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Stenotrophomonas maltophilia Infections: Clinical Characteristics in a Military Trauma Population

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Abstract

Stenotrophomonas maltophilia is a pathogen with unique resistance patterns. We assessed 70 combat casualties with *S. maltophilia* clinical isolates to examine its role as a nosocomial pathogen in critically-ill trauma patients. Incidence density was 0.36 *S. maltophilia* infections per 100 patient-days (95% CI: 0.29–0.44). Patients predominantly had blast trauma (97%) and were critically injured (injury severity score [ISS] >25; 80%). Restricting to patients with ISS >15, 50 patients with *S. maltophilia* infections were compared to 441 patients with infections attributed to other gram-negative bacilli. Patients with *S. maltophilia* infections had significantly more operating room visits prior to isolation, traumatic or early surgical amputations, longer hospitalization (median 71 vs 47 days), and higher overall mortality (10% vs 2%; p=0.01). Initial and serial (≥7 days between initial and subsequent isolation) *S. maltophilia* isolates had high susceptibility to trimethoprim-sulfamethoxazole and minocycline. Evaluation of newer agents awaiting CLSI breakpoints, including moxifloxacin, showed promising results.

Keywords

Stenotrophomonas maltophilia; wound infections; trauma-related infections; combat-related infections

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1. INTRODUCTION

Advancements in point of injury care and medical capabilities have contributed to increased survival following previously fatal injuries for U.S. combat casualties (Murray et al., 2009). Nevertheless, infectious complications remain a leading cause of morbidity and mortality (Blyth et al., 2015) with high rates of multidrug-resistant organism (MDRO) colonization and infections providing further challenges (Campbell et al., 2017; Gilbert et al., 2016; Hospenthal et al., 2011; Tribble et al., 2011; Weintrob et al., 2018). Frequent pathogens associated with combat-related infections include coagulase-negative staphylococci, *Enterococcus* spp. (17–26% vancomycin-resistant), *Escherichia coli* (73–91% MDR), and *Acinetobacter calcoaceticus-baumannii* complex (86–95% MDR) (Weintrob et al., 2018). Other organisms are also increasingly being recognized as clinically-relevant pathogens within this population.

Stenotrophomonas maltophilia has emerged as a concerning nosocomial pathogen in critically ill trauma patients (Hanes et al., 2002). In particular, *S. maltophilia* has demonstrated a trend toward pathogenicity in compromised hosts, including trauma patients with attributable mortality rates of up to 37.5% (Falagas et al., 2009; Hanes et al., 2002; Schaumann et al., 2001; Senol, 2004). Ventilator-associated pneumonia was the most commonly identified syndrome associated with *S. maltophilia*, with the organism recovered from trauma patients following multiple antimicrobial exposures (Mueller et al., 2005). Neutropenia, higher injury severity score (ISS), presence of central venous catheters, use of broad-spectrum antibiotics, and increased length of hospital stay have been independently associated with infection risk (Hanes et al., 2002; Senol, 2004).

S. maltophilia has demonstrated intrinsic resistance to commonly used broad-spectrum antibiotics, including carbapenems, piperacillin-tazobactam, and newer cephalosporin/beta-lactamase combinations (Legacé-Wiens et al., 2014; Nicodemo and Garcia Paez, 2007). Trimethoprim-sulfamethoxazole is currently the first-line therapy, but mechanisms of resistance to this drug, including plasmid-mediated, have been identified (Nicodemo and Garcia Paez, 2007). *In vitro* activity has been reported with newer fluoroquinolones (e.g., clinafoxacin, levofloxacin, gatifloxacin, moxifloxacin, and sitafloxacin), but empiric therapy may prove difficult given regional variations in resistance rates (Nicodemo and Garcia Paez, 2007). Minocycline has shown activity against *S. maltophilia*, but there are concerns that frequent use in treating *A. calcoaceticus-baumannii* complex may have potential for inducing increased resistance in *S. maltophilia* (Milne and Gould, 2012).

While *S. maltophilia* has traditionally been considered a low virulence pathogen, its clinical significance and resistance patterns in a severely-injured trauma population have not yet been fully elucidated. Given this organism's multiple resistance mechanisms, empiric antibiotics in critically ill patients may not provide adequate coverage. We examined the prevalence and clinical features of *S. maltophilia* in U.S. wounded military personnel and evaluated patterns of resistance.

2. METHODS

2.1 Study Population and Design

Clinical and microbiological data collected from June 1, 2009 through September 1, 2014 as part of the Trauma Infectious Disease Outcomes Study (TIDOS) was assessed. Patients were eligible for inclusion in TIDOS if they were active-duty personnel or Department of Defense beneficiaries, 18 years of age or older, injured during deployment and required evacuation through Landstuhl Regional Medical Center (LRMC), Germany, before ultimately being transferred to a participating military hospital in the United States (Brooke Army Medical Center [BAMC] or a hospital in the National Capital Region [NCR]), as previously described (Tribble et al., 2011). The study was approved by the Institutional Review Board of the Uniformed Services University of the Health Sciences.

As part of TIDOS, specimens collected from surveillance cultures and clinical infection work-ups were archived for future study in a microbiological repository. Patients were considered for inclusion if they had *S. maltophilia* isolated from a clinical infection work-up. Exclusion criteria were those patients with *S. maltophilia* isolates without linkage to a corresponding infection syndrome (as defined below). A comparator group was comprised of patients with infections attributed to gram-negative bacilli other than *S. maltophilia*. As preliminary analysis found the patients in the *S. maltophilia* group to have more severe injuries than the comparator group, both groups were restricted to patients with an ISS >15, indicating severe or critical injuries (Copes et al., 1988).

Demographic patient data and clinical history were obtained through the Department of Defense Trauma Registry (Eastridge et al., 2006). Infection syndromes, clinical microbiology, and antimicrobial administration were extracted from the TIDOS supplemental Infectious Disease Module (Tribble et al., 2011). Infections were identified based on a combination of clinical findings and laboratory tests, and classified in accordance with standardized definitions of the Centers for Disease Control and Prevention National Healthcare Safety Network (2019). In the absence of meeting the *a priori* definition, infections were included if there was an indication in the medical chart of a clinical diagnosis, as well as directed antimicrobial treatment (duration of ≥5 days for skin and soft-tissue infections (SSTIs) and ≥21 days for osteomyelitis). Infections were excluded if there was a record of an alternate diagnosis and discontinuation of antimicrobial treatment (Tribble et al., 2011).

Pre-culture antibiotics were defined as those instituted at any point during care prior to the first isolation of *S. maltophilia* and post-culture antibiotics as those initiated within two days following initial isolation. Broad-spectrum antibiotics were specified as any 4^{th} generation cephalosporin, anti-pseudomonal penicillin, or carbapenem. Traumatic or early surgical amputations were defined as amputations occurring prior to admission at a military hospital in the United States. Invasive fungal wound infections (IFIs) were classified in accordance with published criteria (Weintrob et al., 2015).

2.2 Isolate Susceptibility Analysis

Confirmation of *S. maltophilia* speciation and antimicrobial susceptibilities were performed on all archived *S. maltophilia* isolates collected from clinical workups. For isolates cultured from the same patient, only unique initial and serial isolates were included in the analysis, as defined by culture site, resistance pattern, or pulsed-field gel electrophoresis (PFGE) pattern. Serial isolates were defined as isolates collected ≥7 days apart from the first isolate. Any isolate that did not meet inclusion criteria (i.e., was not associated with a clinical infectious workup, including those obtained through routine MDRO screening by groin swabs), was excluded.

S. maltophilia isolates underwent two passages on 5% sheep blood agar prior to confirmed identification using the BD Phoenix™ Automated Microbiology System (BD Diagnostics, Sparks, Maryland). BD Phoenix™ BD Emerge™ (NMIC 300) Panels were utilized for susceptibility testing. Only antibiotics with possible *in vitro* activity against *S. maltophilia* were included in the analysis. Clinical and Laboratory Standards Institute (CLSI) breakpoints were used if available for susceptibility analysis. Isolates with intermediate interpretation were considered non-susceptible. Antimicrobials without CLSI breakpoints were assessed by minimum inhibitory concentration (MIC) with breakpoints assigned for analysis based on published pharmacokinetics/pharmacodynamics data (ciprofloxacin MIC ≤2 μg/mL, moxifloxacin MIC ≤4 μg/mL, and tigecycline MIC ≤2μg/mL being considered susceptible) (Chung et al., 2012; Farrell et al., 2010; Weiss et al., 2000). The PFGE to determine the clonality of the isolates was performed according to the Centers for Disease Control and Prevention standardized PFGE protocol for Gram-negative rods (Centers for Disease Control and Prevention, 2014) with some minor modifications and using a 90% similarity cut-off value.

2.3 Statistical Analysis

Clinical, injury, and infection data of the patients in the *S. maltophilia* and comparator groups were analyzed. Chi-square and Fisher's Exact Test were used to compare categorical variables. Continuous variables were analyzed by Mann-Whitney U. Statistical analysis for the microbiological data was completed using IBM SPSS Statistics 22 (IBM, NY) and SAS version 9.4 (SAS, Cary, NC) was utilized for the analysis of *S. maltophilia* patients and the comparator group.

3. RESULTS

3.1 Epidemiology of *S. maltophilia* infections

A total of 2,699 patients were transferred from LRMC to TIDOS-participating U.S. military hospitals (Figure 1). Seventy (2.6%) of these patients had 71 initial *S. maltophilia* isolates available in the TIDOS microbiological repository (one patient provided two initial isolates). Nine of these patients had subsequent cultures yielding 26 unique serial isolates. The patients were predominantly male (98.6%) who sustained blast-related trauma (97.1%) in Afghanistan (97.1%). Fifty-six (80%) patients had an ISS >25 (critical injury) and 57 (81.4%) patients were admitted to the intensive care unit at participating U.S. military hospitals. The time from injury to diagnosis of an infection (any pathogen) was a median of

4 days (interquartile range [IQR]: 3–6.5 days). For the patients with *S. maltophilia* infections, the time from injury to culture confirmation with growth of *S. maltophilia* was a median of 9 days (IQR: 6–15 days). Sixty-four patients (91.4%) received antibiotics prior to the *S. maltophilia* culture with 45 (64%) patients receiving broad-spectrum antibiotics, 25 (36%) a fluoroquinolone, 3 (4%) trimethoprim-sulfamethoxazole, and 47 (67%) a tetracycline. The length of hospitalization was a median of 65 days (IQR: 42–95 days) and 7 (10%) patients died.

Initial isolates were recovered predominately from wounds (N=44; 62%), followed by respiratory (N=18; 25%), blood (N=5; 7%), urine (N=1; 1%), and other sources (N=3; 4%) with a similar pattern seen in serial isolates [wound (N=18; 69%), respiratory (N=4; 15%), blood (N=2; 8%), urine (N=1; 4%), and other (N=1; 4%)]. Thirty-seven of the 44 (84%) wound isolates were from polymicrobial wound infections. Of these, 25 had other gram-negative bacilli isolated (most frequently *Pseudomonas* spp. [N=11], *A. calcoaceticus-baumannii* complex [N=7], *Enterobacter cloacae* [N=6], *E. coli* [N=5]), 20 had gram-positive organisms (most frequently *E. faecium* [N=14], and coagulase-negative staphylococci [N=5]), and 7 had anaerobes (*Clostridium* spp. [N=3], *Bacteroides* [N=2], and *Prevotella* spp. [N=2]). Fifteen wounds also had fungi isolated, of which 7 were proven, 2 probable, and 4 possible IFIs. Of the 18 *S. maltophilia* respiratory isolates, 13 (72%) were associated with isolation of other gram-negatives (most frequently *P. aeruginosa* [N=4], *E. cloacae* [N=3], *A. calcoaceticus-baumannii* complex [N=2], and *Klebsiella* spp. [N=2]) and only 7 isolates had *Stenotrophomonas*-active agents prescribed following isolation (including 1 trimethoprim-sulfamethoxazole and a fluoroquinolone, 4 fluoroquinolones, and 2 tetracyclines).

On a patient-level, there were a median of 9 operative room (OR) visits (IQR: 5–16) following isolation of *S. maltophilia* in wound infections, but only a median of 3 (IQR: 1–4) OR visits were related to surgeries/procedures for the wound infected with *S. maltophilia* in 18 patients (14 patients with polymicrobial wound infections). In the four patients with monomicrobial *S. maltophilia* wound infections requiring subsequent debridements for management of the infection (1, 3, 4, and 15 debridements, respectively), all were treated with trimethoprim-sulfamethoxazole. Of the 70 patients with initial *S. maltophilia* infections, 59 (84%) received antimicrobials active against *S. maltophilia* following isolation (25 received trimethoprim/sulfamethoxazole, 29 tetracycline, and 22 fluoroquinolones).

Restricting to patients with severe or critical injury severity (ISS >15), 50 patients with an infection syndrome due to *S. maltophilia* were compared to 441 patients with an infection due to other gram-negative bacilli (Figure 1). There were no significant differences between the groups with regards to gender, age, region where the injury was sustained (Afghanistan or Iraq), or rates of intensive care unit (ICU) admission (Table 1). Patients in the *S. maltophilia* group were more likely to have had blast as the primary mechanism of injury, a higher proportion of traumatic or early surgical amputations, and more OR visits prior to isolation. Nevertheless, mechanical ventilation was employed at similar frequencies in each group with the majority of patients continuing ventilation after transfer to the U.S. for ≤ 1 week. The *S. maltophilia* group had later diagnoses of first infection (median of 10 vs 6 days; p=0.001), increased length of hospitalization (median of 71 vs 47 days; p<0.001), and

higher proportion of mortality (10% vs 2%; p=0.01). Furthermore, *S. maltophilia* was identified later than other gram-negative organisms (p=0.001).

On the infection-level, 95 infection syndromes were identified in the *S. maltophilia* group (50 patients) and 866 infections in the comparator group (441 patients) with SSTIs comprising the majority of infections in both groups (Table 2). Incidence density for *S. maltophilia* in this group was 0.36 infections per 100 patient days (95% CI: 0.29–0.44). *P. aeruginosa* (10.1%) was the most common gram-negative bacterium recovered in the comparison group followed by *Escherichia coli* (9.3%), *A. calcoaceticus-baumannii* complex (8.2%), *E. cloacae* (5.5%), *Serratia marcescens* (2.6%), and *Klebsiella pneumoniae* (2.4%).

3.2 Isolate Susceptibility Analysis

A total of 226 *S. maltophilia* isolates were recovered, of which 71 (31.4%) met inclusion criteria for unique, initial isolates and 26 (11.5%) for serial isolates. The PFGE analysis revealed distinct patterns in all except two initial isolates from BAMC (Figure 2). Antimicrobial susceptibilities of initial and serial isolates are shown in Table 3. There were trends towards initial isolate resistance (defined as resistance to any *Stenotrophomonas*-active agent) in patients with an ISS>25 (p=0.056). Among the initial isolates, 21 (47%) of 45 wound, 4 (80%) of 5 blood, 7 (38%) of 18 respiratory, and 1 (33%) of 3 other isolates (p=0.437) had *Stenotrophomonas*-active agents prescribed following isolation. Thirty-six (82%) wound isolates had resistance on initial isolation compared to 9 (50%) respiratory, 3 (60%) blood, 1 (100%) urine, and 1 (33%) other isolate (p=0.060). Treatment status with *Stenotrophomonas*-active agents following initial isolation was not associated with serial isolation (p=1.0).

Initial isolates obtained from patients with ISS >25 had a higher proportion of resistance to ceftazidime (38 [64%] of 60 isolates vs 2 [20%] of 10 isolates; p=0.018). Ceftazidime resistance was also encountered more frequently in levofloxacin-resistant isolates (12 [100%] of 12 isolates vs 29 [49%] of 59 levofloxacin-susceptible isolates; p=0.001). In addition, there was a trend toward increased tigecycline resistance with prior receipt of agents with *Stenotrophomonas*-activity (4 [31%] of 13 isolates vs 5 [9%] of 58 isolates; p=0.052). Overall, there was a more frequent recovery of serial isolates when the initial isolates demonstrated resistance (9 [18%] of 50 isolates vs 0 of 21 isolates; p=0.050) and also with initial isolation at BAMC (6 [43%] of 14 isolates vs 2 [8%] of 26 isolates from LRMC and 1 [3%] of 31 isolates from NCR; p=0.001).

The comparison of the susceptibility data between the 71 initial isolates and 26 serial isolates (collected from 9 patients; 4 with ≥1 serial isolate) revealed an increased percentage of resistance in the serial isolates, with exception of minocycline (Table 3). In particular, the proportion of susceptible isolates decreased from 42% to 4% for ceftazidime, 82% to 31% for levofloxacin, and 87% to 23% for tigecycline. Thirteen of the 26 serial isolates were from the same patient [from wound, respiratory, blood (on two separate occasions), and other specimens], who was treated with varying combinations of carbapenems, aminoglycosides, trimethoprim-sulfamethoxazole, and fluoroquinolones with increasing

MICs to moxifloxacin, ciprofloxacin, and tigecycline, but preserved susceptibilities to minocycline and trimethoprim-sulfamethoxazole.

Restricting to the nine patients with serial isolates, final serial isolates were analyzed against the respective initial isolates, with no significant change in susceptibility patterns. There were minor decreases in susceptibility for trimethoprim-sulfamethoxazole (100% to 78%; p=0.47) without intervening trimethoprim-sulfamethoxazole exposure. Moxifloxacin susceptibility also decreased (89% to 67%; p=0.58) with one of the patients who developed new resistance having had 20 days of levofloxacin in the intervening period (another patient with 14 days of fluoroquinolone exposure had moxifloxacin MIC increase from 0 to 4, but remained within extrapolated susceptibility range). The greatest changes in susceptibility were for levofloxacin and tigecycline, which both decreased from 67% in initial to 11% in the final serial isolate (p=0.05). Of the patients with initial levofloxacin-susceptible isolates, the only patient with continued levofloxacin susceptibility received 8 days of trimethoprim-sulfamethoxazole between cultures. Three patients with newly levofloxacin-resistant isolates had >7 days of interceding fluoroquinolone exposure. Ciprofloxacin susceptibility decreased from 11% to 0 in final isolates. Of the six patients with increased tigecycline MICs (five had new resistance), three had ≥20 days cumulative exposure to tetracyclines (2 doxycycline, 1 minocycline); however, all retained minocycline susceptibility.

4. DISCUSSION

To our knowledge, this is the first study that has examined *S. maltophilia* infections in a previously healthy, young, trauma population. Patients with *S. maltophilia* infections were more severely injured than those acquiring non-*S. maltophilia* gram-negative infections. *S. maltophilia* was most frequently isolated from wound and respiratory sources, and in >70% of these cases in the setting of other organisms.

Similar to prior studies identifying *S. maltophilia* infections at higher frequencies in immunocompromised and ICU patients (Brooke, 2012; Falagas et al., 2009; Garcia Paez and Costa, 2008), we found infections tend to predominate in patients with higher injury severity. Although previously healthy, our study population was likely transiently immunosuppressed from the severity of the trauma (i.e., 80% of patients had an ISS > 25 indicating critical injury, 94% admitted to intensive care, and 10% crude mortality). When the 50 patients with *S. maltophilia* infections were assessed against the comparator group with similarly high ISS severity, *S. maltophilia* was recovered more frequently in patients that had a traumatic amputation or required a surgical amputation prior to reaching definitive care in a U.S. facility. Notably, the majority of *S. maltophilia* isolates were cultured in the setting of polymicrobial infections, which makes interpretation of its attributable morbidity difficult to assess, which is a similar challenge in examining these complex extremity wound infections. Especially notable is the fact that almost a third of *S. maltophilia* wound isolates were associated with IFIs. Interestingly, despite frequent co-isolation of gram-positive organisms in wounds (45%), *S. aureus* was not isolated in any wounds in which *S. maltophilia* was cultured. Additionally, even *S. maltophilia* isolates from respiratory sources were frequently associated with other gram-negative organisms, of which some are also thought to be less virulent. Overall, 84% of patients with isolation of *S. maltophilia* had

antimicrobials targeting this organism prescribed following isolation, including fluoroquinolones and tetracyclines, which were frequently prescribed for other indications (e.g., coverage of other pathogens or continuation of malaria chemoprophylaxis). Despite this, serial isolation was a rare event, potentially due to surgical management. Being ubiquitous in the environment (Brooke, 2012; Denton and Kerr, 1998), this organism has been linked to nosocomial transmission via water sources, disinfectant solutions, and other healthcare-related modes of transmission (Khardori et al., 1990; Mukhopadhyay et al., 2003; Sakhnini et al., 2002), raising the suspicion that infections occur primarily through a common contaminated source. Nevertheless, our analysis showed no evidence for clonal spread, suggesting that trauma patients are acquiring unique healthcare-associated infections selected through antimicrobial pressure, again emphasizing the role for antimicrobial stewardship in these critically ill patients.

When examining the susceptibility of *S. maltophilia* isolates, susceptibility to trimethoprim-sulfamethoxazole was documented in 99% of initial isolates with levofloxacin susceptibility in only 83%, confirming the role of trimethoprim-sulfamethoxazole as a first-line therapy for *S. maltophilia* in the absence of contraindications to the drug (Farrell et al., 2010). Susceptibility to minocycline was high (100%) and persisted in serial isolates, demonstrating a similar potential for minocycline to be employed as an alternative therapy, as described in other studies (Hand et al., 2016; Neela et al., 2012). Furthermore, MICs to moxifloxacin appeared favorable in 97% of initial isolates when using previously described cutoffs (Weiss et al., 2000), suggesting that it may be a more effective agent than levofloxacin and warrants further clinical evaluation. Although serial isolates are less common, these isolates were noted to harbor more resistance to *S. maltophilia*-targeted antibiotics versus the unique initial isolates with 81% retaining susceptibility to trimethoprim-sulfamethoxazole, but only 31% being susceptible to levofloxacin. Previous studies have described various resistance mechanisms employed by *S. maltophilia* and that increased resistance to trimethoprim-sulfamethoxazole may be associated with acquisition of the *sul1* gene and class 1 integron (Chang et al., 2007; Song et al., 2010; Toleman et al., 2007). Moreover, the presence of *smeDEF* RNA increases resistance to multiple antimicrobial agents through action of an efflux pump (Alonso and Martinez, 2000). As the nine patients with serial isolates in our study had severe injuries, predisposing them to longer hospital stays and duration of antibiotic use, it may suggest activation or new acquisition of these resistance genes over the course of their care, which warrants further investigation. Minocycline susceptibility was preserved against all isolates and moxifloxacin MICs were favorable in 89% of the serial isolates, indicating that these may be useful alternative agents. Despite favorable MICs for moxifloxacin, recent data suggests poor bactericidal activity of fluoroquinolones against *S. maltophilia* in time-kill studies (Grillon et al., 2016), and perhaps limiting *in vivo* effectiveness.

This study includes limitations inherent to its retrospective nature. Despite starting with 226 isolates from 2,699 eligible patients, only 71 isolates met criteria as a unique initial isolate and only nine patients had unique serial isolates, limiting the statistical power to identify predisposing factors for infection. Taking the study limitations into consideration, our analysis reveals that *S. maltophilia* is an uncommon pathogen in trauma patients. When isolated, it is most frequent in later, polymicrobial wound and respiratory infections. We

again demonstrate the utility of trimethoprim-sulfamethoxazole and suggest minocycline and moxifloxacin as potential alternatives, though further clinical data is needed.

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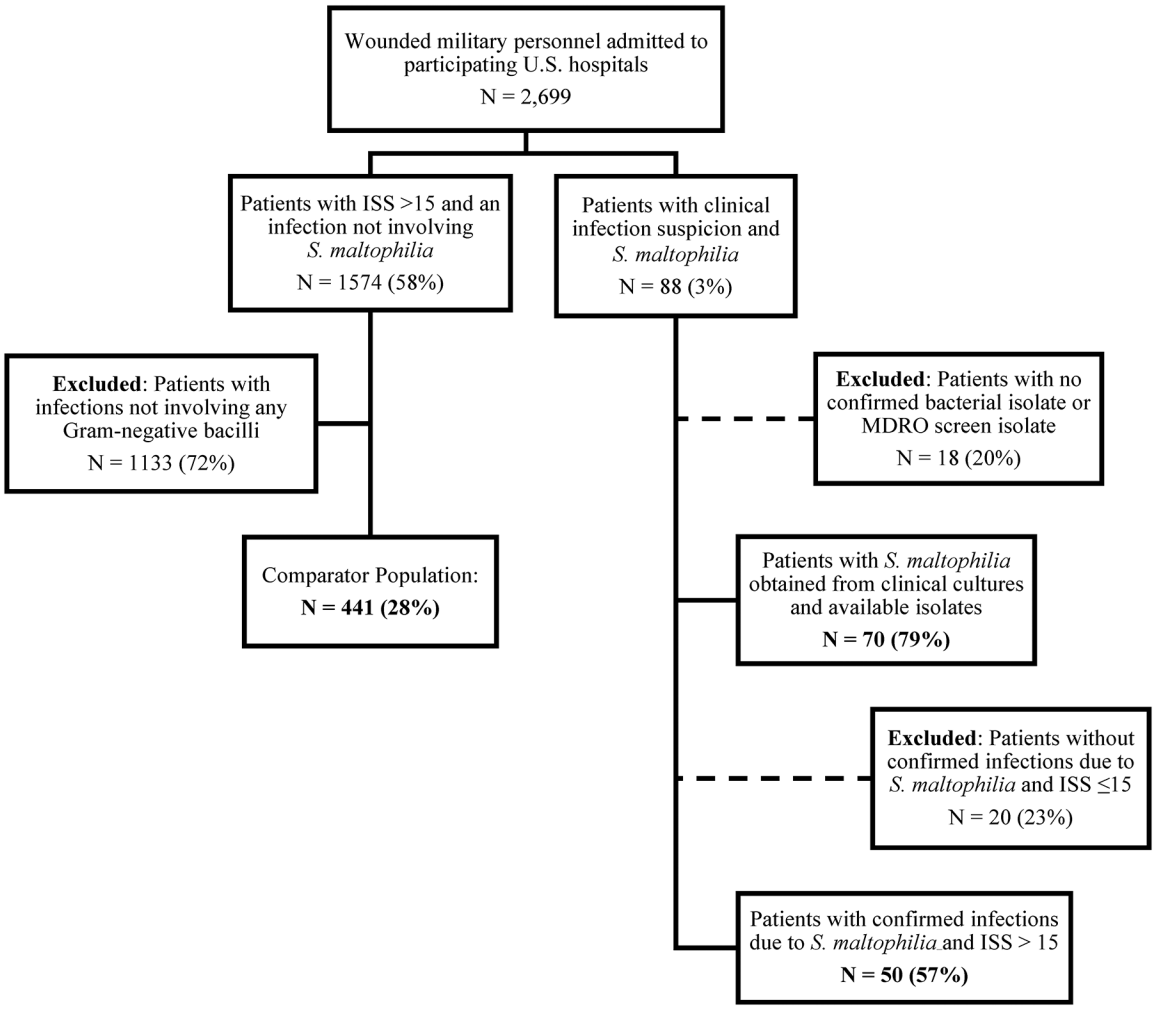

Figure 1.
Flowchart of Study Population. ISS – injury severity score. MDRO – multidrug-resistant organisms

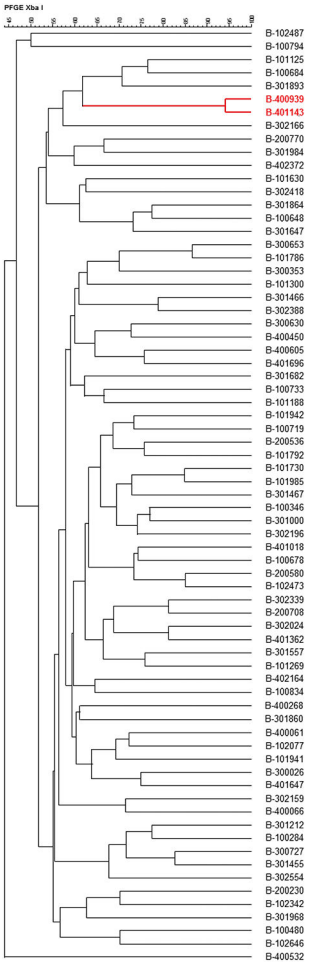

Figure 2.

Dendrogram for 71 unique initial *Stenotrophomonas maltophilia* isolates. Two isolates, highlighted in red, showed the same pulsed-field gel electrophoresis (PFGE) type. All other initial isolates had unique PFGE types.

Table 1.

Characteristics, No. (%), of Severely Injured Trauma Patients by Infection[a]

Characteristic	Patients with *S. maltophilia* Infection (N = 50)	Patients with Other Gram-negative Infection (N = 441)	P-value
Age, median years (IQR)	24 (22–27)	24 (21–28)	0.95
Male	50 (100)	435 (98.6)	1.00
Afghanistan theater	49 (98.0)	410 (93.0)	0.50
U.S. Admission Facility			0.52
National Capital Region[b]	37 (74.0)	344 (78.0)	
Brooke Army Medical Center	13 (26.0)	97 (22.0)	
Composite ISS			0.26
16 – 25 (severe)	6 (12.0)	81 (18.4)	
> 25 (critical)	44 (88.0)	360 (81.6)	
Injury Mechanism			<0.01
Blast	50 (100)	358 (81.2)	
Other (e.g., gunshot, motor vehicle crash)	0	79 (17.9)	
Pre-culture Antibiotics[c]			
None	2 (4.0)	15 (3.4)	0.69
Broad-spectrum[d]	38 (76.0)	131 (29.7)	<0.01
Fluoroquinolone	19 (38.0)	129 (29.3)	NA[e]
Fluoroquinolones without broad-spectrum antibiotics	7 (14.0)	78 (17.7)	0.51
Trimethoprim-sulfamethoxazole	3 (6.0)	2 (0.5)	NA[e]
Tetracycline	43 (86.0)	302 (68.5)	NA[e]
Post-culture Antibiotics[c]			
None	4 (8.0)	11 (2.5)	0.06
Broad-spectrum[d]	28 (56.0)	331 (75.1)	<0.01
Fluoroquinolone	16 (32.0)	184 (41.7)	NA[e]
Fluoroquinolones without broad-spectrum antibiotics	7 (14.0)	51 (11.6)	0.61
Trimethoprim-sulfamethoxazole	24 (48.0)	17 (3.9)	NA[e]
Tetracycline	19 (38.0)	228 (51.7)	NA[e]
Hospitalization, median days (IQR)	71 (46–117)	47 (34–66)	<0.01
Time to Culture, median days post-injury (IQR)	10 (6–17)	7 (4–13)	<0.01
OR Visits Pre-culture[c], median (IQR)	3 (1–6)	2 (1–4)	0.02
Injury to 1st infection diagnosis[f], median days post-injury (IQR)	9.5 (6, 17)	6 (3,13)	<0.01
ICU Admission			0.34
None	3 (6.0)	40 (9.1)	
LRMC only	4 (8.0)	61 (13.8)	

Characteristic	Patients with *S. maltophilia* Infection (N = 50)	Patients with Other Gram-negative Infection (N = 441)	P-value
U.S. hospital with/without LRMC	43 (86.0)	336 (76.2)	
Traumatic/Early Surgical Amputation[g]	39 (78.0)	240 (54.4)	<0.01
Inpatient Mechanical Ventilation			0.11
None	7 (14.0)	104 (23.5)	
LRMC Only	7 (14.0)	103 (23.3)	
LRMC plus U.S. hospital ≤ 1 week	33 (66.0)	219 (49.6)	
LRMC plus U.S. hospital ≥ 2 weeks	1 (2.0)	6 (1.3)	
Died	5 (10.0)	10 (2.3)	0.01

ICU – intensive care unit; ISS – injury severity score; IQR – interquartile range; LRMC – Landstuhl Regional Medical Center; OR – operating room

[a]Patients are restricted to those with an injury severity score >15. Comparator group includes patients with infections attributed to gram-negative bacillus other than *Stenotrophomonas maltophilia*. In the *S. maltophilia* infection group, 2 patients did not have documentation of mechanical ventilation status and in the comparator group, the operation theater, mechanism of injury, ICU status, and mechanical ventilation status was not known for 8, 4, 4, and 9 patients respectively. As such, these numbers were excluded from the analysis.

[b]Includes National Naval Medical Center and Walter Reed Army Medical Center, which merged to become Walter Reed National Military Medical Center in September 2011

[c]Pre-culture is the period prior to the date of collection of the culture that grew *S. maltophilia*. Post-culture is defined as at least one day after the date of collection of the culture that grew *S. maltophilia*.

[d]4^{th} generation cephalosporin, anti-pseudomonal penicillin, or carbapenem

[e]Use of antibiotics was not mutually exclusive for the patients, a p-value could not be calculated.

[f]Initial infection post-injury regardless of infecting pathogen.

[g]Amputations occurred prior to admission at U.S. hospitals

Table 2.

Infectious Syndromes among Subjects with *Stenotrophomonas maltophilia* Infections and Other Gram-negative Bacilli Infections (Comparator Group)

Infection Syndrome, No. (%)	*S. maltophilia* Infections N=95	Other Gram-negative bacilli Infections N=866	P-value
Skin and soft-tissue infection	56 (59.0)	394 (45.5)	0.07
Bloodstream infection	9 (9.5)	101 (11.7)	0.37
Osteomyelitis	6 (6.3)	68 (7.9)	0.85
Pneumonia[a]	11 (11.6)	143 (16.5)	0.15
Sepsis	9 (9.5)	48 (5.5)	0.19
Urinary tract infection	1 (1.1)	73 (8.4)	NC
Central nervous system infection	0	10 (1.2)	NC
Other[b]	3 (3.2)	29 (3.3)	NC

[a]Includes ventilator and non-ventilator associated pneumonia

[b]Includes sinusitis, empyema without pneumonia, lung abscess without pneumonia, tracheobronchitis, intra-abdominal infection

Table 3.

Antimicrobial Susceptibilities of Initial and Serial *Stenotrophomonas maltophilia* Isolates, No. (%)

	Ceftazidime	Levofloxacin	Minocycline	TIM	SXT	Ciprofloxacin[a]	Moxifloxacin[a]	Tigecycline[a]
Initial Isolates (N=71)	30 (42.3)	59 (83.1)	71 (100)	48 (67.6)	70 (98.6)	10 (28.2)	69 (97.2)	62 (87.3)
Serial Isolates (N=26)	1 (3.8)	8 (30.8)	26 (100)	8 (30.8)	21 (80.8)	2 (7.7)	23 (88.5)	6 (23.1)

SXT – trimethoprim-sulfamethoxazole; TIM – ticarcillin-clavulanic acid

[a]Susceptibility defined for ciprofloxacin, moxifloxacin, and tigecycline by MIC ≤ 2 μg/ml, ≤ 4 μg/ml, and ≤ 2 μg/ml respectively based on values used in published literature

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