

## Dueling Antibiotics: Should dual antibiotic therapy be considered for *Stenotrophomonas maltophilia* infections

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## What is it?

- ***Stenotrophomonas maltophilia*** (*S. maltophilia*)
  - “Steno”
  - Aerobic, non-fermentative, gram negative bacilli
  - Opportunistic bacteria
  - Adheres to foreign material and creates biofilm
  - Ubiquitous
    - Found in: soil, water, animals, plants, and **hospital equipment**



## What does it cause?

- Colonization vs. Infection
- Pneumonia
- Bacteremia
- Other less common infections:
  - Meningitis
  - Ocular infection
  - Mastoiditis
  - Endocarditis
  - Peritonitis
  - Urinary tract infection
  - Soft tissue infection
  - Wound infection

Stenotrophomonas Maltophilia, UpToDate Accessed March 3, 2014

## Who is at risk?

- Admission to an ICU
- Mechanical ventilation
- Central venous catheters
- Broad spectrum antibiotics use
- Neutropenia
- Recent surgery
- Trauma
- HIV infection
- Malignancy
- Cystic fibrosis

Journal of Hospital Infection. 2004;57:1-7.

## What therapies are effective?

Published Breakpoints	Other Agents
<ul style="list-style-type: none"> <li>• <b>Co-trimoxazole (TMP-SMX)</b></li> <li>• <b>Minocycline</b></li> <li>• <b>Ticarcillin / Clavulanate</b></li> <li>• Levofloxacin</li> <li>• Ceftazidime</li> <li>• Chloramphenicol</li> </ul>	<ul style="list-style-type: none"> <li>• Combination therapy</li> <li>• Moxifloxacin</li> <li>• Tigecycline</li> <li>• Rifampin</li> <li>• Polymyxins</li> </ul>

\*Based on Clinical and Laboratory Standards Institute

Stenotrophomonas Maltophilia, UpToDate Accessed March 3, 2014  
 Eur J Clin Microbiol Infect Dis. 2007;26:229-37.

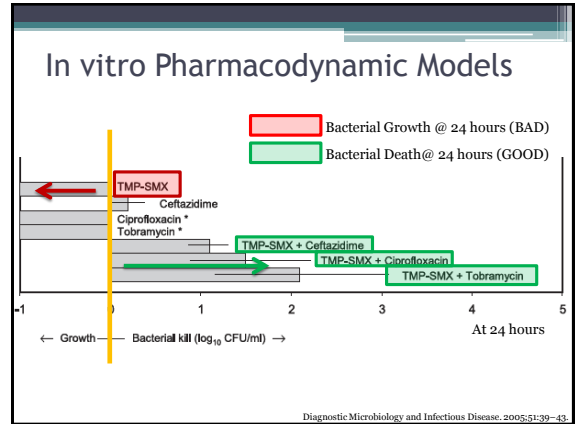
## Why is it difficult to target?

- Intrinsic and acquired resistance mechanisms
  - Inducible  $\beta$ -lactamases
  - Penicillinase
  - Cephalosporinase
  - Aminoglycoside acetyl-transferase
  - Target modifications
  - Efflux pumps

Eur J Clin Microbiol Infect Dis. 2007;26:229-37.

### Why Combine Therapies?

Therapy	Mechanism	Effect
TMP-SMX	Anti-metabolite	Static
Minocycline	Inhibit protein synthesis	Static
Ticarcillin / Clavulanate	Inhibit cell wall synthesis	Cidal
Ceftazidime	Inhibit cell wall synthesis	Cidal
Ciprofloxacin	Inhibit topoisomerases	Cidal
Chloramphenicol	Inhibits protein synthesis	Static



<b>P</b>	In a patient a <i>S. maltophilia</i> infection				
<b>I</b>	Combination antibiotics				
<b>C</b>	Monotherapy				
<b>O</b>	<table border="1"> <tr> <td>Efficacy</td> <td>Mortality Time to resolution of symptoms Hospital length of stay</td> </tr> <tr> <td>Safety</td> <td>SAE Withdrawals due to ADR Total ADRs</td> </tr> </table>	Efficacy	Mortality Time to resolution of symptoms Hospital length of stay	Safety	SAE Withdrawals due to ADR Total ADRs
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<b>Database</b>	EMBASE, Pubmed, IPA, Cochrane Library, clinicaltrials.gov
<b>Search Terms</b>	Stenotrophomonas maltophilia, synerg*, Combination therapy, drug combination
<b>Results</b>	<ul style="list-style-type: none"> <li>•0 SR</li> <li>•0 RCT</li> <li>•0 Cohort</li> <li>•1 Prospective Surveillance</li> <li>•1 Systematic Review of Case Reports / Series</li> <li>•9 Editorials</li> <li>•14 In-vitro studies</li> </ul>

Prospective Surveillance (PS)	Systematic Review of Cases (SRC)
<p><b>Bacteremia Due to <i>S. maltophilia</i>: A Prospective, Multicenter Study of 91 Episodes</b></p> <p>Clinical Infectious Diseases, 1996;22:508-12.</p>	<p><b>Therapeutic options for <i>S. maltophilia</i> infections beyond co-trimoxazole: a systematic review</b></p> <p>Journal of Antimicrobial Chemotherapy, 2008;62:889-94.</p>

### PS - Muder et al.

<b>Intent</b>	In a patient with <i>S. maltophilia</i> bacteremia: <ol style="list-style-type: none"> <li>1. Define the spectrum of illness</li> <li>2. Identify the clinical determinants of outcome</li> <li>3. Assess the impact of antimicrobial therapy on survival</li> </ol>
<b>Design</b>	Multicentre, Prospective surveillance for invasive <i>S. maltophilia</i> bacteremia
<b>Population</b>	91 patients 66 already hospitalized 55 were <i>S. maltophilia</i> alone 8 were TMP-SMX resistant

Clinical Infectious Diseases, 1996;22:508-12.

### PS - Results - Severity

Based on 55 patients with bacteremia due to *S. maltophilia* alone

Factor	No. of patients who died/total no. with indicated factor (%)	No. of patients who died/total no. without indicated factor (%)	P value
Hematologic malignancy	14/32 (44)	2/23 (9)	.005
Organ transplantation	7/11 (64)	9/44 (20)	<.01
Neutropenia	12/26 (46)	4/29 (14)	<.01
Immunosuppressive therapy	16/45 (36)	0/10 (0)	<.01
Severity score of >4	7/11 (64)	9/44 (20)	<.01

#### Severity Scoring

1. Temperature
2. Hypotension
3. Altered mental status
4. Need for ventilator support

Clinical Infectious Diseases, 1996;22:508-12.

### PS - Results - 14 day Mortality

Based on 55 patients with bacteremia due to *S. maltophilia* alone

Therapy	WITH use of Drug	WITHOUT use of Drug
TMP-SMX	24%	34%
3 <sup>rd</sup> Generation Cephalosporin	10%	40%
Extended spectrum Penicillin	20%	32%

#### 14 day Mortality with:

None of the above classes	55%
Only one of the above classes	31%
More than one of the above classes	11%

Clinical Infectious Diseases, 1996;22:508-12.

### PS - Evaluation

#### Major Limitations

- **Prospective Surveillance**
  - Hypothesis generating
  - Small number of cases
- **Poor definitions**
  - Specific antibiotics
  - Specific doses used
  - Specific combinations
- **Outcomes**
  - No association between illness and antibiotic used
  - No association between mortality and appropriate antibiotic use

### PS - Bottom Line

In patients with bacteremia due to *S. maltophilia* alone, **mortality** may be:

1. ↑ if patient has a **temperature, hypotension, altered mental status** and **ventilator support**
2. ↓ with use of any **TMP-SMX, 3<sup>rd</sup> generation Cephalosporin, extended spectrum Penicillin** alone or in combination

Prospective Surveillance (PS)	Systematic Review of Cases (SRC)
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### SCR - Falagas et al.

<b>Question</b>	Beyond TMP-SMX, what alternative antibiotic agents may be used for the treatment of <i>S. maltophilia</i> ?
<b>Search</b>	PubMed and Scopus
<b>Inclusion</b>	<ol style="list-style-type: none"> <li>1. No TMP-SMX use</li> <li>2. True infection</li> <li>3. Systemic therapy</li> </ol>
<b>Cases</b>	49
<b>Outcomes</b>	Survival

Journal of Antimicrobial Chemotherapy, 2008;62:889-94.

### SCR - Results

Therapy	Cases	Outcome
<b>Ciprofloxacin</b>	<b>12</b>	12 cured
<b>Ciprofloxacin in Combination</b>	<b>8</b>	6 cured / improvement <b>2 died (combined with Amikacin)</b>

Antibiotics combined with Amikacin, Ceftazidime, Chloramphenicol, Gentamicin, Piperacillin, Ticarcillin/clavulanate, Tobramycin

Journal of Antimicrobial Chemotherapy, 2008;62:889-94.

### SCR - Results

Therapy	Cases	Outcome
<b>3<sup>rd</sup> Generation Cephalosporin</b>	<b>6</b>	5 cure / improvement <b>1 death (Ceftazidime)</b>
<b>3<sup>rd</sup> Generation Cephalosporin in Combination</b>	<b>6</b>	5 cure / improvement <b>1 death (Combined Ceftriaxone, Ceftazidime with Tobramycin)</b>

Antibiotics combined with Amikacin, Ampicillin, Ciprofloxacin, Netilmicin, or Tobramycin

Journal of Antimicrobial Chemotherapy, 2008;62:889-94.

### SCR - Results

Therapy	Cases	Outcome
<b>Ticarcillin in Combination</b>	<b>1</b>	1 cure
<b>Ticarcillin / Clavulanate</b>	<b>3</b>	2 cure <b>1 died</b>
<b>Ticarcillin / Clavulanate in Combination</b>	<b>2</b>	1 cure <b>1 died (Combined with Amikacin)</b>

Antibiotics combined with Amikacin, Teicoplanin, or Tobramycin

Journal of Antimicrobial Chemotherapy, 2008;62:889-94.

### SCR - Evaluation

Major Limitations
<ul style="list-style-type: none"> <li>• <b>Case series</b> <ul style="list-style-type: none"> <li>• Hypothesis generating</li> <li>• Publication bias</li> </ul> </li> <li>• <b>Search</b> <ul style="list-style-type: none"> <li>• Not exhaustive</li> </ul> </li> <li>• <b>Population</b> <ul style="list-style-type: none"> <li>• Heterogenous ages</li> <li>• Heterogenous infections</li> </ul> </li> </ul>

### SCR - Bottom Line

In patients who are unable to receive TMP-SMX, **Ciprofloxacin, Ceftazidime, Ceftriaxone, and Ticarcillin/Clavulanate**, alone or in combinations may be effective therapies

### Potential Therapeutic Algorithm

- *S. maltophilia* therapy:
  - Colonized or Infection
    - Find source - Remove/replace catheters
  - Consider monotherapy as first line in uncomplicated infection:
    - TMP-SMX
    - Unable to tolerate: minocycline

## Potential Therapeutic Algorithm

- Critically ill - consider 4 points of severity
  1. Temperature
  2. Hypotension
  3. Altered mental status
  4. Need for ventilator support
- Consider TMP-SMX + Ceftazidime
- Unable to tolerate: Ceftazidime + Ciprofloxacin