Comparison of Monotherapy Versus Combination Therapy for *Stenotrophomonas maltophilia* Pneumonia Including Trimethoprim-Sulfamethoxazole-Containing and -Sparing Regimens

#2029

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ABSTRACT

Background: Trimethoprim-sulfamethoxazole (TS) is recommended for the treatment of *Stenotrophomonas maltophilia* infections due to high levels of *in vitro* susceptibility, but tolerability and increasing resistance may limit its utility. Studies have identified fluoroquinolones, tetracyclines, polymyxins, ceftazidime, and ticarcillin-clavulanate, as alternatives but clinical data are limited regarding the role of these agents and their role in combination therapy (CT).
Methods: Retrospective cohort study of adult patients at NewYork-Presbyterian Hospital with *S. maltophilia* pneumonia defined by CDC/NHSN criteria from 2009-2015. Patients were excluded if treatment was initiated > 5 days after the index culture (IC), they received <48 hours of therapy, resistance to both TS and levofloxacin were identified, or the patient died within 3 days of IC. The primary outcome was 30-day mortality. Secondary outcomes included clinical response (CR) at end of therapy (EOT), microbiologic eradication (ME) at EOT, and the development of resistance (DOR) within 90 days. Outcomes were compared between monotherapy (MT) and CT as well as TS-containing and -sparing regimens.
Results: 106 patients were included. Patients were 50% male with median age of 64 years and 47% were immunosuppressed. Compared to MT, patients with CT had higher median Charlson Comorbidity Index (2 vs. 4; p=0.014), higher median modified APACHE II scores (13 vs. 14; p<0.001), and were more often in severe sepsis/septic shock (38% vs. 62%; p=0.021). CT was associated with increased mortality (16% vs. 40%; p=0.012), decreased CR at EOT (72% vs. 49%; p=0.025), and increased DOR (26% vs. 65%; p=0.012) with no difference in ME. On multivariable analysis only the modified APACHE II score (p=0.001) and continuous renal replacement therapy (p=0.011) were associated with increased risk of mortality. No difference in mortality (22% vs. 29%; p=0.547), CR (56% vs. 66%; p=0.404), ME (63% vs. 72%; p=0.455), or DOR (52% vs. 37%; p=0.467) was identified between TS-sparing (n=41) and TS-containing (n=65) regimens.
Conclusion: Combination therapy for *S. maltophilia* pneumonia did not improve outcomes and outcomes may be driven more by severity of illness than susceptible drug therapy. No differences were identified for TS-containing or -sparing regimens. Additional data are needed to identify optimal therapy.

BACKGROUND

- *Stenotrophomonas maltophilia* is an increasingly more common cause of nosocomial infection[1]
- A known colonizer of the respiratory tract, this opportunistic pathogen causes significant morbidity and mortality in debilitated patients[1-2]
- Treatment options for *S. maltophilia* infections are limited by the intrinsic resistance to several classes of antimicrobials
- Trimethoprim-sulfamethoxazole (TS) has long been considered the drug of choice due to high rates of *in vitro* susceptibility, but treatment is limited by toxicity as well as increasing rates of resistance[3]
- *In vitro* activity against *S. maltophilia* has been demonstrated for fluoroquinolones, tetracyclines, ceftazidime, ticarcillin-clavulanate, and polymyxins[4-6]
- There is limited clinical evidence available comparing these alternative agents to TS and no clinical evidence on their use as part of combination therapy

METHODS

Study Design:
- Retrospective chart review at NewYork-Presbyterian/Columbia University Irving Medical Center, a 750-bed academic medical center in New York, NY
- Inclusion criteria:
  - Adult patients (at least 18 years of age) with *S. maltophilia* pneumonia defined by CDC/NHSN criteria treated with TS, levofloxacin, minocycline, polymyxin B, ceftazidime, or ticarcillin/clavulanic acid from 2009 to 2015[7]

METHODS (cont.)

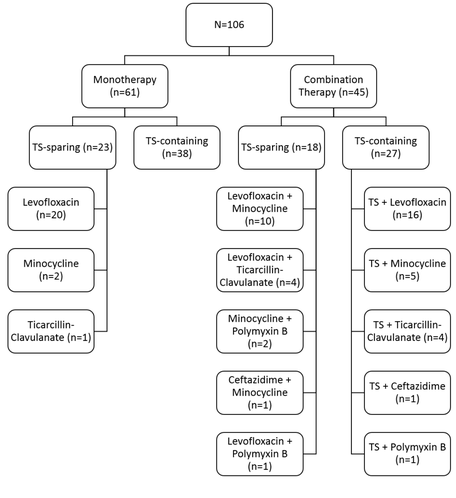
- Exclusion criteria:
  - Treatment initiated >5 days after the index culture
  - <48 hours of targeted therapy
  - Microbiologic resistance to both TS and levofloxacin
  - Death within 3 days of index culture.

Outcomes:
- Primary: mortality within 30 days of index culture
- Secondary: clinical response at end of therapy, development of microbiologic resistance to any of the agents used within 90 days of the end of therapy
- Outcomes were compared between subjects treated with monotherapy and combination therapy as well as TS-containing and -sparing regimens.

Statistical analysis:
- Univariate analysis was performed using Chi-squared or Fisher's exact test for categorical variables and Student's t test or the Mann-Whitney U test for continuous variables, as appropriate
- A multivariable analysis was conducted to identify independent predictors of mortality
- All p-values ≤0.05 were considered significant
- Performed using IBM SPSS Statistics, version 23

RESULTS

Figure 1: Enrollment



RESULTS (cont.)

Table 1: Demographics and Clinical Characteristics

	Monotherapy (n=61)	Combination Therapy (n=45)	p-value
Age, median (IQR), years	65 (50,76)	63 (49,75)	NS
Male, n (%)	27 (44)	26 (58)	NS
Time to index culture, median (IQR), days	8 (4,16)	16 (5,24)	0.047
Length of stay, median (IQR), days	28 (17,43)	41 (22,78)	0.024
Length of stay after index culture, median (IQR), days	17 (12,24)	23 (12,35)	NS
ICU within 48 hours of index culture, n (%)	44 (72)	40 (89)	NS
Charlson comorbidity index, median (range)	2 (0-12)	4 (0-13)	0.014
mAPACHE II[a,8-9], median (IQR)	13 (10,15)	14 (13,19)	<0.001
Immunocompromised[b], n (%)	24 (39)	26 (58)	NS
Antibiotic exposure in the previous 3 months, n (%)	59 (97)	45 (100)	NS
Mechanical ventilation at the time of index culture, n (%)	45 (74)	33 (73)	NS
Concurrent infection, n (%)	46 (75)	33 (73)	NS
Continuous renal replacement therapy, n (%)	9 (15)	12 (27)	NS
Hemodialysis, n (%)	2 (3)	4 (9)	NS
Severe sepsis or septic shock[c], n (%)	23 (38)	28 (62)	0.021
TS-containing therapy, n (%)	38 (62)	27 (60)	NS
Minocycline-containing therapy, n (%)	2 (3)	20 (44)	<0.001

NS=not significant; [a] Modified acute physiology and chronic health evaluation; [b] Immunocompromised defined as hematologic malignancy within 1 year of culture, other malignancy within 1 year of culture, chemotherapy within 1 year of culture, HIV, equivalent of 20 mg/day of prednisone for ≥14 days 30 days prior to culture, solid organ transplant, bone marrow transplant, neutropenia, or immunosuppressant therapy; Severe sepsis or septic shock defined as sepsis-induced tissue hypoperfusion or organ dysfunction

Figure 2: Treatment Outcomes

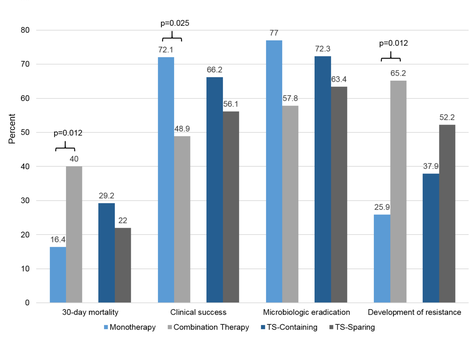


Table 2: Predictors of 30-day Mortality

Characteristic	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Combination Therapy	3.4 (1.4-8.4)	0.008	1.4 (0.5-4.2)	NS
mAPACHE II	1.3 (1.2-1.5)	0.001	1.3 (1.1-1.5)	0.001
Immunocompromised	2.6 (1.1-6.3)	0.037	1.7 (0.6-5.1)	NS
Continuous Renal Replacement Therapy	5.8 (1.1-6.3)	0.037	4.6 (1.4-14.6)	0.011
TS-Containing Regimen	1.5 (0.6-3.7)	0.409	2.3 (0.7-7.2)	NS

CONCLUSIONS

- This retrospective chart review did not find combination therapy to improve patient outcomes in the treatment of *S. maltophilia* pneumonia
- It is possible that disease severity plays a larger role in determining a patient's response to therapy than the specific regimen chosen
- Combination therapy may be associated with more development of resistance
- There were no statistically significant differences in outcomes for TS-sparing and -containing regimens
- TS-sparing regimens may be potential treatment alternatives for patients who are allergic to or cannot tolerate TS
- Limitations in this study included the retrospective and non-randomized design, significant differences in the monotherapy and combination therapy groups in severity of illness scores, heterogeneity of combination regimens, uncontrolled antimicrobial dosing, and a lack of adverse event reporting

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