MAD-ID Newsletter

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MAD-ID
MAKING A DIFFERENCE IN INFECTIOUS DISEASES®

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In this issue

A Message from the MAD-ID Board of Directors

We hope all of you are doing well and are safe during this pandemic. It is unfortunate that MAD-ID had to cancel its annual meeting this year due to the current COVID-19 crisis. We wanted you to know that **we appreciate all of your work and dedication to antimicrobial stewardship efforts during the pandemic**.

Over the summer, the MAD-ID Annual Meeting Planning Committee has been planning the 2021 Meeting slated to be held May 19-22nd. The meeting will include many of the same topics and speakers which were slated for this year's meeting. The exact model for the meeting (in person, virtual or a combination of both) has not been decided but we will inform you as possible. Of course, a lot depends on how things are with the pandemic going into 2021. At this point, we are hoping and planning for a live meeting!

In the meantime, MAD-ID has been busy developing and delivering complementary continuing education webinars, moving forward with promoting our online training program, and continuing our partnerships and advocacy for antimicrobial stewardship. Please continue to follow MAD-ID for our Twitter announcements @MAD_ID_ASP, our Facebook page at https://www.facebook.com/madidasp/ and via our website at www.mad-id.org for upcoming programs and antimicrobial stewardship resources. We look for forward to seeing you in the near future!

MAD-ID 2020 Virtual Sessions are available online as Enduring CE content

MAD-ID held three virtual sessions featuring exceptional speakers and timely topics. If you missed the live sessions, the events are available online as enduring content.

The webinars are available on the MAD-ID online learning platform. After you log in, look for these sessions under the heading "MAD-ID Webinars 2020". For those who didn't catch them live, you can access the quiz and claim CE after completing the online webinars.

https://mad-idtraining.org/certification/login/index.php

Implementing the 2020 Vancomycin Guidelines: What Every Clinician Needs to Know	• Presented by Emily L. Heil, PharmD (University of Maryland Medical Center) Erin K. McCreary, PharmD (University of Pittsburgh Medical Center) • Enduring content available now!
Sepsis 2020	• Presented by Edward Septimus, MD (Texas A&M Medical School) and Mary Millard, MEd (International Patient Advocate Speaker) • Enduring content available now!
Guideline Updates: Community-Acquired Pneumonia and Asymptomatic Bacteriuria	• Presented by Thomas M. File, Jr., MD, MSc (Summa Health and Northeast Medical University) and Emily S. Spivak, MD, MHS (University of Utah College of Medicine) • Enduring content available after 9/25

New CE Webinar on HAP/VAP Coming Soon

Please join us for a free continuing pharmacy education webinar developed by Academy for Continued Healthcare Learning (ACHL) in collaboration with MAD-ID on Wednesday, October 7, 2020 from 12:30 to 2:00PM ET.

ACHL
ACADEMY for CONTINUED HEALTHCARE LEARNING

Applying Institutional Susceptibility Data in Treatment Decisions for HAP/VAP

This interactive webinar will feature expert faculty Jason Pogue, PharmD of the University of Michigan and James Lewis, PharmD of the Oregon Health & Science University

For more information and registration instructions see this URL: https://www.achlcme.org/MAD-ID-Education

Antibiotic Awareness Week is Nov 18th – 24th

Antibiotic Awareness Week is just around the corner, November 18th – 24th. Every year, antimicrobial stewardship programs use this as an opportunity to raise awareness of the importance of antibiotic, resistance, and stewardship.

Look for tips and resources from the Centers for Disease Control and Prevention and from the World Health Organization.

U.S. Antibiotic Awareness Week Resources
https://www.cdc.gov/antibiotic-use/week/index.html

World Antibiotic Awareness Week Resources
https://www.who.int/news-room/events/detail/2020/11/18/default-calendar/world-antimicrobial-awareness-week-2020

Antimicrobial Resistance Updates from PACCARB

On September 9-10, 2020, the U.S. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) held public meetings to address the impact of COVID-19 on antimicrobial resistance. Antimicrobial stewardship and resistance were discussed from a wide range of presenters representing national and global agencies, organizations, and healthcare institutions. Of note, past MAD-ID presenters Emily Heil and Arjun Srinivasan presented sessions, and Jason Newland and Elizabeth (Libby) Dodds-Ashley were sworn in as designated representatives for the Pediatric Infectious Diseases Society and Society of Infectious Diseases Pharmacists, respectively.

Read the full agenda, listen to the webcast, and find upcoming meetings at the PACCARB website:
https://www.hhs.gov/ash/advisory-committees/paccarb/meetings/index.html

Highlighted Virtual Abstracts from the Annual Meeting
insights from the MAD-ID Research Network

One of the usual highlights of the MAD-ID annual meeting is interacting with investigators at the live poster sessions. While we didn't have a chance to see each other this year, many MAD-ID members did share their findings by submitting abstracts that they have shared online at our website. https://mad-id.org/wp-content/uploads/2020/06/MAD-ID-2020-Approved-Abstracts-c-logo.pdf

Here are a few notable highlights.

(Abstract 36) Paula Politis and her colleagues at Summa Health shared their intervention to implement an algorithm for management of suspected urinary tract infections in home-bound adult patients. The service increased appropriate antibiotic use from 52% to 71%. They also observed reductions in emergency department visits and demonstrated high provider confidence with the intervention.

MAD-ID Research Network Grant Recipient

(Abstract 19) The team at Intermountain Healthcare described their experience with a drug recovery assistance service partnering with outpatient parenteral antimicrobial therapy in people who inject drugs. The collaborative service was associated with improvements in efficiency, length-of-stay, and cost.

(Abstract 16) Josh Eudy and colleagues from multiple institutions shared the results of a national survey of ambulatory antimicrobial stewardship practices. They identify important drivers for meeting the core elements of antimicrobial stewardship in outpatient settings, including dedicated pharmacist support and availability of institutional guidelines.

Keep up with the latest

It's easy to be overwhelmed with the pace of new information in infectious diseases and antimicrobial stewardship. Be sure to follow MAD-ID and our media partners to stay in touch.

- Follow MAD-ID on social media (now curated by the talented Helen Newland!) https://twitter.com/mad_id_asp and https://www.facebook.com/madidasp .

Or keep up with our media partners.

- Infectious Diseases Special Edition, https://www.idse.net/
- ContagionLive, https://www.contagionlive.com/

Review of *Stenotrophomonas maltophilia*

Continuing Education Activity

Authors: Shelbye Herbin, PharmD and Marco Scipione, PharmD, BCPS AQ-ID

Disclosures: Doctors Herbin and Scipione have no conflicts of interest to disclose relevant to this learning activity.

Learning Objectives:
At the end of this article, learners will be able to:

1. Describe common methods of resistance and virulence in *Stenotrophomonas maltophilia*
2. Select an appropriate treatment option for a patient with an infection caused by *Stenotrophomonas maltophilia*
3. Recognize new treatment options and synergistic combinations for the treatment of *Stenotrophomonas maltophilia*

Disclaimer: The information contained in this newsletter is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner. We are not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in any practice setting.

Background:
Stenotrophomonas maltophilia is an emerging nosocomial and opportunistic pathogen. It has been reclassified multiple times since its isolation in the 1940s. *S. maltophilia* was first known as *Bacterium bookeri*, followed by *Pseudomonas maltophilia*. The discovery of bacterial ribosomal ribonucleic acid homologies allowed the genus *Pseudomonas* to be divided into distinct groups including *Xanthomonas.* (1,2) The ability to perform polymerase chain reactions (PCR) to amplify 16s RNA helped differentiate *Xanthomonas from Stenotrophomonas*. (2,3) *S. maltophilia* is a Gram-negative, aerobic, glucose non-fermenting, motile bacillus that has a reported incidence of 7.1 to 37.7 cases/10,000 discharges (regarding nosocomial infections). This pathogen is associated with significant morbidity and mortality; crude mortality rates range from 24 up to 69%. (1) *S. maltophilia* can be found in different water sources and is also commonly found in soils and plant rhizospheres due to a preferred growth medium rich in sulfurated amino acids. It's most commonly isolated from the respiratory tract but has also been associated with urinary tract, bone, and bloodstream infections. Risk factors for infection with *S. maltophilia* may include admission in an intensive care unit (ICU), malignancy, immunosuppression, chronic respiratory diseases, or previous carbapenem use. (4, 5) Several risk factors for mortality have been identified and include malignancy and failure to remove central venous catheters. (1) Due to the intrinsic resistance profile and ability to sequester different genes of resistance, treatment options for *S. maltophilia* are limited.

Resistance and Virulence

Intrinsic resistance

S. maltophilia is a difficult organism to eradicate due to its intrinsic resistance to many classes of antibiotics (including carbapenems) in addition to its ability to sequester genes of resistance via horizontal transfer. *S. maltophilia's* intrinsic resistance to different antibiotics is thought to stem from its large genome that allows it to live in diverse environments. (1) These environments may harbor toxic compounds that only allow bacteria to survive if they have mechanisms to withstand or remove harmful compounds from their environment. Mechanisms of resistance that *S. maltophilia* express include low membrane permeability, beta-lactamases (including metallo-beta-lactamases), efflux pumps, antibiotic modifying enzymes, and antibiotic target site mutations such as quinolone resistance genes. (1)

Low membrane permeability can act synergistically with beta-lactamases by slowing down antibiotic entry into the periplasm and increasing enzymatic degradation in Gram-negative bacteria. (6) *S. maltophilia* has two inducible beta-lactamases, L1 and L2, that drive its intrinsic resistance to most beta-lactam agents. L1 is an Ambler class B3 metallo-beta-lactamase that can hydrolyze a multitude of beta-lactamases, including carbapenems, but is unable to hydrolyze aztreonam. Additionally, L1 is impervious to all beta-lactamase inhibitors. L2 is an Ambler class A cephalosporinase that exhibits resistance to extended spectrum beta-lactams and aztreonam, but it can be inhibited by beta-lactamase inhibitor such as clavulanic acid and avibactam. However, isolates that are resistant to combinations with clavulanic acid, such as ticarcillin-clavulanate, are increasingly common. (4)

Multidrug efflux pumps are a component of the genetic makeup of all bacteria. *S. maltophilia* utilizes several different classes of efflux pumps that allow it to be resistant to many different classes of antibiotics. Following the sequencing of the K279 strain of *S. maltophilia*, three superfamilies have been identified of which eight efflux pumps belong to the resistance-nodulation-cell division (RND) superfamily, four efflux pumps belong to the major facilitator superfamily (MFS), and two efflux pumps belong to the ATP-binding cassette (ABC) superfamily. (7)

Six of the eight RND efflux pumps have been identified and of those, four (SmeDEF, SmeIJK, SmeOP, and SmeY) have been shown to contribute to *S. maltophilia*'s vast resistant genome. SmeDEF and SmeVWX both mediate resistance to chloramphenicol and quinolones while SmeDEF is also responsible for resistance to tetracyclines and trimethoprim-sulfamethoxazole (TMP/SMX). SmeOP encodes for low susceptibility to aminoglycosides, doxycycline, and macrolides and SmeIJK offers additional resistance to the fluroquinolone levofloxacin when overexpressed. The additional RND efflux pumps, SmeABC and SmeVWX, do not contribute to intrinsic resistance but still amplify the resistance profile of *S. maltophilia*. (7) MacABCsm is one of the two ABC type efflux pumps that provide intrinsic resistance to aminoglycosides, macrolides, and polymyxins. The data on SmrA is less well known in regard to its intrinsic contributions; however, it does confer resistance to fluroquinolones and tetracyclines. A lesser studied class of efflux pumps, the MFS superfamily has four known efflux pumps, EmrCABsm, Smlt0032, MfsA, and SmtcrA, however its unclear how these contribute to resistance in *S. maltophilia*. (7)

N-acetyltransferases, or AACs, generally make modifications on the amino group which confers resistance to aminoglycosides that have amino groups, such as gentamicin, neomycin, and tobramycin. Intrinsic AAC in *S. maltophilia* was first described in 1978 and when the AAC (6')-Iz gene was deleted, the susceptibility increased for tobramycin and neomycin, and gentamicin. (8)

S. maltophilia also contains a chromosomally encoded *qnr* gene, Smqnr, which aids in its natural resistance to fluroquinolones. Gene expression has also been documented to be higher when it was plasmid encoded versus chromosomally encoded. Overexpression of the Sm*qnr* gene was followed by reduced susceptibility to fluroquinolones due to increased protection of DNA and DNA gyrase. (9)

Additional Virulence Factors

In addition to mechanisms that decrease susceptibility to antibiotics, *S. maltophilia* has additional virulence factors that allow it to adapt to an array of environments and colonize its host. These additional factors should be considered while treating patients because it may make eradication of the pathogen more difficult. Some of the virulence factors include the presence of flagella and pili, the production of biofilm, and ability to create small-colony variants. (1,10). Flagella and pili help mediate adherence to surfaces, such as host tissue, glass and plastic. Once adhered, *S. maltophilia* has the ability to form biofilms. This feature allows it to colonize items such as catheters, I.V lines, and tubing used for dialysis. Even contamination in sinks and drains has been reported. This feature gives more opportunities for *S. maltophilia* to infect or colonize patients. (1) Small colony variants (SCV) are phenotypically distinctive sub-populations that are slow growing and thought to arise from antibiotic pressure. SCV are clinically challenging because they may have decreased susceptibility to antibiotics, but they may be difficult to identify and *in vitro* susceptibilities may be difficult to obtain with current microbiology laboratory techniques. (10)

Treatment

Currently, there are no specific guidelines on the treatment of specific infections caused by *S. maltophilia*, but instead treatment is based off of local susceptibility (antibiograms), published *in vitro* data, and clinical expertise. Antibiotics with *in vitro* activity against *S. maltophilia* that have been used for treatment include ceftazidime, ticarcillin-clavulanate, TMP/SMX, fluoroquinolones (levofloxacin and ciprofloxacin), and minocycline. If no viable options are available then newer agents, in addition to synergic combinations, have shown promising *in vitro* data. (1)

Flouroquinolones

Flouroquinolones have *in vitro* activity and are bactericidal against *S. maltophilia* however, until more recently, clinical data supporting there use has been limited to case reports. Two recent studies have compared the effectiveness of TMP/SMX monotherapy versus fluroquinolone monotherapy. (11,12) The first study consisted of 98 patients with mostly pulmonary infections. Microbiological and clinical response data were evaluated at the end of treatment (EOT) for 35 patients who received TMP/SMX and 63 patients who received a fluroquinolone. Twenty-three of these patients were admitted in an ICU during the time of culture and the most common comorbidity was solid organ malignancy (39%). There was an overall microbiological cure rate of 63%, a clinical success rate of 55% and an in-hospital mortality rate of 24% in all patients. Both microbiological (65% vs. 62%, p=0.832) and clinical success (61% vs 52%, p=0.546) were similar in the TMP/SMX and fluroquinolone treatment groups, respectively. Clinical response at the end of treatment (EOT) was determined by improvement in all signs and symptoms of infection and no additional treatment was required. Microbiological cure was defined as a negative culture, from the same site as the original sample, at the EOT. In-hospital mortality was 20% for the TMP/SMX treatment group and 25% for the fluroquinolone group. Out of the 63 patients who received a fluroquinolone, 48 received levofloxacin and 15 received ciprofloxacin. Comparing levofloxacin with ciprofloxacin, the microbiological cure at EOT was 60% vs. 71%, the clinical success at EOT was 48% vs. 70%, and the in-hospital mortality was 31% vs. 7%, respectively. Of interest, there were a total of 75 (77%) patients with a polymicrobial infection with the most common Gram-negative organism isolated being *Pseudomonas aeruginosa*. The number of patients with a polymicrobial infection is a potential limitation to this study because it could have impacted outcomes. Additionally, it may not have been possible to distinguish whether these polymicrobial infections, including *S. maltophilia*, were a colonizer or true infection. (11)

The second study was a systematic review and meta-analysis of 7 retrospective cohort and 7 case-control studies which analyzed 663 patients. Of the 663 patients, 332 received TMP/SMX (50.1%) and 331 received fluroquinolones (49.9%). Levofloxacin was the most commonly used fluroquinolone (187/331, 56.6%) followed by ciprofloxacin (114/331, 34.4%). The pooled analysis showed similar effectiveness between the two treatment arms with an overall survival benefit with fluroquinolones (OR 0.62, 95% CI 0.39-0.99) over TMP/SMX. There was no significant difference between ciprofloxacin (OR 0.44, 95% CI 0.17-1.12), or levofloxacin (OR 0.78, 95% CI 0.48-1.26) when individually compared to TMP/SMX. However, the results should be interpreted with caution due to the lack of randomized controlled trials available to be included in this study. Additional limitations to this study include missing data and not being able to analyze patient-specific data, therefore, a pooled analysis could not be completed on adjusted values and confounding factors were not adjusted for. (12)

Minocycline

Minocycline has bacteriostatic *in vitro* activity against *S. maltophilia* but there is limited clinical data on its use in patients infected with *S. maltophilia*. A multicenter, observational study of minocycline for the treatment of non-pseudomonal Gram-negative bacteria at six US hospitals included 35 patients with *S. maltophilia.* Overall, 29 patients with *S. maltophilia* were evaluated for clinical and microbiological response. A majority of patients (24/29, 83%) were diagnosed with pneumonia and 18/24 (75%) experienced clinical cure or improvement. Microbiological response was documented as either microbiologic eradication or presumed eradication. Microbiologic eradication was defined as a negative bacterial culture from the original isolation site and presumed eradication was the absence of follow-up microbiological data in a patient with a clinical response of cure or improvement. In this study, five patients had *S. maltophilia* bacteremia and all experienced a positive clinical response. When assessing all non-fermenters who received combination therapy, the most common concomitant antibiotic was meropenem, followed by ceftazidime or cefepime. Therefore, even though minocycline demonstrated activity against *S. maltophilia,* most patients (20/29, 70%) received combination therapy with another non-minocycline agent which may have impacted clinical outcomes. (14)

Minocycline monotherapy has also been compared to TMP/SMX monotherapy in a retrospective analysis of 45 patients. *S. maltophilia* was most commonly isolated from sputum, followed by bronchoalveolar lavage and urine. There were 22 patients who received TMP/SMX and 23 patients who received minocycline. Overall mortality was 9%, which was comparable between the two groups. Treatment failure, defined as isolation within 30 days of the initial culture, was seen in 9/22 (41%) patients who received TMP/SMX and 7/23 (30%) patients who received minocycline. Treatment duration was significantly longer in patients who received minocycline as compared to TMP/SMX (13 days versus 7 days, p=0.009). A similar limitation in this study was inability to distinguish true infection from colonization. (13)

Additional Options

Examining resistance rates throughout a 10-year time frame (2008-2012) found 12.1% of *S. maltophilia* isolates to be resistant to TMP/SMX and 8.9% resistant to levofloxacin. However, with the global burden of *S. maltophilia* increasing the current rate of resistance may be even higher. (5, 16) As a result, clinicians may need to look into older agents, such as tigecycline, newly approved novel agents, or synergistic combinations if first line agents are no longer effective in patients.

Tigecycline is a glycylcycline that was approved in 2005 and it has activity against a range of Gram-positive and Gram-negative bacteria. Tigecycline was tested against 22,005 isolates from the SENTRY Antimicrobial Surveillance Program of which 362 were *S. maltophilia*. Broth microdilution susceptibility testing was performed according to CLSI methods and susceptibility ranged from 89.3% to 98.3% across the varying

participating regions with a breakpoint of ≤2 mg/L. The MIC_{50}/MIC_{90} for tigecycline for *S. maltophilia* was 0.5 and 2 mg/L, respectively. (17)

Newer tetracycline derivatives have also been recently added to the resistant Gram-negative armamentarium. Eravacycline and omadacycline are novel tetracyclines that can bypass common tetracycline resistance mechanisms, such as ribosomal protection and efflux resistance genes (20, 21). Omadacycline demonstrated *in vitro* activity against 315 *S. maltophilia* isolates that were collected for the 2016 SENTRY Antimicrobial Surveillance program. The MIC_{50} was 2 mg/L and the MIC_{90} was 8 mg/L for *S. maltophilia*. (20). In a three-year global surveillance study comparing eravacycline against comparators, 619 isolates of *S. maltophilia* were gathered. MICs were determined by CLSI broth microdilution. Eravacycline showed *in vitro* activity against *S. maltophilia* with an MIC_{50} of 1 mg/L and a MIC_{90} of 2 mg/L. (21)

Cefiderocol is a new injectable cephalosporin that utilizes the siderophore-iron complex pathway to cross the outer membrane of Gram-negative organisms. The *in vitro* activity of cefiderocol was compared to levofloxacin, minocycline, polymyxin B, and TMP/SMX against 37 *S. maltophilia* isolates that were not susceptible to levofloxacin and/or TMP/SMX. The MIC_{50} and MIC_{90} for cefiderocol were determined to be 0.125 and 0.5 mg/L, respectively. Nine of these isolates, with varying MICs, were selected for time-kill experiments. Out of these 9 isolates, 5 (55.5%) were susceptible to levofloxacin, 8 (88.9%) were susceptible to minocycline, 6 (66.7%) were intermediate to polymyxin B, and 3 (33.3%) were susceptible to TMP/SMX. Cefiderocol was bactericidal, defined as ≥3-log_{10} CFU/mL reduction at 24-hours from the starting inoculum, against 2/9 (22.2%) of the isolates.

Combination Therapy

Combining antibiotics to either increase the activity of one or both agents, or to restore susceptibility of an agent has been increasing in practice due to the emergence of MDR pathogens and results from *in vitro* analyses. Data from *in vitro* studies can be used in conjunction with clinical judgement in patients who may not have alternatives available. A large *in vitro* study conducted by the Cystic Fibrosis Referral Center from 1996 through 2001 analyzed 673 *S. maltophilia* isolates from Cystic Fibrosis centers throughout the United States to further look into synergistic combinations among antimicrobials. (23) Upon reviewing 10 different antimicrobial agents, synergy studies using checkerboard dilutions of pairs of antimicrobial agents tested at clinically achievable concentration were performed. Synergy and additive effects were defined by calculating the fractional inhibitory concentrations (FIC). A FIC of ≤0.5 was interpreted as synergistic and a FIC of > 0.5 to 1.0 was interpreted as additive. TMP/SMX coupled with ticarcillin-tazobactam was synergistic in 317/643 (47%) and additive in 124/673 (18%) of isolates. This was closely followed by ciprofloxacin and ticarcillin-tazobactam, which was synergistic in 296/673 (44%) and additive in 132/673 (20%) of isolates. (23) Synergy with colistin in combination with either tigecycline or rifampicin was tested both *in vitro* and in animal models compared to colistin alone. Both the combination with colistin and rifampicin and colistin and tigecycline were superior to monotherapy.The animal model analysis results indicated that colistin and rifampicin was more successful in the treatment of *S. maltophilia* than the colistin and tigecycline combination. This suggests that both pairs might be options in patients with difficult to treat *S. maltophilia* infections. (24) In another study, 252 patients were retrospectively evaluated comparing monotherapy with TMP/SMX, levofloxacin, ciprofloxacin, moxifloxacin, minocycline, ceftazidime or any combination of these. No difference was observed for the primary outcome of 7-day clinical response after controlling for immunocompromised state, polymicrobial pneumonia, and APACHE II scores. The most common combination therapy used was TMP/SMX with ciprofloxacin. However, overall there were more patients in the monotherapy group (N= 214) compared to the combination therapy group (N=38). (25) In vitro activity of cefiderocol in combination with TMP/SMX, levofloxacin, minocycline, or polymyxinB has also been evaluated in time-kill experiments. Cefiderocol acted synergistically, defined as ≥2-log_{10} CFU/mL difference between the combination and the most active

single agent alone, with 6/9 (66.7%) minocycline and TMP/SMX isolates, and with 5/9 (55.5%) polymyxin B isolates. (22) A listing of potential monotherapy agents with respective MIC data is located in Table 1. (17-22)

Table 1: MIC Distribution of Treatment Options for Multidrug Resistant *Stenotrophomonas maltophilia*

Drug	CLSI Category			Number of Isolates	MIC50 (mg/L)	MIC90 (mg/L)	MIC Range (mg/L)	Source Reference
	S	I	R					
Ceftazidime	</=8	16	>/=32	77	>256	>256	2→ >256	18
Cefiderocol	</=4	8	>/16	165	0.12	0.5	0.004 →64	19
Ciprofloxacin	-	-	-	80	16	>32	0.50 → >32	18
Colistin	-	-	-	619	1	8	<0.12→ 32	21
Eravacycline	-	-	-	619	1	2	0.03→16	21
Levofloxacin	</=2	4	>/=8	80	4	>32	0.25 → >32	18
Minocycline	</=4	8	>/=16	80	2	4	0.25 → 16	18
Omadacycline	-	-	-	315	2	8	0.25 →>32	20
TMP/SMX	</=2/38		>/=4/76	37	8	>8	0.03 → >8	22

CLSI: Clinical and Laboratory Standards Institute; S: Susceptible; I: Intermediate; R: Resistant

Conclusions and Recommendations

S. maltophilia is considered to be a nosocomial pathogen that often most affects the respiratory tract, causing significant morbidity and mortality. Its broad resistance profile limits the number of potential treatment options with TMP/SMX, levofloxacin, and minocycline having the most clinical data to support their use. Unfortunately, patient factors in addition to susceptibilities may not always allow for these agents to be used for the treatment of *S. maltophilia*.

Patient allergies and concomitant conditions also need to be considered prior to selecting therapy. Allergies to sulfa containing medications and concerns for myelosuppression in certain patient populations may limit the ability to use TMP/SMX. Fluoroquinolones are associated with many adverse effects and black box warnings, therefore certain comorbidities or concomitant medications that can prolong the QT, or increase risk of tendonitis, may be a limiting factor and deter the clinician from using them. There is still a paucity of data to recommend one agent over another and continued evaluation of *in vivo* data is necessary to examine susceptibility patterns of *S. maltophilia* to reassess first line treatment options. Newer agents that have *in vitro* activity against *S. maltophilia*, such as omadacycline and eravacycline, may have a role in the treatment of *S. maltophilia* in patients who are not able to tolerate or use first line agents. *In vitro* data with tetracyclines have maintained effectiveness against *S. maltophilia*, but randomized controlled trials are needed to compare the agents against standard treatment. The novel tetracyclines can also be a resource in patients with a penicillin or cephalosporin allergy who are not able to use first line recommendations. If the isolate of *S. maltophilia* is resistant to all first line agents and the newer agents are not an option, using a synergistic combination of antimicrobials may be the next step. Current literature on synergistic combinations for treating *S. maltophilia* are conflicting and therefore additional *in vivo* and *in vitro* data is needed to understand the most effective combination and how they compare to monotherapy.

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Instructions for Obtaining CE

The self-assessment quiz that can be found at the end of this article can be completed for 0.1 CEU of Continuing Pharmacy Education credit. The quiz may be completed online (http://madidtraining.org/newsletter/) at no cost for MAD-ID members. Non-members should print and mail the completed quiz, along with a $15.00 check made payable to MAD-ID to: MAD-ID, 537 Calico Retreat, Mt. Pleasant, SC 29464-2765. Your CE credit will be reported on CPE monitor within 4 weeks of receipt.

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Self Assessment Questions

(To be completed online (http://mad-idtraining.org/newsletter/) or, in the case of non-MAD members, printed and mailed. You must achieve a grade of 80% of better to receive continuing education credit.)

1) What are the classes of the L1 and L2 beta-lactamase enzymes that *Stenotrophomonas maltophilia* expresses? (Learning Objective 1)
    a. Both are Ambler Class B3 Beta-Lactamases
    b. L1 is an Ambler Class B3 Beta-Lactamase and L2 is an Ambler Class A Beta-Lactamase
    c. L1 is an Ambler Class A Beta-Lactamase and L2 is an Ambler Class C Beta-Lactamase
    d. Both are Ambler Class A Beta-Lactamases

2) Which virulence factor is NOT expressed by *Stenotrophomonas maltophilia*? (Learning Objective 1)
    a. Toxin production
    b. Biofilm production
    c. Presence of Flagella
    d. Ability to create Small Colony Variants (SCV)

3) Which antibiotic is NOT likely to have *in vitro* activity against *Stenotrophomonas maltophilia*? (Learning Objective 2)
    a. Trimethoprim-Sulfamethoxazole (TMP-SMX)
    b. Minocycline
    c. Fluroquinolones
    d. Meropenem

4) Which is not a limitation to the studies mentioned for the treatment of *Stenotrophomonas maltophilia*? (Learning Objective 2)
    a. Potential polymicrobial infections
    b. Lack of randomized controlled studies
    c. Inability to distinguish between colonization and true infection
    d. These are all limitations to the studies mentioned

5) Which new treatment option has shown *in vitro* activity against *Stenotrophomonas maltophilia*? (Learning Objective 3)
    a. Intravenous eravacycline
    b. Intravenous fosfomycin
    c. Intravenous meropenem-vaborbactam
    d. Intravenous Lefamulin

Learning Activity Assessment

Please provide your honest assessment of the value of this learning activity so that we can continue to improve our offerings.

Please indicate your degree of agreement or disagreement with the following statements regarding this learning activity by indicating strong agreement (a), general agreement (b), no opinion (c), mild disagreement (d), or strong disagreement (e):

Criteria	Strong agreement	General agreement	No opinion	General disagreement	Strong disagreement
The information presented was relevant to my practice	a	b	c	d	e
This program/session met the stated learning objectives	a	b	c	d	e
The information was presented in an objective and balanced manner without commercial bias	a	b	c	d	e
The information presented will alter/affect my practice (usefulness)	a	b	c	d	e
The educational materials enhanced my learning	a	b	c	d	e
The learning method was effective	a	b	c	d	e
The learning assessment activity (self-assessment quiz) was appropriate	a	b	c	d	e
The faculty/authors were of appropriate quality	a	b	c	d	e

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