 have not been explored; however, the associated SIRS with cytokine storm and indirect measures used in the ICU including fluid loading and administration of vasoactive drugs suggest that it may be plausible for ARC to be present in these patients.

HOW DOES THE LITERATURE OF AUGMENTED RENAL CLEARANCE IN PATIENTS WITH COVID-19 COMPARE WITH OTHER PUBLISHED ARC LITERATURE?

As of November 29, 2021, five articles were identified across three databases (Pubmed, Embase, and Web of Science) that discussed patients with COVID-19 exhibiting ARC (**Supplemental Table**, http://links.lww.com/CCX/A898). Each article defined ARC as CrCl greater than 130 mL/min/1.73 m^2 using measured urinary CrCl (15–19). Beunders et al (15) and Murt et al (17) also calculated renal function using Modified Diet in Renal Disease, while Murt et al (17) and Tomasa-Irriguible et al (19) also determined renal function by calculating CrCl based on Chronic Kidney Disease Epidemiology Collaboration. Prevalance of ARC among these five articles ranged from 25% to 72% (15, 17–19) with almost half of patients with ARC in Beunders et al (15) also experienced a decrease in serum creatinine from baseline. While Dhaese et al (16) identified onset of ARC to be anywhere from hospital 2 to 39, skewed toward the first week of hospitalization, Beunders et al (15) and Murt et al (17) reported ARC on median hospital day 28 and 13, respectively, with Murt et al (17) specifying a duration of 5 ± 1 day. Additionally, Murt et al (17) determined that male gender, younger age (age not specified), and increase in inflammatory markers, notably peak ferritin, peak C-reactive protein (CRP), and peak D-dimer, were all associated with development of ARC. Dhaese et al (16) was the only other article to report risk factors where younger patients were more likely to exhibit ARC. Importantly, clinical outcomes were reported in both Selles et al (18) and Tomasa-Irriguible et al (19). Specifically, Selles et al (18) indicated failure to achieve therapeutic vancomycin concentrations, while Tomasa-Irriguible et al (19) reported a significant increase in deep vein thrombosis and pulmonary embolism (44 vs 31; 33 vs 10, respectively; $p = 0.025$) and subtherapeutic anti-Xa levels in patients with ARC despite appropriate chemoprophylaxis. Additionally, Murt et al (17) commented on the increased possibility of therapeutic failure of renally cleared drugs, although they did not report specific instances of drug failure.

Regarding patients without COVID-19 exhibiting ARC, we searched for original research articles on November 29, 2021, that described ARC in a mixed ICU population and/or in patients with sepsis. A total of 16 articles were identified and included in the Supplemental Table (http://links.lww.com/CCX/A898) (20–35). The general consensus definition of ARC among these reviews is a CrCl greater than or greater than or equal to 130 mL/min/1.73 m^2 (20, 22–25, 28, 29, 31, 33–35); however, the two studies in pediatric patients used different definitions including CrCl or greater than or equal to 160 mL/min/1.73 m^2 (21) and measured CrCl exceeding age-adjusted reference values plus two SDs (26).

Most studies reported using measured urinary CrCl as a means to quantify renal function with collection times ranging from 4 to 24 hours; however, 24-hour collection was used in seven of the 16 studies. Prevalance of ARC among the included studies ranged from 24.9% to 67.4% (20–35). Eight of the studies provided insight into the ARC onset and time course (Supplemental Table, http://links.lww.com/CCX/A898). While the reporting of this data is variable, making it difficult to make definitive conclusions, it appears that patients may experience ARC for at least half of their ICU admission days (29) with some may have ARC across the entire ICU stay (22, 24, 27, 31, 33). Tomasa-Irriguible et al (22) followed patients twice weekly for 2 months to provide insight into the natural history of ARC. They reported that patients who experience ARC in the ICU maintained ARC for 3 weeks and that some of the non-ARC patients in the ICU developed ARC after the third follow-up. This study highlighted that ARC is a dynamic phenomenon without a clear established pattern but could last several weeks (22).

Young age was the most commonly reported risk factor for ARC reported in nine of the studies (22–25, 27, 29, 31, 33, 34). Other specific risk factors are listed in the Supplemental Table (http://links.lww.com/CCX/A898). With respect to the clinical implication of

ARC, no study reported an impact on clinical outcomes. Four of the studies in septic patients reported an increase in renally eliminated drugs and commented on the need for increased drug dosing to achieve appropriate pharmacokinetic/pharmacodynamic; however, antibiotics is the only drug class studied to date (30, 31, 35).

While there are similarities in the literature of ARC in patients with and without COVID-19, there are also some notable differences (22, 24, 26, 27, 29, 31, 33, 35). Younger age is the most frequently reported risk factor for ARC both in COVID-19 and non-COVID-19 patients. This is an important consideration as new variants of COVID-19 emerge since the delta variant occurred more frequently in younger patients including pediatric patients (36). Therefore, the prevalence of ARC in COVID-19 patients may be variable depending on the variant. There are notable differences, however, between patients presenting with COVID-19 and those who exhibited ARC without coinfection. First is the pronounced variation in onset of ARC. Patients with COVID-19 are reported to have a much-delayed onset of ARC compared with those without (13–28 d vs 1–3 d, respectively) (15–17, 21, 26, 27, 29, 31, 33, 35). The duration of ARC has been less extensively studied; however, Murt et al (17) suggested ARC lasts 5 days in the COVID patients they studied, while the non-COVID-19 ARC population varies from 1 day to 3 weeks (15–17, 21, 22, 26, 27, 29, 31, 33, 35).

The new COVID-19 articles uniquely include interesting and novel biomarkers that could be associated with ARC, whereas the non-COVID-19 studies did not explore these thoroughly. Most importantly, and promising for future ARC research, is the identification of novel biomarkers from COVID-19 patients to predict ARC. While Cook and Hatton-Kolpek (1) in their ARC review mentioned increased atrial natriuretic peptide and brain natriuretic peptide as hypothesized possible contributing factors to ARC. Murt et al (17) found significant correlations between the first day of ARC and peak ferritin, CRP, and D-dimer, biomarkers not before assessed in the ARC literature. These newfound biomarkers provide a major area for future exploration in identifying patients at risk for ARC. Furthermore, the ARC in COVID-19 literature has highlighted the first definitive case of therapeutic drug failure in patients likely due to ARC. While antimicrobial drug studies have either not shown or not evaluated clinical outcomes, Tomasa-Irriguble et al (19) found significant increase in thromboembolic events in patients with COVID-19 being treated with heparin-based chemoprophylaxis who exhibited ARC compared with those without ARC, evidenced by subtherapeutic anti-Xa levels. This new outcome data increases the clinical importance of screening for ARC and the need to make appropriate pharmacotherapy interventions in this subsect of patients; herein lies the heart of future research in ARC.

CONCLUSIONS

While much attention has been paid to renal injury in COVID-19, ARC is another important clinical phenomenon to consider, but there is a paucity of data in this population. It appears to manifest differently compared with other patient populations, occurring much later in a patient's clinical course, and has been associated with negative clinical outcomes including deep vein thrombosis and pulmonary embolism. Given that younger age is a strong risk factor for ARC, the clinician should be cognizant that the different variants of COVID-19 may display age differences and thus varying prevalence of ARC may be observed. This new biomarker data from COVID-19 ARC patients provides new avenues for other populations to further elucidate the mechanism behind ARC and additional predictive methods. Clinicians should be aware of the potential spectrum of both reduced and augmented renal function while caring for patients with COVID-19.

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