American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2022; 23: e936889
DOI: 10.12659/AJCR.936889

Received: 2022.04.09
Accepted: 2022.05.30
Available online: 2022.06.13
Published: 2022.07.19

Stenotrophomonas maltophilia Infection Associated with COVID-19: A Case Series and Literature Review

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Financial support: None declared
Conflict of interest: None declared

Case series
Patients: Female, 52-year-old • Male, 80-year-old • Male, 48-year-old • Male, 80-year-old
Final Diagnosis: COVID pneumonia
Symptoms: Cough
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease
Background: We aimed to identify the risk factors for *Stenotrophomonas maltophilia* infection in patients with COVID-19.
Case Reports: **Case 1.** A 52-year-old COVID-19-positive woman with systemic lupus erythematosus was administered remdesivir (RDV) and methylprednisolone (mPSL) 1000 mg/day for 3 days, and subsequently administered baricitinib and ceftriaxone. Following respiratory deterioration, she was transferred to the Intensive Care Unit (ICU) and the antibiotics were switched to meropenem (MEPM). Blood and sputum cultures were positive for *S. maltophilia*. Administration of trimethoprim-sulfamethoxazole (TMP-SMX) showed clinical improvement.
Case 2. An 80-year-old COVID-19-positive man was treated with RDV, dexamethasone, and baricitinib. Owing to severe hypoxia, he was transferred to the ICU and MEPM was administered. Sputum culture was positive for *S. maltophilia*. TMP-SMX administration temporarily improved his symptoms; however, he died from COVID-19-associated invasive aspergillosis.
Case 3. A 48-year-old COVID-19-positive man who was mechanically intubated was transferred to our hospital and treated with RDV, mPSL, and piperacillin/tazobactam. Sputum culture revealed *S. maltophilia*; treatment with TMP-SMX improved his respiratory status.
Case 4. An 80-year-old COVID-19-positive man was treated with RDV and dexamethasone. Owing to severe hypoxemia, he was transferred to the ICU and the antibiotics were switched to MEPM. Sputum culture revealed *S. maltophilia.* Administration of TMX-SMX improved his respiratory status.
Conclusions: Isolation of *S. maltophilia* in respiratory specimens of patients with COVID-19 should prompt clinicians to administer treatment for *S. maltophilia*-associated pneumonia in ICU-admitted patients who have been intubated, have been administered broad-spectrum antibiotics, or have immunocompromised status.

Keywords: *Stenotrophomonas maltophilia* • *Stenotrophomonas maltophilia* Bacteremia • COVID-19 Breakthrough Infections • Healthcare-Associated Pneumonia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936889

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Background

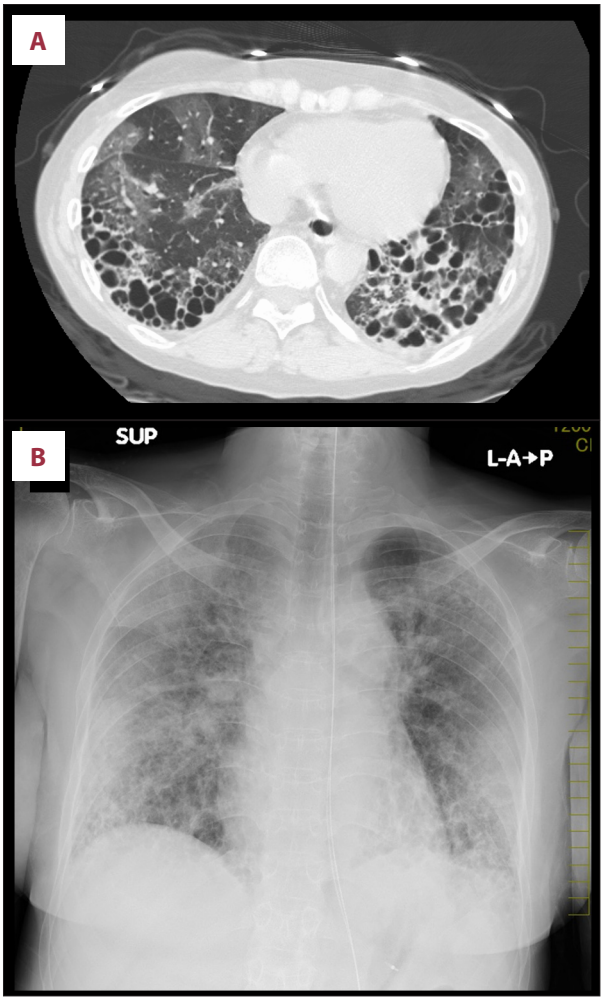
Stenotrophomonas maltophilia, a multidrug resistant, gram-negative bacterial rod is found in aquatic environments, such as water, soil, and plants. Owing to its ability to form biofilms on medical equipment and to grow in disinfectants, it is an emerging opportunistic pathogen known to cause bacteremia, pneumonia, endocarditis, and meningitis, as well as urinary tract, ocular, bone and joint, skin and soft tissue, and gastrointestinal infections in hospitals settings [1]. *S. maltophilia* infections include ventilator-associated pneumonia (VAP) and central venous catheter (CVC)-related bacteremia [2]. *S. maltophilia* bacteremia has a mortality rate of over 20%, and risk factors include Intensive Care Unit (ICU) admission, indwelling devices such as CVC and ventilators, exposure to carbapenems and anti-*Pseudomonas aeruginosa* cephalosporins within 14 days prior to bacteremia, and *S. maltophilia* isolation within 30 days [3]. *S. maltophilia* pneumonia has been reported to cause opportunistic infections in some patients, such as those with hematologic malignancy [4]. *S. maltophilia* colonizes the sputum, and a high sequential organ failure assessment score is seen in patients who are immunocompromised and exposed to broad-spectrum antimicrobial agents [5]. It is difficult to determine whether *S. maltophilia* simply colonizes the lungs or causes true infection leading to pulmonary inflammation. Despite a few reports of *S. maltophilia* pneumonia in patients with COVID-19, the risk factors for *S. maltophilia* infection in COVID-19-positive patients are unknown. Herein, we aimed at identifying the risk factors for *S. maltophilia* infection in patients with COVID-19 based on the information available in the literature and on our cases in St Luke's International Hospital between January 1, 2020, and August 31, 2021.

Case Reports

This study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (No: 21-R107). Although written informed consent was obtained from all patients in this case series, the requirement for patient consent was waived by the Institutional Review Board due to the study's retrospective nature.

Case 1

A 52-year-old woman using prednisolone (PSL) and baricitinib (BARI) with a medical history of systemic lupus erythematosus,



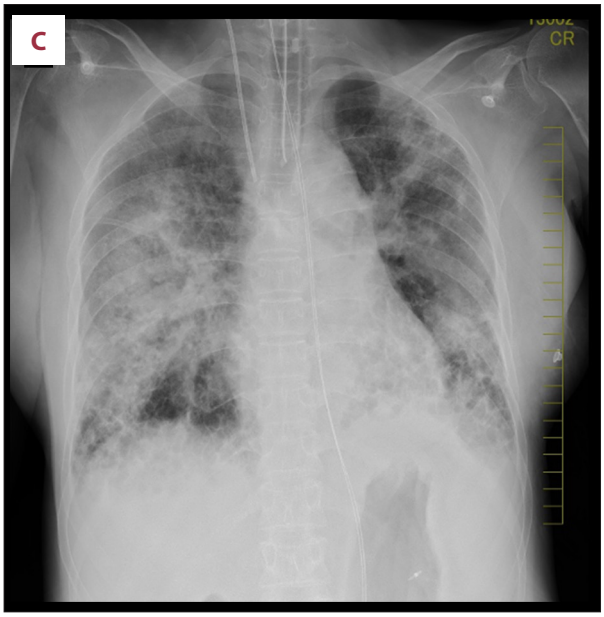


Figure 1. Chest computed tomgraphy (**A**) and X-ray (**B,** X-ray on hospital admission; **C,** X-ray on ICU admission). (**A**) Non-segmental bilateral ground-glass opacities in the diffuse area and honeycomb associated with interstitial pneumonia in the bilateral dorsal aspects of the inferior lung lobe, (**B, C**) Two chest X-rays reveal bilateral diffuse grand-glass opacity.

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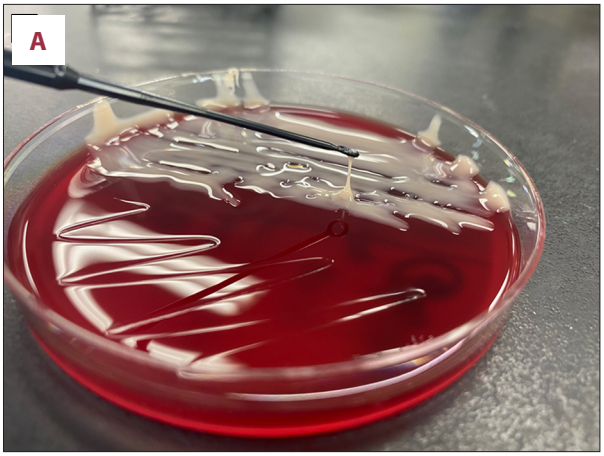

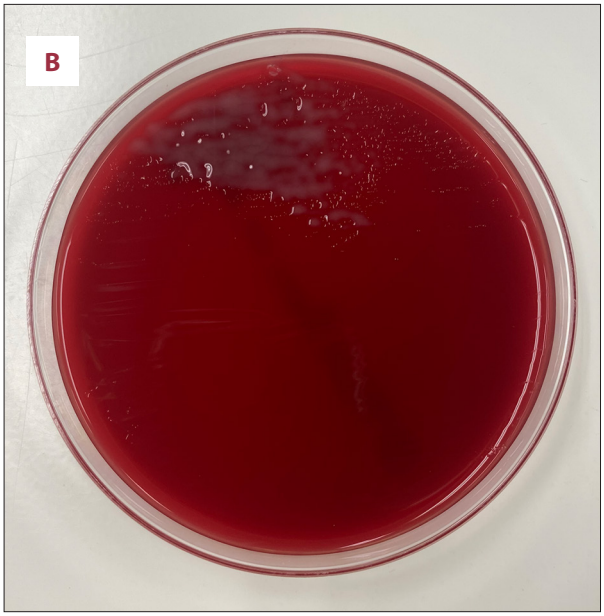

Figure 2. Mucoid-type *S. maltophilia* colony. String-positive (**A**), *S. maltophilia* on blood agar (**B**).

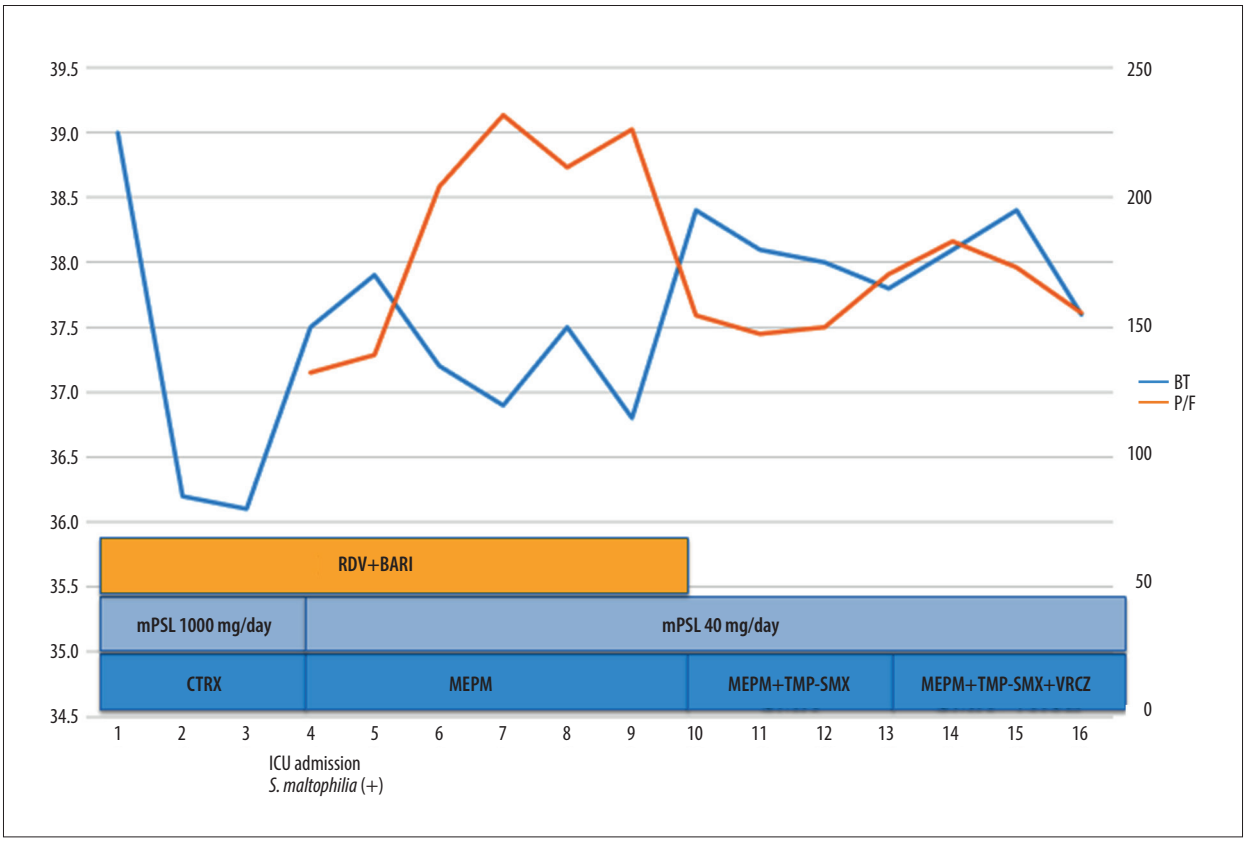

Figure 3. Clinical course of Case 1. RDV – remdesivir; ICU – Intensive Care Unit; mPSL – methylprednisolone; CTRX – ceftriaxone; MEPM – meropenem; TMP-SMX – trimethoprim-sulfamethoxazole; VRCZ – voriconazole; BT – body temperature; P/F – PaO_2/FIO_2; BARI – baricitinib.

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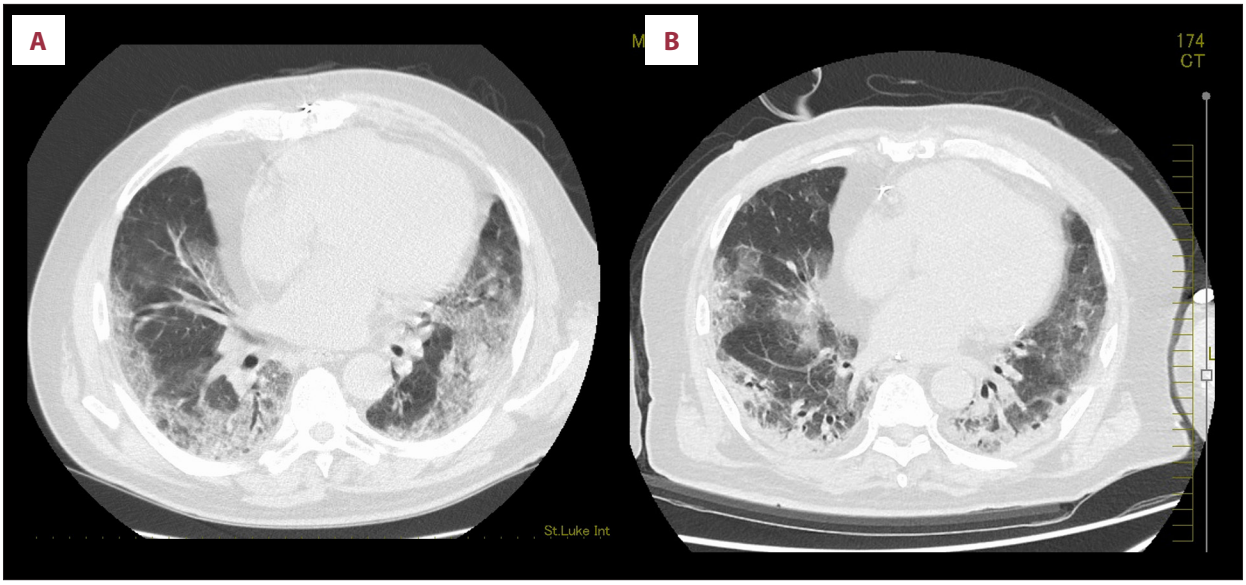

Figure 4. Chest computed tomography scan on admission (**A**), on *S. maltophilia* culture (+) (**B**). (**A**) bilateral ground-glass opacities and reticulation with subpleural distribution; (**B**) bilateral consolidation with bronchiectasis and expansion of bilateral ground-glass opacity area.

rheumatoid arthritis, liver cirrhosis, and interstitial pneumonia was admitted to our Emergency Department with high fever and headache. On admission, her vital signs were as follows: clear consciousness; temperature, 37.2°C; blood pressure, 101/77 mmHg; pulse rate, 100 beats/min; respiratory rate, 22 breaths/min; and oxygen saturation, 94% on room air. The patient's COVID-19 polymerase chain reaction (PCR) test result was positive. Chest computed tomography (CT) revealed bilateral, non-segmental, ground-glass opacities in the diffuse area, and honeycomb appearance associated with interstitial pneumonia in the bilateral dorsal aspects of the inferior lung lobe (**Figure 1A-1C**). We initiated administration of remdesivir (RDV) and methylprednisolone (mPSL) 1000 mg/day for 3 days followed by mPSL 40 mg/day, BARI 4 mg/day, and ceftriaxone (CTRX) 1 g intravenously (i.v.) every 24 h. On day 4 of hospital admission, her respiratory status worsened, she was moved to the ICU, and a nasal high flow cannula was inserted. We switched the antibiotics to meropenem (MEPM). On day 8, the patient developed a fever of 37.9°C with 90% oxygen saturation with FIO_2 60% and nasal high flow gas 40 L/min, and was intubated. Blood and sputum cultures were positive for *S. maltophilia* (**Figure 2A, 2B**). Mucoid-type *S. maltophilia* was detected by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Biotyper, Bruker Daltonics, Germany). Adjustment to 0.5 McFarland in the mucoid-type *S. maltophilia* was difficult; thus, susceptibility testing could not be performed. Intravenous trimethoprim-sulfamethoxazole (TMP-SMX) (equivalent to 15 mg/kg/day TMP) was initiated. Her respiratory status improved; however, the *Aspergillus* galactomannan antigen level was 1.1. We administered voriconazole to treat COVID-19-associated invasive aspergillosis. The patient's respiratory condition stabilized, although the duration of intubation was extended; consequently, tracheostomy was performed. Sputum culture revealed elimination of *S. maltophilia*. At the time of writing this review, the patient's clinical status had improved (**Figure 3**).

Table 1. MINO, TMP-SMX, LVFX, and CAZ were susceptible to *Stenotrophomonas maltophilia*.

Antibiotics	MIC (µg/mL)	Susceptibility
MINO	≤2	S
TMP-SMX	≤2	S
LVFX	≤0.5	S
CAZ	≤2	S

MIC breakpoint reference: M100 in Clinical and Laboratory Standards Institute (CLSI). S – susceptible; MINO – minocycline; TMP-SMX – trimethoprim-sulfamethoxazole; LVFX – levofloxacin; CAZ – ceftazidime; MIC – minimum inhibitory concentration.

Case 2

An 80-year-old man with a medical history of hypertension and acute myocardial infarction status after coronary artery bypass graft was admitted to our Emergency Department with high fever. On admission, the vital signs were as follows: clear consciousness; temperature, 37.6°C; blood pressure, 101/77 mmHg; pulse rate, 98 beats/min; respiratory rate, 22 breaths/min; and oxygen saturation, 96% (10 L/min on reservoir mask). The patient's COVID-19 PCR result was positive. Chest CT revealed

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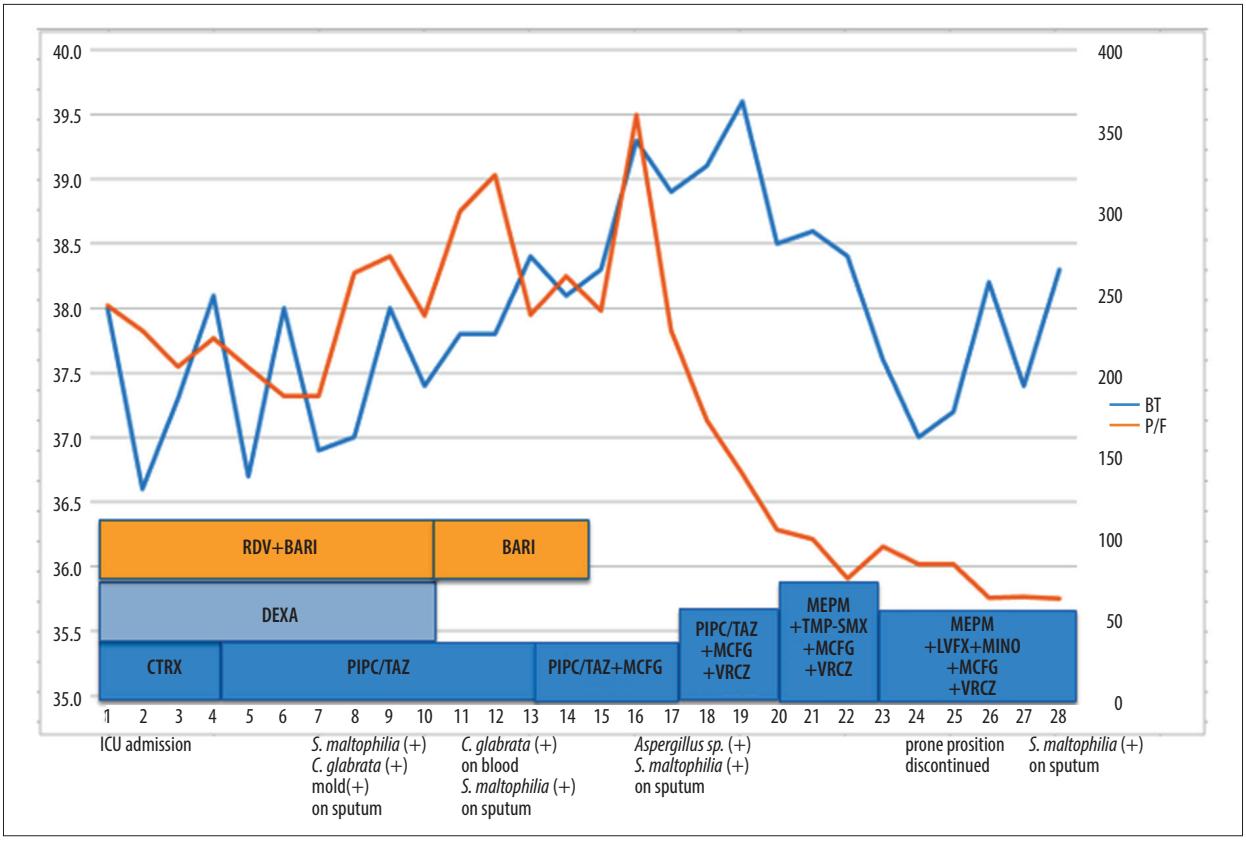

Figure 5. Clinical course of Case 2. On day 24 of hospital admission, the prone position was not effective in improving saturation; therefore, it was discontinued. BARI – baricitinib; RDV – remdesivir; CTRX – ceftriaxone; PIPC/TAZ – piperacillin/tazobactam; MCFG – micafungin; VRCZ – voriconazole; MEPM – meropenem; TMP-SMX – trimethoprim-sulfamethoxazole; LVFX – levofloxacin; MINO – minocycline; DEXA – dexamethasone; ICU – Intensive Care Unit; *S. maltophilia* – *Stenotrophomonas maltophilia*; *C. glabrata* – *Candida glabrata*; BT – body temperature; P/F – PaO_2/FIO_2.

bilateral ground-glass opacity and reticulation with subpleural distribution (**Figure 4A, 4B**). We initiated administration of RDV, dexamethasone (DEXA) 6.6 mg/day, BARI 4 mg/day, and CTRX 1 g i.v. every 24 h. Owing to severe hypoxemia, he was transferred to the ICU and mechanically intubated, and a CVC was inserted. On day 4 of hospital admission, he developed a fever of 38°C, and antibiotics were switched to piperacillin/tazobactam (PIPC/TAZ). A sputum culture on day 8 revealed the presence of *Candida glabrata* (mold) and *S. maltophilia*; however, we did not administer any treatment for these as we assumed them to be colonizing organisms. The minimum inhibitory concentrations were measured using the MicroScan WalkAway 96 Plus and NC-NF2J panel (Beckman Coulter Inc). Levofloxacin (LVFX), minocycline (MINO), TMP-SMX, and ceftazidime were all effective (**Table 1**). The patient had persistent prominent fever; however, and a blood culture on day 11 indicated *C. glabrata* infection. We administered micafungin and replaced the CVC. Follow-up blood cultures were negative for *C. glabrata*; however, the fever did not abate, and on day 18 the patient showed increased hypoxia. Switching antibiotics from PIPC/TAZ to MEPM did not improve the clinical symptoms. Therefore, we administered TMP-SMX (equivalent to 15 mg/kg/day TMP) for treating *S. maltophilia*-associated pneumonia, and the fever resolved. Owing to acute kidney injury, we switched from TMP-SMX to LVFX and MINO. *Aspergillus* galactomannan sputum antigen was >5.0, and we administered voriconazole. However, the patient's respiratory status worsened. He died on day 28 of hospital admission due to COVID-19-associated invasive aspergillosis (**Figure 5**).

Case 3

A 48-year-old man with COVID-19 and a medical history of hypertension, diabetes, and obesity was admitted to another hospital, where he was treated with RDV and DEXA. His respiratory condition deteriorated, and he was mechanically intubated and treated with mPSL 1000 mg/day for 3 days. On day 7 following COVID-19 onset, his PaO_2/FiO_2 ratio was about 80. He was transferred to our hospital for COVID-19 treatment with extracorporeal membrane oxygenation (ECMO). Chest CT revealed bilateral diffuse consolidation (**Figure 6**). He was treated with RDV, mPSL 125 mg/day, and PIPC/TAZ. His respiratory

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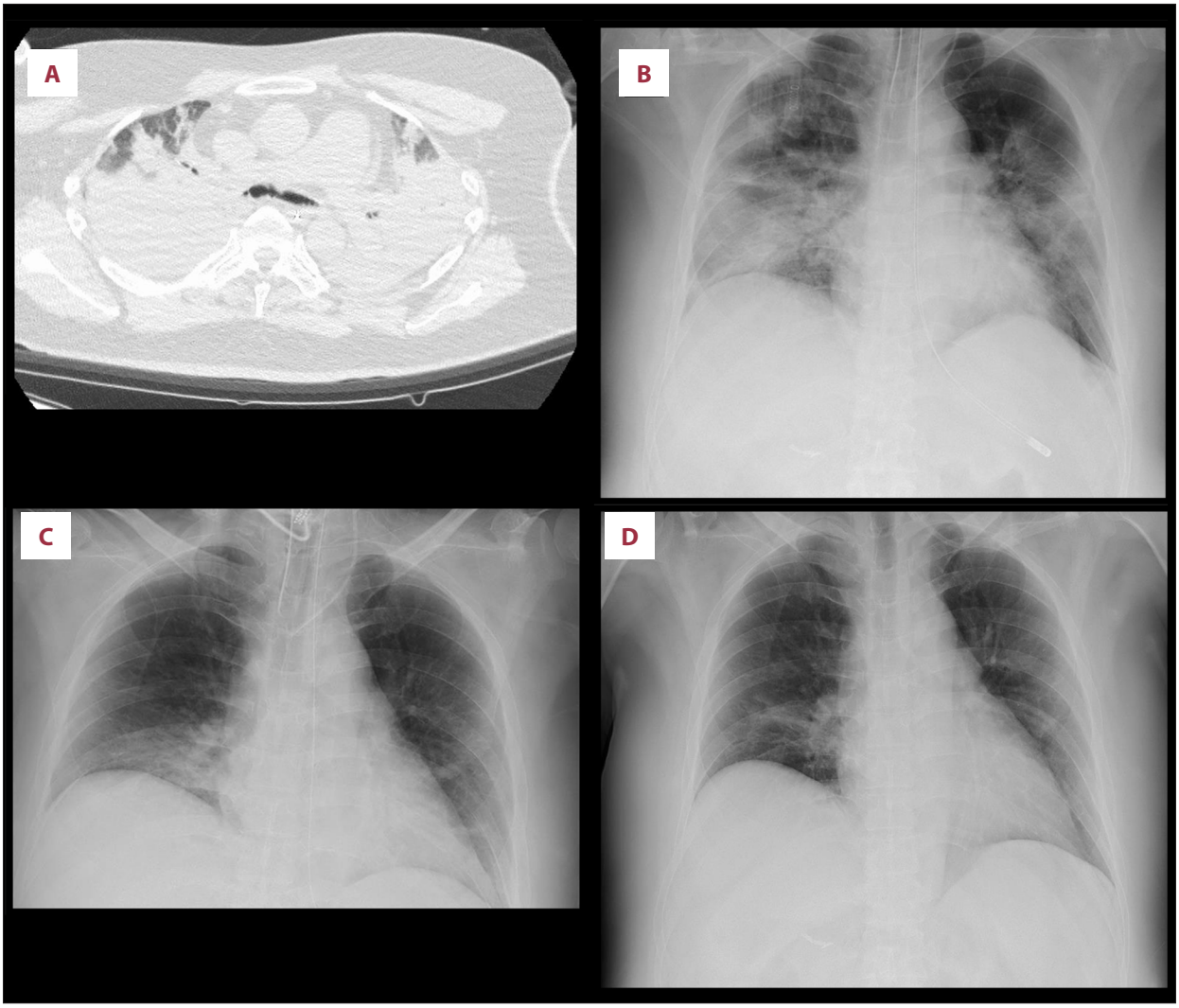

Figure 6. Chest computed tomography scan on admission (**A**) and X-ray on admission (**B**), on *S. maltophilia* (+) (**C**), and on day 22 of hospital admission (**D**). (**A**) bilateral diffuse consolidation; (**B**) consolidation in the bilateral lung on admission; (**C**) right lower lung field on *S. maltophilia* (+); and (**D**) consolidation improves on day 22 of hospital admission.

status stabilized; therefore, ECMO was discontinued, and he was extubated on day 9. On day 10 of hospital admission, he had increased sputum production and his C-reactive protein level increased to 23.7 mg/dL. Chest radiography revealed consolidation in the right lower lung field (**Figure 6**). The sputum culture revealed the presence of *S. maltophilia*; therefore, he was treated with TMP-SMX (equivalent to 15 mg/kg/day TMP). By the time of this report, the patient was clinically stable and preparing for transfer to a rehabilitation hospital (**Figure 7**).

Case 4

An 80-year-old man with a medical history of dementia developed COVID-19 four days before admission. The patient was medically monitored at a health care institute. When his O_2 saturation level gradually decreased, he was admitted to our hospital. Chest CT revealed ground-glass opacity with subpleural distribution (**Figure 8**). We started RDV, DEXA 6.6 mg/day, AZM 500 mg/day, and CTRX 1 g i.v. every 24 h. Owing to severe hypoxemia, he was transferred to the ICU and mechanically intubated on day 6 after hospital admission. On day 9, his sputum culture revealed *S. maltophilia*, *Klebsiella aerogenes*, and *Enterococcus faecalis*. Although susceptible to LVFX, MINO, and TMP-SMX, the bacteria were resistant to ceftazidime (**Table 2**). The patient was treated with LVFX 500 mg/day. On day 18 of hospital admission, he was extubated. However, his sputum production increased, and he was re-intubated on day 34. He was treated with TMP-SMX (equivalent to 15 mg/kg/day TMP) and MEPM. His respiratory status improved, although a tracheostomy had to be performed because of CO_2 retention. He was finally transferred to a rehabilitation hospital on day 56 of hospital admission (**Figure 9**).

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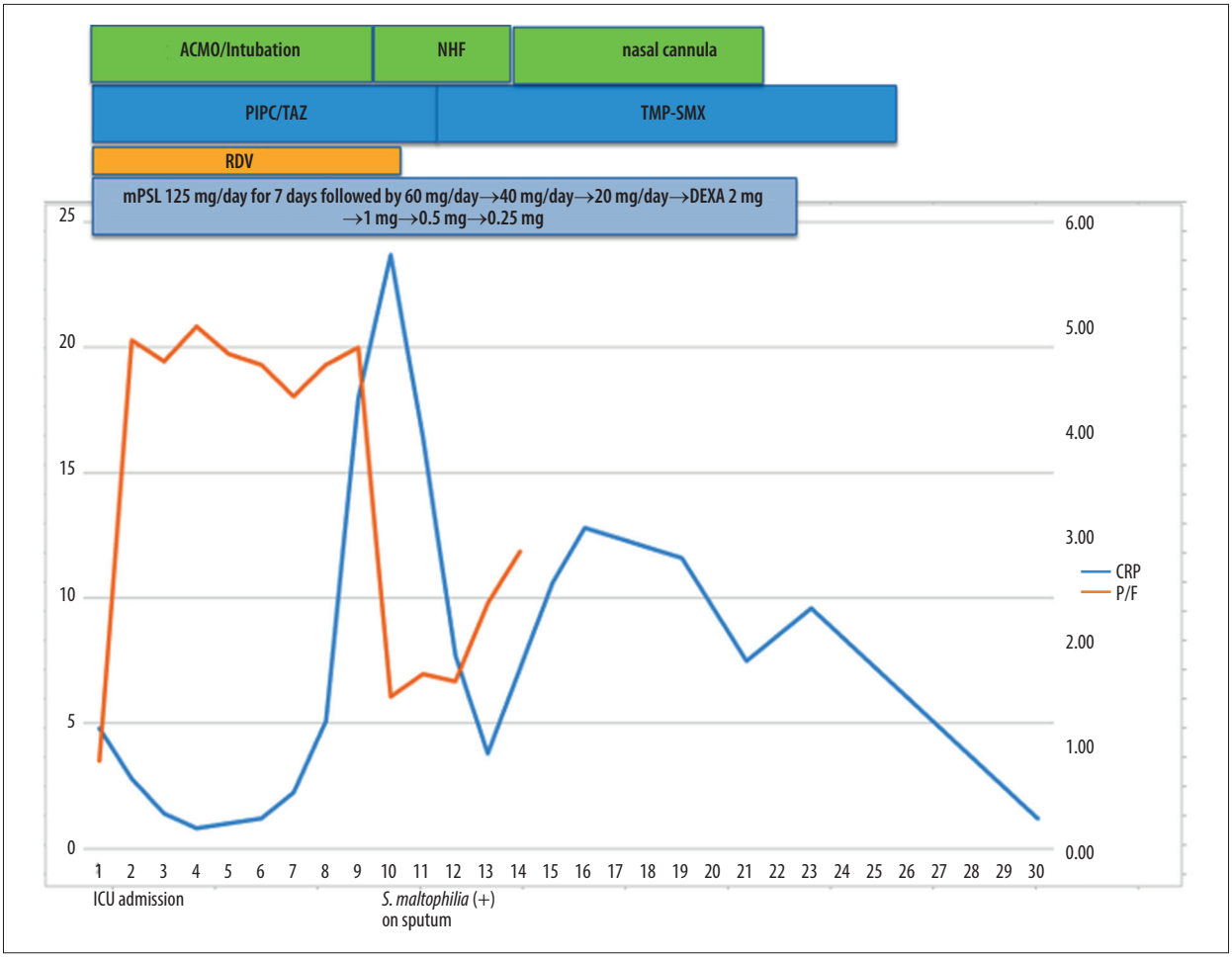

Figure 7. Clinical course of Case 3. RDV – remdesivir; PIPC/TAZ – piperacillin/tazobactam; TMP-SMX – trimethoprim-sulfamethoxazole; ICU – Intensive Care Unit; ECMO – extracorporeal membrane oxygenation; NHF – nasal high flow; mPSL – methylprednisolone; DEX – dexamethasone; CRP – C-reactive protein; P/F – PaO_2/FIO_2.

Discussion

Two authors independently reviewed the relevant titles and abstracts in the database records, retrieved full texts for eligibility assessment, and extracted the information from these cases. We performed a search using the keywords "*Stenotrophomonas maltophilia*" and "COVID-19" in the electronic databases PubMed, Embase, and Ichushi from January 1, 2020, to April 4th, 2022 (**Table 3**).

We found 68 articles and 8 case reports on COVID-19-associated *S. maltophilia* infection (**Figure 10**). The clinical characteristics of the patients in the 8 published cases, including the 4 in this review, are shown in **Table 4**. Furthermore, we extracted 13 retrospective studies on COVID-19-associated *S. maltophilia* infections, which are shown in **Table 5**.

We extracted the data of 8 patients with COVID-19 and positive *S. maltophilia* cultures at St. Luke's International Hospital, a 520-bed teaching hospital in Tokyo (**Figure 10**). Four patients were diagnosed with *S. maltophilia* colonization, while the other 4 had COVID-19-associated *S. maltophilia* infection (**Table 4**).

The median age of the 12 patients, including the 4 patients in this review, with COVID-19-associated *S. maltophilia* infection was 64 years (**Table 4**). Among them, 10 (83%) were men. Eleven patients (92%) were admitted to the ICU, and 12 (100%) were mechanically intubated. Immunosuppressants such as steroids, BARI, and tocilizumab were used in 9 (75%) patients; however, only DEXA, a short-term steroid used for COVID-19, was administered in 2 patients. Antimicrobial agents were administered to almost all patients, including MEPM to 5 patients, PIPC/TAZ to 2 patients, and cefepime to 1 patient. The treatment against *S. maltophilia* was TMP-SMX in 7 patients, and 2 were switched from TMP-SMX to LVFX owing to acute renal injury; LVFX was used in 5 patients, including 2 patients who were switched from TMP-SMX, as mentioned above. There were 3 deaths. In our hospital, there were 4 patients with *S.*

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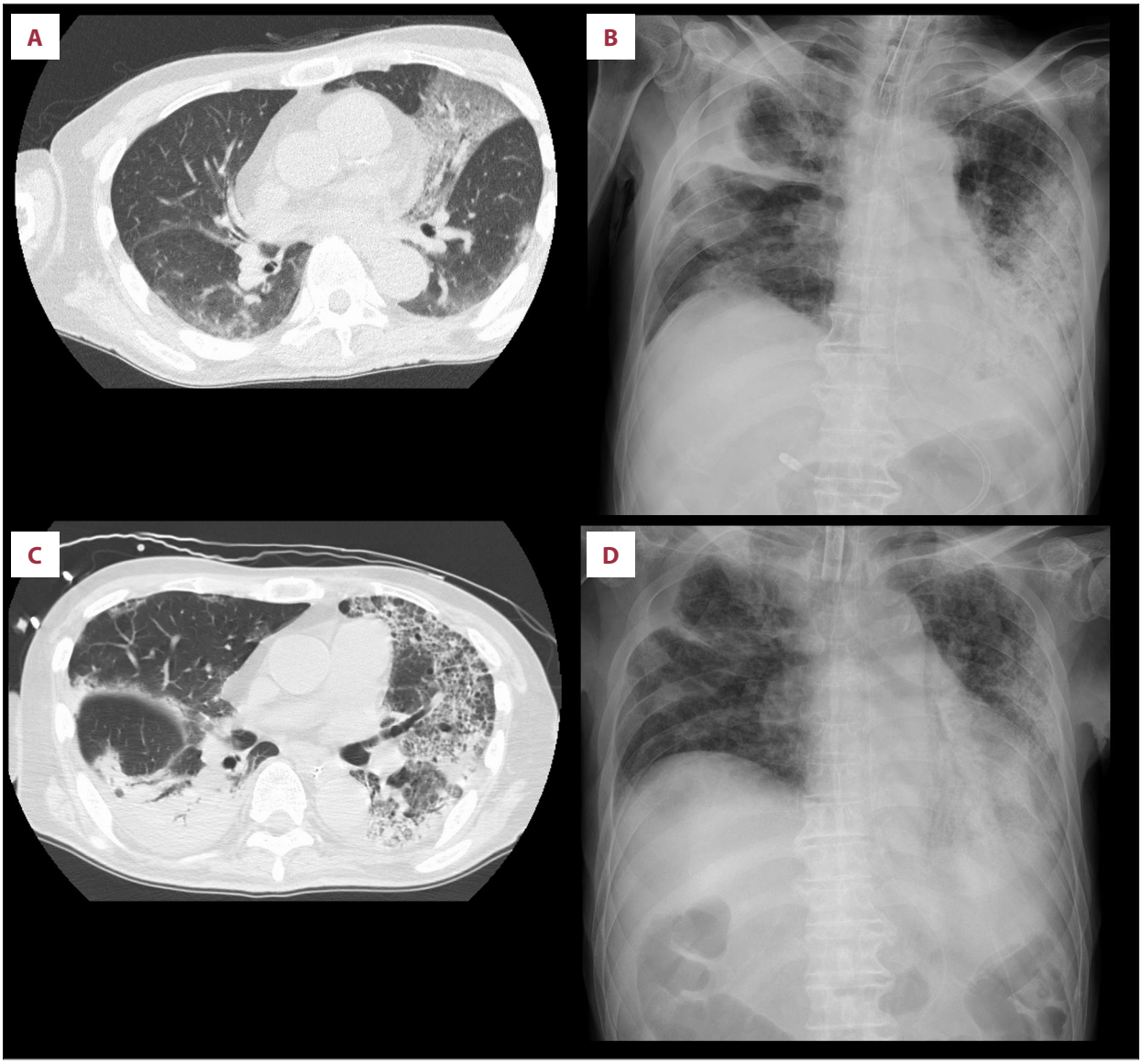

Figure 8. Chest computed tomography (CT) scan and X-ray on admission (**A, B**) and on maltophilia (+) (**C, D**). Chest CT and X-ray show ground-glass opacity with subpleural distribution on admission (**A, B**), non-segmental consolidation with air bronchogram on the right lower lobe, and the progression of bronchiectasis on maltophilia (+) (**C, D**).

Table 2. MINO, TMP-SMX, and LVFX were susceptible to *Stenotrophomonas maltophilia*.

Antibiotics	MIC (μg/mL)	Susceptibility
MINO	≤2	S
TMP-SMX	≤2	S
LVFX	≤0.5	S
CAZ	>16	R

MIC breakpoint reference: M100 in Clinical and Laboratory Standards Institute (CLSI). S – susceptible; MINO – minocycline; TMP-SMX – trimethoprim-sulfamethoxazole; LVFX – levofloxacin; CAZ – ceftazidime; MIC – minimum inhibitory concentration.

maltophilia colonization, all of whom were admitted to the ICU, 3 who were administered steroids, and 3 who were administered broad-spectrum antibiotics such as cefepime, PIPC/TAZ, or MEPM. Two patients had positive sputum cultures; however, they were resolved without treatment. Autopsy blood cultures from 2 patients were positive for *S. maltophilia*, although their antemortem blood cultures were negative.

Among the 13 observational studies (**Table 5**), 4 were from China, 2 from Italy, 2 from Spain, and 5 from the United States. Nine of the 13 studies were conducted in the ICU (2 studies had mixed ICU and non-ICU patients). Eleven studies included respiratory infections, such as VAP and hospital-acquired

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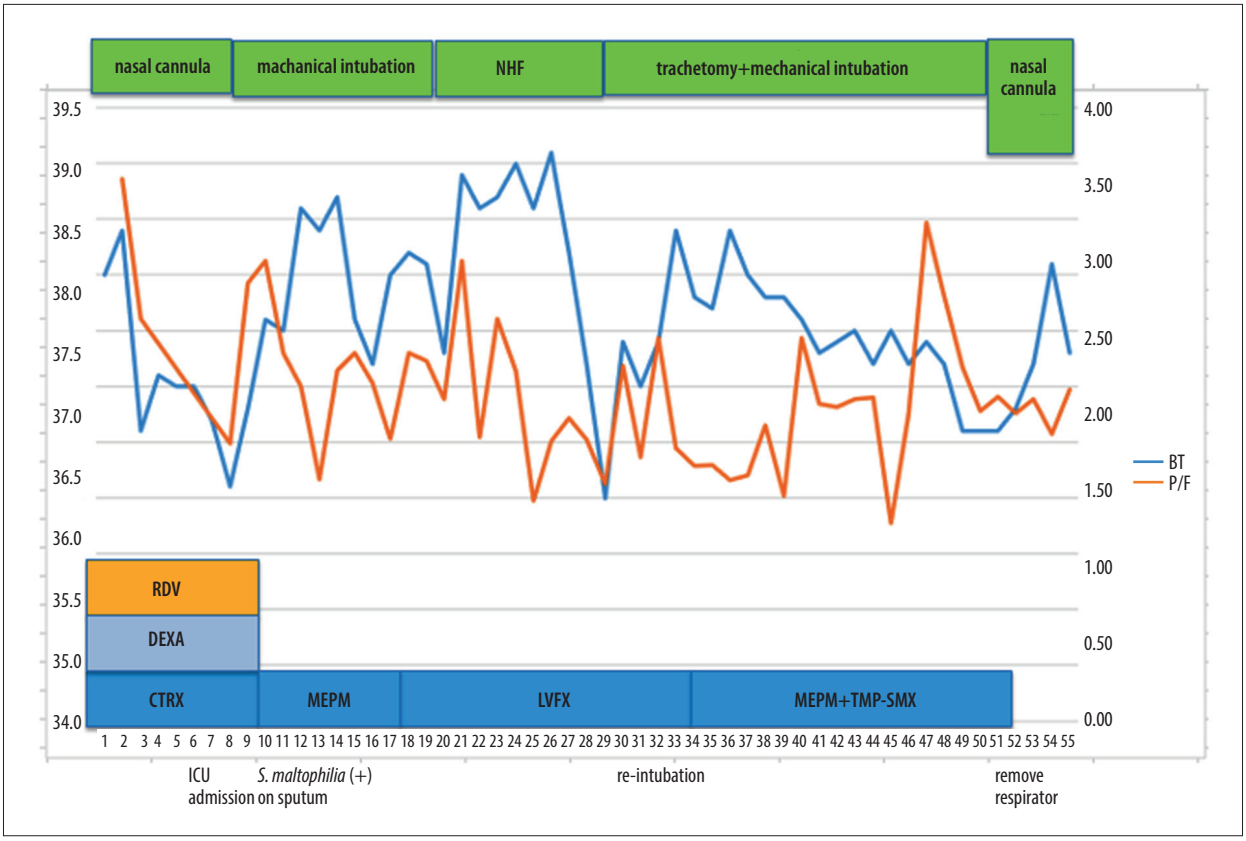

Figure 9. Clinical course of Case 4. RDV – remdesivir; DEXA – dexamethasone; CTRX – ceftriaxone; LVFX – levofloxacin; TMP-SMX – trimethoprim-sulfamethoxazole; ICU – Intensive Care Unit; NHF – nasal high flow; mPSL – methylprednisolone; BT – body temperature; P/F – PaO_2/FIO_2.

pneumonia (HAP). Mortality rates ranged from 15.4% to 52.4%, although we did not find any mortality rate for *S. maltophilia*-associated VAP or HAP. In addition to *S. maltophilia*, the organisms *Acinetobacter spp.*, *P. aeruginosa*, and *Enterobacter spp.* were the causative or isolated organisms in VAP and HAP.

Here, we report 4 cases of COVID-19-associated *S. maltophilia* infection. To the best of our knowledge, this is the first literature review on COVID-19-associated *S. maltophilia* infection. It may help clinicians make treatment choices by presenting clinical data on patient backgrounds, treatment choices, and outcomes of COVID-19-associated *S. maltophilia* infection, for which no consensus has been reached.

S. maltophilia can form small colony variants [6], and the one detected in Case 1 was considered to be of the mucoid type as it was a large, viscous colony with a positive string test. Reports of mucoid-type *S. maltophilia* are rare: only 1 case from Japan has been previously reported [7]. Further studies are needed to clarify the mechanism of mucoid-type *S. maltophilia*.

Among patients without COVID-19, the risk of *S. maltophilia* infection was higher in patients who were admitted to the ICU, intubated, and had exposure to broad-spectrum antimicrobials and used immunosuppressants [3,5]. In this review, patients with COVID-19 had similar risk factors for *S. maltophilia* infection. In our observational study at St Luke's International Hospital, *S. maltophilia* colonization was 50% in 8 patients. It is difficult to distinguish between patients with *S. maltophilia* colonization and infection as they have similar baseline characteristics. The previous study reported that VAP caused by *S. maltophilia* is associated with high morbidity and mortality [6]. Another study reported a mortality rate due to *S. maltophilia* bacteremia ranging from 12.5% to 41% [7]. According to the Infectious Diseases Society of America guideline, the overall VAP mortality rate is 20% to 50% [8]. Therefore, the mortality rate for *S. maltophilia* is also high enough. Owing to the high mortality rate of COVID-19-associated *S. maltophilia* infection, we believe that this condition should be treated in clinically unstable patients. In general, *S. maltophilia*-associated pneumonia was diagnosed 11 days after intubation and 11 days after ICU admission [8]. In the present study, COVID-19-associated *S. maltophilia* was either isolated from the culture immediately after ICU admission or was positive in the PCR test for *S. maltophilia* if not detected in the culture [9,10]. Therefore, *S. maltophilia* infection should be considered immediately after ICU admission

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Table 3. Search terms used to search 3 databases (PubMed, Embase, and Ichushi) for literature review of COVID-19-associated *Stenotrophomonas maltophilia*.

Pubmed	("Stenotrophomonas maltophilia"[MeSH Terms] OR "Stenotrophomonas maltophilia"[Text Word] OR "Stenotrophomonas maltophilia bacteremia"[Supplementary Concept] OR "Pseudomonas maltophilia"[Title/Abstract] OR "Xanthomonas maltophilia"[Title/Abstract] OR "s maltophilia"[Title/Abstract]) AND ("Pneumonia"[MeSH Terms] OR "pneumoni*"[Text Word] OR ("pulmonary infect*"[Title/Abstract] OR "lung infect*"[Title/Abstract]) OR "Respiratory Tract Infections"[MeSH Terms]) AND ("COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines"[All Fields] OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy"[All Fields] OR "COVID-19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "NCOV"[All Fields] OR "2019 NCOV"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COV"[All Fields]) AND 2019/11/01: 3000/12/31[Date – Publication]))
Embase	(('severe acute respiratory syndrome coronavirus 2'/exp OR '2019-ncov': ti,ab,kw OR 'cov 2': ti,ab,kw OR 'sars cov 2': ti,ab,kw OR 'coronavirus 2': ti,ab,kw OR 'covid 19': ti,ab,kw OR '2019 ncov': ti,ab,kw OR '2019ncov': ti,ab,kw OR 'corona virus disease 2019': ti,ab,kw OR 'cov2': ti,ab,kw OR 'covid-19': ti,ab,kw OR 'covid19': ti,ab,kw OR 'ncov 2019': ti,ab,kw OR 'ncov': ti,ab,kw OR 'new corona virus': ti,ab,kw OR 'new coronaviruses': ti,ab,kw OR 'novel corona virus': ti,ab,kw OR 'novel coronaviruses': ti,ab,kw OR 'sars coronavirus 2': ti,ab,kw OR 'sars2': ti,ab,kw OR 'sars-cov-2': ti,ab,kw OR 'severe acute respiratory syndrome coronavirus 2': ti,ab,kw OR ((19: ti,ab,kw OR 2019: ti,ab,kw OR '2019-ncov': ti,ab,kw OR 'beijing': ti,ab,kw OR 'china': ti,ab,kw OR 'covid-19': ti,ab,kw OR epidem*: ti,ab,kw OR epidemic*: ti,ab,kw OR epidemy: ti,ab,kw OR new: ti,ab,kw OR 'novel': ti,ab,kw OR 'outbreak': ti,ab,kw OR pandem*: ti,ab,kw OR 'sars-cov-2': ti,ab,kw OR 'shanghai': ti,ab,kw OR 'wuhan': ti,ab,kw) AND ('coronavirinae'/exp OR 'coronavirus infection'/exp OR coronavirus*: ti,ab,kw OR 'corona virus*': ti,ab,kw OR cov: ti,ab,kw OR 'pneumonia-virus*': ti,ab,kw))) AND (2019: py OR 2020: py OR 2021: py)) AND ('Stenotrophomonas maltophilia'/exp OR 'Stenotrophomonas maltophilia' OR maltophilia) AND (pneumoni* OR ('pulmonary infect*' OR 'lung infect*') OR 'respiratory tract infection'/exp)
Ichushi	(SARS coronavirus[Japanese] -2/TH or COVID-19/TH or COVID-19/AL or (corona[Japanese]/TA and DT=2020: 2021)) and (("Stenotrophomonas maltophilia"/TH) or (maltophilia[Japanese]/TA or maltophilia/TA))

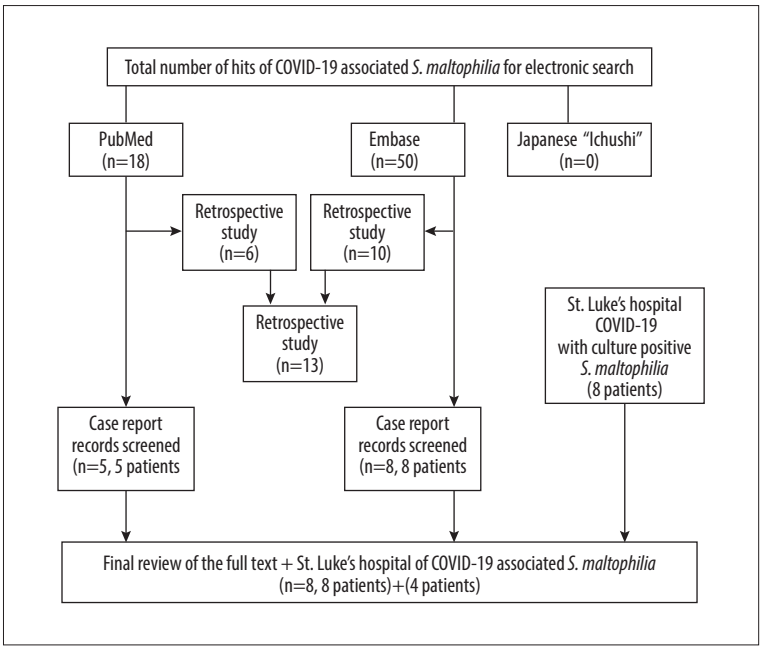

Figure 10. Flow chart of the systematic review process.

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Table 4. Literature review of COVID-19-associated *Stenotrophomonas maltophilia* + cases at our hospital.

No	Case reference	Age	Sex	Publisheddate/ country	Diagnosis/ complications	Underlying diseases	Ward
1	Su XW [19]	72	Male	2020/ USA	*S. maltophilia* VAP/ Guillain-Barré syndrome	HTN, CAD, alcohol abuse	ICU
2	Mohamed AM [20]	64	Male	2020/ USA	*S. maltophilia* VAP	DM, HTN, ESRD, post-renal transplant recipient taking TAC, MMF and PSL 5 mg/day	ICU
3	Zachary P [21]	60s	Male	2021/ USA	*S. maltophilia* VAP, bacteremia/septic shock, MOF, myopericarditis	Asthma, hyperlipidemia, elevated BMI	N/A
4	Vikas P [22]	55	Male	2021/ USA	*S. maltophilia* VAP/ARDS, pneumothorax	No	ICU
5	Nicole N [23]	51	Male	2021/ Lebanon	*S. maltophilia* VAP, bacteremia/ bacterial pneumonia	hemodialysis, Von Hippel-Lindau disease, renal cell carcinoma leading to bilateral nephrectomy and adrenalectomy, cystadenoma of the pancreas, DM, HTN, CAD	ICU
6	Miraç Öz [24]	61	Male	2020/ Turkey	*S. maltophilia* VAP	COPD, bronchiectasis, previous TB, bilateral upper lobectomies nearly 30 years ago. tracheostomy and had been ventilating with a home-type of mechanical ventilator for two years	ICU
7	David D [25]	71	Male	2021/Iran	*S. maltophilia* VAP	Hodgkin's lymphoma	ICU
8	Velamakanni S [26]	70	Female	2021/ USA	*S. maltophlia* VAP	HTN, PAD, COPD	ICU
9	Our case	52	Female	2021/ Japan	*S. maltophilia* VAP, bacteremia/CAPA	SLE, RA, IP, LC	ICU
10	Our case	79	Male	2021/ Japan	*S. maltophilia* VAP	dementia	ICU
11	Our case	80	Male	2021/ Japan	*S. maltophilia* VAP/CAPA, candidemia	HTN. post-CABG	ICU
12	Our case	48	Male	2021/ Japan	*S. maltophilia* VAP	Af, DM, HTN, obesity	ICU
Contamination							

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Table 4 continued. Literature review of COVID-19-associated *Stenotrophomonas maltophilia* + cases at our hospital.

No	Case reference	Age	Sex	Publisheddate/ country	Diagnosis/ complications	Underlying diseases	Ward
1	Our case	64	Male	2020/ Japan		Post-AVR, hyperlipidemia, Af	ICU
2	Our case	85	Female	2020 Japan		Af, DM, distal radius fracture	ICU
3	Our case	79	Male	2020/ Japan		TB, DM, HTN, hyperlipidemia	ICU
4	Our case	52	Female	2021/ Japan		HTN	ICU

No	Case reference	Mechanical intubation	COVID-19 treatment	Antibiotics prior to *S. maltophilia* infection	Specimen	*S. maltophilia* treatment	Outcome	Other pathogen
1	Su XW [19]	Yes	N/A	No	Sputum	TMP-SMX	Under treatment	N/A
2	Mohamed AM [20]	Yes	HCQ, AZM, mPSL 60 mg/kg	CFPM	Sputum	TMP-SMX→ LVFX due to AKI	Death	N/A
3	Zachary P [21]	Yes	Steroid (N/A), DEXA	MEPM	Sputum, blood	TMP-SMX	Death	N/A
4	Vikas P [22]	Yes	Tocilizumab, RDV	N/A	N/a	N/A	Cured	N/A
5	Nicole N [23]	Yes	AZM, HCQ, hydrocortisone 50 mg QID, Tocilizumab	MEPM	Sputum	LVFX+CAZ	Cured	N/A
6	Miraç Öz [24]	Yes	HCQ, AZM, Favipiravir	MEPM	Sputum	Colistin+FOM	Cured	*P. aeruginosa*
7	David D [25]	Yes	N/A	N/A	Sputum	TMP-SMX	Cured	N/A
8	Velamakanni S [26]	Yes	HCQ, Sarilumab	CTRX	Sputum	LVFX	Cured	no
9	Our case	Yes	RDV, BARI, mPSL (including mPSL pulse)	MEPM	Sputum, blood	TMP-SMX	Under treatment	no
10	Our case	Yes	RDV, DEXA, AZM	PIPC/TAZ	Sputum	LVFX	Cured	*K. aerogenes, E. faecalis*
11	Our case	Yes	RDV, BARI, DEXA	MEPM	Sputum	LVFX+MINO due to AKI	Death	*Aspergillus sp., Hafnia alvei*
12	Our case	Yes/ECMO	RDV, DEXA, mPSL (including mPSL pulse)	PIPC/TAZ+VCM	Sputum	TMP-SMX	Under treatment	*K. aerogenes*
Contamination								

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Table 4 continued. Literature review of COVID-19-associated *Stenotrophomonas maltophilia* + cases at our hospital.

No	Case reference	Mechanical intubation	COVID-19 treatment	Antibiotics prior to *S. maltophilia* infection	Specimen	*S. maltophilia* treatment	Outcome	Other pathogen
1	Our case	No	CTRX, MINO, LPV/RTV	CFPM	Sputum		Cured	*E. faecalis*
2	Our case	Post-intubation	CFPM, MINO, Favipiravir, mPSL	MEPM	Sputum		Cured	*E. faecalis*, *C. albicans*
3	Our case	Yes	CTRX, favipiravir, mPSL	CAZ+TOB	Blood at autopsy		Death	*P. aeruginosa*, *A. fumigatus*
4	Our case	Yes/ECMO	CTRX, AZM, RDV, DEXA	PIPC/TAZ+VCM	Blood at autopsy		Death	Mold

Table 5. List of retrospective cohort studies on *Stenotrophomonas maltophilia* secondary infection to COVID-19.

No	Study	Published year/ Country	Ward	number	Site of infection or isolation	Specimen	Mortality of respiratory infection	Top 5 pathogen
1	Li J [18]	2020/ China	ICU	*102/**110 *all patients developing secondary bacterial infection ** lung infection	Respiratory infection	Sputum endotracheal aspiration, BAL	*49% *all patients developing secondary bacterial infection	*A. baumannii* 42.7%, *K. pneumoniae* 30.9%, *S. maltophilia* 9.1%, *P. aeruginosa* 6.4%, *E. coli* 3.6%
2	Foschi C [27]	2021/ Italy	ICU	178/**230 *patients developing respiratory infection ** number of lower respiratory samples	Respiratory infection	BAL, bronchial aspiration	N/A	*P. aeruginosa* 14.7%, *K. pneumoniae* 6.9%, *S. aureus* 3.4%, *A. baumannii* 3.4%, *S. maltophilia* 3.4%
3	Yang S [9]	2021/ China	ICU	*13/**96 *critical group patients *number of specimens (BAL, sputum)	Respiratory infection	Sputum, BAL in the critical group	N/A	*B. cepacia* 18.8%, *S. maltophilia* 15.6%, *S. aureus* 7.3%, *A. baumannii* 6.3%, *M. morganii* 5.2%, * pathogens detected only in the critical group
4	Garcia-Vidal C [28]	2021/ Spain	ICU, non-ICU	*11(VAP), *4(HAP) *patients developing *S. maltophilia* infection	VAP, HAP	sputum, BAL	N/A	VAP *S. aureus* 36.4%, *P. aeruginosa* 27.3%, *S. maltophilia* 18.2%, *S. marcescens* 9% HAP *S. aureus* 25%, *P. aeruginosa* 25%, *S. maltophilia* 25%, *K. pneumoniae* 25%

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Table 5 continued. List of retrospective cohort studies on *Stenotrophomonas maltophilia* secondary infection to COVID-19.

No	Study	Published year/ Country	Ward	number	Site of infection or isolation	Specimen	Mortality of respiratory infection	Top 5 pathogen
5	Moretti M [29]	2021/ Belgium	ICU	*21 * VAP patients	VAP	Endotracheal aspiration BAL	52.4% (VAP)	*K. pneumoniae* 25.93%, *P. aeruginosa* 18.52%, *K. oxytoca* 11.11%, *Enterobacter* spp. 11.11%, *K. aerogenes* 7.41%, 7th *S. maltophilia* 3.70%
6	Puzniak L [30]	2021/ USA	N/A	*5012 *all specimens	isolation	Urinary, respiratory, blood, skin/ wound, intra-abdominal and other specimen	N/A	*Enterobacteriaceae* 31.8%, *S. aureus* 13.7%, *Enterococcus* spp. 7.1%, *P. aeruginosa* 6.5%, *S. pneumoniae* 1.9%, *S. maltophilia* 0.8%, only SARS-CoV-2 positive group
7	Baiou A [31]	2021/ Qatar	ICU	*78/**98 *patients who has isolation of multi-drug-resistant gram-negative bacteria (MDR GNB) **the number of MDR GNB specimens	Respiratory infection, bacteremia, UTI	Respiratory tract, blood, urine	15.4% (all-cause mortality by 28 day)	*S. maltophilia* 24.25%, *K. pneumoniae* 23.24%, *E. cloacae* 18.18%, *E. coli* 12.12%, *S. marcescens* 12. 12%
8	Bardi T [32]	2021/ Spain	ICU	*57/**30(VAP 21, HAP 9 *patients developing nosocomial infection during ICU **number of episodes	VAP, HAP	Tracheal aspiration	*36%/*37% *all-cause mortality by 28 day ** death within all-cause mortality by refractory respiratory failure	VAP *P. aeruginosa* 38%, MRSA 24%, *S. maltophilia* 9%, *A. baumannii* 5%, *E. cloacae* 5% HAP *P. aeruginosa* 33%, MRSA 21%, *H. influenzae* 9%, MSSA 9%, *S. maltophilia* 9%
9	Zhang D [33]	2021/ China	N/A	23 *number of sputum, BAL specimens	Respiratory infection	Sputum, BAL	NA	*Acinetobacter* 26.1%, *S. maltophilia* 21.7%, *K. pneumoniae* 13.0%, *B. multivorans*, *R. mannitolilytica*, *E. cloacae* complex 8.7%
10	Signorini L [10]	2021/ Italy	ICU	*53/**75 *patient developing super infection **VAP infection	VAP, HAP	BAL	49.1% (28 day mortality of superinfection)	*P. aeruginosa* 34.7%, *S. maltophilia* 18.7%

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Table 5 continued. List of retrospective cohort studies on *Stenotrophomonas maltophilia* secondary infection to COVID-19.

No	Study	Published year/ Country	Ward	number	Site of infection or isolation	Specimen	Mortality of respiratory infection	Top 5 pathogen
11	Martinez-Guerra BA [34]	2021/ Mexico	ICU, non-ICU	*69/**56 * number of specimens of VAP, HAP **number of VAP, HAP episode	VAP, HAP	N/A	N/A	*Enterobacter* complex 42.0%, *P. aeruginosa* 14.5%, *Klebsiella* spp. 13.0%, *E. coli* 13.0%, *S. maltophilia* 8.7%
12	Sang L [35]	2021/ China	ICU	165/**935 *number of positive culture patients **number of lower respiratory samples	HAP, VAP	Lower respiratory tract aspiration	51.6% at positive culture group (28 days ICU mortality rate)	*K. pneumoniae* 24.6%, *A. baumaninii* 24.3%, *S. maltophilia* 11.1%, *P. aeruginosa* 5.7%, *B. cepacia* 4.2%
13	Luyt C-E [36]	2020/ France	ICU	*43 number of VAP patients	VAP	BAL	9% Died on VAP treatment	*P. aeruginosa* 37%, *K. aerogenes* 26%, *E. cloacae* 7%, *Enterococcus* spp. 7%, *Streptococcus* spp. 7%, MRSA 5% *Hafnia alvei* 5%, *S. maltophilia* 5%

HAP – hospital-acquired pneumoniae; VAP – ventilator-associated pneumonia; MOF – multiple organ failure; ARDS – acute respiratory distress syndrome; CAPA – COVID-19 associated pulmonary aspergillosis; Af – atrial filtration; HTN – hypertension; CAD – coronary artery disease; DM – diabetes; ESRD – end stage renal disease; TAC – tacrolimus; MMF – mycophenolate mofetil; PSL – prednisolone; BMI – body mass index; COPD – chronic obstructive pulmonary disease; TB – tuberculosis; SLE – systemic lupus erythematous; RA – rheumatic arthritis; IP – interstitial pneumonia; LC – liver cirrhosis; CABG – coronary artery bypass graft; ICU – Intensive Care Unit; ECMO – extracorporeal membrane oxygenation; N/A – not applicable; HCQ – hydroxychloroquine; AZM – azithromycin; mPSL – methylprednisolone; RDV – remdesivir; DEXA – dexamethasone; QID – quater in die; BARI – baricitinib; CFPM – cefepime; MEPM – meropenem; PIPC/TAZ – piperacillin/tazobactam; VCM – vancomycin; CAZ – ceftazidime; TOB – tobramycin; TMP-SMX – trimethoprim/sulfamethoxazole; LVFX – levofloxacin; MINO – minocycline; AKI – acute kidney injury; FOM – fosfomycin; *P. aeruginosa – Pseudomonas aeruginosa; K. aerogenes – Klebsiella aerogenes; E. faecalis – Enterococcus faecalis; C. albicans – Candida albicans; A. fumigatus – Aspergillus fumigatus;* UTI – urinary tract infection; BAL – bronchoalveolar lavage; *A. baumannii – Acinetobacter baumannii; K. pneumoniae – Klebsiella pneumoniae; S. maltophilia – Stenotrophomonas maltophilia; E. coli – Escherichia coli; S. aureus – Staphylococcus aureus; B. cepacia – Burkholderia cepacia; M. morganii – Morganella morganii; S. marcescens – Serratia marcescens; K. oxytoca – Klebsiella oxytoca; S. pneumoniae – Streptococcus pneumoniae; E. cloacae – Enterobacter cloacae; MRSA* – methicillin-resistant *S. aureus; H. influenzae – Haemophilus influenzae; B. multivorans – Burkholderia multivorans; R. mannitolilytica – Ralstonia mannitolilytica.*

in patients with COVID-19. Chest CT imaging abnormalities in COVID-19-associated pneumonia manifest as rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progress to or co-exist with consolidations within 1 to 3 weeks [11]. Chest CT imaging abnormalities in *S. maltophilia* infections also appear as ground-glass opacity [12,13], which is difficult to distinguish from that of COVID-19. In the 4 patients in this review, we did not find any new ground-glass opacity when the *S. maltophilia* culture was positive. In these 4 patients, *S. maltophilia* was susceptible to TMPX-SMX, LVFX, and MINO. *S. maltophilia* is a multidrug-resistant organism exhibiting intrinsic metallo-beta-lactamases, cephalosporinases, and efflux pumps [14]. Therefore, *S. maltophilia* is resistant to penicillin, cephalosporins, and carbapenems. It is important for the clinician to note that beta-lactams such as carbapenems target extended-spectrum beta-lactamase-producing Enterobacteriaceae and is not effective for *S. maltophilia*. We have to administer TMP-SMX or LVFX to treat *S. maltophilia* infection.

There is limited evidence on effective antimicrobials against *S. maltophilia*. TMP-SMX is the most commonly used drug showing good susceptibility [15]. In the presence of TMP-SMX-induced hypersensitivity reactions and acute kidney injury, LVFX is an alternative; however, 1 study showed no difference in its efficacy compared to that of TMP-SMX [16]. Moreover, LVFX-resistant *S. maltophilia* has emerged worldwide [17]. The aforementioned

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study showed that a history of fluoroquinolone use, previous ICU stay, and the number of previous exposures to different classes of antibiotics were significantly associated with LVFX-resistant *S. maltophilia*. Another study described the antimicrobial susceptibility of COVID-19-related *S. maltophilia* [18], and the resistant strains were ceftazidime (90%), LVFX (30%), TMP-SMX (0%), and MINO (0%). In our review, *S. maltophilia* infection was associated with higher mortality; therefore, we suggest empirically administering TMX-SMP. Further studies are needed to confirm this hypothesis.

This study had some limitations. As VAP and HAP definitions differed among the studies, it was not possible to discern whether *S. maltophilia* was colonizing or infectious. In addition, no retrospective studies have analyzed the risk factors and mortality associated with *S. maltophilia*. However, this case review suggested that a history of broad-spectrum antimicrobial use, steroid use, and ICU admission are risk factors for COVID-19-associated *S. maltophilia* infection.

Conclusions

S. maltophilia is detected in sputum cultures of clinically unstable ICU patients with COVID-19 who are receiving immunosuppressive drugs, are intubated, or are on broad-spectrum antimicrobial agents. We suggest administering treatment for *S. maltophilia*-associated pneumonia.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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