Stenotrophomonas maltophilia Resistance in Military Trauma Patients

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Abstract

Background: *Stenotrophomonas maltophilia* is as an emerging pathogen in critically ill trauma patients. This study identifies *S. maltophilia* distribution, susceptibility, and risk factors for resistance in a military trauma population.
Methods: All *S. maltophilia* isolates prospectively collected during the Trauma Infectious Disease Outcomes Study (TIDOS) were included (9/09-9/14). Unique initial isolates were defined as differing in site, resistance and pulse-field gel electrophoresis (PFGE) patterns; serial isolates as ≥7 days between isolation. BD Phoenix™BD Emerge™(NMIC300) panels were used for susceptibility testing. Clonality was assessed with PFGE. Demographics, trauma-related characteristics, isolate source, presence of polymicrobial infection, and antimicrobial exposure before and after initial isolation were evaluated. Susceptibilities were defined by CLSI criteria [trimethoprim-sulfamethoxazole (TS), ticarcillin-clavulanate (TC), ceftazidime (CZ), levofloxacin (LV) minocycline (MC)] or MIC [moxifloxacin (MX), ciprofloxacin (CP), tigecycline (TG)].
Results: Of 2,699 TIDOS patients, 66 patients with 67 unique initial isolates were included. Sources were wound (62%), respiratory (27%), blood (7%), urine (1%), and other (3%) with 72% resistant to ≥1 antimicrobial. There was no evidence of clonal spread by PFGE. There was a trend towards increased resistance in wound isolates and patients with injury severity scores (ISS) >25 (p=0.05). Higher initial CP MICs were associated with increasing time from injury to initial isolate (p=0.01). CZ resistance was associated with LV resistance, and higher MX, CP, and TG MICs (p<0.01). Of 9 patients identified with 26 unique serial isolates, all had an ISS >25 and resistance to ≥1 antimicrobial. Comparing all initial to serial isolates, susceptibilities decreased for TS (from 99% to 81%), CZ (42% to 4%), LV (82% to 31%), and TC (67% to 31%). All isolates remained susceptible to MC. Initial and serial isolate MICs for CP, MX, and TG were ≤2µg/mL in 28% and 8%, ≤4µg/mL in 97% and 89% and ≤2µg/mL in 86% and 23% respectively.
Conclusions: *S. maltophilia* resistance in trauma patients may be seen with higher injury severity, increased time from injury to isolation, and in serial isolates.

Background

- Improvements in personal protective gear and medical capabilities lead to improved battlefield survival for US combat casualties, increasing hospitalizations and the potential for multidrug-resistant organism (MDRO) infection
- MDRO colonization of evacuated US personnel from Iraq and Afghanistan reached 13% in 2009
- Multiple inherent resistance mechanisms are found within *Stenotrophomonas maltophilia* resulting in few effective antibiotics
- In this study, we assessed antibiotic susceptibility patterns in initial and serial *S. maltophilia* isolates across combat trauma patients

Methods

Study Design:
- TIDOS eligibility criteria include active duty personnel or Department of Defense beneficiaries ≥18 years who are injured during deployment requiring evacuation to Landstuhl Regional Medical Center (LRMC) in Germany and ultimately transferring to a participating clinical site in the US
- As part of TIDOS, bacterial and yeast isolates are archived for future study at -80°C
- We utilized all initial unique (differing in site, resistance and pulse-field gel electrophoresis (PFGE) patterns) and serial (≥7 days between cultures) *S. maltophilia* isolates collected during infectious work-ups between 2009-2014
- Isolates obtained through routine MDRO screening by groin swabs were excluded
- After 2 passages on 5% sheep blood agar, the BD Phoenix™ Automated Microbiology System (BD Diagnostics, Sparks, Maryland) was used for identification of archived isolates
- BD Phoenix™ BD Emerge™ Panels were utilized for susceptibility testing
- Clonality was determined using PFGE with a ≥ 90% relatedness breakpoint

CLSI and MIC interpretations:
- CLSI breakpoints were used where available for susceptibility analysis
- MICs with intermediate susceptibility results were considered non-susceptible
- Antimicrobials without CLSI breakpoints were assessed by MIC with breakpoints assigned for analysis based on published pharmacokinetics/pharmacodynamics data

Statistical Analysis:
- Univariate analysis by χ^2 and Fisher's Exact Test for categorical variables, as appropriate, and Mann-Whitney U for continuous variables was performed

Results

Overall Demographics:
- 2,699 patients were transferred to TIDOS-participating clinical facilities with 226 *S. maltophilia* isolates cultured
- Of these, 66 (2.4%) patients with 67 unique initial isolates were included
- 9 of the 66 patients had subsequent cultures yielding 26 unique serial isolates; 22 from San Antonio (SAMMC) and 4 from the National Capital region (NCC)
- All except for 2 initial isolates from SAMMC had unique PFGE patterns

Table 1. Antimicrobial Susceptibility Percentages in Initial and Serial Isolates

	No.	Ceftazidime	Levofloxacin	Minocycline	Tic-Clav	TMP-SMX	Ciprofloxacin*	Moxifloxacin*	Tigecycline*
Initial Isolates N (%)	67	28 (42)	55 (82)	67 (100)	45 (67)	66 (99)	19 (28)	65 (97)	58 (87)
Serial Isolates N (%)	26	1 (4)	8 (31)	26 (100)	8 (31)	21 (81)	2 (8)	23 (88)	6 (23)

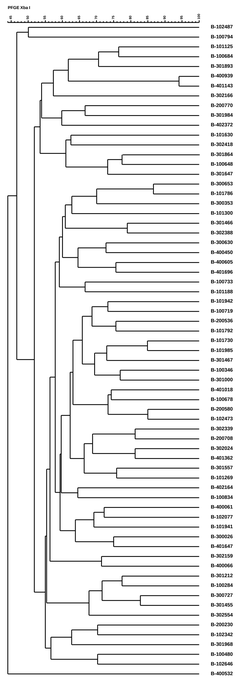
*Susceptibility defined for ciprofloxacin, moxifloxacin, and tigecycline by MIC ≤ 2, ≤ 4, and ≤ 2 respectively based on values used in published literature

Results (cont.)

Table 2. Comparison of Susceptible and Non-Susceptible Initial *S. maltophilia* Isolates

	Susceptible No (%) N=19	Non-susceptible* No (%) N=48
Culture Facility		
LRMC	9 (47)	17 (35)
NCC	6 (32)	22 (46)
SAMMC	4 (21)	9 (19)
Infection Type		
SSTI	6 (32)	17 (35)
Osteomyelitis	0	4 (8)
BSI	1 (5)	3 (6)
Sepsis	0 (0.0)	6 (13)
Pneumonia	3 (16)	1 (2)
Unspecified	9 (47)	17 (35.4)
Specimen Site		
Wound	7 (37)	35 (73)
Respiratory	9 (47)	8 (17)
Blood	2 (11)	3 (6)
Urine	0	1 (2)
Other	1 (5)	1 (2)
1st US Facility		
NCC	11 (69)	37 (80)
SAMMC	5 (31)	9 (19)
Prior Stenotrophomonas active[a] antimicrobial		
Fluoroquinolone	3 (16)	3 (6)
Tetracycline	1 (5)	3 (6)
TMP-SMX	0	1 (2)
Broad spectrum[b]	6 (32)	15 (31)
Composite ISS >25[T]	13 (68)	42 (88)
Blast Injury	18 (95)	46 (96)
Blast Type		
IED	16 (89)	43 (94)
Non-IED	2 (11)	3 (6)
Polymicrobial infection		
Yes	6 (32)	29 (60)
No	1(5)	6 (13)
Serial Isolates Recovered		
Yes	0	9 (19)
No	19 (100)	39 (81)

Dendrogram for 67 unique initial isolates



BSI, bloodstream infection; IED, improvised explosive device; ISS, injury severity score; LRMC = Landstuhl Regional Medical Center , NCC = National Capital Consortium (former Walter Reed Army Medical Center, National Navy Medical Center, and Walter Reed National Military Medical Center), SAMMC = San Antonio Military Medical Center; SSTI, skin and soft-tissue infection
*Non-susceptibility for 1 or more assessed antimicrobials (ceftazidime, levofloxacin, minocycline, ticarcillin-clavulanate, trimethoprim-sulfamethoxazole, ciprofloxacin, moxifloxacin, and tigecycline) Susceptibility defined for ciprofloxacin, moxifloxacin, and tigecycline by MIC ≤ 2, ≤ 4, and ≤ 2 respectively based on values used in published literature
TDenotes a p-value ≤ 0.05
[a] Steno active agents were defined as any fluoroquinolone, trimethoprim-sulfamethoxazole or tetracycline
[b] Broad spectrum agents were define as any 4th gen cephalosporin, anti-Pseudomonal penicillin, or carbapenem

Results (cont.)

Risk factors for resistance in initial isolates:
- Isolates were significantly more likely to be resistant to ceftazidime when there was documented levofloxacin resistance (p=0.001)
- There was significantly more ceftazidime resistance in isolates from patients with an ISS >25 (p = 0.02)
- Tigecycline resistance was seen more often in cultures obtained from SAMMC (p=0.04) and when agents active against *S. maltophilia* were employed prior to the 1st culture

Serial isolate demographics:
- Serial isolates were recovered more frequently when initial isolates demonstrated resistance (p=0.05) and were recovered more frequently from SAMMC (p<0.001)

Conclusions

- A high percentage of initial infecting *S. maltophilia* isolates show susceptibility to trimethoprim-sulfamethoxazole
- Levofloxacin and ciprofloxacin MICs were higher than expected for initial isolates and few serial isolates maintained low MICs, whereas a high percentage of initial and serial isolates maintained low moxifloxacin MICs
- Initial and serial *S. maltophilia* isolates were uniformly susceptible to minocycline
- Findings indicate that *S. maltophilia* resistance may be more likely with higher injury severity, longer post-injury duration to isolation, and serial collection of isolates
- Future analyses are needed to assess antibiotic exposure in relation to *S. maltophilia* resistance

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