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The COVID-Kidney Controversy: Can SARS-CoV-2 Cause Direct Renal Infection?

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Keywords

COVID-19 · SARS-CoV-2 · Kidney pathology · Immunohistochemistry · Ribonucleic acid

Abstract

Context: Determining whether SARS-CoV-2 causes direct infection of the kidneys is challenging due to limitations in imaging and molecular tools. **Subject of Review:** A growing number of conflicting kidney biopsy and autopsy reports highlight this controversial issue. **Second Opinion:** Based on the collective evidence, therapies that improve hemodynamic stability and oxygenation, or dampen complement activation, are likely to ameliorate acute kidney injury in COVID-19. At this time, whether inhibition of viral infection and replication directly modulates kidney damage is inconclusive.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus outbreak in China at the end of 2019 led to the COVID-19 pandemic, which has claimed over 1 million lives as of October 1, 2020. SARS-CoV-2 demonstrates broad organotropism, that is, cells in many or-

gan systems can be directly infected and may act as a reservoir for the virus. Angiotensin-converting enzyme 2 (ACE2) is the functional receptor of SARS-CoV-2 and is expressed in most organs, with highest expression in the kidneys (proximal tubular cells and podocytes) and ileum [1]. Given what is known about ACE2 tissue distribution, the association between acute kidney injury and increased mortality risk in COVID-19, and the urgent need to identify therapeutic targets, it is no surprise that SARS-CoV-2-associated kidney injury is an area of active research.

Several indirect pathways of SARS-CoV-2 acute kidney injury have been elucidated. Kidney pathology shows varying degree of acute tubular injury which includes necrosis when severe, due to a combination of a virus-induced cytokine storm, hypoxemia, and polypharmacy. Complement and coagulation cascades are triggered and may activate each other [2]; however, kidney thrombotic microangiopathy is present only in a subset of cases [3–6]. A few cases of glomerular disease have been reported, with the most common being collapsing glomerulopathy [6–10] which can be associated with high-risk APOL1 gene variants [7–9]. Minimal change disease, membranous glomerulopathy, anti-GBM disease, infection-associated glomerulonephritis, and ANCA-associated vasculitis have also been reported concurrently with SARS-CoV-2 infection [3, 6, 7, 11–13].

Table 1. Summary of studies as of November 30, 2020, that have investigated direct kidney infection by SARS-CoV-2

Source	Kidney samples assessed for SARS-CoV-2, <i>n</i>	Kidney biopsy versus postmortem	Methods used to detect SARS-CoV-2	Details
Studies that detected SARS-CoV-2 in kidney tissue				
Abbate et al. [18]. Nephron. Italy	1	Postmortem	TEM	Suggestive morphology of coronavirus with recognizable spikes
Bradley et al. [19]. Lancet. USA	2–4	Postmortem	RT-PCR TEM IHC: anti-SARS-S antibody, mouse, GeneTex	RT-PCR: 3/3 samples positive TEM: 2/2 samples with viral-like particles, diameter 70–100 nm IHC: 2/4 samples positive
Braun et al. [20]. Lancet. Germany	63	Postmortem	RT-PCR	SARS-CoV-2 detected in 38/63 samples
Diao et al. medRxiv preprint. [†] China	6	Postmortem	TEM IHC: anti-SARS-NP antibody from clone ID: 019, rabbit, Sino Biological	TEM: 2/2 samples with viral-like particles, diameter 80–160 nm IHC: 6/6 samples positive
Farkash et al. [21]. J Am Soc Nephrol. USA	1	Postmortem	TEM	Viral-like particles, diameter 76 μm
Puelles et al. [22]. N Engl J Med. Germany	6	Postmortem	RT-PCR, RNA-ISH	SARS-CoV-2 detected in 3/6 samples
Su et al. [23]. Kidney Int. China	6–9	Postmortem	TEM IHC: anti-SARS-NP antibody from clone ID: 019, rabbit, Sino Biological	TEM: 7/9 samples with virus-like particles, diameter 65–136 nm with 20–25 nm spikes IHC: 3/6 samples positive
Studies that were negative for SARS-CoV-2 in kidney tissue				
Akilesh et al. [3, 11]. Am J Kidney Dis. USA	17	Kidney biopsy	RNA-ISH (4 biopsies) TEM (all biopsies) IHC: anti-SARS-NP antibody, 40143-T62, Sino Biological (4 biopsies)	No SARS-CoV-2 detected
Golmai et al. [15]. J Am Soc Nephrol. USA	12	Postmortem	TEM	Clathrin-coated vesicles closely resembling viral particles, diameter <20 to >500 nm. No true viral particles identified.
Kudose et al. [7]. J Am Soc Nephrol. USA	17 (14 native kidneys and 3 transplant allografts)	Kidney biopsy	RNA-ISH TEM IHC 1. Anti-SARS-NP antibody from clone ID: 001, rabbit, Sino Biological 2. Anti-SARS-S2 antibody from clone ID: 1A9, GTX632604, mouse, GeneTex	No SARS-CoV-2 detected
Larsen et al. [8]. Kidney Int Rep. USA	1	Kidney biopsy	RNA-ISH	No SARS-CoV-2 detected This study notes that they tested a widely used IHC antibody under numerous conditions and found nonspecific staining (anti-SARS-NP antibody from clone ID: 019, rabbit, Sino Biological)
Nasr et al. [9]. Am J Kidney Dis. USA	13	Kidney biopsy	RNA-ISH (1 biopsy) TEM (all biopsies)	No SARS-CoV-2 detected
Peleg et al. [10]. Kidney Int Rep. USA	1	Kidney biopsy	RNA-ISH TEM	No SARS-CoV-2 detected
Rossi et al. [24]. Kidney Int Rep. Italy	1	Kidney biopsy	RT-PCR	No SARS-CoV-2 detected
Santoriello et al. [5]. J Am Soc Nephrol. USA	10	Postmortem	RNA-ISH	No SARS-CoV-2 detected

Table 1 (continued)

Source	Kidney samples assessed for SARS-CoV-2, <i>n</i>	Kidney biopsy versus postmortem	Methods used to detect SARS-CoV-2	Details
Sharma et al. [6]. J Am Soc Nephrol. USA	10	Kidney biopsy	TEM IHC: SARS-CoV-2 nucleocapsid protein, clone 1C7; Bioss, Woburn, MA	No SARS-CoV-2 detected
Xia et al. [25]. Am Soc Nephrol. China	10	Postmortem	RT-PCR IHC: anti-SARS-S from clone ID: HA14FE2402, Sino Biological	No SARS-CoV-2 detected

IHC, immunohistochemistry; NP, nucleocapsid protein antigen; RNA-ISH, in situ hybridization for detection of target ribonucleic acids within cells; S, spike antigen; RT-PCR, quantitative real-time reverse transcriptase polymerase chain reaction for detection of ribonucleic acids; TEM, transmission electron microscopy. † B. Diao, C.H. Wang, R.S. Wang, Z.Q. Feng, Y.J. Tan, H.M. Wang, et al.: Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (preprint posted online April 10, 2020). medRxiv. doi: 10.1101/2020.03.04.20031120.

Whether direct viral kidney infection occurs with SARS-CoV-2 is a controversial topic. Detection methods include histology, that is, immunohistochemistry (IHC) and transmission electron microscopy (TEM), and ribonucleic acid (RNA) assays, that is, in situ hybridization (RNA-ISH) and quantitative real-time reverse transcriptase polymerase chain reaction (RT-PCR). These methods have inherent limitations.

IHC is valid only if the antibody probe is specific; unfortunately, the commercially available antibodies targeting the SARS-CoV-2 nucleocapsid protein (NP) and spike (S) antigens have not been well validated. In particular, there are concerns with the anti-SARS-NP antibody from clone ID: 019 (Sino Biological, Beijing, China) which has been tested under numerous conditions and has shown nonspecific positive staining in the kidney parenchyma [8]. Moreover, proximal tubules are prone to nonspecific staining of many antibodies due to their intense absorptive capacity.

TEM is challenging as numerous ultrastructures (termed viral-like particles) can mimic viruses [14]. For example, multivesicular bodies in podocyte cytoplasm and clathrin-coated endocytosed vesicles in tubular epithelial cells can have the appearance of a viral corona [8, 15]. Several investigations of pre-COVID era biopsies have demonstrated structures morphologically identical to those reported as “SARS-CoV-2 viral particles” [16, 17]. To date, no studies utilizing immunoelectron microscopy for specific viral antigens have been reported.

RNA assays are regarded as the most sensitive and specific, but may be limited if the virus is present below the level of detection. RT-PCR requires homogenization of a tissue sample and may report a false positive if blood is not

carefully washed out from the sample, such that the test is actually detecting extracellular circulating virus. Moreover, if tissue samples are obtained at time of autopsy, extent of postmortem autolysis and cell degeneration can complicate interpretation of viral detection assays.

Conflicting studies published between April and November 2020 have provoked an ongoing debate about whether SARS-CoV-2 causes direct kidney infection (Table 1). Several postmortem studies have reported detection of SARS-CoV-2 by electron microscopy, IHC, and/or RNA assays [18–23] (including one medRxiv preprint by Diao et al.). Of note, 2 of these studies utilized the anti-SARS-NP antibody that has raised concerns for a nonspecific signal as discussed above [8]. Puelles et al. [22] provided compelling evidence of punctate staining of viral RNA in glomeruli and tubules by in situ hybridization, and their study included multiple SARS-CoV-2 negative controls. The study by Braun et al. [20] demonstrated successful infection of cultured primate kidney tubular epithelial cells, utilizing homogenized kidney specimens obtained at time of autopsy from SARS-CoV-2 patients; however, the possibility of virus present within residual blood in the kidney tissue could also explain this observation.

Of note, difficulty interpreting RNA-ISH in autopsy tissue has been reported [5] whereby there is rare tubular positivity in both SARS-CoV-2-positive and -negative patients. Thus, in autopsy tissue, RNA-ISH may show false positives, and the threshold as well as characteristics for true positive staining remains to be established.

In contrast, biopsy data from live patients and other autopsy studies have not detected SARS-CoV-2 in the kidney via IHC, RT-PCR, and RNA-ISH [3, 5–11, 15, 24, 25]. It is possible that the absence of virus detection may

reflect viral clearing from the kidney as there is frequently delay between initial SARS-CoV-2 infection and either renal biopsy or autopsy. Nonetheless, the negative reports are more consistent with the fact that SARS-CoV-2 is rarely detected in the urine, and urinary levels do not correlate with degree of kidney injury [26, 27]. Furthermore, blood levels are also generally low or nondetectable [27]. These data support the notion that the majority of SARS-CoV-2 renal complications likely result from indirect mechanisms, even if a minority of cases may indeed show direct kidney viral infection.

Given this controversy, future studies should utilize rigorous controls including both SARS-CoV-2-positive and -negative tissue. Multimodal detection strategies including IHC, RNA-ISH, and immunoelectron microscopy are warranted. We believe without immunoelectron detection, morphologic evaluation by electron microscopy alone is not sufficient to confirm the presence of viral particles. Fortunately, published validation studies of SARS-CoV-2 antibodies and RNA-ISH are emerging [28] which will help guide the use of appropriate commercially available antibodies and RNA-ISH probes.

Proof of viral replication in human kidney cells remains to be confirmed [29, 30]. Based on the collective evidence, therapies that improve hemodynamic stability and oxygenation, or dampen complement activation, are likely to ameliorate acute kidney injury in COVID-19. At this time, whether inhibition of viral infection and replication directly modulates kidney damage is inconclusive.

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Conflict of Interest Statement

W.L. Lau has received honoraria and/or support from Fresenius, Hub Therapeutics, Roche, Sanofi, and ZS Pharma. J.E. Zuckerman is a paid consultant for Leica Biosystems. A. Gupta has filed 3 provisional patent applications for use of PGD2 and thromboxane A2 antagonists, including ramatroban, as a treatment for COVID-19 (Application Nos. 63/003,286 filed on March 31, 2020; 63/005,205 filed on April 3, 2020; and 63/027,751 filed on May 2, 2020). K. Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, Ardelyx, Astra-Zeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Kissei, Novartis, Pfizer, Regulus, Relpyssa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS Pharma.

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Author Contributions

W.L.L. and J.E.Z. drafted the manuscript. W.L.L., J.E.Z., A.G., and K.K.Z. made revisions and approved the final manuscript version.

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