

Clinical characteristics of *Stenotrophomonas maltophilia* infection in hematopoietic stem cell transplantation recipients: a single center experience

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Abstract

Background Recipients of hematopoietic stem-cell transplantation (HSCT) are at high risk for infections caused by *Stenotrophomonas maltophilia*.

Methods We conducted a retrospective analysis of all infections caused by *S. maltophilia* in HSCT recipients in a single center in Israel during a 4 year period.

Results Of 570 patients undergoing HSCT, 19 patients with an invasive *S. maltophilia* infection were identified. Sixteen had allogeneic HSCT and 3 had autologous HSCT. Seventeen patients (90%) had an indwelling central venous catheter (CVC) at the time of infection. *S. maltophilia* infections were detected in three clinical settings: as a complication of prolonged neutropenia ($n = 9$), as a CVC-related non-neutropenic infection occurring after CVC manipulation ($n = 8$) and as a respiratory tract infection ($n = 2$). Eleven patients (58%) had a polymicrobial infection. Ten patients (52.6%) received carbapenems during the previous month. The treatment for all patients included

broad spectrum antibiotics, which were switched according to susceptibilities upon identification of the isolates. All isolates were susceptible in vitro to TMP-SMX. CVCs were removed in 12 patients (70%). Six patients, all after allogeneic HSCT, died. The CVC was removed in only two of the five patients with CVCs who died.

Conclusions *Stenotrophomonas maltophilia* is an emerging nosocomial pathogen in HSCT recipients, both in the early neutropenic phase and in the non-neutropenic phase. It is commonly associated with the presence and manipulation of an indwelling CVC. Removal of the CVC in addition to appropriate antibiotic therapy (TMP-SMX) is crucial for infection control.

Keywords *Stenotrophomonas maltophilia* · Hematopoietic stem cell transplantation · Central venous catheter · Bloodstream infection · Neutropenia · TMP-SMX

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Introduction

Invasive bacterial infections are common complications following hematopoietic cell transplantation (HSCT) and are associated with significant morbidity and mortality. During the early post-transplant period, HSCT recipients have two critical risk factors for invasive infections: prolonged neutropenia and breaks in the mucocutaneous barrier, resulting from the HSCT preparative regimen and from frequent vascular access required for patient care. The use of long-term central venous catheters (CVC) has become an essential part of the management of bone marrow transplant recipients and its importance in the pathogenesis of bacterial, as well as invasive fungal blood stream infections is well established [1–3]. A recent German multicenter study of a total of 1899

patients who had undergone bone marrow transplant or peripheral blood stem cell transplant demonstrated incidences of bloodstream infections (BSIs) of 22.4 BSIs per 100 patients following allogeneic transplantation and 18.2 BSIs per 100 patients following autologous transplantation. The majority (57%) of pathogens associated with BSI were coagulase-negative staphylococci [4].

Stenotrophomonas maltophilia is a glucose nonfermentative Gram-negative bacillus previously known as *Pseudomonas maltophilia* or *Xanthomonas maltophilia*, the sole member of the genus *Stenotrophomonas*. Despite reports in the earlier literature that *Stenotrophomonas* was of strictly limited pathogenicity, *S. maltophilia* has risen to prominence over the last two decades as an important nosocomial pathogen associated with significant case/fatality ratios in certain patient populations, especially in severely debilitated or immunosuppressed patients [5]. Therefore, HSCT recipients may be at particularly high risk for severe infections caused by *S. maltophilia*.

The objective of this study was to investigate the incidence, clinical characteristics, treatment, antibiotic susceptibility patterns and outcomes of HSCT recipients with *S. maltophilia* infections in a single center in Israel.

Materials and methods

Patient identification and data collection

This retrospective cohort study included all patients who underwent HSCT at the Chaim Sheba Medical Center, Israel, during a 4 year period. Patients with invasive infections caused by *S. maltophilia* were retrospectively identified from patients' records and from the computerized microbiological database of the hospital. Data from the medical charts were recorded and analyzed including demographic features, indication for transplantation, conditioning regimens (myeloablative vs. reduced intensity), source of transplanted graft (autologous vs. allogeneic), presence and duration of neutropenia (neutrophils <500/mcl), bacterial isolation site, number of positive cultures, concomitant isolates of other infectious agents, presence of mucositis, clinical presentation (e.g. fever, rigors, septic shock, hypoxemia), recent antimicrobial therapy during the month before the present infection by *S. maltophilia*, antimicrobial susceptibility, medical interventions and patients' outcomes. In our center antibacterial prophylaxis with fluoroquinolones following HSCT was not routinely administered.

Definitions

An episode of *S. maltophilia* bacteremia was defined as one or more positive blood cultures for *S. maltophilia* with

clinical symptoms and signs of infection. Isolations of coagulase-negative staphylococci or Gram-positive bacilli in a single bottle were considered contaminants and excluded from this analysis.

Stenotrophomonas maltophilia infections other than bacteremia were defined as invasive in cases of isolation from tissue biopsy, broncho-alveolar lavage or sinus lavage.

Prior antibiotic therapy was defined as administration of intravenous antibiotics for more than 24 h within 30 days before the onset of the *S. maltophilia* infection.

Microbiology

Blood culture samples were processed by the Bactec 9240 microbial system (Becton–Dickinson, Franklin Lakes, NJ, USA). Susceptibility to antibiotics was tested by the disk diffusion method on Mueller–Hinton agar, according to Clinical and Laboratory Standards Institute (formerly NCCLS) procedures.

Results

Patient characteristics

Throughout the 4-year study period, 570 adult patients underwent HSCT at the Chaim Sheba Medical Center, Israel. Of these, 287 had allogeneic HSCT and 283 had autologous HSCT. A total of 19 patients (3.3% of all HSCT recipients) had an invasive infection caused by *S. maltophilia* during or after HSCT. Of these, 16 patients had allogeneic HSCT (5.6% of all allogeneic HSCTs) and three patients had autologous HSCT (1% of all autologous HSCTs). The clinical characteristics of the patients are described in Table 1.

Clinical settings

Stenotrophomonas maltophilia infections were detected in three clinical settings: as a complication of prolonged neutropenia ($n = 9$), as a CVC-related non-neutropenic infection ($n = 8$) and as a respiratory tract infection ($n = 2$).

Four patients presented with septic shock and/or multi-organ failure. Eight patients had concomitant mucositis, one had severe intestinal graft-versus-host disease (GVHD) and one had a paralytic ileus.

Seventeen patients had a CVC at the time of infection, of these 15 were bacteremic and two had other invasive infections.

Eight patients, all non-neutropenic, developed bacteremia shortly after CVC manipulation by the nursing team. They presented clinically with shivers, fever, shortness of

Table 1 Clinical characteristics of 19 patients with *Stenotrophomonas maltophilia* infection

Characteristic	No. (%)
Age (median, range)	50 years (18–69)
Gender	
Male/female	13/6
Underlying disease	
Acute leukemia	8 (42)
NHL	8 (42)
Multiple myeloma	1 (5)
CML	1 (5)
Aplastic anemia	1 (5)
Source of transplant	
Allogeneic	16 (84)
Autologous	3 (15.7)
Concurrent neutropenia	
Neutropenic	9 (47)
Not neutropenic	10 (53)
Duration of neutropenia (median, range)	28 days (6–84)
Duration of neutropenia until <i>S. maltophilia</i> infection (median, range)	17 days (3–69)
Site of infection	
Total cases of bacteremia	17 (90)
Isolated bacteremia	15 (79)
Concomitant bacteremia and soft tissue abscess	2 (10.5)
Pneumonia	1 (5.3)
Sinuses	1 (5.3)
Prior antibiotic therapy with carbapenem	10 (52.6)
Polymicrobial infection	11 (58)
Presence of CVC	17 (89)

NHL non-Hodgkin's lymphoma, CML chronic myeloid leukemia, CVC central venous catheter

breath, hypotension or shock within 2 h following routine flushing of heparin locked CVCs with aseptic precautions. Patients with bacteremia following CVC manipulation had their CVCs installed a median of 4.5 months before infection (range, 1–14 months), while those with bacteremia unrelated to CVC manipulation were mostly neutropenic (7 of 9) and had their CVCs installed a median of 2 months before infection (range, 1–6 months).

There were two patients with respiratory infection: one with sinusitis, one with pneumonia. Both patients were non-neutropenic.

Stenotrophomonas maltophilia isolates

Concomitant isolation of other infectious agents was common both in neutropenic (66%) and non-neutropenic (50%) patients, as well as in blood stream (53%) and soft tissue (100%) infections. Nine patients had bacteremia with

S. maltophilia and one or more of the following infective organisms: *coagulase negative Staphylococci*, *Corynebacterium*, *Pseudomonas*, *Acinetobacter* and *Candida*. The patient with pneumonia had concomitant respiratory syncytial virus (RSV) in his broncho-alveolar lavage, and the patient with sinusitis had concomitant *Pseudomonas* in his sinus lavage.

All isolates were susceptible in vitro to TMP-SMX, none were susceptible to carbapenems, and 10.6% were susceptible to fluoroquinolones. Ten patients (52.6%) received prior antibiotic therapy during the previous month with carbapenems.

Treatment and outcome

The treatment for all patients included empiric broad spectrum antibiotic therapy at the onset of signs of infection, and after identification of *S. maltophilia*, antibiotics were changed according to susceptibility. Specific therapy against *S. maltophilia* consisted of high dose (>15 mg/kg/day) trimethoprim—sulfamethoxazole (TMP-SMX) (two patients), ofloxacin (two patients) or both (four patients). Five patients died before specific identification of *S. maltophilia* and therefore did not receive appropriate antibiotics. There were no cases of persistent bacteremia despite adequate therapy.

Seventeen patients had a CVC at the time of infection, 15 of them were bacteremic and two had other invasive infections. Twelve patients out of the 17 patients with CVCs at the time of infection had their CVCs removed (70%). All of them were bacteremic. Only three patients with *S. maltophilia* bacteremia, two neutropenic and one non-neutropenic, did not have their CVCs removed. In the two neutropenic patients this was due to non-reversible multi-organ failure and non-engraftment, which technically did not enable CVC removal.

Of the eight non-neutropenic patients with bacteremia, six had their CVCs removed within hours following CVC manipulation and corresponding sepsis, without awaiting culture results. Indeed, five of them had an uneventful recovery and only one patient died with multi-organ failure. One additional patient had his CVC removed only upon identification of *S. maltophilia* in blood cultures; he fully recovered. The eighth patient had his CVC preserved and was successfully treated with intravenous (IV) antibiotics.

Both non-neutropenic patients with respiratory tract infections (pneumonia and sinusitis) had their CVCs preserved. The patient with sinusitis fully recovered, and the patient with pneumonia died from multi-organ failure.

In all, six patients with *S. maltophilia* bacteremia died (a mortality rate of 31.5%). Data regarding their characteristics are depicted in Table 2.

Table 2 Clinical characteristics of the patients with fatal *Stenotrophomonas maltophilia* infection

Patient number	Neutropenia at time of infection	CVC at time of infection	CVC removal	Poly-microbial infection	Cause of death, time of death
1	Yes	Yes	No	Yes	Septic shock, lack of engraftment, day +22 post-alloHSCT
2	Yes	Yes	No	No	Septic shock, lack of engraftment, day +22 post-alloHSCT
3	Yes	No	Not relevant	Yes	ARDS and acute GVHD, day +54 post-alloHSCT
4	Yes	Yes	Yes	Yes	Bilateral pneumonia, septic shock, day +56 post-alloHSCT
5	No	Yes	Yes	No	Multiorgan failure, day +32 post-alloHSCT
6	No	Yes	No	Yes	Pneumonia, septic shock, multiorgan failure day +66 post-autoHSCT

ARDS acute respiratory distress syndrome, GVHD graft versus host disease, alloHSCT allogeneic hematopoietic stem cell transplant, autoHSCT autologous hematopoietic stem cell transplant

Discussion

In this study we present data of a cohort of 19 patients with invasive *S. maltophilia* infection following HSCT.

Stenotrophomonas maltophilia and other glucose non-fermentative Gram-negative bacteria, such as *pseudomonas* and *acinetobacter* species, have emerged as frequent offenders of immunocompromised patients, especially those with hematological malignancies and prolonged neutropenia [5].

In our series, the blood was the most common site of *S. maltophilia* infection, as 90% of our patients had bacteremia. Of note, 90% of them had CVCs at the time of bacteremia. The use of long-term central venous catheters has become an essential part of the management of HSCT recipients and the importance of intravascular devices in the pathogenesis of *S. maltophilia* bacteremia is well recognized [6]. Moreover, the presence of a CVC is not only a risk factor for *S. maltophilia* bacteremia but also an important source of bacteremia [7]. Other ports of entry of *S. maltophilia* are the respiratory, urinary and gastrointestinal tracts [5]. Our results are in concert with other series in which CVCs were present in more than 80% of the cases with *S. maltophilia* bacteremias [7, 8].

We found that *S. maltophilia* invasive infections are relatively common in HSCT patients. Specifically, they are more common in allogeneic transplants (5.6%) as compared with autologous transplants (1%). Recently, Labarca et al. reported an outbreak of *S. maltophilia* bacteremia in eight allogeneic bone marrow transplant recipients in a bone marrow transplant center in the USA. Compared with concurrently hospitalized allogeneic bone marrow transplant recipients, these patients were more likely to have severe and prolonged neutropenia as well as severe mucositis [9]. In our study, the higher incidence of bacteremia in the allogeneic HSCT group may also be due to higher incidence of prolonged neutropenia and non-engraftment in these patients. In addition, patients after allogeneic transplants are immunocompromised more deeply and for

longer periods of time, cutaneous and gastrointestinal GVHD in allogeneic transplantations could facilitate bacterial seeding into the blood, and possibly most importantly, CVCs were kept during longer periods following allogeneic transplants as compared with autologous transplants (median, 4.5 vs. 2 months, respectively) and were more frequently manipulated (e.g. for blood sampling and transfusions). Both long duration of catheterization and number of manipulations have been linked to increased risk of CVS infection [10, 11].

In our cohort, polymicrobial blood and soft tissue infections were present in 58% of the patients. Although invasive infections with *S. maltophilia* are frequently polymicrobial, our frequency is even higher than in previous studies. Jang et al. reported 44% polymicrobial cases out of 32 cases with bacteremia [12], while Lai et al. reported 27% polymicrobial infections [7].

Ten patients (52.6%) were treated with carbapenems during the month prior to the infection. The emergence of *S. maltophilia* as a common offender in immunocompromised patients has been linked to antibiotic selection pressure and induction of extended spectrum chromosomal beta-lactamases after the use of beta-lactams, including carbapenems. *S. maltophilia* is intrinsically resistant to carbapenems and exposure to these antibiotic agents may perpetuate the infection [13].

Most of our non-neutropenic patients (six of eight) had their CVCs removed promptly upon showing symptoms and signs of sepsis following CVC manipulation, without waiting for culture results. They fully recovered. Of the five patients with CVCs who died, only two had their CVCs removed. Our results confirm results from previous studies which showed that catheter related bacteremia responds well to removal of the catheter [5, 7]. Removal of the infection source in addition to appropriate antibiotic therapy is crucial to control infection.

Our results underscore the need for strict infection control measures while manipulating CVCs. Special focus should be given on proper hand hygiene and skin

disinfection, as demonstrated in a recent randomized controlled trial which compared the efficacy of two commercially available, alcohol-based antiseptic solutions for preparation and care of CVC insertion sites, with and without octenidine dihydrochloride. It demonstrated that octenidine in alcoholic solution may be a better option than alcohol alone for the prevention of CVC-associated infections, due to significantly fewer positive cultures of the catheter tip and a non-significant reduction in catheter-associated bloodstream infections in the octenidine group [14].

Since all of our isolates were susceptible to TMP-SMX, this strengthens previous reports that show that TMP-SMX has the most potent in vitro activity against *S. maltophilia* and should probably be regarded as first line therapy [5, 7]. Similar to previous studies, *S. maltophilia* isolates were resistant to many antimicrobial agents [5, 7, 8].

The patients in our study could be divided into three groups based on the clinical setting of infection. The first group included patients with invasive *S. maltophilia* infection with the classic predisposing factors of severe neutropenia and mucositis [5, 9] following transplant conditioning. This was a relatively late infection during the neutropenic course and common in patients with engraftment failure. This group of patients had a high mortality rate, partially related to the underlying complicated course of transplantation. The second group consisted of non-neutropenic patients, usually 1–2 months post-transplant, with *S. maltophilia* bacteremia and sepsis following CVC manipulation; this group of patients fully recovered and infection promptly resolved following CVC removal and short term treatment by systemic antibiotics. The third group was comprised of patients with respiratory tract infections. Importantly, all groups had a high frequency of concomitant infections with other bacteria.

Our study has several limitations. It includes a relatively small number of patients and most of the patients had catheter-related bacteremia, thus we could not assess bacteremias from other sources which are usually associated with high treatment failure. In addition, we could not assess less common forms of invasive *S. maltophilia* infection such as endocarditis and pulmonary infections.

In summary, we describe *S. maltophilia* infections in a population of HSCT recipients. *S. maltophilia* is an emerging nosocomial pathogen that may infect these patients in the early neutropenic phase, but also in the non-neutropenic phase. It is commonly associated with an indwelling CVC. Attempts should be made to remove CVCs once infection is detected. Moreover, while neutropenia duration and mucositis are factors that are difficult to control, unnecessary CVCs should be avoided and removed as soon as possible. Although resistant to many

antimicrobial agents, the infection usually responds well to the combination of appropriate antibiotic therapy with TMP-SMX and CVC removal.

Conflict of interest statement None.

References

1. Howell PB, Walters PE, Donowitz GR, Farr BM. Risk factors for infection of adult patients with cancer who have tunneled central venous catheters. *Cancer*. 1995;75:1367–75.
2. Goetz AM, Wagener MM, Miller JM, Muder RR. Risk of infection due to central venous catheters: effect of site of placement and catheter type. *Infect Control Hosp Epidemiol*. 1998;19:842–5.
3. Wolf HH, Leithauser M, Mascchmeyer G, Salwender H, Kleine U, Chaberny I, et al. Central venous catheter-related infections in hematology and oncology: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol*. 2008;87:863–76.
4. Dettenkofer M, Wenzler-Röttle S, Babikir R, Bertz H, Ebner W, Meyer E, et al. Surveillance of nosocomial sepsis and pneumonia in patients with a bone marrow or peripheral blood stem cell transplant: a multicenter project. *Clin Infect Dis*. 2005;40:926–31.
5. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis*. 2007;45:1602–9.
6. Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. *Clin Microbiol Rev*. 1998;11:57–80.
7. 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;37:350–8.
8. 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;22:508–12.
9. Labarca JA, Leber AL, Kern VL, Territo MC, Brankovic LE, Bruckner DA, et al. Outbreak of *Stenotrophomonas maltophilia* bacteremia in allogeneic bone marrow transplant patients: role of severe neutropenia and mucositis. *Clin Infect Dis*. 2000;30:195–7.
10. Hampton AA, Sherertz RJ. Vascular-access infections in hospitalized patients. *Surg Clin North Am*. 1988;68:57–71.
11. Snyderman DR, Murray SA, Kornfeld SJ, Majka JA, Ellis CA. Total parenteral nutrition-related infections. Prospective epidemiologic study using semiquantitative methods. *Am J Med*. 1982;73:695–9.
12. Jang TN, Wang FD, Wang LS, Liu CY, Liu IM. *Xanthomonas maltophilia* bacteremia: an analysis of 32 cases. *J Formos Med Assoc*. 1992;91:1170–6.
13. Sanyal SC, Mokaddas EM. The increase in carbapenem use and emergence of *Stenotrophomonas maltophilia* as an important nosocomial pathogen. *J Chemother*. 1999;11:28–33.
14. Dettenkofer M, Wilson C, Gratwohl A, Schmoor C, Bertz H, Frei R, Heim D, Luft D, Schulz S, Widmer AF. Skin disinfection with octenidine dihydrochloride for central venous catheter site care: a double-blind, randomized, controlled trial. *Clin Microbiol Infect*. 2009. doi:10.1111/j.1469-0691.2009.02917.x.