



Stenotrophomonas maltophilia Infections in Pediatric Patients – Experience at a European Center for Pediatric Hematology and Oncology

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Stenotrophomonas maltophilia is an important nosocomial pathogen in immunocompromised individuals and characterized by intrinsic resistance to broad-spectrum antibacterial agents. Limited data exists on its clinical relevance in immunocompromised pediatric patients, particularly those with hematological or oncological disorders. In a retrospective single center cohort study in pediatric patients receiving care at a large European pediatric hematology and oncology department, ten cases of invasive *S. maltophilia* infections (blood stream infections (BSI), 4; BSI and pneumonia, 3, or soft tissue infection, 2; and pneumonia, 1) were identified between 2010 and 2020. Seven patients had lymphoblastic leukemia and/or were post allogeneic hematopoietic cell transplantation. Invasive *S. maltophilia* infections occurred in a setting of indwelling central venous catheters, granulocytopenia, defective mucocutaneous barriers, treatment with broad-spectrum antibacterial agents, and admission to the intensive care unit. Whole genome sequencing based typing revealed no genetic relationship among four individual *S. maltophilia* isolates. The case fatality rate and mortality at 100 days post diagnosis were 40 and 50%, respectively, and three patients died from pulmonary hemorrhage. Invasive *S. maltophilia* infections are an emerging cause of infectious morbidity in patients receiving care at departments of pediatric hematology and oncology and carry a high case fatality rate.

Keywords: children, cancer, transplantation, *Stenotrophomonas maltophilia*, blood stream infection, pulmonary hemorrhage

INTRODUCTION

Stenotrophomonas maltophilia (formerly: *Pseudomonas* or *Xanthomonas maltophilia*) is an aerobic non-fermenting Gram-negative bacillus (NGNB) that can be found ubiquitously in the environment (1). Next to *Pseudomonas aeruginosa* and *Acinetobacter* spp., the organism is considered the third most frequent nosocomial pathogen among non-fermentative bacteria (2, 3).

Pneumonia and bloodstream infection (BSI) are the most common clinical manifestations of *S.maltophilia* infections. Less frequently, *S.maltophilia* can cause urinary tract infections, cholangitis, peritonitis, wound infections, eye infections, arthritis, meningitis, and endocarditis (4, 5). Patients with hematologic malignancies are at high risk for *S.maltophilia* infection because of chemotherapy-induced neutropenia and immunodeficiency. Frequent exposure to broad-spectrum antibiotics and the presence of central venous catheters further enhance the risk of *S.maltophilia* infection (6, 7). The rate of *S.maltophilia* BSI among BSIs in this patient population has been reported to be as high as 60% (8–11).

Treatment of *S.maltophilia* infection can be difficult because of the organisms inherent resistance to a variety of antibiotics (12, 13). Trimethoprim-sulfamethoxazol (TMP-SMX) is the drug of choice, and fluoroquinolones are the proposed alternative. Similar to the treatment of *Pneumocystis jirovecii* pneumonia, up to five-fold higher than regular doses of TMP-SMX are recommended for severe infections (5, 14). Thus, the therapeutic options for *S.maltophilia* infections are quite different from those available for other NGNB, and appropriate antimicrobial therapy is often delayed through ineffective treatment during initial empirical therapy (15). Accordingly, mortality rates are high in immunocompromised and critically ill patients (11, 16), with 30-day mortality rates of *S.maltophilia* BSIs ranging from 11% to 53% (8, 11–13, 17–19).

While series of adult cancer patients with invasive *S.maltophilia* infections have been published in regular intervals, few reports exist for pediatric patients with cancer and/or allogeneic hematopoietic cell transplantation (HCT) (20–22). We therefore analyzed the incidence, genetic relatedness, clinical course and outcomes of invasive *S.maltophilia* infections observed during the past ten years at our institution, a high volume European pediatric cancer center with an active allogeneic HCT program.

METHODS

Study Design and Setting

The study was a retrospective observational single center cohort study of children and adolescents with oncological or hematological disease including patients with autologous or allogeneic HCT receiving care at the Department of Pediatric Hematology and Oncology of the University Children's Hospital of Münster between January 2010 and July 2020 with the last follow-up in October 2020. The Department's referral patterns

and admission data at the time of the study have been reported recently (23). Patients with *S.maltophilia* infection or colonization were identified through the Hospital's central electronic medical information system. Inclusion criteria were medical care at the Department of Pediatric Hematology and Oncology; a diagnosis of either solid tumor, hematological malignancy, a non-neoplastic hematological disorder, or status post allogeneic HCT; and microbiology confirmation of *S.maltophilia* in blood, usually sterile body sites or respiratory secretions in the presence of pneumonia. Patient demographics, disease related parameters, clinical course and outcome data were retrieved from the medical information system and analyzed. The primary endpoint of outcome was survival at day +100 post diagnosis. Written informed consent for data collection and analysis was obtained within the consent procedure for cancer treatment, HCT, and specialized medical care approved by the local institutional review board. Data collection was accomplished by a pseudonymized standardized case report form.

Standard Operating Procedures

All patients received treatment for their underlying condition according to standard protocols of the German Society for Oncology and Hematology (GPOH) or individual recommendations of the respective study groups. Up to December 2014, antibacterial prophylaxis was given to patients undergoing HCT and consisted of penicillin, ciprofloxacin and metronidazole in allogeneic and penicillin and ciprofloxacin in autologous HCT recipients, respectively. Antibacterial prophylaxis was discontinued starting 2015. Initial empirical antibacterial therapy for fever and neutropenia consisted of ceftazidime plus gentamycin until December 2016 and was then replaced by piperacillin/tazobactam. Unstable patients were to start with meropenem plus vancomycin and were subsequently deescalated, as feasible. This regimen was also used for escalation in patients with fever persisting for more than 48–72 hours or a new fever after defervescence, with or without additional empirical antifungal therapy at the discretion of the attending physician. Suspected or proven infections were treated according to current management recommendations. All patients received TMP-SMX 8 mg/kg (max. 320 mg) twice weekly as prophylaxis for prevention of *Pneumocystis jirovecii* pneumonitis, and topical polyenes or azoles for prevention of oropharyngeal candidiasis. Prophylaxis with TMP-SMX was continued until three months after end of therapy in cancer patients and until immunoreconstitution in allogeneic HCT recipients. Standard antifungal prophylaxis consisted of fluconazole for allogeneic HCT recipients, and either posaconazole or voriconazole for patients with acute myeloid leukemia or recurrent leukemia (24, 25). Blood cultures were drawn in case of fever and daily until defervescence and negative results. Aerobic and anaerobic cultures with age-appropriate blood volumes were obtained from each lumen of an indwelling catheter or from a peripheral vein, if no catheter was present. Respiratory cultures were obtained by tracheal aspiration in intubated patients (n=4) and by sputum induction in non-intubated patients, respectively. Cultures

form other body sites were obtained only when infection was clinically or radiologically suspected or on a case-by-case basis to monitor bacterial colonization by swabs from the throat and the perianal region. All patients were routinely screened for colonization with methicillin-resistant *Staphylococcus aureus* by a combined swab from the throat and the nares at each hospital admission.

Definitions

Blood stream infection was defined as \geq one positive blood culture for either *S.maltophilia* or any other bacterial and fungal pathogens obtained in a patient with fever and other signs of infection, where present. Infections at other body sites were defined by clinical and/or radiographic criteria. Pulmonary infection was considered to be radiological evidence of pneumonic infiltrates together with detection of *S.maltophilia* in respiratory secretions and BSI. In the absence of documented BSI, respiratory evidence of *S.maltophilia* together with direct detection of *S.maltophilia* in the intraoperative tissue cultures, as in patient 3 after open abscess surgery (**Table 1**), was considered pulmonary infection.

Identification and Susceptibility Testing

Standard blood culture systems (BACTEC[®], Becton Dickinson, Sparks, Maryland, USA) were used for detection of bloodstream isolates. Blood culture vials were incubated for up to 14 days. Subsequent species identification was performed by Matrix-Assisted Laser Desorption/Ionization Time of Flight-Mass Spectrometry (MALDI TOF MS[®], Microflex, Bruker, Bremen, Germany). Susceptibility testing was done using disk diffusion method in accordance with the standards of European Committee on Antimicrobial Susceptibility Testing (EUCAST) and interpreted using zone diameter breakpoints (EUCAST clinical breakpoints [version 6.0]) for TMP-SMX.

Whole Genome Sequencing-Based Typing

To determine the clonal relationship of *S.maltophilia* strains isolated from blood cultures, available isolates were subjected to whole genome sequencing (WGS)-based typing using the Illumina MiSeq platform (Illumina Inc., San Diego, USA) as described previously (26). Due to the retrospective character of this study, only four individual samples from four different patients were available for testing. Using SeqSphere+ software version 2.0 beta (Ridom GmbH, Münster, Germany), all coding regions were extracted and compared in a gene-by-gene approach (core genome multilocus sequence typing, cgMLST) using SM K279a strain (GenBank accession number AM743169.1) as a reference sequence. Instead of a published cgMLST scheme, which is not yet available, this *ad hoc* scheme was used to differentiate the cluster. SeqSphere+ software was used to display the clonal relationship in a minimum spanning tree. For backwards compatibility with classical molecular typing, i. e. MLST, the MLST sequence types were extracted from the WGS data *in silico*.

Statistical Analysis

Statistical analyses were carried out with SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA) software package. Overall survival (OS) was calculated from primary diagnosis to death or last follow-up. Comparison of the frequency of *S.maltophilia* infections over time and statistical exploration of associations between patient- and disease related parameters and mortality were performed by the Fisher's Exact test; univariate and multivariate analyses were not performed due to the limited sample size. The level of statistical significance was set at $p < 0.05$ (two-sided).

RESULTS

Demographic and Clinical Characteristics

Between January 2010 and July 2020, a total of 502 distinct BSIs were identified in children with oncological or hematological disease including patients with autologous or allogeneic HCT receiving care at the Department of Pediatric Hematology and Oncology of the University Children's Hospital of Münster. Of these, nine BSIs were due to *S.maltophilia*, accounting for a rate of *S.maltophilia* BSIs of 1.8% among all BSIs and of 7% among all Gram-negative BSIs, respectively. Considering one additional patient with documented pulmonary infection and positive cultures from all other sources, there were a total of ten invasive *S.maltophilia* infections in ten patients. Over time, there was a numerical, but not statistically significant increase in infected patients in the second half (2016–2020) of the study (**Figure 1**).

The demographic and clinical characteristics of the ten patients with invasive infections are listed in **Table 1**. Five patients each were male and female, and the median age was 10.4 years (range, 0.8 to 17.9 years). Five patients had acute lymphoblastic leukemia, and five patients had received allogeneic HCT and were between 13 and 523 days (median: 63) post-transplant. Seven patients were receiving antineoplastic or immunosuppressive therapy, and all had an indwelling central venous catheter at the time of diagnosis (Broviac-type, $n=6$; percutaneous transient catheter, $n=3$; port-a-cath-type, $n=1$). Among the 10 patients with invasive *S.maltophilia* infections, four had isolated BSIs, three a BSI and concomitant pneumonia, two a BSI and concomitant soft tissue infection, and one patient had pneumonia with an intrapulmonary abscess without positive blood cultures. In seven patients, superficial colonization by *S.maltophilia* was detected. Most affected patients ($n=8$) were receiving broad-spectrum antibacterial agents at the time of diagnosis, most frequently carbapenems ($n=8$), glycopeptides ($n=7$), and quinolones ($n=6$). All had an increased C-reactive protein level, and seven patients were profoundly granulocytopenic with an absolute neutrophil count $< 500/uL$. Six patients required admission to the intensive care unit at presentation, and four of these patients received mechanical ventilation because of pneumonia ($n=3$) and respiratory failure not related to pneumonia but to multiorgan failure ($n=1$) (**Table 1**).

TABLE 1 | Demographics, underlying condition and principal treatment, central venous cannulation, infection and colonization data, concomitant clinical data, treatment and outcome of ten pediatric patients with oncological or hematological disease including patients with autologous or allogeneic hematopoietic cell transplantation and invasive *S.maltophilia* infections.

Patient No.	Gender	Age (years)	Diagnosis	Allo HCT; time after HCT (days)**	Chemotherapy	IST	CVC	SM BSI	SM Pneumonia	SM Tissue Infection	Concomitant SM Colonization
1	M	9.2	HLH	Yes (MMUD); 523	No	No	Yes	Yes	No	Yes ****	Skin
2	M	4.6	DSP Mutation*	No	No	No	Yes	Yes	No	No	Skin
3	F	11.6	ALL	No	Yes	No	Yes	No	Yes***	No	Anus, skin, trachea
4	F	15.8	VSAA	Yes (MRD); 63	No	Yes	Yes	Yes	Yes***	No	No
5	M	17.9	ALL	Yes (MUD); 231	No	Yes	Yes	Yes	Yes***	No	Anus, trachea
6	M	5.2	ALL	No	Yes	No	Yes	Yes	No	No	Skin, pharynx
7	M	14.7	ALL	Yes (MMUD); 15	No	Yes	Yes	Yes	No	No	Anus
8	F	11.8	ALL	Yes (MUD); 13	No	Yes	Yes	Yes	No	Yes ****	No
9	F	2.8	EwS	No	Yes	No	Yes	Yes	No	No	No
10	F	0.8	SCID	No	No	No	Yes	Yes	Yes	No	Anus, skin, pharynx

Patient No.	Broad-spectrum Antibiotics	Defective Skin Barrier	CRP (mg/dL)	WBC (10 ³ /μL)	ANC (10 ³ /μL)	ICU Admission	Mechanical Ventilation	Concomitant BSI	CVC Removal	Antibiotic Treatment	Total Duration of Treatment (days)	Survival *****	Follow-up (days)
1	No	Yes	3.5	8.2	0.7	No	No	No	No	Meropenem; moxifloxacin	14	Yes	2053
2	Yes	Yes	11.3	27.5	21.7	Yes	Yes	Yes ¹	Yes	TMP-SMX; meropenem; moxifloxacin; tigecyclin	20	Yes	395
3	Yes	No	25.5	0.2	0	Yes	Yes	No	No	Meropenem; fosfomycin; tigecyclin	45	No	45
4	No	No	19.8	0	0	Yes	No	No	No	Meropenem; ciprofloxacin	1	No	2
5	Yes	Yes	37.9	0.3	0	Yes	Yes	Yes ²	Yes	TMP-SMX; meropenem	2	No	3
6	Yes	No	6.1	0.7	0.2	No	No	No	Yes	Ceftazidim; colistin; moxifloxacin; tigecyclin	18	Yes	167
7	Yes	No	23.0	0	0	No	No	No	Yes	Ceftazidim; colistin; moxifloxacin; tigecyclin	27	Yes	497
8	Yes	Yes	3.3	0	0	Yes	No	No	Yes	Meropenem; colistin; moxifloxacin; tigecyclin	10	No	10
9	Yes	No	9.7	0	0	No	No	No	Yes	Meropenem; ciprofloxacin	15	Yes	2446
10	Yes	Yes	15.2	23.3	18.0	Yes	Yes	Yes ³	Yes	Ceftazidim; tobramycin	14	No	79

ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; BSI, blood stream infection; CRP, C-reactive protein; CVC, central venous catheter; DSP, desmoplakin; EwS, Ewing sarcoma; F, female; HCT, hematopoietic stem cell transplantation; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; IST, immunosuppressive therapy; M, male; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; SCID, severe combined immunodeficiency; SM, *Stenotrophomonas maltophilia*; WBC, white blood cell count; VSAA, very severe aplastic anemia.

* Associated with recurrent infections, especially skin; care at the Department of Hematology and Oncology; ** Conditions in allo-HCT recipients: Patient 1, chronic graft-versus-host disease (GVHD) of the skin, off immunosuppression, low dose steroids (< 0.3 mg/kg prednisone equivalent); patient 4, primary graft failure; patient 5, chronic GVHD of the skin and the gastrointestinal tract, immunosuppression with sirolimus, anti-inflammatory antibodies, methylprednisolone 2 mg/kg/d; patients 7 and 8 were prior to engraftment. *** including pulmonary hemorrhage (please see **Figure 3** for details); **** patient 1 had a catheter exit-site infection, and patient 8 had necrotizing fasciitis involving the lower extremities and buttocks. ***** Four patients died in direct causal relationship to the infection from pulmonary hemorrhage (patients 3,4,5) and necrotizing fasciitis (patient 7) with multiorgan failure, and one patient (patient 10) died two months after completion of treatment from unrelated causes in hospice care.

¹ *Staphylococcus hemolyticus*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Candida albicans* in the week prior to diagnosis of *S.maltophilia* infection and another blood culture positive for *Staphylococcus hemolyticus* in the week after; ² *Escherichia coli*, *Enterococcus faecium*, *Staphylococcus epidermidis* in the week prior to diagnosis of *S.maltophilia* infection; ³ *Pseudomonas aeruginosa*, *Staphylococcus hemolyticus*, and *Enterococcus faecium* in the week prior to diagnosis of *S.maltophilia* infection.

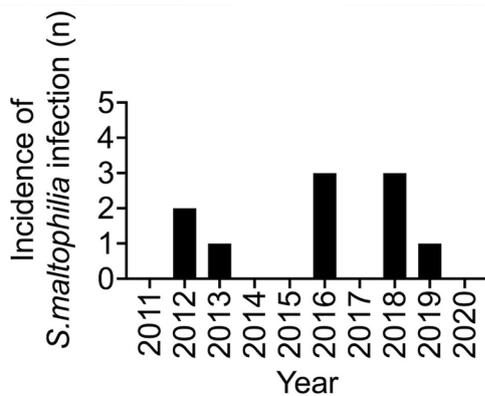


FIGURE 1 | Annual frequency of *S. maltophilia* infection in children with oncological or hematological disease including patients with autologous or allogeneic hematopoietic cell transplantation between 2011 and 2020. For 2020, cases until March are included. $p = 0.34$ for the comparison of the proportion of *S. maltophilia* blood stream infections (BSI) ($n = 9$) among all BSIs in 2016–2020 relative to 2011–2015 (n.s.).

Concomitant Infections

Three patients were diagnosed with other BSIs in the week prior and/or the week after *S. maltophilia* infection and were receiving antibiotic treatment (patient 2 with *Staphylococcus hemolyticus*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Candida albicans* in the week prior and another blood culture positive for *Staphylococcus hemolyticus* in the week after; patient 5 with *Escherichia coli*, *Enterococcus faecium*, *Staphylococcus epidermidis* in the week prior; and patient 10 with *Pseudomonas aeruginosa*, *Staphylococcus hemolyticus*, and *Enterococcus faecium* in the week prior to *S. maltophilia* infection, respectively). Two patients (patient 4 and patient 5) showed concomitant low-level systemic *Epstein-Barr virus* reactivation, and one patient (patient 4) had systemic *Herpes simplex virus 1* reactivation (**Table 1**).

Antimicrobial Susceptibilities and Genotyping

Using disk diffusion methodology in accordance with the standards of European Committee on Antimicrobial Susceptibility Testing (EUCAST) and an agar diffusion diameter of > 16 mm assumed as susceptible (increased exposure), 70% of all ten initial isolates were susceptible to TMP-SMX. However, in one of the seven patients with a TMP-SMX-susceptible initial isolate, a follow-up blood stream isolate obtained three days after the initial one was tested non-susceptible. WGS-based typing and gene by gene comparison of four initial *S. maltophilia* blood culture isolates obtained from four different patients showed allelic differences between strains of at least 1604 alleles, thereby excluding any genetic relatedness of subjected *S. maltophilia* isolates (**Figure 2**).

Antimicrobial Management and Outcome

The indwelling central venous catheter was removed shortly after diagnosis in seven of the nine patients with positive blood cultures. One patient (patient 7, **Table 1**) received repeated granulocyte transfusions. Antimicrobial treatment of *S. maltophilia* infection was highly heterogeneous and included combinations of meropenem (7), fluoroquinolones (7), tigecyclin (5), colistin (3), TMP-SMX (2), ceftazidime (1), fosfomycin (1), and tobramycin (1) administered for a total treatment duration of 1 to 45 days (median: 14.5 days). Of note, in retrospect, it is difficult to distinguish precisely between therapy directed at *S. maltophilia*, empiric treatment for suspected infections or directed treatment of confirmed concomitant infections, but the agents TMP-SMX and moxifloxacin were added only when *S. maltophilia* was detected. The 30-day mortality rate and the overall mortality rate were 30% and 50%, respectively, after a median follow-up time of 123 days (range, 2 to 2446 days). Four patients died in direct causal relationship to the infection after 2, 3, 10 and 45 days after diagnosis from pulmonary hemorrhage (patients 3,4,5, **Figure 3**) and necrotizing fasciitis (patient 7) with multiorgan failure (**Table 1**). Explorative statistical analysis of factors associated with overall mortality in patients with invasive *S. maltophilia*

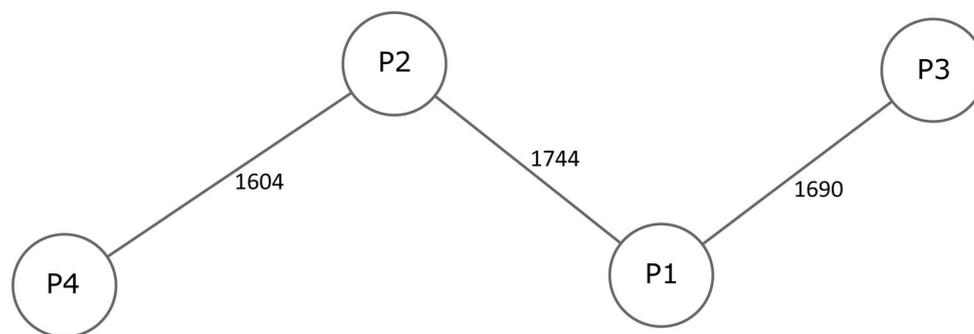


FIGURE 2 | Minimum spanning tree of four *S. maltophilia* blood culture isolates obtained from four different patients. The tree is based on up to 1876 target genes, pairwise ignoring missing values. Each dot represents one genotype (P1–P4). Different connecting lines and numbers on these lines show the number of alleles differing between two genotypes.

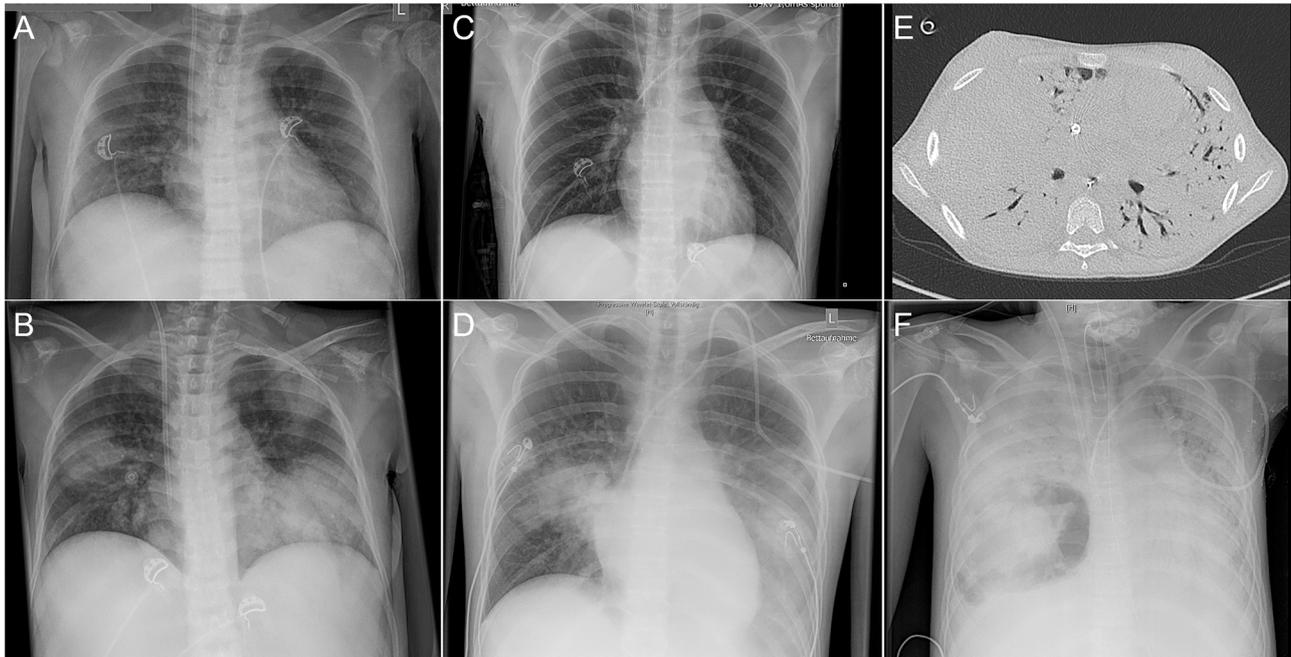


FIGURE 3 | Radiographic findings in three patients with *S. maltophilia* infection and pulmonary hemorrhage. **(A, B)** 15-years old girl post allogeneic HCT for aplastic anemia (patient 4). **(A)** Normal chest x-ray at day +1 following allogeneic HCT; **(B)** *S. maltophilia*-related sepsis and ultimately fatal diffuse pulmonary hemorrhage at day +12 with detection of *S. maltophilia* in tracheal aspirates. **(C, D)** 17-years old male post allogeneic HCT for acute lymphoblastic leukemia (ALL) (patient 5). **(C)** Normal chest x-ray obtained during evaluation prior to transplantation; **(D)** *S. maltophilia*-related sepsis with ultimately fatal diffuse pulmonary hemorrhage on day +1 post-transplant. **(E, F)** 11-years old female with ALL (patient 3). First tracheal detection of *S. maltophilia* four days after microbiologically proven methicillin-susceptible *Staphylococcus aureus* pneumonia. **(E)** Middle lobe bleeding and atelectasis on chest CT-scans twenty-four days after first *S. maltophilia* detection. **(F)** Intrapulmonary abscess thirty-one days after first *S. maltophilia* detection; in the context of surgical resection, documentation of *S. maltophilia* from intraoperative tissue. Death forty-five days after first *S. maltophilia* detection.

infections revealed the presence of pneumonia ($p=0.047$) and admission to the intensive care unit ($p=0.047$) as being associated with dismal outcome (**Supplementary Table 1**).

DISCUSSION

Stenotrophomonas maltophilia is a non-fermentative, Gram-negative bacillus that has emerged as important nosocomial pathogen in immunocompromised and critically ill patients (16, 27). Published experience in pediatric patients with cancer and/or allogeneic HCT is limited to two separate studies reporting on a total of 24 *S. maltophilia* BSIs (22, 28) and several larger pediatric series that include a relevant proportion of patients with hematological malignancies or solid tumors (24, 25, 29, 30) (**Table 2**). In the study presented here, *S. maltophilia* accounted for 1.8% of all BSIs and for 7% of those caused by Gram-negative rods. Invasive *S. maltophilia* infection was associated with a diagnosis of acute leukemia and/or allogeneic HCT, or immunodeficiency, and occurred in a setting of impaired host defences, defective mucocutaneous barriers, indwelling central venous catheters, treatment with broad-spectrum antibacterial agents, and admission to the intensive care unit. Four patients

died in direct relationship to the infection, including three patients with pneumonia and pulmonary hemorrhage (**Figure 3**), which has been reported to be associated with *S. maltophilia* infection and status post allogeneic HCT (29, 44, 45). Similar to others (28), we found a numerical increase in *S. maltophilia* infections over time. Molecular typing of a limited number of blood culture isolates, however, confirmed that isolates were genetically not related and suggests the absence of a nosocomial outbreak (46).

The exact route of acquisition of *S. maltophilia* often remains unknown. Nevertheless, isolation of the organism from mucosal surfaces of the respiratory and/or the lower gastrointestinal tract may herald later infection as many patients with *S. maltophilia* BSIs were reported to be colonized prior to infection (5, 17). Indeed, the oral microbiome has recently been described as a potential reservoir, and real-time monitoring of the oral *S. maltophilia* relative abundance has been suggested to identify patients at risk for invasive infection (30). In our limited cohort, concomitant colonization was detected in the majority of cases with invasive *S. maltophilia* infection, but overall, there was no apparent relationship between pharyngeal or respiratory colonization and invasive infection.

Similar to previous reports (20), the majority of invasive *S. maltophilia* infections in our cohort was associated with

indwelling central venous catheters. Six of the ten patients were treated at the intensive care unit and four were on invasive ventilation. Intensive care, mechanical ventilation, and/or central venous catheterization have been identified as risk factors for *S. maltophilia* BSI and/or dismal outcome (**Table 2**). Several studies suggest a survival benefit for removal of indwelling central venous catheters (8, 9, 17, 47–49), and international guidelines strongly recommend prompt catheter removal in *S. maltophilia* associated BSIs (50), independent on whether the catheter is considered the source of the infection or being colonized secondary to ongoing bacteremia.

Patients with *S. maltophilia* BSIs often have polymicrobial infections (5), and their relative frequency in children seems to be higher as observed with *Pseudomonas aeruginosa* (35). In the cohort presented here, concomitant BSI occurred in 30% of patients with *S. maltophilia* infection, which is below the rate in previous series of pediatric patients (31, 33). Bacteria most commonly recovered in temporal context with *S. maltophilia* were coagulase-negative *Staphylococcus* and *Enterococcus* spp (8, 45). It remains unclear whether the detection of *S. maltophilia* is a consequence of appropriate antimicrobial therapy for other BSIs or whether the concurrent invasive infections simply reflect the sum of immunodeficiency in the affected patients.

In eight of the ten cases, *S. maltophilia* infection occurred as breakthrough infection in patients receiving broad-spectrum antibacterial agents. Prior use of carbapenems has been repeatedly described as a risk factor for *S. maltophilia* infection (12, 17, 44, 51–53), and cumulative carbapenem use has been identified to be associated with *S. maltophilia* in leukemia patients with altered oral microbiome (30). Similarly, in the majority of studies in pediatric patients investigating factors related with outcome, prior use of carbapenems was associated with dismal outcome of *S. maltophilia* BSI (22, 35, 39) (**Table 2**). As a consequence, clinicians should be aware that breakthrough infection with *S. maltophilia* may occur in severely ill patients being treated with carbapenems.

Antibacterial therapy for *S. maltophilia* infections is challenging because most clinical isolates are resistant to agents commonly used for empirical treatment of febrile neutropenia or documented infections by Gram-negative organisms, including extended-spectrum penicillins, third-generation cephalosporins, carbapenems, and aminoglycosides (53). In addition, current recommendations for treatment are based on historical evidence, case series, and *in vitro* susceptibility data rather than pharmacokinetic/pharmacodynamic considerations and results of controlled clinical trials (5). In general, TMP-SMX is the drug of choice for infections by susceptible *S. maltophilia* isolates based on its potent *in vitro* activity and documented clinical efficacy (10, 46). Nevertheless, susceptibility varies between geographic regions and resistance is an emerging threat (2, 5, 10, 16, 54, 55). Alternatives to treatment with TMP-SMX include fluoroquinolones and tigecycline (12, 13). However, in contrast to TMP-SMX, clinical breakpoints for these agents have not been defined, which makes a valid interpretation of *in vitro* susceptibility testing results with regards to the prediction of clinical efficacy difficult. In our study, seven of ten *S. maltophilia* initial isolates from patients with invasive

infections were susceptible *in vitro* to TMP-SMX, and in one of these patients, isolates became resistant during treatment. Apart from primary or secondary resistance, further concerns in immunocompromised patients with cancer and/or allogeneic HCT include the myelotoxicity of therapeutic doses of TMP-SMX (18) and the widespread use of low and intermittent doses of the agent for antibacterial or anti-*Pneumocystis* prophylaxis that may result in the selection of resistant *S. maltophilia* strains (17). Indeed, based on emerging resistance, it has been suggested by individual experts to consider escalating therapies in immunocompromised or critically ill patients (49, 56). Previous observations on the use of fluoroquinolones against invasive *S. maltophilia* infections have demonstrated comparable patient survival relative to TMP-SMX (12, 13, 57), and quinolone prophylaxis in adult cancer patients has been associated with a reduced incidence of invasive *S. maltophilia* infections (58). Nevertheless, quinolone monotherapy for *S. maltophilia* BSIs should be critically reflected (19), as rapid emergence of resistance to these agents has been observed both *in vitro* and *in vivo* (5, 59).

Considering the small number of patients, the 30-day mortality rate of 30% in patients with invasive *S. maltophilia* infections in our study is in line with 30-day mortality rates of *S. maltophilia* BSIs of 33% and 38% reported by others (17, 60). In pediatric studies, the reported all-cause mortality rates in patients with *S. maltophilia* infections range from 12.5% to 61% with an attributable mortality of 0% to 18%, respectively (22, 31, 33, 37–39, 41) (**Table 2**). Many studies across all age groups have reported risk factors for mortality associated with *S. maltophilia* BSIs including prolonged hospitalization prior to BSI onset, previous exposure to antimicrobial agents, use of indwelling medical devices, a compromised health status, complex medical care, granulocytopenia and/or transplantation, and inappropriate therapy (5, 8–10, 15, 17, 18, 36, 48, 61–64). While the limited number of patients included precluded robust statistical assessments, the presence of pneumonia and admission to the intensive care unit were both significantly associated in explorative analyses with mortality in the present study (**Supplementary Table 1**). Nevertheless, as it is often difficult to distinguish between colonization and infection, identification of risk factors for mortality is ultimately limited to BSIs and may not consider the full spectrum of diseases caused by the organism (7).

To conclude, as reflected in this limited series of heterogeneous patients, defined therapeutic strategies for invasive *S. maltophilia* infections in immunocompromised pediatric patients, including those with cancer and/or allogeneic HCT, so far lack uniformity but remain an important goal. Clinicians should be aware that breakthrough infections by *S. maltophilia* may occur during the administration of broad-spectrum antibiotics, especially following carbapenem use, and that these infections may be associated with fulminant and fatal pulmonary hemorrhage, in particular in allogeneic HCT patients (29). Detection of BSI by *S. maltophilia* should prompt the removal of indwelling central venous catheters and the immediate initiation of therapeutic doses of TMP-SMX. Initial combination with second generation fluoroquinolones and tigecycline until return of resistance testing

TABLE 2 | Literature overview of case series reporting blood stream infections of *S. maltophilia* in pediatric patients.

Patient Collective	Study Duration (years)	<i>S. maltophilia</i> Pts. (number)	Isolates (number)	Source	All-cause Crude Mortality (%)	Attributed Mortality (%)	Risk Factors (RF)	Positive Effect on Survival	Reference	Publication Date
Pediatric pts	6.5	79	85	non-respiratory	12.5	6.3	NA	NA	(31)	2000
Pediatric pts	5	8	8	blood	NA	NA	NA	NA	(32)	2002
Pediatric cancer pts	4	6	6	blood	NA	NA	NA	NA	(28)	2006
Infants <180 days with heart disease	5	32	47	blood, CSF, urine, eye, wound, BAL	37.5	NA	RF for <u>outcome</u> : prolonged positive SM cultures (p=0.008) need for renal dialysis (p=0.04) presence of stroke (p=0.05)	<u>outcome</u> -related: High ALC prior infection (p=0.01) Less mechanical ventilation days (p=0.006)	(33)	2015
Pediatric pts	5	18	18	blood	NA	NA	NA	NA	(34)	2016
Pediatric pts	2	19	NA	blood	NA	NA	RF for <u>BSI</u> : prior use of carbapenems within 7 d (p=0.02) prior ICU stay (p=0.03) mechanical ventilation (p=0.01)	<u>BSI</u> -related: Consultation with ID physician (p=0.04)	(35)	2016
Pediatric cancer pts	13	18	18	blood	NA	0	RF for <u>BSI</u> : severe neutropenia (<100/mm ³ ; p=0.002) hospital-acquired infection (p<0.0001) breakthrough infection (p<0.0001)	NA	(22)	2017
PICU	0.3	NA	16	blood	NA	NA	NA	NA	(36)	2017
Pediatric pts	0.7		23	blood, respiratory, urine	35	NA	NA	NA	(37)	2017
PICU	5	31	91	blood, respiratory, soft tissues	61	16	RF for <u>outcome</u> : prior prolonged hospitalization (p=0.002) septic shock (p=0.003) mechanical ventilation (p=0.004) indwelling central vein catheter (p=0.03) prior use of steroids (p=0.04) prior use of carbapenems (p=0.004) mechanical ventilation (p=0.02)	<u>outcome</u> -related: combination of ciprofloxacin, TMP-SMX, and/or minocycline (p<0.001)	(38)	2018
Critically ill children	5	NA	68	blood	42	18	RF for <u>outcome</u> : prior prolonged	<u>outcome</u> -related: combination of	(39)	2019

(Continued)

TABLE 2 | Continued

Patient Collective	Study Duration (years)	<i>S. maltophilia</i> Pts. (number)	Isolates (number)	Source	All-cause Crude Mortality (%)	Attributed Mortality (%)	Risk Factors (RF)	Positive Effect on Survival	Reference	Publication Date
							hospitalization (p=0.03) nosocomial source of infection (p=0.02) septic shock (p<0.001) chemotherapy (p=0.007) carbapenems (p=0.05)	ciprofloxacin, TMP-SMX, and minocycline (p<0.01)		
Pediatric pts	2	NA	104	blood, respiratory, soft tissues, CSF	NA	NA	NA	NA	(40)	2020
Pediatric pts	10	12	20	blood and/or catheter	33.3	NA	NA	NA	(41)	2020
Pediatric pts	7.3	128	161	blood, respiratory, CSF, wound	NA	3.9	RF for <u>severe <i>S.maltophilia</i> infection</u> : mechanical ventilation (p=0.021) prior ICU stay within 30 d (p=0.005) prior use of carbapenems (p=0.007)	NA	(42)	2020
Pediatric pts	2	NA	NA	blood	NA	NA	NA	NA	(43)	2020

ALC, absolute lymphocyte count; BAL, bronchio-alveolar lavage; BSI, blood stream infection; CSF, cerebral spinal fluid; d, days; ICU, intensive care unit; ID, infectious diseases; NA, not annotated; PICU, pediatric intensive care unit; pts, patients; TS, tracheostoma.
Type of risk factor is underlined.

and achievement of a stable clinical response may be considered in view of the high case fatality rates.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Clinical data. Requests to access these datasets should be directed to (andreas.groll@ukmuenster.de).

ETHICS STATEMENT

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Retrospective analysis of single-center data and literature review was conducted by SKZ, supported by HH and with clinical input by CR, AH, KM, AR, and AHG. Identification and susceptibility testing by NJF, whole genome sequencing based typing was performed and analyzed by SK. Statistical analysis was performed by AR, SKZ and AHG. Manuscript was written by

SKZ and was edited by SK and AHG. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2021.752037/full#supplementary-material>

Supplementary Table 1 | Explorative statistics of the association between demographic or clinical factors with non-survival.

REFERENCES

- Denton M, Kerr KG. Microbiological and Clinical Aspects of Infection Associated With *Stenotrophomonas Maltophilia*. *Clin Microbiol Rev* (1998) 11(1):57–80. doi: 10.1128/CMR.11.1.57
- Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J. Emerging Importance of Multidrug-Resistant *Acinetobacter* Species and *Stenotrophomonas Maltophilia* as Pathogens in Seriously Ill Patients: Geographic Patterns, Epidemiological Features, and Trends in the SENTRY Antimicrobial Surveillance Program (1997–1999). *Clin Infect Dis* (2001) 32 Suppl 2:S104–13. doi: 10.1086/320183
- Jones RN, Sader HS, Beach ML. Contemporary In Vitro Spectrum of Activity Summary for Antimicrobial Agents Tested Against 18569 Strains Non-Fermentative Gram-Negative Bacilli Isolated in the SENTRY Antimicrobial Surveillance Program (1997–2001). *Int J Antimicrob Agents* (2003) 22(6):551–6. doi: 10.1016/S0924-8579(03)00245-0
- Brooke JS. *Stenotrophomonas Maltophilia*: An Emerging Global Opportunistic Pathogen. *Clin Microbiol Rev* (2012) 25(1):2–41. doi: 10.1128/CMR.00019-11
- Looney WJ, Narita M, Muhlemann K. *Stenotrophomonas Maltophilia*: An Emerging Opportunist Human Pathogen. *Lancet Infect Dis* (2009) 9(5):312–23. doi: 10.1016/S1473-3099(09)70083-0
- Chang YT, Lin CY, Chen YH, Hsueh PR. Update on Infections Caused by *Stenotrophomonas Maltophilia* With Particular Attention to Resistance Mechanisms and Therapeutic Options. *Front Microbiol* (2015) 6:893. doi: 10.3389/fmicb.2015.00893
- del Toro MD, Rodriguez-Bano J, Herrero M, Rivero A, Garcia-Ordóñez MA, Corzo J, et al. Clinical Epidemiology of *Stenotrophomonas Maltophilia* Colonization and Infection: A Multicenter Study. *Medicine (Baltimore)* (2002) 81(3):228–39. doi: 10.1097/00005792-200205000-00006
- Araoka H, Baba M, Yoneyama A. Risk Factors for Mortality Among Patients With *Stenotrophomonas Maltophilia* Bacteremia in Tokyo, Japan, 1996–2009. *Eur J Clin Microbiol Infect Dis* (2010) 29(5):605–8. doi: 10.1007/s10096-010-0882-6
- Friedman ND, Korman TM, Fairley CK, Franklin JC, Spelman DW. Bacteraemia Due to *Stenotrophomonas Maltophilia*: An Analysis of 45 Episodes. *J Infect* (2002) 45(1):47–53. doi: 10.1053/jinf.2002.0978
- Muder RR, Harris AP, Muller S, Edmond M, Chow JW, Papadakis K, et al. Bacteremia Due to *Stenotrophomonas (Xanthomonas) Maltophilia*: A Prospective, Multicenter Study of 91 Episodes. *Clin Infect Dis* (1996) 22(3):508–12. doi: 10.1093/clinids/22.3.508
- Senol E, Desjardin J, Stark PC, Barefoot L, Snyderman DR. Attributable Mortality of *Stenotrophomonas Maltophilia* Bacteremia. *Clin Infect Dis* (2002) 34(12):1653–6. doi: 10.1086/340707
- Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy With Fluoroquinolone or Trimethoprim-Sulfamethoxazole for Treatment of *Stenotrophomonas Maltophilia* Infections. *Antimicrob Agents Chemother* (2014) 58(1):176–82. doi: 10.1128/AAC.01324-13
- Cho SY, Kang CI, Kim J, Ha YE, Chung DR, Lee NY, et al. Can Levofloxacin be a Useful Alternative to Trimethoprim-Sulfamethoxazole for Treating *Stenotrophomonas Maltophilia* Bacteremia? *Antimicrob Agents Chemother* (2014) 58(1):581–3. doi: 10.1128/AAC.01682-13
- Ice LL, Barreto JN, Dao BD, Wolf RC, Dierkhising RA, Jannetto PJ, et al. Relationship of Sulfamethoxazole Therapeutic Drug Monitoring to Clinical Efficacy and Toxicity: A Retrospective Cohort Study. *Ther Drug Monit* (2016) 38(3):319–26. doi: 10.1097/FTD.0000000000000282
- Fihman V, Le Monnier A, Corvec S, Jauregui F, Tankovic J, Jacquier H, et al. *Stenotrophomonas Maltophilia*—The Most Worrisome Threat Among Unusual Non-Fermentative Gram-Negative Bacilli From Hospitalized Patients: A Prospective Multicenter Study. *J Infect* (2012) 64(4):391–8. doi: 10.1016/j.jinf.2012.01.001
- Victor MA, Arpi M, Bruun B, Jonsson V, Hansen MM. *Xanthomonas Maltophilia* Bacteremia in Immunocompromised Hematological Patients. *Scand J Infect Dis* (1994) 26(2):163–70. doi: 10.3109/00365549409011780
- Hotta G, Matsumura Y, Kato K, Nakano S, Yunoki T, Yamamoto M, et al. [Risk Factors and Clinical Characteristics of *Stenotrophomonas Maltophilia* Bacteremia: A Comparison With Bacteremia Due to Other Glucose-Non

- Fermenters]. *Kansenshogaku Zasshi* (2013) 87(5):596–602. doi: 10.11150/kansenshogakuzasshi.87.596
18. Lakatos B, Jakopp B, Widmer A, Frei R, Pargger H, Elzi L, et al. Evaluation of Treatment Outcomes for Stenotrophomonas Maltophilia Bacteraemia. *Infection* (2014) 42(3):553–8. doi: 10.1007/s15010-014-0607-3
 19. Sumida K, Chong Y, Miyake N, Akahoshi T, Yasuda M, Shimono N, et al. Risk Factors Associated With Stenotrophomonas Maltophilia Bacteremia: A Matched Case-Control Study. *PLoS One* (2015) 10(7):e0133731. doi: 10.1371/journal.pone.0133731
 20. Wu PS, Lu CY, Chang LY, Hsueh PR, Lee PI, Chen JM, et al. Stenotrophomonas Maltophilia Bacteremia in Pediatric Patients—A 10-Year Analysis. *J Microbiol Immunol Infect* (2006) 39(2):144–9.
 21. Kagen J, Zaoutis TE, McGowan KL, Luan X, Shah SS. Bloodstream Infection Caused by Stenotrophomonas Maltophilia in Children. *Pediatr Infect Dis J* (2007) 26(6):508–12. doi: 10.1097/INF.0b013e318059c285
 22. Averbuch D, Avaky C, Harit M, Stepensky P, Fried I, Ben-Ami T, et al. Non-Fermentative Gram-Negative Rods Bacteremia in Children With Cancer: A 14-Year Single-Center Experience. *Infection* (2017) 45(3):327–34. doi: 10.1007/s15010-017-0988-1
 23. Barking C, Masjosthusmann K, Rellensmann G, Ehlert K, Zollner S, Jocham S, et al. Treatment of Children With Cancer and/or Hematopoietic Stem Cell Transplantation in the Intensive Care Unit: Experience at a Large European Pediatric Cancer Center. *J Pediatr Hematol Oncol* (2020) 42(7):e583–e8. doi: 10.1097/MPH.0000000000001718
 24. Linke C, Tragiannidis A, Ahlmann M, Frohlich B, Waltermann M, Burkhardt B, et al. Epidemiology and Management Burden of Invasive Fungal Infections After Autologous Hematopoietic Stem Cell Transplantation: 10-Year Experience at a European Pediatric Cancer Center. *Mycoses* (2019) 62(10):954–60. doi: 10.1111/myc.12968
 25. Yunus S, Pieper S, Kolve H, Goletz G, Jurgens H, Groll AH. Azole-Based Chemoprophylaxis of Invasive Fungal Infections in Paediatric Patients With Acute Leukaemia: An Internal Audit. *J Antimicrob Chemother* (2014) 69(3):815–20. doi: 10.1093/jac/dkt438
 26. Mellmann A, Bletz S, Boking T, Kipp F, Becker K, Schultes A, et al. Real-Time Genome Sequencing of Resistant Bacteria Provides Precision Infection Control in an Institutional Setting. *J Clin Microbiol* (2016) 54(12):2874–81. doi: 10.1128/JCM.00790-16
 27. Micozzi A, Venditti M, Monaco M, Friedrich A, Taglietti F, Santilli S, et al. Bacteremia Due to Stenotrophomonas Maltophilia in Patients With Hematologic Malignancies. *Clin Infect Dis* (2000) 31(3):705–11. doi: 10.1086/314043
 28. Teo WY, Chan MY, Lam CM, Chong CY. Skin Manifestation of Stenotrophomonas Maltophilia Infection—A Case Report and Review Article. *Ann Acad Med Singap* (2006) 35(12):897–900.
 29. Tada K, Kurosawa S, Hiramoto N, Okinaka K, Ueno N, Asakura Y, et al. Stenotrophomonas Maltophilia Infection in Hematopoietic SCT Recipients: High Mortality Due to Pulmonary Hemorrhage. *Bone Marrow Transplant* (2013) 48(1):74–9. doi: 10.1038/bmt.2012.87
 30. Aitken SL, Sahasrabhojane PV, Kontoyiannis DP, Savidge TC, Arias CA, Ajami NJ, et al. Alterations of the Oral Microbiome and Cumulative Carbapenem Exposure are Associated With Stenotrophomonas Maltophilia Infection in Patients With Acute Myeloid Leukemia Receiving Chemotherapy. *Clin Infect Dis* (2020) 72(9):1507–13. doi: 10.1093/cid/ciaa778
 31. Sattler CA, Mason EO Jr, Kaplan SL. Nonrespiratory Stenotrophomonas Maltophilia Infection at a Children's Hospital. *Clin Infect Dis* (2000) 31(6):1321–30. doi: 10.1086/317473
 32. Ladhani S, Gransden W. Septicaemia Due to Glucose non-Fermenting, Gram-Negative Bacilli Other Than Pseudomonas Aeruginosa in Children. *Acta Paediatr* (2002) 91(3):303–6. doi: 10.1111/j.1651-2227.2002.tb01719.x
 33. Arthur C, Tang X, Romero JR, Gossett JG, Harik N, Prodhon P. Stenotrophomonas Maltophilia Infection Among Young Children in a Cardiac Intensive Care Unit: A Single Institution Experience. *Pediatr Cardiol* (2015) 36(3):509–15. doi: 10.1007/s00246-014-1041-0
 34. Tariq TM, Rasool E. Emerging Trends of Bloodstream Infections: A Six-Year Study at a Paediatric Tertiary Care Hospital in Kabul. *J Coll Physicians Surg Pak* (2016) 26(11):887–91.
 35. Furuichi M, Ito K, Miyairi I. Characteristics of Stenotrophomonas Maltophilia Bacteremia in Children. *Pediatr Int* (2016) 58(2):113–8. doi: 10.1111/ped.12745
 36. Motamedifar M, Heidari H, Yasemi M, Sedigh Ebrahim-Saraie H. Molecular Epidemiology and Characteristics of 16 Cases With Stenotrophomonas Maltophilia Bacteraemia in Pediatric Intensive Care Units. *Ann Ig* (2017) 29(4):264–72. doi: 10.7416/ai.2017.2154
 37. Nayyar C, Thakur P, Tak V, Saigal K. Stenotrophomonas Maltophilia: An Emerging Pathogen in Paediatric Population. *J Clin Diagn Res* (2017) 11(1):DC08–11. doi: 10.7860/JCDR/2017/24304.9318
 38. Tokatly Latzer I, Paret G, Rubinstein M, Keller N, Barkai G, Pessach IM. Management of Stenotrophomonas Maltophilia Infections in Critically Ill Children. *Pediatr Infect Dis J* (2018) 37(10):981–6. doi: 10.1097/INF.0000000000001959
 39. Tokatly Latzer I, Nahum E, Cavari Y, Lazar I, Ben-Ari Y, Ben-Shimol S, et al. Treatment Outcomes of Stenotrophomonas Maltophilia Bacteremia in Critically Ill Children: A Multicenter Experience. *Pediatr Crit Care Med* (2019) 20(5):e231–9. doi: 10.1097/PCC.0000000000001919
 40. Duan Z, Qin J, Li C, Ying C. Clinical and Molecular Epidemiology of Stenotrophomonas Maltophilia in Pediatric Patients From a Chinese Teaching Hospital. *Front Cell Infect Microbiol* (2020) 10:411. doi: 10.3389/fcimb.2020.00411
 41. Buyukcam A, Bicakcigil A, Cengiz AB, Sancak B, Ceyhan M, Kara A. Stenotrophomonas Maltophilia Bacteremia in Children - A 10-Year Analysis. *Arch Argent Pediatr* (2020) 118(3):e317–23. doi: 10.5546/aap.2020.eng.e317
 42. Wang L, Zhou W, Cao Y, Yang C, Liu H, Chen T, et al. Characteristics of Stenotrophomonas Maltophilia Infection in Children in Sichuan, China, From 2010 to 2017. *Medicine (Baltimore)* (2020) 99(8):e19250. doi: 10.1097/MD.00000000000019250
 43. Qiu Y, Yang J, Chen Y, Yang J, Zhu Q, Zhu C, et al. Microbiological Profiles and Antimicrobial Resistance Patterns of Pediatric Bloodstream Pathogens in China, 2016–2018. *Eur J Clin Microbiol Infect Dis* (2020) 40(4):739–49. doi: 10.1007/s10096-020-04069-2
 44. Ansari SR, Hanna H, Hachem R, Jiang Y, Rolston K, Raad I. Risk Factors for Infections With Multidrug-Resistant Stenotrophomonas Maltophilia in Patients With Cancer. *Cancer* (2007) 109(12):2615–22. doi: 10.1002/cncr.22705
 45. Garazi M, Singer C, Tai J, Ginocchio CC. Bloodstream Infections Caused by Stenotrophomonas Maltophilia: A Seven-Year Review. *J Hosp Infect* (2012) 81(2):114–8. doi: 10.1016/j.jhin.2012.02.008
 46. Nicodemo AC, Paez JL. Antimicrobial Therapy for Stenotrophomonas Maltophilia Infections. *Eur J Clin Microbiol Infect Dis* (2007) 26(4):229–37. doi: 10.1007/s10096-007-0279-3
 47. Lai CH, Wong WW, Chin C, Huang CK, Lin HH, Chen WF, et al. Central Venous Catheter-Related Stenotrophomonas Maltophilia Bacteraemia and Associated Relapsing Bacteraemia in Haematology and Oncology Patients. *Clin Microbiol Infect* (2006) 12(10):986–91. doi: 10.1111/j.1469-0691.2006.01511.x
 48. Cheong HS, Lee JA, Kang CI, Chung DR, Peck KR, Kim ES, et al. Risk Factors for Mortality and Clinical Implications of Catheter-Related Infections in Patients With Bacteraemia Caused by Stenotrophomonas Maltophilia. *Int J Antimicrob Agents* (2008) 32(6):538–40. doi: 10.1016/j.ijantimicag.2008.05.011
 49. Boktour M, Hanna H, Ansari S, Bahna B, Hachem R, Tarrand J, et al. Central Venous Catheter and Stenotrophomonas Maltophilia Bacteremia in Cancer Patients. *Cancer* (2006) 106(9):1967–73. doi: 10.1002/cncr.21846
 50. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* (2009) 49(1):1–45. doi: 10.1086/599376
 51. Metan G, Hayran M, Hascelik G, Uzun O. Which Patient is a Candidate for Empirical Therapy Against Stenotrophomonas Maltophilia Bacteraemia? An Analysis of Associated Risk Factors in a Tertiary Care Hospital. *Scand J Infect Dis* (2006) 38(6-7):527–31. doi: 10.1080/00365540500452481
 52. Safdar A, Rolston KV. Stenotrophomonas Maltophilia: Changing Spectrum of a Serious Bacterial Pathogen in Patients With Cancer. *Clin Infect Dis* (2007) 45(12):1602–9. doi: 10.1086/522998

53. Sanyal SC, Mokaddas EM. The Increase in Carbapenem Use and Emergence of *Stenotrophomonas Maltophilia* as an Important Nosocomial Pathogen. *J Chemother* (1999) 11(1):28–33. doi: 10.1179/joc.1999.11.1.28
54. Al-Jasser AM. *Stenotrophomonas Maltophilia* Resistant to Trimethoprim-Sulfamethoxazole: An Increasing Problem. *Ann Clin Microbiol Antimicrob* (2006) 5:23. doi: 10.1186/1476-0711-5-23
55. Toleman MA, Bennett PM, Bennett DM, Jones RN, Walsh TR. Global Emergence of Trimethoprim/Sulfamethoxazole Resistance in *Stenotrophomonas Maltophilia* Mediated by Acquisition of Sul Genes. *Emerg Infect Dis* (2007) 13(4):559–65. doi: 10.3201/eid1304.061378
56. Elting LS, Bodey GP. Septicemia Due to *Xanthomonas* Species and Non-Aeruginosa *Pseudomonas* Species: Increasing Incidence of Catheter-Related Infections. *Medicine (Baltimore)* (1990) 69(5):296–306. doi: 10.1097/00005792-199009000-00003
57. Ko JH, Kang CI, Cornejo-Juarez P, Yeh KM, Wang CH, Cho SY, et al. Fluoroquinolones Versus Trimethoprim-Sulfamethoxazole for the Treatment of *Stenotrophomonas Maltophilia* Infections: A Systematic Review and Meta-Analysis. *Clin Microbiol Infect* (2019) 25(5):546–54. doi: 10.1016/j.cmi.2018.11.008
58. Krupova I, Kaiserova E, Foltinova A, Kovacicova G, Kiskova M, Krchnakova A, et al. Bacteremia and Fungemia in Pediatric Versus Adult Cancer Patients After Chemotherapy: Comparison of Etiology, Risk Factors and Outcome. *J Chemother* (1998) 10(3):236–42. doi: 10.1179/joc.1998.10.3.236
59. Ba BB, Feghali H, Arpin C, Saux MC, Quentin C. Activities of Ciprofloxacin and Moxifloxacin Against *Stenotrophomonas Maltophilia* and Emergence of Resistant Mutants in an In Vitro Pharmacokinetic-Pharmacodynamic Model. *Antimicrob Agents Chemother* (2004) 48(3):946–53. doi: 10.1128/AAC.48.3.946-953.2004
60. Ebara H, Hagiya H, Haruki Y, Kondo E, Otsuka F. Clinical Characteristics of *Stenotrophomonas Maltophilia* Bacteremia: A Regional Report and a Review of a Japanese Case Series. *Intern Med* (2017) 56(2):137–42. doi: 10.2169/internalmedicine.56.6141
61. Cho SY, Lee DG, Choi SM, Park C, Chun HS, Park YJ, et al. *Stenotrophomonas Maltophilia* Bloodstream Infection in Patients With Hematologic Malignancies: A Retrospective Study and In Vitro Activities of Antimicrobial Combinations. *BMC Infect Dis* (2015) 15:69. doi: 10.1186/s12879-015-0801-7
62. Demiraslan H, Sevim M, Pala C, Durmaz S, Berk V, Kaynar L, et al. Risk Factors Influencing Mortality Related to *Stenotrophomonas Maltophilia* Infection in Hematology-Oncology Patients. *Int J Hematol* (2013) 97(3):414–20. doi: 10.1007/s12185-013-1296-x
63. Falagas ME, Valkimadi PE, Huang YT, Matthaiou DK, Hsueh PR. Therapeutic Options for *Stenotrophomonas Maltophilia* Infections Beyond Co-Trimoxazole: A Systematic Review. *J Antimicrob Chemother* (2008) 62(5):889–94. doi: 10.1093/jac/dkn301
64. Lai CH, Chi CY, Chen HP, Chen TL, Lai CJ, Fung CP, et al. Clinical Characteristics and Prognostic Factors of Patients With *Stenotrophomonas Maltophilia* Bacteremia. *J Microbiol Immunol Infect* (2004) 37(6):350–8.

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