View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by RERO DOC Digital Library

Infection (2014) 42:553–558
DOI 10.1007/s15010-014-0607-3

BRIEF REPORT

Evaluation of treatment outcomes for *Stenotrophomonas maltophilia* bacteraemia

B. Lakatos · B. Jakopp · A. Widmer · R. Frei · H. Pargger · L. Elzi · M. Battegay

Received: 23 December 2013 / Accepted: 22 February 2014 / Published online: 14 March 2014
© Springer-Verlag Berlin Heidelberg 2014

Abstract
Objective The goal of this study was to retrospectively collect data about treatment outcomes in patients diagnosed with *Stenotrophomonas maltophilia* bacteraemia over a period of 20 years and evaluate these data with respect to the efficacy of treatment options.
Methods The setting was a 700-bed tertiary care hospital in a large urban area. Hospital databases and medical records provided information about episodes of *S. maltophilia*, patient characteristics and treatment outcomes. Patients with at least one positive blood culture for *S. maltophilia* were included in the study. Data were analysed with respect to clinical improvement and mortality ≤30 days after the onset of infection. We compared patient characteristics, laboratory values and treatments by using the Chi-square or Fisher's exact tests and the Mann–Whitney test.
Results We investigated 27 patients with *S. maltophilia* bacteraemia. The focus of infection was a central venous catheter in 18 (67 %) cases. The 30-day mortality rate was 11 %. All patients who were treated with an antibiotic that was effective in vitro against the pathogen recovered clinically and survived ≥30 days after the onset of infection. The most frequently used antibiotic was trimethoprim–sulfamethoxazole administered alone or in combination with a fluoroquinolone.
Conclusions Despite the fact that *S. maltophilia* is resistant to multiple antibiotics, the prognosis for patients with *S. maltophilia* bacteraemia is good when they are treated with antibiotics that are effective against this pathogen in vitro.

Keywords *Stenotrophomonas maltophilia* · Bacteraemia · Antimicrobial therapy · Trimethoprim–sulfamethoxazole · Bacteraemia mortality

Introduction

Stenotrophomonas maltophilia, a Gram-negative, non-fermentative bacillus, is increasingly being recognised as a cause of nosocomial infections [1], but the treatment of a *S. maltophilia* infection is challenging. This is primarily due to the inherent resistance of *S. maltophilia* to multiple classes of antibiotics, including beta-lactams, aminoglycosides and carbapenems [2]. Given the lack of randomised clinical trials to test treatment options for *S. maltophilia* bacteraemia, current recommendations for treatment are based mostly on in vitro susceptibility tests and expert opinion. Trimethoprim–sulfamethoxazole (TMP/SMX) is the usual drug of choice because of its excellent in vitro activity against *S. maltophilia*. A high dose of TMP (15 mg/kg/day) is generally recommended to reduce the risk of emerging resistance to TMP/SMX [1]. However,

B. Lakatos and B. Jakopp contributed equally to this work.

B. Lakatos · B. Jakopp · A. Widmer · L. Elzi · M. Battegay (✉)
Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland
e-mail: manuel.battegay@usb.ch

R. Frei
Division of Clinical Microbiology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland

H. Pargger
Department of Anesthesiology and Intensive Care Medicine, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland

allergic reactions and toxicities related to the administration of TMP/SMX in patients limit the use of this drug in clinical practice [3]. Fluoroquinolones are an alternative option for treatment, if the pathogen is shown to be susceptible to the specific antimicrobial in vitro [1, 2]. The reported mortality rates of *S. maltophilia* infections are high, i.e. 15–62 %. However, most studies did not focus on therapeutic aspects [4–7].

The goal of this study was to retrospectively collect information about the treatment of *S. maltophilia* bacteraemia and its outcomes over a period of 20 years in a single-centre setting and to describe the effectiveness of the treatment.

Patients and methods

The setting for this study was a 700-bed tertiary care hospital that is associated with a university in a large urban area of approximately half a million inhabitants. To retrospectively study outcomes for the treatment of *S. maltophilia* bacteraemia, we chose to review all episodes of *S. maltophilia* bacteraemia over a 20-year period beginning in January 1993 and ending in January 2013. Data were collected by first reviewing the microbiology database at the University Hospital Basel to identify episodes of *S. maltophilia* bacteraemia and then by cross-checking this information with data in the databases of the Clinical Microbiology Laboratory and the Infection Control Division at the hospital to identify the specific patient cases associated with these episodes of bacteraemia. All patients who had one or more blood cultures that were positive for *S. maltophilia* were included in the study. Hospital medical records provided information about patient demographic characteristics, co-morbidities, the focus of the infection attributed to *S. maltophilia*, the number of positive blood cultures, time to positivity of blood cultures, the susceptibility of the identified pathogen in each case to specific antimicrobial agents in vitro, and the type and duration of both empirical and targeted antibiotic therapy. Treatment outcomes were assessed with respect to clinical improvement and 30-day mortality in the patients.

Empirical therapy was defined as the administration of antibiotics at the onset of symptoms of bacteraemia. Adequate treatment was defined as the targeted administration of at least one antimicrobial agent to which *S. maltophilia* was susceptible in vitro.

Nosocomial infections and sepsis were defined according to the Centers for Disease Control and Prevention (CDC) and international consensus definitions [8]. In brief, a positive blood culture with *S. maltophilia* was defined as 'catheter-related' if a central venous line was in place $\geq$48 h and *S. maltophilia* was cultured from the catheter tip with more than 15 colony-forming units. We used the term 'catheter-associated' for cases having a central venous catheter for 48 h or more and without any evidence for another source.

A patient was considered immunosuppressed if they were receiving chemotherapy or radiotherapy for malignancies, immunosuppressive therapies with a daily dose $\geq$10 mg prednisolone-equivalent steroid, monoclonal antibodies, antimetabolite drugs or T cell inhibitors within the preceding 30 days of the positive blood culture. Neutropaenia (absolute neutrophil granulocyte cell count of $<0.5 \times 10^9$/L) at the time of bacteraemia was also defined as immunosuppression.

The *S. maltophilia* isolates from infection episodes that were reported in the microbiology database had been detected in the Clinical Microbiology Laboratory by using standard assays, including API20 NE (bioMérieux, France), VITEK 2 (bioMérieux, France) and MALDI Biotyper (Bruker Daltonik, Germany), or, in special cases, by sequencing of the 16S rRNA gene. For susceptibility testing in vitro, the commercial systems Micronaut (Merlin, Germany), VITEK 2 (bioMérieux, France) or Etest (bioMérieux, France) were used [9]. From 1993 through May 2011, the results for antimicrobial susceptibility were interpreted according to the standards of the Clinical and Laboratory Standards Institute [CLSI, formerly National Committee for Clinical Laboratory Standards (NCCLS)]. From June 2011 onwards, they were interpreted according to the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Patient characteristics, laboratory values and treatments were compared by using the Chi-square or Fisher's exact tests for categorical variables and the Mann–Whitney test for continuous variables. Analyses were performed by using SPSS version 21 software (SPSS Inc., USA).

To more definitively characterise treatment outcomes, patients were assigned to one of two groups. The two groups were defined by the adequacy of treatment.

The study was approved by the Ethical Committee of Basel (178/13).

Results

S. maltophilia was identified in almost 1,000 microbiological samples over the 20-year study period. From these data, we identified 29 patients with at least one positive blood culture for *S. maltophilia*. Two patients were excluded from the study because detailed medical data were not available for them. Table 1 shows the baseline patient characteristics for the two treatment groups to which patients were assigned: the group which received adequate treatment and the group which did not receive

Table 1 Baseline characteristics of 27 patients diagnosed with *Stenotrophomonas maltophilia* bacteraemia in a single-centre study over a period of 20 years

Variable	Group receiving adequate treatment[a] ($n = 21$)	Group not receiving adequate treatment ($n = 6$)	*p*-Value
Median age in years (IQR)	59 (43–69)	72 (71–77)	<0.001
Number of males	9 (43 %)	3 (50 %)	0.756
Number of patients with:			
Comorbidity			
Cardiovascular disease	9 (43 %)	4 (66 %)	0.352
Renal impairment[b]	5 (24 %)	3 (50 %)	0.245
Diabetes mellitus	3 (14 %)	2 (33 %)	0.318
Immunosuppression	9 (43 %)	3 (50 %)	0.829
Sepsis	19 (90 %)	5 (83 %)	0.623
Polymicrobial infection	8 (38 %)	1 (17 %)	0.617
Median length (in days) of hospital stay prior to onset of bacteraemia (IQR)	10 (6–13)	18 (5–38)	0.387
ICU stay within 30 days	4 (19 %)	5 (83 %)	0.004
Prior hospitalisation within 30 days	8 (38 %)	3 (50 %)	0.662
Number of patients with a bacteraemia focus that was:			
Central line	15 (71 %)	3 (50 %)	0.326
Pneumonia	4 (29 %)	3 (50 %)	0.289
Other[c]	2 (10 %)	0	1.000
Median C-reactive protein in mg/l (IQR)	116 (77–229)	121 (63–165)	0.887
Median creatinine in µmol/l (IQR)	76 (58–93)	102 (97–108)	0.307
Median number of hours between onset of symptoms and a positive blood culture (IQR)	24 (22–29)	24 (22–24)	0.563
Number of patients who died within 30 days after onset of symptoms of bacteraemia	0	3 (50 %)	0.007

IQR interquartile range, *ICU* intensive care unit

[a] Adequate treatment: defined as the targeted administration of at least one antimicrobial agent to which *S. maltophilia* was susceptible in vitro

[b] Renal impairment: defined as a creatinine clearance of <60 ml/min

[c] Other: urinary tract infection (patient 2), surgical site infection (patient 25)

adequate treatment. Table 2 describes in more detail the therapeutic treatment for each patient.

All of the patients had multiple co-morbidities, and 12 (44 %) of them were immunosuppressed. Twenty-five (93 %) patients had been seen by a specialist in the Infectious Diseases Consultant Service. All bacteraemia episodes except for one were nosocomial infections. The most common focus of bacteraemia was a central line, followed by a focus in the respiratory tract (Table 1). Detailed data on central venous catheter insertion and removal could be analysed in 17 of 18 patients. The duration of central venous catheter use was 15 days (median; IQR 12–21) at the diagnosis of *S. maltophilia* in blood culture. After obtaining blood culture results, catheters were removed within 1 day (median; IQR 0–3). The majority of patients had also been diagnosed with sepsis (24; 89 %), of whom seven had septic shock. Most patients (78 %) had been treated with broad-spectrum antibiotics within the 30 days prior to the onset of *S. maltophilia* bacteraemia symptoms. The median number of *S. maltophilia*-positive blood cultures was 1 (IQR 1–2), and the median time to positivity was 24 h in the blood culture system. *S. maltophilia* was identified as the single pathogen present in cultures for 18 (67 %) of the patients. All isolates of *S. maltophilia* were susceptible to TMP/SMX, 12 isolates (41 %) were intermediate susceptible or resistant to ciprofloxacin and only one isolate was resistant to levofloxacin from the 17 isolates tested. Six patients were treated with antimicrobial agents that were not active in vitro. In this latter group, patients 15, 24 and 27 (Table 2) died before their treatment was changed as recommended by the specialist in infectious diseases, and patients 5, 11 and 16 (Table 2) survived their bacteraemia episodes. Ventilator-associated pneumonia (VAP) was identified as the source of bacteraemia in two out of three patients (patients 24 and 27) with fatal outcome. For patients 5 and 16 (Table 2), central catheters were removed and no further antibiotic treatment was administered. The positive blood culture of patient 11 (Table 2) was retrospectively considered as a contamination.

Of the 21 patients who were defined as having received adequate treatment, 16 (76 %) were treated with TMP/SMX alone, two were treated with TMP/SMX in combination with fluoroquinolones and three were treated with fluoroquinolones alone. Detailed information about the dosages and side effects of TMP/SMX monotherapy for patients in this study is shown in Table 3.

The 30-day mortality rate of patients with *S. maltophilia* bacteraemia was 11 % (3 of 27 patients). All patients who received treatment with an antibiotic shown to be effective

Table 2 Focus of infection and type of antibiotic treatment for 27 patients diagnosed with *S. maltophilia* bacteraemia

Patient	Age (years)	Gender	Focus of *S. maltophilia* bacteraemia/associated clinical condition	Empirical therapy antimicrobials	Targeted therapy antimicrobials	Duration of targeted therapy (days)	Survived ≥30 days?
1	63	F	CLR/metastatic breast cancer	Cefepime	TMP/SMX	13	Yes
2	66	M	Urosepsis/bladder urothelial carcinoma	Ciprofloxacin	TMP/SMX	18	Yes
3	46	F	CLR/severe cellulitis	Piperacillin/ tazobactam	TMP/SMX	14	Yes
4	60	F	VAP/necrotising fasciitis	Piperacillin/ tazobactam	TMP/SMX	14	Yes
5	67	F	CLA/secondary amyloidosis	Imipenem	–	–	Yes
6	76	F	CLA/abdominal injury, multimorbidity	Ciprofloxacin	TMP/SMX	14	Yes
7	59	M	CLA/septic shock with *Staphylococcus aureus*	Piperacillin/ tazobactam	TMP/SMX	4	Yes
8	30	M	CLR/intravenous drug use, community-acquired sepsis	Piperacillin/ tazobactam	Ciprofloxacin	14	Yes
9	58	M	CLA/multiple myeloma	TMP/SMX	TMP/SMX, ciprofloxacin	17	Yes
10	50	M	Pneumonia/severe pulmonary fibrosis	Piperacillin/ tazobactam	TMP/SMX, levofloxacin	17	Yes
11	71	M	Pneumonia/bowel ischaemia and resection/hypovolaemic shock	Piperacillin/ tazobactam, metronidazole	–	–	Yes
12	15	F	CLR/polytrauma	Cefepime	TMP/SMX	13	Yes
13	48	M	CLA/acute myeloid leukaemia	Meropenem	TMP/SMX	14	Yes
14	69	M	Pneumonia/prostate cancer	Piperacillin/ tazobactam	Ciprofloxacin	14	Yes
15	71	M	CLA/metastatic prostate carcinoma	Amoxicillin/ clavulanate	–	–	No
16	72	M	CLA/hepatic abscess	Vancomycin, tobramycin	–	–	Yes
17	71	M	CLA/parkinsonism and severe pneumonia	Piperacillin/ tazobactam	TMP/SMX	9	Yes
18	25	F	CLA/acute lymphoblastic leukaemia	TMP/SMX	TMP/SMX	14	Yes
19	76	M	Pneumonia/urinary tract infection	Piperacillin/ tazobactam	Ciprofloxacin	14	Yes
20	71	F	CLA/complicated hip prosthesis infection	TMP/SMX, ertapenem	TMP/SMX	14	Yes
21	80	F	CLR/*Staphylococcus aureus* sepsis	Piperacillin/ tazobactam	TMP/SMX	15	Yes
22	68	F	CLA/acute myeloid leukaemia	Ciprofloxacin	TMP/SMX	16	Yes
23	44	F	CLA/HIV, endometrial cancer	Piperacillin/ tazobactam	TMP/SMX	20	Yes
24	80	F	VAP/myocardial infarction and brain death	–	–	–	No
25	39	F	Surgical site infection/distortion trauma	Piperacillin/ tazobactam	TMP/SMX	14	Yes
26	35	F	CLA/complications from Caesarean section	Amoxicillin/ clavulanate	TMP/SMX	14	Yes
27	78	F	VAP/chronic heart failure	Piperacillin/ tazobactam	–	–	No

F female, *M* male, *TMP/SMX* trimethoprim–sulfamethoxazole, *CLR* central line-related, *CLA* central line-associated, *VAP* ventilator-associated pneumonia, *HIV* human immunodeficiency virus

Table 3 Details about TMP/SMX monotherapy in 16 patients diagnosed with *S. maltophilia* bacteraemia

Median number of days of treatment with TMP/SMX (IQR)	13 (8–14.5)
Median daily dose of trimethoprim (in mg/kg) at the end of the treatment period (IQR)	6.6 (4.2–13.2)
Number of patients to whom TMP/SMX was being administered at a lower than recommended high dose (<5 mg TMP/kg; TID) [1] at the start of the treatment period (patients 1, 2, 3, 4, 6, 7, 12, 17, 18, 22 and 26 in Table 2)	11 (69 %)
Number of patients for whom a dose reduction was required because of a reaction to the medication (renal toxicity; patients 2 and 13 in Table 2)	2 (13 %)
Number of patients for whom TMP/SMX was changed to fluoroquinolones because of treatment complications (i.e. delirium; patient 10 in Table 2)	1 (6 %)
Median percentage of the recommended dose (5 mg TMP/kg; TID) that was adjusted to the weight and renal function of the patient (IQR)	44.2 % (33.1–70.5)
Median percentage of normal dose (5 mg TMP/kg; BID) that was adjusted to the weight and renal function of the patient (IQR)	66.3 % (49.7–105.8)

TMP/SMX trimethoprim–sulfamethoxazole, *IQR* interquartile range

against *S. maltophilia* in vitro clinically recovered and none of them died in the 30-day period following the onset of the infection. No differences in outcomes were observed with respect to the use of different TMP/SMX dosages.

Discussion

Various studies have reported a mortality rate for *S. maltophilia* infections of 15–29 % and the mortality rate for bacteraemia was even higher, reaching up to 62 % [4–7, 10]. However, in this study, we observed an excellent prognosis with clinical improvement and no 30-day mortality when adequate treatment with TMP/SMX and/or a fluoroquinolone was provided, even when the daily TMP dose was lower than 15 mg/kg [1]. The most striking finding of the current analysis was a zero mortality rate in adequately treated patients diagnosed with *S. maltophilia* bacteraemia. We identified four factors that might have contributed to these excellent outcomes for treatment.

First, the *S. maltophilia* isolates in this study were all susceptible to TMP/SMX in vitro. This is in agreement with an overall low rate of TMP/SMX resistance (3.7 %) for *S. maltophilia* in Switzerland (http://www.anresis.ch). This is in contrast to higher rates of TMP/SMX resistance reported in other European countries and in North America [11].

Second, the use of TMP/SMX in most of our patients very likely contributed to the positive outcomes in this study, given that TMP/SMX is known to be the most efficient antimicrobial for either monotherapy or combination therapy against susceptible *S. maltophilia* isolates [1, 2]. Newer fluoroquinolones, minocycline or tigecycline might be future alternatives to combat emerging TMP/SMX resistance; however, the selection of resistant *S. maltophilia* strains with the use of quinolones remains a concern [2]. The administration of TMP/SMX can be associated with adverse events such as neutropaenia, hepatopathy or decreased tubular secretion of creatinine and also with more uncommon severe skin diseases such as Stevens–Johnson syndrome or with central nervous system side effects [3]. However, the complication rate in this study was low. It is, therefore, noteworthy that the average dose of TMP used in the study was lower than the normally recommended dose of 15 mg/kg body weight per day. It is especially noteworthy in light of the low toxicity rate among these patients and the generally excellent outcomes. However, prospective, well-controlled and larger studies are required in order to confirm these retrospective findings on TMP/SMX dosages for treating *S. maltophilia* bacteraemia.

Third, the patients in the group whose antimicrobial therapy conformed with our definition of adequate treatment were somewhat younger ($p < 0.001$) and also required less time in the intensive care unit (ICU) than other patients in the study whose therapy did not conform to the definition of adequate treatment ($p = 0.004$), which indicates lower morbidity in the group.

Fourth, a central line was the focus identified in two-thirds of the cases, which has been shown in earlier studies to be associated with a lower mortality rate [5, 6].

The limitations of the study are the rather small number of cases and the retrospective design of the study. The strengths of the study include the amount of information that was provided by the detailed work-ups of patients with *S. maltophilia* bacteraemia, in particular the information about therapeutic aspects and outcome in each case. In addition, the involvement of an infectious disease specialist in all but two cases provided specialised and detailed data about the cases that are still useful years after the events occurred.

In conclusion, *S. maltophilia* bacteraemia is a serious condition, but it appears to have a low mortality rate when central lines are removed as quickly as possible after the onset of infection and patients receive adequate treatment, preferably treatment with TMP/SMX, if the identified pathogen is shown to be susceptible to this antimicrobial agent in vitro.

Acknowledgments We would like to thank Sigrid Strom, Seattle, WA, for her excellent editing of the manuscript. This work was supported by the Stiftung Forschung Infektionskrankheiten, Basel,

Switzerland (SFI 43/2013). The study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data, in writing the manuscript or in the decision to submit the manuscript for publication.

Conflict of interest The authors declare that there are no conflicts of interest.

References

1. Looney WJ, Narita M, Mühlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. Lancet Infect Dis. 2009;9:312–23.
2. Nicodemo AC, Paez JI. Antimicrobial therapy for *Stenotrophomonas maltophilia* infections. Eur J Clin Microbiol Infect Dis. 2007;26:229–37.
3. Nguyen AT, Gentry CA, Furrh RZ. A comparison of adverse drug reactions between high- and standard-dose trimethoprim–sulfamethoxazole in the ambulatory setting. Curr Drug Saf. 2013;8:114–9.
4. Yeshurun M, Gafter-Gvili A, Thaler M, Keller N, Nagler A, Shimoni A. Clinical characteristics of *Stenotrophomonas maltophilia* infection in hematopoietic stem cell transplantation recipients: a single center experience. Infection. 2010;38:211–5.
5. Garazi M, Singer C, Tai J, Ginocchio CC. Bloodstream infections caused by *Stenotrophomonas maltophilia*: a seven-year review. J Hosp Infect. 2012;81:114–8.
6. 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.
7. Senol E, DesJardin J, Stark PC, Barefoot L, Snydman DR. Attributable mortality of *Stenotrophomonas maltophilia* bacteremia. Clin Infect Dis. 2002;34:1653–6.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36:309–32.
9. Carroll KC, Cohen S, Nelson R, Campbell DM, Claridge JD, Garrison MW, et al. Comparison of various in vitro susceptibility methods for testing *Stenotrophomonas maltophilia*. Diagn Microbiol Infect Dis. 1998;32:229–35.
10. Fihman V, Le Monnier A, Corvec S, Jaureguy 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;64:391–8.
11. Gales AC, Jones RN, Forward KR, Liñares 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:S104–13.