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Renal Transplant Recipient with Concurrent COVID-19 and *Stenotrophomonas maltophilia* Pneumonia Treated with Trimethoprim/Sulfamethoxazole Leading to Acute Kidney Injury: A Therapeutic Dilemma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BEF 1 Mohamed A. Mohamed
CDEF 2 Jasleen Kaur
BF 1 Farah Wani
ADE 1 Asim Kichloo
ACDEF 3 Ravinder Bhanot

1 Division of Internal Medicine, Central Michigan University, Saginaw, MI, U.S.A.
2 Division of Rheumatology, Detroit Medical Center, Wayne State University, Detroit, MI, U.S.A.
3 Division of Pulmonary and Critical Care, Ascension St Mary's Hospital, Saginaw, MI, U.S.A.

Corresponding Author: Ravinder Bhanot, e-mail: rdbhanot@gmail.com
Conflict of interest: None declared

Patient: Male, 64-year-old
Final Diagnosis: COVID-19 pneumonia
Symptoms: Cough • fever • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine • Pulmonology

Objective: Rare co-existance of disease or pathology

Background: Although coronavirus disease 2019 (COVID-19) manifests primarily as a lung infection, its involvement in acute kidney injury (AKI) is gaining recognition and is associated with increased morbidity and mortality. Concurrent infection, which may require administration of a potentially nephrotoxic agent, can worsen AKI and lead to poor outcomes. *Stenotrophomonas maltophilia* is a multidrug-resistant gram-negative bacillus associated with nosocomial infections, especially in severely immunocompromised and debilitated patients. Trimethoprim/sulfamethoxazole combination (TMP/SMX) is considered the treatment of choice but can itself lead to AKI, posing a significant challenge in the management of patients with concomitant COVID-19 and *S. maltophilia* pneumonia.

Case Report: A 64-year-old male with end-stage renal disease and post renal transplant presented with severe respiratory symptoms of COVID-19 and was intubated upon admission. His renal functions were normal at the time of admission. The patient subsequently developed superimposed bacterial pneumonia with *S. maltophilia* requiring administration of TMP/SMX. However, TMP/SMX led to the development of AKI, which continued to worsen despite appropriate management including hemodialysis. This coincided with and most likely resulted in the patient's clinical deterioration and ultimate death.

Conclusions: The etiology of kidney disease involvement in patients with COVID-19 is still evolving and appears to be multifactorial. The condition can significantly worsen especially when nephrotoxic agents are given, probably due to a cumulative or synergistic effect. Great caution should be taken when administering nephrotoxic agents in the setting of COVID-19 as it can lead to adverse patient outcomes.

MeSH Keywords: Acute Kidney Injury • COVID-19 • *Stenotrophomonas maltophilia* • Trimethoprim-Sulfamethoxazole Combination • Kidney Transplantation

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/926464

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Background

Since the global outbreak of the coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has been established that the disease manifests mainly as a lower respiratory tract infection [1,2]. Although its involvement in other systems has been noted, the extended effects have not yet been fully studied. However, the renal system is commonly affected and acute kidney injury (AKI) has been reported in 3% to 37% of COVID-19 patients, often with increased morbidity and mortality [3–5]. This poses a significant challenge in the treatment of such patients who may require nephrotoxic drug administration to treat a concurrent infection or underlying pathology.

Stenotrophomonas maltophilia is a gram-negative bacillus and an opportunistic pathogen responsible for various infectious diseases and deaths in hospitalized patients, especially in patients who are immunosuppressed, immunocompromised, or have medical implants [6]. *S. maltophilia* is inherently resistant to multiple classes of antibiotics, and trimethoprim/sulfamethoxazole combination (TMP/SMX) is considered the treatment of choice because it has the most reliable *in vitro* activity against the organism [7]. However, TMP/SMX has a narrow therapeutic index and nephrotoxic properties which can lead to AKI [8]. We present a patient with COVID-19 and concomitant *S. maltophilia* pneumonia for whom the administration of TMP/SMX led to the accelerated deterioration of renal function and clinical condition. In the midst of rapidly increasing evidence of kidney dysfunction due to COVID-19, our case illustrates the therapeutic dilemma clinicians can face when the use of a nephrotoxic drug is unavoidable.

Case Report

A 64-year-old Caucasian man with a medical history including type 2 diabetes and hypertension presented to the emergency department with symptoms of progressive shortness of breath, recurrent fever, and cough for 4 days. He was also a kidney transplant recipient (deceased donor) maintained on immunosuppressive drugs including 5 mg tacrolimus twice per day, 250 mg mycophenolic acid twice per day, and 5 mg prednisone once per day. His renal parameters were normal upon admission with serum creatinine of 0.7 mg/dL and a glomerular filtration rate (GFR) >60 ml/min/1.73 m^2. Relevant workup included a chest radiography (CXR) which revealed diffuse interstitial and airspace opacities in the bilateral lungs, suggestive of multifocal pneumonia (Figure 1). The gram stain on the sputum sample was negative for any organism, and a rapid influenza test and pneumococcal and legionella urinary antigen test were negative. His nasopharyngeal swab results returned positive for SARS-CoV-2 infection by a real-time reverse transcriptase

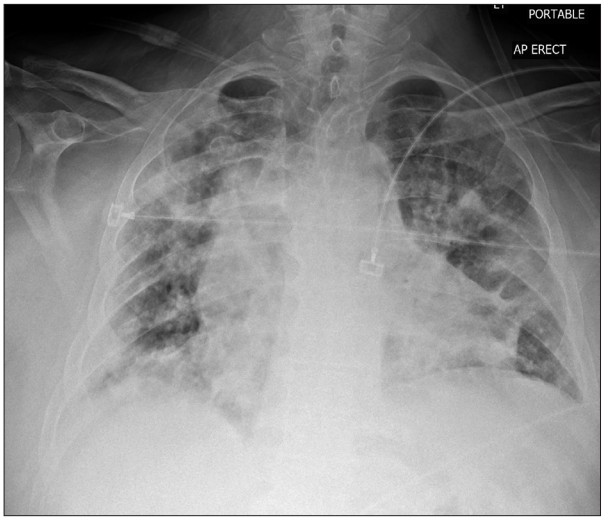

Figure 1. CXR upon admission showing diffuse interstitial and airspace opacities in the bilateral lungs, right >left.

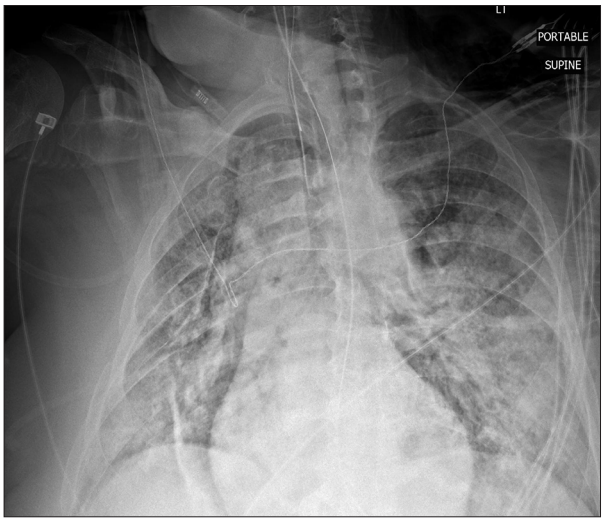

Figure 2. CXR on day 3 showing worsening of bilateral diffuse interstitial and airspace opacities.

polymerase chain reaction test (RT-PCR), done using the Abbott ID Now SARS-CoV-2 RT-PCR testing system. He was admitted to the intensive care unit and was electively intubated because of his worsening respiratory status and severe acute hypoxic respiratory failure. The patient was started on compassionate use of hydroxychloroquine with azithromycin for COVID-19 infection, which was standard care during the time of his hospitalization and our institution's policy. While awaiting the final sputum culture report, he was also started on cefepime for broad antibiotic coverage because of the severity of his disease. His immunosuppressive medications were adjusted and included the suspension of mycophenolic acid, reduction of tacrolimus to 2.5 mg twice per day, and the continuation of prednisone at his home dose of 5 mg per day. For mechanical ventilation, a low tidal volume lung-protective strategy was employed along

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Table 1. Lab results during the clinical course of the patient.

	Admission	Day 3*	Day 5**	Day 7	Day 8***	Day 11	Reference value
Creatinine (mg/dL)	0.7	0.8	1.0	2.1	3.4	2.8	0.5–1.3
BUN (mg/dL)	18	34	43	64	73	56	7–26
GFR (ml/min/1.73 m^2)	>60	>60	>60	27	18	29	>60
Arterial pH	7.34	7.25	7.29	7.22	7.19	7.19	7.35–7.45
Arterial PO2 (mmHg)	108	75	84	76	92	67	80–108
FiO2 (in%)	100	80	80	90	100	100	Up to 100

* Day3: Sputum cultures re-sent; ** Day 5: Cultures positive for *Stenotrophomonas maltophilia*, Sulfamethoxazole/Trimethoprim (TMP/SMX) initiated; *** Day 8: Dialysis initiated.

with prone positioning and neuromuscular blockade (atracurium) under sedation. High positive end-expiratory pressure therapy was also instituted to maintain adequate oxygenation.

On day 3, the patient's sputum sample was redrawn because of increased endotracheal secretions, worsening results of the CXR, and hypoxemia (Figure 2). The patient was switched to a high dose of corticosteroids (60 mg IV methylprednisolone once daily). The sputum examination came back positive for gram-negative bacilli on hospitalization day 4, and on day 5 the automated culture with antibiogram identified the bacterium *S. maltophilia*, which is sensitive only to TMP/SMX. Antibiotic coverage was thus tailored to TMP/SMX to treat this new ventilator-associated pneumonia (VAP) and the cefepime was discontinued. From day 7 onward, the patient developed AKI with worsening serum creatinine (2.1 mg/dL) and oliguria, which did not respond to fluid administration and continuation of his immunosuppressive drugs (Table 1). TMP/SMX was discontinued on day 8 and switched to levofloxacin while we awaited the susceptibility results, which later came back as intermediately sensitive. The patient's kidney function continued to deteriorate as indicated by serum creatinine increasing as high as 3.4 mg/dL on day 8, GFR decreasing to 18 ml/min/1.73 m^2, and hyperkalemia (serum potassium of 6.1 mmol/L); the patient was therefore started on hemodialysis (Table 1). The urinalysis did not reveal eosinophiluria or white cell casts, so the patient was continued on the same dose of steroids as before (5 mg per day). His tacrolimus levels remained therapeutic at between 5–8 ng/ml (reference range 5–20 ng/ml). A kidney biopsy to rule out transplant rejection was considered unsafe because of the patient's poor oxygenation, high ventilatory requirement, and overall very ill clinical status. Our institution had no access to remdesivir at the time, and convalescent plasma was also unavailable. He was continued on supportive therapy along with hemodialysis and mechanical ventilation. Despite extensive medical care, the patient's oxygenation and overall clinical status continued to decline (Table 1, Day 11). Due to the patient's poor prognosis, the family decided to proceed with comfort care measures, and the patient died on day 12 of his hospitalization. An autopsy was offered to the patient's family but they declined.

Discussion

There is increasing evidence that AKI and kidney abnormalities are associated with COVID-19 and lead to a higher risk of morbidity and mortality [3–5]. Although the exact mechanism remains unclear, it is postulated that SARS-CoV-2 can penetrate the cells of the kidney tubule and cause direct cytotoxic effects through rapid replication within each cell [3]. Renal histopathological analysis of patients with COVID-19 has revealed distinct features of injury involving the direct injury to the parenchyma, likely due to endothelial damage from severe acute tubular necrosis with lymphocyte and macrophage infiltration [9,10]. The main binding site for cell entry of SARS-CoV-2 is the angiotensin-converting enzyme 2 protein, which is found on a much larger scale in the proximal and distal tubules of the kidney than in those found in the lung alveoli [11]. Morphological findings of RBC fragments and fibrin thrombi in renal vasculature have also been seen leading to small vessel occlusion, suggesting another theory of AKI in patients with COVID-19 [9,10]. Kidney disease in patients with COVID-19 can manifest as proteinuria, hematuria, or AKI, and each of these presentations can be an independent risk factor for in-patient hospital death as shown in a recent prospective analysis of 701 COVID-19 patients [3]. Another large observational study from New York showed that AKI occurs frequently among patients with COVID-19 and in temporal association with respiratory failure and is associated with a 35% mortality rate [12]. In addition to having been severely affected by COVID-19, our patient had underlying risk factors to develop AKI, namely, his single-functioning transplanted kidney, diabetes, hypertension, and immunosuppressed status.

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S. maltophilia is a multidrug resistant gram-negative bacillus mostly seen in clinical practice as an opportunistic pathogen predominantly in mechanically ventilated patients [13]. It is responsible for approximately 6% of the VAPs that usually occur after a prolonged duration of mechanical ventilation [14]. Prior exposure to broad-spectrum antibiotics, including cefepime, has been significantly associated with VAP due to *S. maltophilia,* as was the case in our patient [14,15]. The drug of choice for its treatment has been TMP/SMX because it has the most reliable *in vitro* activity against the organism and its extensive drug resistance [7]. However, TMP/SMX has nephrotoxic properties which cause acute tubular necrosis in the majority of cases and acute interstitial nephritis in the minority of cases [16]. In hindsight, a different antimicrobial agent could have been preferable over TMP/SMX, but our patient's sputum cultures showed sensitivity solely to it, and there was no evidence of renal impairment at the onset of the treatment. Our patient's AKI can be explained by the concurrent COVID-19 infection and administration of a nephrotoxic antimicrobial agent (i.e., TMP/SMX) in the setting of worsening sepsis, hemodynamic instability, and need for mechanical ventilation. Although possible, transplant rejection was a less likely cause since our patient was continued on steroids and tacrolimus (with normal therapeutic levels) throughout his hospital stay. The risk of AKI should raise concerns in clinical practice when the need arises to administer TMP/SMX or other known nephrotoxic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) or diuretics in COVID-19 patients as they can potentiate renal dysfunction.

We question how much of our patient's AKI burden was attributable to TMP-SMX and how much was attributable to the COVID-19 infection. In a previous study, the adverse effects of TMP/SMX were assessed in 573 patients, of which 5.8% developed AKI solely due to the drug without confounding factors, and only 1 patient required dialysis [8]. These results agreed with other studies which showed that, although AKI is a common adverse effect of TMP/SMX, it is usually transient and often subsides after discontinuation of the medication [17]. On the other hand, a recent epidemiological study showed that renal replacement therapy was required in 5% (14) of 278 pooled patients with COVID-19, indicating a relatively high prevalence [18]. Considering the speed and severity of our patient's renal decline, we believe that the nephrotoxic effects of COVID-19, even after discontinuation of the TMP/SMX, played an independent role in his poor outcome. More research is needed to analyze the additive or possible synergistic nephrotoxic effects of COVID-19 and common nephrotoxic agents administered during clinical practice. Currently data on AKI in association with COVID-19 infection is minimal and is based mostly on case reports and small-scale retrospective studies. Larger scale studies are needed to fully assess the role of COVID-19 on renal function.

Conclusions

The burden of COVID-19 needs to be considered as a contributing factor in patients with worsening AKI, even in the setting of shock, sepsis, and nephrotoxic agents. This burden is believed to be secondary to the direct tubular damage caused by virus replication inside cells or by microthrombi formation leading to microangiopathy [3,9]. Caution should be taken when administering nephrotoxic agents in cases of severe COVID-19 as it can lead to poor outcomes.

Conflicts of interest

None.

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