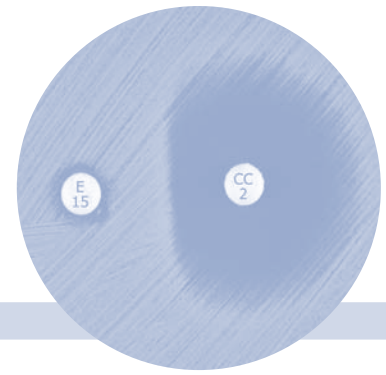


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Study of the Month

A five-day course of nitrofurantoin is shown to be microbiologically and clinically equivalent to the standard three-day course of TMP/SMX.

Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med* 2007; 167(20): 2207-2212.

Review of the Month

A comprehensive summary of the current state of knowledge regarding *Bacteroides* species, the most predominant anaerobes in the GI tract.

Wexler HM. *Bacteroides*: the good, the bad, and the nitty-gritty. *Clin Microbiol Rev* 2007; 20(4): 593-621.

Quote of the Month

"A fool with a plan can outsmart a genius with no plan."

—T. Boone Pickens

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Stenotrophomonas maltophilia: A Treatment Challenge

Introduction

Stenotrophomonas maltophilia is a non-lactose fermenting, oxidase-negative motile Gram-negative bacillus. First described in 1960 and named *Pseudomonas maltophilia*, it underwent a name change in 1983 to *Xanthomonas maltophilia*. Recognition of significant differences from other xanthomonads led to reclassification into the newly created genus *Stenotrophomonas*.¹ *S. maltophilia* is an environmental organism found in water, soil, and on plants. It has been isolated from oxygen humidifier water reservoirs in ambulances, disinfectants, ice-making machines, tracheal suction catheters, a cardiopulmonary bypass pump, "sterile" water, and the hands of hospital staff.²

S. maltophilia infection was a relatively rare occurrence in the pre-carbapenem era. A naturally occurring gene on the bacterial chromosome encodes a broad-spectrum carbapenemase (known as L1, discussed below), and it is likely that heavy use of imipenem/cilastatin (and other carbapenems) beginning in 1985 has helped foster the emergence of the organism.

S. maltophilia, an opportunistic pathogen, is associated with a variety of infections including pneumonia, bacteremia, endocarditis, central nervous system infection, urinary tract infection, and endophthalmitis.³ The single most important risk factor for *S. maltophilia* infection is the presence of a compromised immune system. Other risk factors include prior broad-spectrum antibiotic therapy, extended hospitalization, catheterization, and admission to an intensive care unit.² *S. maltophilia* has been isolated with increasing frequency from the lung secretions of patients with cystic fibrosis.⁴ There is mounting evidence that clinical outcome, including mortality risk, is dependent on appropriate antibiotic selection.⁵⁻⁷

In vitro susceptibility

A striking feature of *S. maltophilia* is its inherent resistance to many commonly used antibiotics. Sader and Jones collected 2,076 strains of *S. maltophilia* from 1997-2003 as part of the worldwide SENTRY Antimicrobial Surveillance Program.⁸ Their data are summarized in Table 1. Trimethoprim/sulfamethoxazole (TMP/SMX) was the most active drug tested; 95.3% of strains were susceptible according to Clinical and Laboratory Standards Institute (CLSI) breakpoints established for non-Enterobacteriaceae. 55.7% of the strains were susceptible to ticarcillin/clavulanate, compared to 20.1% for piperacillin/tazobactam. Ceftazidime was the most active cephalosporin tested; 52.9% of isolates were susceptible. 86.1% of the isolates were susceptible to levofloxacin whereas only 30.9% were susceptible to ciprofloxacin. Activity of aztreonam and the aminoglycosides (gentamicin, tobramycin, and amikacin) was uniformly poor.

The polymyxins are cyclic polypeptides that damage bacterial cell membranes, causing leakage of cellular contents and cell death. Colistin (polymyxin E) differs from polymyxin B by a single phenylalanine residue. The polymyxins have largely been replaced by drugs that are less toxic and pharmacokinetically superior, although they have enjoyed a recent resurgence due to the emergence of resistant bacteria. Unfortunately, their role in the treatment of *S. maltophilia* appears to be limited. Resistance is generally greater than that observed in *Pseudomonas aeruginosa*.⁹ In one study, all the isolates of *S. maltophilia* tested were resistant to colistin.¹⁰

Stenotrophomonas maltophilia: A Treatment Challenge (continued)

Mechanisms of antibacterial resistance

S. maltophilia possesses at least two inducible β -lactamases, L1 and L2, encoded by genes located on the bacterial chromosome. L1 is a tetrameric broad-spectrum zinc-dependent metallo- β -lactamase (Bush group 3) that can hydrolyze all β -lactam antibiotics except monobactams (aztreonam) and is not inhibited by clavulanate. L2 is a serine-based cephalosporinase (Bush group 2e) that also hydrolyzes penicillins and aztreonam; L2 is inhibited by clavulanate and, to a lesser extent, by the other β -lactamase inhibitors (sulbactam and tazobactam).^{11, 12} There is heterogeneity among the L1 and L2 β -lactamases produced by *S. maltophilia*; in isoelectric focusing studies, 17 isolates of *S. maltophilia* produced seven different types of metallo- β -lactamases and at least eight different types of serine-based β -lactamases.¹³

Other important mechanisms of resistance in *S. maltophilia* include production of aminoglycoside-modifying enzymes, target site alteration (e.g., ribosomal mutations), reduced permeability of the outer membrane, and multidrug efflux pumps.

A biofilm is a structured community of bacterial cells enclosed in an exopolysaccharide matrix produced by the cells and adherent to an inert surface. *S. maltophilia* is capable of forming biofilms on catheters and other prosthetic surfaces (such as heart valves), a property that aids in defense against antimicrobial agents.¹²

Trimethoprim/sulfamethoxazole (TMP/SMX)

TMP/SMX is bacteriostatic *in vitro* against most isolates of *S. maltophilia*.¹⁴ More important, there is a conspicuous lack of published randomized controlled trials establishing its clinical efficacy. Nevertheless, TMP/SMX is generally considered the drug of first choice for infections caused by *S. maltophilia* based mainly on *in vitro* susceptibility and case reports.

The optimum dose of TMP/SMX for a serious infection due to *S. maltophilia* has not been established, but a suggested dose can be inferred from serum concentration data. Administration of TMP/SMX at a dose of 12-15 mg/kg/day (TMP component) produces maximum trimethoprim serum concentrations of 5-10 μ g/ml; increasing the dose to 20 mg/kg/day (TMP component) achieves maximum trimethoprim serum concentrations of 13.6 μ g/ml.¹⁵ Most isolates of *S. maltophilia* will be inhibited at these concentrations (see Table 1). Therefore, a starting TMP/SMX dose of 15 mg/kg/day (TMP component) seems reasonable.

S. maltophilia can acquire resistance through integrons, transposons, and plasmids.⁹ Recent data suggest that resistance to TMP/SMX among *S. maltophilia* is increasing, although the specific mechanism has not been thoroughly investigated. In a multicenter study of 842 strains of *S. maltophilia* collected from 1997-1999, rates of resistance to TMP/SMX were 2-10%. More recent studies have reported resistance rates as high as 58%.¹⁶ The bacteriostatic activity of TMP/SMX, increasing resistance rates, and reports of suboptimal outcomes have fueled

consideration of combination antibiotic regimens against *S. maltophilia* based primarily on *in vitro* synergy testing (see below).

β -lactam/ β -lactamase inhibitors

As discussed above, naturally occurring resistance mechanisms in *S. maltophilia* limit the therapeutic usefulness of β -lactam antibiotics, although there are notable exceptions. Ticarcillin-clavulanate is generally considered a second-line option for treatment of *S. maltophilia* infection, particularly in patients who cannot tolerate TMP/SMX.¹² The activity of ticarcillin-clavulanate is consistently superior to other β -lactam/ β -lactamase inhibitors such as piperacillin-tazobactam and ampicillin-sulbactam, for reasons that are not entirely clear.^{3, 17} In one study, ticarcillin was hydrolyzed less efficiently by L1 than piperacillin; in addition, tazobactam was found to be a good substrate for the enzyme, being hydrolyzed more efficiently than imipenem.¹⁸ L2 is more susceptible to inhibition by clavulanate than by sulbactam or tazobactam, as mentioned above. Finally, it has been suggested that strains of *S. maltophilia* susceptible to ticarcillin-clavulanate produce relatively little L1, whereas resistant strains produce relatively more.¹⁹

Cephalosporins

Among the cephalosporins (including ceftobiprole²⁰), ceftazidime exhibits the greatest activity against *S. maltophilia* (Table 1). However, there is considerable variability among susceptibility studies; Vartivarian et al. found only 15% of 130 isolates of *S. maltophilia* to be susceptible to ceftazidime.¹⁵ Moreover, the activity of ceftazidime has declined steadily since 1981, when 76% of 70 strains of *S. maltophilia* in one study were susceptible.¹ Therefore, ceftazidime cannot be recommended as a monotherapy alternative for treatment of *S. maltophilia*, although it may have a role in combination therapy (see below).

Fluoroquinolones

In contrast to TMP/SMX, levofloxacin and the 8-methoxy fluoroquinolones (gatifloxacin, moxifloxacin) tend to be rapidly bactericidal against *S. maltophilia*.¹⁴ The *in vitro* activity of levofloxacin is superior to that of ciprofloxacin, as seen in Table 1 and documented in several investigations.^{21, 22} The MIC₅₀ and MIC₉₀ of moxifloxacin for 109 isolates of *S. maltophilia* were 0.06 μ g/ml and 0.5 μ g/ml, respectively.²³ These data suggest a possible role for newer fluoroquinolones, alone or in combination, in the treatment of *S. maltophilia*. However, published clinical experience is essentially nonexistent at this time.

Tetracyclines and glycylicyclines

Minocycline and doxycycline exhibit good activity against *S. maltophilia*. Tigecycline, a semisynthetic glycylicycline derived from minocycline, demonstrated promising activity in 131 isolates of *S. maltophilia* (MIC₅₀ 1 μ g/ml, MIC₉₀ 2 μ g/

Stenotrophomonas maltophilia: A Treatment Challenge (continued)

ml, range 0.12 – 8 µg/ml).¹² As with the fluoroquinolones, clinical experience with these agents for *S. maltophilia* is extremely limited.^{3, 16}

Combination therapy

Many combinations of antimicrobial agents have been examined for the presence of *in vitro* synergy against *S. maltophilia*. Because of strain-to-strain variation, differing methodologies for assessing synergy, and the wide variety of antibiotic combinations tested, firm conclusions are difficult to draw.³ Nevertheless, a few of the more relevant combinations tested deserve mention.

Given that aztreonam is not a substrate of L1 (as discussed above) and clavulanate inhibits L2, the combination of aztreonam plus ticarcillin-clavulanate seems particularly logical. Krueger et al. showed that the addition of aztreonam to ticarcillin-clavulanate results in enhanced activity compared to ticarcillin-clavulanate alone, using three different testing methods.²⁴ In earlier work, Bellido et al. found the combination of aztreonam plus ticarcillin-clavulanate to be two- to four-fold more active than aztreonam plus clavulanate.²⁵

Other combinations demonstrating *in vitro* synergy include TMP/SMX plus ticarcillin-clavulanate,^{26, 27} ticarcillin-clavulanate plus ciprofloxacin,^{26, 27} ticarcillin-clavulanate plus doxycycline,²⁶ ceftazidime plus ciprofloxacin,^{27, 28} ceftazidime plus levofloxacin,²⁹ colistin plus rifampin,³⁰ and colistin plus TMP/SMX.³⁰ A few combinations that seem promising, such as TMP/SMX plus levofloxacin (or moxifloxacin), have not yet been investigated.

In an *in vitro* pharmacodynamic infection model, TMP/SMX at “clinical” doses (10 mg/kg/day, TMP component) was studied alone and in combination with one of four drugs (ceftazidime, ciprofloxacin, gentamicin, or tobramycin) against four isolates of *S. maltophilia*. The isolates were susceptible to TMP/SMX and at least one of the four other drugs. All antibiotic combinations were more active than monotherapy as assessed by reduction in bacterial colony count at 24 and 48 hours.³¹

The key question is whether *in vitro* synergy translates into *in vivo* benefit. Supportive data, as might be expected, are sparse and far from conclusive. Muder et al. identified 91 immunocompromised patients with *S. maltophilia* bacteremia in a prospective, multicenter, observational study. Mortality was 11% in patients who received any combination of TMP/SMX, extended-spectrum penicillin, or third generation cephalosporin compared to 31% in patients who were treated with monotherapy. Most patients had an underlying malignancy, had received immunosuppressive therapy, and had an indwelling vascular catheter.³²

The remaining published data supporting combination antibiotic therapy for *S. maltophilia* are limited to case reports. For example, Landrum et al. successfully treated a patient with refractory vertebral osteomyelitis due to

S. maltophilia with the combination of TMP/SMX (2 DS tablets TID) and ticarcillin-clavulanate (18.6 grams per day by continuous infusion) for six weeks. The patient required intravenous desensitization with TMP/SMX at the initiation of treatment. Monotherapy with TMP/SMX was continued for an additional six months.¹⁴ In another report, a patient with *S. maltophilia* endocarditis associated with a central venous catheter was treated initially with intravenous TMP/SMX (10 mg/kg/day TMP component) and cefepime 2 grams Q12H. Ciprofloxacin was substituted for the TMP/SMX after the patient developed hyperkalemia on or about day 18 of therapy. Ciprofloxacin plus cefepime was administered for six additional weeks. Thirty months after treatment, no subsequent bloodstream infections had occurred.³³

Summary

S. maltophilia is an opportunistic pathogen of increasing significance. Emerging data emphasize the importance of appropriate therapy; however, natural and acquired antibiotic resistance mechanisms render treatment of *S. maltophilia* infection more challenging than ever. There is general agreement that TMP/SMX is the agent of first choice, and ticarcillin-clavulanate is a reasonable second-line option. However, the precise role of other drugs active against *S. maltophilia* is very difficult to state with certainty. Many drug combinations are synergistic *in vitro*, but specifically which combination is superior—and who should receive it—remains unestablished. There is a clear need for further clinical study, particularly in the immunocompromised host.

Table 1. *In vitro* susceptibility of *S. maltophilia*⁸

ANTIBIOTIC	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)	RANGE (µg/ml)
Amikacin	>32	>32	0.5 – >32
Aztreonam	>16	>16	≤0.12 – >16
Cefepime	16	>16	≤0.12 – >16
Ceftazidime	8	>16	≤2 – >16
Ceftriaxone	>32	>32	≤0.25 – >32
Ciprofloxacin	2	>2	≤0.25 – >2
Gentamicin	>8	>8	≤2 – >8
Imipenem	>8	>8	0.25 – >8
Levofloxacin	1	4	≤0.5 – >4
Meropenem	>8	>8	≤0.06 – >8
Piperacillin	>128	>128	≤1 – >128
Piperacillin/tazobactam	>64	>64	≤0.5 – >64
Polymyxin B*	2	8	≤1 – >8
Tetracycline	>8	>8	≤4 – >8
Ticarcillin/clavulanate	16	128	≤16 – >128
Tobramycin	>16	>16	0.25 – >16
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2

* isolates were collected in 2001–2003

Stenotrophomonas maltophilia: A Treatment Challenge (continued)

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