

Treatment refractory *Stenotrophomonas maltophilia* bacteraemia and pneumonia in a COVID-19-positive patient

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SUMMARY

Stenotrophomonas maltophilia is an opportunistic pathogen that most often infects patients requiring mechanical ventilation, indwelling central venous catheters and broad-spectrum antibiotics. The reported incidence of *S. maltophilia* infection has increased over the past two decades, and many of its risk factors are commonly seen in patients with severe COVID-19 infection. Our case regards a patient with severe COVID-19 pneumonia, who subsequently developed disseminated *S. maltophilia* infection, refractory to first-line treatment and optimal medical management. This case highlights the high index of suspicion required for diagnosing secondary complications in patients with COVID-19 infection and highlights the difficulty in treating disseminated *S. maltophilia* infection in critically ill patients.

BACKGROUND

Stenotrophomonas maltophilia is an opportunistic, and frequently multidrug-resistant Gram-negative bacteria of increasing clinical significance, coinciding with an increased use of mechanical ventilation, indwelling central venous catheters and the widespread use of broad-spectrum antibiotics.¹ The reported incidence of *S. maltophilia* infection ranges from 7.1 to 37.7 cases per 10 000 hospital discharges.^{2–5} *S. maltophilia* is most frequently hospital-acquired, with pneumonia being the most common manifestation and bacteraemia being second most common.⁶ Pulmonary infection is often preceded by respiratory tract colonisation, with mechanical ventilation being an important risk factor for both colonisation and infection. In cases of bacteraemia, central venous catheters are a major risk factor, with approximately 72% of *S. maltophilia* bacteraemia being primarily catheter-related, and 22% thought to be secondary to pneumonia.⁷ There is high mortality associated with *S. maltophilia* infection, with a recent retrospective review of 282 patients with *S. maltophilia* hospital-acquired pneumonia reporting a mortality rate of nearly 50%.⁵

The COVID-19 pandemic, which has caused an increase in prolonged intensive care unit (ICU) stays for mechanical ventilation, has likely increased the incidence of opportunistic infections such as *S. maltophilia* infection. To our knowledge, there are only 12 reported cases in the literature documenting concomitant *S. maltophilia* and COVID-19 infection, of which all cases were of *S.*

maltophilia pneumonia.^{8–10} Our case represents the first reported case of *S. maltophilia* pneumonia with concomitant bacteraemia in a COVID-19-positive patient.

CASE PRESENTATION

A man in his 60s with a history of asthma, hyperlipidaemia and elevated body mass index, with no active alcohol/tobacco or illicit drug use, was admitted to an affiliated community hospital for symptomatic COVID-19 pneumonia diagnosed by PCR. He remained stable on steroids and low-flow oxygen therapy for the first 6 days, but subsequently developed worsened respiratory failure requiring non-invasive positive pressure ventilation. At that time, there was concern for a developing secondary bacterial pneumonia and empiric broad spectrum antibiotics were initiated, with piperacillin/tazobactam (3.375 g intravenously every 8 hours given over 4 hours) and vancomycin intravenous (target trough 15–20 mg/L). A sputum culture collected at the admitting hospital grew *Serratia marcescens* and *Enterobacter aerogenes*, at which point antibiotics were promptly switched to cefepime 2 g intravenously every 8 hours monotherapy per organism susceptibilities. The patient's respiratory failure continued to worsen, and on hospital day 10 he was intubated and transferred to our hospital for further management of severe acute respiratory distress syndrome (ARDS).

Investigations

On arrival at our hospital, a peripherally inserted central catheter (PICC) was placed. A chest X-ray showed pulmonary findings of multifocal pneumonia. At that time, routine infectious work-up was negative for bacteraemia; sputum culture grew mixed respiratory flora. Intermittent fevers were noted, so antibiotics were continued to complete a 7-day course for treatment of previously isolated *S. marcescens* and *E. aerogenes* pneumonia. On antibiotic day 7, the fever curve worsened, and the antibiotic regimen was transitioned from cefepime 2 g intravenously every 8 hours to meropenem 500 mg intravenously every 6 hours in an effort to broaden antibiotic therapy while maintaining coverage against organisms previously isolated in the patient's sputum culture. Repeat blood cultures remained without growth. The following week, the patient's fevers again increased in range and frequency; blood cultures were repeated and continued without growth. However, a chest X-ray



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showed worsening multifocal pneumonia, and a tracheal aspirate grew *S. maltophilia*, with the following susceptibilities: trimethoprim-sulfamethoxazole (TMP-SMX) $\leq 0.5/9.5$ susceptible; minocycline ≤ 4 susceptible; levofloxacin ≤ 2 susceptible and ceftazidime >16 resistant. The decision was made to start targeted therapy against *S. maltophilia* with intravenous TMP-SMX and complete a 7-day course for hospital-acquired pneumonia. Despite first-line antibiotic therapy, the patient developed refractory septic shock on day 7 of this regimen. A repeat tracheal aspirate showed persistent *S. maltophilia*, with unchanged susceptibilities. At this time, a peripheral blood culture also grew *S. maltophilia*, and treatment with TMP-SMX was continued. Repeat peripheral blood cultures drawn 5 days later for ongoing septic shock with fevers showed persistent *S. maltophilia*, as did a repeat tracheal aspirate. The patient's PICC line was exchanged for an internal jugular central venous catheter. PICC tip culture only grew *Staphylococcus epidermidis*, favoured to be a contaminant given insufficient quantities of organism seen. A transthoracic echocardiogram did not show valvular vegetations. The patient was too unstable for a follow-up transesophageal echocardiogram or CT chest to evaluate for abscesses. Two days later on hospital day 38, repeat peripheral blood cultures were finally without growth.

Differential diagnosis

The differential diagnosis for persistent *S. maltophilia* bacteraemia in this case is limited and included catheter-related bloodstream infection (CRBSI), complicated parapneumonic effusion, infectious endocarditis (IE) or necrotising pneumonia with abscess formation. Our leading diagnosis was pneumonia with possible complicated parapneumonic effusion as the persistent source. Focal lung necrosis and haemorrhage are frequent histologic features of *S. maltophilia*, but cavitory lesions are uncommon.¹¹ *S. maltophilia* post viral superinfection has been documented in immunosuppressed patients.¹⁰ Our patient had also been diagnosed with COVID-19 pneumonia, which in some cases has led to temporary immunosuppression while the virus is active, potentially predisposing our patient to more severe bacterial illness. Necrotising *S. maltophilia* pneumonia is a serious complication, and despite appropriate therapy, many patients may die because of progressive infection.¹² Unfortunately, our patient was too unstable to obtain a chest CT scan, and chest X-rays might not be sufficiently sensitive or specific to detect a more complicated respiratory infection.

CRBSI was felt to be less likely given sterility of central line tip culture, and the central line was exchanged after he was found to be bacteremic. IE was felt to be less likely, as IE from *S. maltophilia* is rare. Most patients who develop IE usually have identifiable risk factors such as recent cardiothoracic surgery with or without valve replacement, or a history of injection drug use. Our patient did not meet any of these risk factors, and a transthoracic echocardiogram did not demonstrate any vegetations.

Treatment

At the affiliate community hospital, the patient was treated with a 10-day course of dexamethasone for COVID-19 pneumonia.

For *S. maltophilia*, the treatment of choice regardless of site of infection is TMP-SMX at a dose of 15 mg/kg/day intravenously or by mouth, when susceptible, as it has reliable in vitro activity. Shortly after starting intravenous TMP-SMX, the patient developed hyperkalemia and volume overload refractory to intravenous furosemide. He ultimately required continuous renal replacement therapy for management of these drug

related adverse effects. Consideration of an antibiotic switch was limited by the isolate's resistance pattern as well as drug-drug interactions. The patient remained on mechanical ventilation for persistent ARDS throughout the duration of his hospitalisation.

The patient's refractory septic shock despite appropriate antibiotic treatment for *S. maltophilia* was likely multifactorial and due in part to severe COVID-19 pneumonia. This patient was hospitalised early in the pandemic when antiviral medications or monoclonal antibodies were not yet available to treat COVID-19 pneumonia. Consideration was given to transitioning from TMP-SMX to an alternative antibiotic for treatment of persistent *S. maltophilia* infection, however, there were no available alternatives, as follows: levofloxacin was contraindicated due to concomitant amiodarone for atrial fibrillation with rapid ventricular response, and corrected QT interval prolongation at 530 ms; tetracyclines are not indicated for treatment of bacteraemia due to its large volume of distribution and lack of proven efficacy in bacteraemia; ceftazidime-avibactam susceptibility testing was unable to be performed by our microbiology laboratory due to lack of standardised breakpoints; colistin is not available at our institution and procurement of this medication would not have been timely.

OUTCOME AND FOLLOW-UP

Bacteraemia clearance was documented on hospital day 38. Repeat tracheal aspirate cultures remained positive with *S. maltophilia*; at this point the patient was deemed to be colonised. Ventilator setting remained unchanged. Three days after bacteraemia clearance, he developed worsened septic shock, multi-organ failure and myopericarditis. He ultimately expired on hospital day 43.

Discussion

Secondary bacterial infections (SBIs) are commonly seen in patients admitted with prolonged hospitalisation for COVID-19 pneumonia. The largest case series was from Wuhan, China, which reported on 1495 patients hospitalised for COVID-19 pneumonia, 102 of which developed SBI, with bacterial pneumonia being the most common secondary infection. In the medical literature, there are 12 reported cases of *S. maltophilia* pneumonia complicating COVID-19 pneumonia. To our knowledge, there are no reported cases of concomitant *S. maltophilia* pneumonia and bacteraemia in a COVID-19-positive patient. The primary risk factor for SBI is severe COVID-19 pneumonia on admission, and SBI was associated with increased mortality at 49% during hospitalisation.⁸⁻¹⁰

Regarding *S. maltophilia* infection, some key issues complicate treatment with TMP-SMX, especially in the ICU setting.

Learning points

- ▶ Complications of severe COVID-19 pneumonia are common. There should be a high index of suspicion and low threshold for evaluation for secondary bacterial pneumonia and bacteraemia when a patient is clinically worsening.
- ▶ *Stenotrophomonas maltophilia* bacteraemia requires prompt initiation of antimicrobial treatment and consideration of central venous catheter exchange if one is present.
- ▶ Treatment of *S. maltophilia* bacteraemia in a critically ill patient is limited by drug-related adverse effects and the large intravenous fluid load of intravenous trimethoprim-sulfamethoxazole.

These include the risk for drug-related adverse effects such as hyperkalemia, renal injury and fluid overload arising from the required high dilution volumes of the intravenous formulation, all of which are seen in this case. Consideration may be given to switching to oral formulation, but in this case the patient's high-dose vasopressor requirement prevented this, as there was concern oral absorption could be compromised. Alternative antibiotic options may be limited, as discussed above. Our case highlights the high mortality of *S. maltophilia* infection, especially in the setting of COVID-19 pneumonia, in addition to the challenges of intravenous TMP-SMX treatment in the intensive care setting.

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