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

Stefan K. Zöllner1,2,3*, Stefanie Kampmeier4, Nele J. Froböse5, Heidrun Herbrüggen1, Katja Masjosthusmann2, Alijda van den Heuvel2, Christian Reicherts6, Andreas Ranft3 and Andreas H. Groll1*

1 Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Onco, University Children’s Hospital Münster, Münster, Germany, 2 Intensive Care Medicine, Department of General Pediatrics, University Children’s Hospital Münster, Münster, Germany, 3 Pediatric Oncology & Hematology, Pediatrics III, University Hospital of Essen, Essen, Germany, 4 Institute of Hygiene, University Hospital Münster, Münster, Germany, 5 Institute of Medical Microbiology, University Hospital Münster, Münster, Germany, 6 Center for Bone Marrow Transplantation and Department of Medicine A, University Hospital Münster, Münster, Germany

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


tolophomonas 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 pneumonia, 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 allogenic 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 ≥ 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/μL. 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 hematological disease including patients with ambiguous or ambiguous hematopoietic cell transplantation and invasive *Stenotrophomonas 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     | No     | No     | No        | Skin                     |****                          |
| 3           | F      | 11.6        | ALL       | No                                | Yes           | No  | No     | Yes    | Yes    | Yes       |*** Anus, skin, trachea          |
| 4           | F      | 15.8        | VSAA      | Yes (MRD); 63                     | Yes           | Yes | Yes    | Yes    | Yes    | Yes       |*** No                     |
| 5           | M      | 17.9        | ALL       | Yes (MUD); 231                    | No            | Yes | Yes    | Yes    | Yes    | Yes       |*** Anus, trachea            |
| 6           | M      | 5.2         | ALL       | No                                | Yes           | No  | No     | Yes    | Yes    | No        | Skin, pharynx               |
| 7           | M      | 14.7        | ALL       | Yes (MMUD); 15                    | No            | Yes | No     | Yes    | No     | No        | Anus                     |
| 8           | F      | 11.8        | ALL       | Yes (MUD); 13                     | Yes           | No  | No     | Yes    | Yes    | No        |**** No                     |
| 9           | F      | 2.8         | EwS       | No                                | Yes           | No  | No     | No     | No     | No        |**** No                     |
| 10          | F      | 0.8         | SCID      | No                                | No            | No  | No     | Yes    | Yes    | Yes       | Anus, skin, pharynx         |

### Table 2: \( \text{Antibiotic Treatment Total Duration of Treatment (days)} \)

| Patient No. | Broad-spectrum Antibiotics | Defective Skin Barrier | CRP (mg/dL) | WBC (10³/μL) | ANC (10³/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          | No                  | Meropenem; moxifloxacin       | 14                      | Yes 2053 |
| 2           | Yes                       | Yes                    | 11.3        | 27.5         | 21.7         | Yes            | Yes                   | Yes             | Yes         | Yes                 | Ticagrelor; meropenem; moxifloxacin; tigecycline | 20                      | 395     |
| 3           | Yes                       | No                     | 25.5        | 0            | 0            | No             | No                    | No              | No          | Yes                 | Ticagrelor; meropenem; moxifloxacin | 45                      | 45      |
| 4           | No                        | No                     | 19.8        | 0            | 0            | Yes            | No                    | No              | No          | Yes                 | Ticagrelor; meropenem; moxifloxacin | 1                       | 2       |
| 5           | Yes                       | Yes                    | 37.9        | 0.3          | 0            | Yes            | Yes                   | Yes             | Yes         | Yes                 | Ticagrelor; meropenem; moxifloxacin | 2                       | 2       |
| 6           | Yes                       | No                     | 6.1         | 0.7          | 0            | No             | No                    | No              | No          | Yes                 | Ticagrelor; meropenem; moxifloxacin | 20                      | 167     |
| 7           | Yes                       | No                     | 23.0        | 0.2          | 0            | Yes            | No                    | No              | No          | Yes                 | Ticagrelor; meropenem; moxifloxacin | 27                      | 497     |
| 8           | Yes                       | Yes                    | 18.9        | 0            | 0            | Yes            | No                    | No              | Yes         | Yes                 | Ticagrelor; meropenem; moxifloxacin | 10                      | 10      |
| 9           | Yes                       | No                     | 9.7         | 0            | 0            | Yes            | No                    | No              | No          | Yes                 | Ticagrelor; meropenem; moxifloxacin | 15                      | 2446    |
| 10          | Yes                       | Yes                    | 15.2        | 23.3         | 18.0         | Yes            | Yes                   | Yes             | Yes         | Yes                 | Ticagrelor; meropenem; moxifloxacin | 14                      | 79      |

### Notes:
- **All CAH-SSTIs included: MRSA, S. aureus, E. coli, Enterococcus faecalis and Candida albicans in the week prior to diagnosis of *S. maltophilia* infection.
- **Associated with recurrent infections, especially skin care at the Department of Hematology and Oncology.**
- **Conditions in allo-HCT recipients:**
  - Patient 1, chronic 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.
- **Concomitant BSI:***
  - Patient 3 and 4 had catheter exit-site infection, and patient 7 had a catheter exit-site infection with pulmonary hemorrhage and patient 8 had necrotizing fasciitis involving the lower extremities and buttocks.
- **Antibiotic Treatment:**
  - Patients 1 and 10 died from 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.
- **Follow-up:**
  - Patient 1 had a catheter exit-site infection, and patient 8 had necrotizing fasciitis involving the lower extremities and buttocks.

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**References:**
- Zöllner et al. *Stenotrophomonas maltophilia* in Pediatric Immunocompromised Patients. Frontiers in Oncology, 2021.
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*
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

![FIGURE 3](image-url) | 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.
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 heterogenous 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
| Patient Collective | Study Duration (years) | S. maltophilia 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                          | (26)      | 2006            |
| Infants <180 days with heart disease | 5 | 32                          | 47                | blood, CSF, urine, eye, wound, BAL | 37.5 | NA | RF for outcome: prolonged positive SM cultures (p=0.008) need for renal dialysis (p=0.04) presence of stroke (p=0.05) | NA | (33) | 2015 |
| Pediatric pts     | 5                     | 18                          | 18                | blood          | NA              | NA                   | NA              | NA                          | (34)      | 2016            |
| Pediatric cancer pts | 2         | 19                          | NA                | blood          | NA              | NA                   | RF for BSI: prior use of carbapenems within 7 d (p=0.02) prior ICU stay (p=0.03) mechanical ventilation (p=0.01) severe neutropenia (<100/mm³; p=0.002) hospital-acquired infection (p=0.0001) breakthrough infection (p=0.0001) | NA | (35) | 2016 |
| PICU              | 0.3                   | NA                          | 16                | blood          | NA              | NA                   | NA              | NA                          | (22)      | 2017            |
| Pediatric pts     | 0.7                   | NA                          | 23                | blood, respiratory, urine | 35 | NA | RF for BSI: 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) combination of ciprofloxacin, TMP-SMX, and/or minocycline (p<0.001) | NA | (36) | 2017 |
| PICU              | 5                     | 31                          | 91                | blood, respiratory, soft tissues | 61 | 16 | RF for outcome: prior prolonged | NA | (37) | 2017 |
| Critically ill children | 5         | NA                          | 68                | blood          | 42              | 18                   | RF for outcome: prior prolonged | outcome-related: combination of | (39) | 2018 |

(Continued)
| Patient Collective | Study Duration (years) | S. maltophilia Pts. (number) | Isolates (number) | Source | All-cause Crude Mortality (%) | Attributed Mortality (%) | Risk Factors (RF) Positive Effect on Survival | Reference Publication Date |
|--------------------|-----------------------|-----------------------------|-------------------|--------|-----------------------------|-------------------------|-----------------------------------|--------------------------|
| Pediatric pts      | 2                     | NA                          | 104               | blood, respiratory, soft tissues, CSF | NA                        | NA                      | NA                                               | (43)                     | 2020 |
| Pediatric pts      | 10                    | 12                          | 20                | blood and/or catheter                   | 33.3                      | NA                              | NA                                               | (41)                     | 2020 |
| Pediatric pts      | 7.3                   | 128                         | 161               | blood, respiratory, CSF, wound          | NA                        | 3.9                             | RF for severe S. maltophilia infection: mechanical ventilation (p=0.021), prior ICU stay within 30 days (p=0.005), prior use of carbapenems (p=0.007) | (42)                     | 2020 |
| Pediatric pts      | 2                     | NA                          | NA                | blood                                    | NA                        | NA                              | NA                                               | (43)                     | 2020 |

- ALC, absolute lymphocyte count; BAL, broncho-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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