MAD-ID Newsletter

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MAD-ID
MAKING A DIFFERENCE IN INFECTIOUS DISEASES®

Making the Most of Virtual MAD-ID

MAD-ID 2021 is just around the corner. This spring, instead of catching a flight/driving to ChampionsGate to get together in person we'll be attending in the comfort of home. Here are some tips to make Virtual MAD-ID a success!

- Arrange your meeting space with your usual conference routine in mind. What do you usually have with you at sessions in person? A notebook? Coffee and water? Maybe a snack? But don't forget you need an outlet for your computer nearby!
- Take advantage of virtual networking and engagement through the meeting app. Message other attendees, speakers, and poster presenters to ask questions, share insights, or tell them you like their work.
- Review the session logistics. Should you ask questions in the chat? In Q&A? Do you need to log in a little early? For the MAD-ID workshops, you'll have live, face-to-face interaction, so make sure your audio and video settings are working appropriately if you want to be seen and heard.
- Give your conference your full attention, just like you would in person. Make time in your schedule for your sessions. It can be hard not to multitask, but you deserve some time to refocus, re-energize, and engage with the MAD-ID community.

In this issue

MAD-ID 2021 Agenda and Speakers

Thursday May 20

Thursday Workshops: 2:15pm – 4:15pm (choose 2 of 4)

- Antimicrobial Stewardship in Challenging Environments, *Eddie Stenehjem, MD, MSc*
- How to Interpret Data from *In Vitro* Studies and Apply to Patient Care, *Katie E. Barber, PharmD*
- How to Win Friends and Influence Outpatient Antibiotic Use, *Lisa Dumkow, PharmD*
- Tales from the Trenches: Difficult Stewardship Challenges from our Community, *Kate E. DeSear, PharmD, Lynne C. Krop, PharmD, and David L. Lourwood, PharmD*

Thursday Plenary Sessions

- 4:15pm – 5:45pm: A New Era in HIV Management
  - New Therapies, New Problems; *Roger Bedimo, MD*
  - Real-Life Challenges in Antiretroviral Therapy; *Melissa Badowski, PharmD*

Friday May 21

Friday Plenary Sessions

- 10:45am – 12:15pm: COVID-19
  - Public Health and Clinical Challenges; *Roger Bedimo, MD*
  - Treatment Challenges, Access and Impact of AMS; *Julie Ann Justo, PharmD, MS*
- 12:15pm – 1:45pm: The Public Health Crisis of Vaccines
  - Advances in Vaccines; *Jeff Goad, PharmD, MPH*
  - Vaccine Mythbusters; *Marc Hutchison, PhD*
- 3:00pm – 4:30pm: Combination therapy for serious infections
  - *Staphylococcus aureus* infections; *George Sakoulas, MD*
  - Gram-negative Infections; *Ryan Shields, PharmD, MS*
- 4:30pm – 6:00pm: Update on Vancomycin
  - Demystifying Two-sample and Bayesian Estimated AUC: Simple but no Simpler; *Manjunath (Amit) P. Pai, PharmD, FCP*
  - Implementing the 2020 Vancomycin Dosing and Monitoring Guidelines: Finding a Path Forward; *Emily Heil, PharmD, MS*
- 6:15pm – 7:45pm: Antimicrobial Stewardship in Special Populations
  - Pediatrics; *Tracy Zembles, PharmD*
  - Adults with Cystic Fibrosis; *Wendy Bullington, PharmD*

Follow MAD-ID and share your experience, #MADID2021

https://twitter.com/MAD_ID_ASP

https://www.facebook.com/madidasp/

Saturday May 22

Saturday Plenary Sessions

- 10:30am – 12:00pm: Hot Topics
  - Top 10 Papers from 2020; *Ryan K. Shields, PharmD, MS and Erin K. McCreary, PharmD*

- 2:15pm – 3:45pm: Emerging and Difficult to Treat Infections
  - *Candida auris*; *Jeffrey Rybak, PharmD, PhD*
  - Non-tuberculous Mycobacterial Infections; *Wendy Bullington, PharmD*

Saturday Workshops: 12:00pm – 2:00pm (choose 2 of 4)

- Effective use of EMR Programming to Implement Antibiotic Guidelines and Pathways; *David Ha, PharmD*
- Dose Optimization of Beta-lactams; *Chuck Peloquin, PharmD*
- Supporting ID/ASP Professionals, Preventing Burnout in an Era of Doing More with Less; *Erin McCreary, PharmD*
- Developing and Using Your Antibiogram, *John Bosso, PharmD*

Registration Details are Here:
https://mad-id.org/2021-mad-id-annual-meeting/registration-2/

MAD-ID Welcomes New Scientific Committee Members

Welcome Dr. Kenneth Lawrence and Dr. Jacinda Abdul-Mutakabbir to the MAD-ID Scientific Committee! The Scientific Committee provides guidance on educational initiatives, invited speakers, collaborative relationships, and other priorities of MAD-ID.

Don't Forget to Visit the MAD-ID Vancomycin AUC Dosing Resource Page

Find all of the tools you need including guidelines, literature, calculators, implementation resources, and the opportunity to contact an expert, for FREE.

https://mad-id.org/vancomycin/

5 Questions with the MAD-ID Organizers

Is the "travel grant" program still available for the virtual meeting?
Registration waiver awards are available for a limited number of trainees who are presenting original research at the MAD-ID meeting. See the website for information on how to apply. https://mad-id.org/2021-mad-id-annual-meeting/id-resident-fellow-program/

The abstract submission deadline is Monday May 10th!

How will posters be presented at the conference?
Abstracts submitted for presentation at MAD-ID will be shared in the conference app, and posters will be posted to the MAD-ID website for attendees to view during the meeting. To ask questions and engage with poster presenters, attendees are encouraged to use the messaging features of the conference app!

Is the AASP available this year?
The Advanced Antimicrobial Stewardship Program (AASP) is a training program for practitioners who already have some experience and basic skills in antimicrobial stewardship implementation. The live, didactic portion is delivered through the MAD-ID conference and is available in 2021. The practical component is completed at the participant's home within the next 12 months. For more information see: https://mad-id.org/antimicrobial-stewardship-programs/advanced-program/

Will sessions be recorded?
All plenary sessions will be recorded and available for review after the conference for all registered attendees. Instructions for accessing recorded content will be shared in post-conference mailings. Due to the active, collaborative nature of workshops, classroom sessions will not be recorded.

Will there be Satellite Symposia at MAD-ID 2021
Yes! Watch your email for information on how to register for satellite sessions:

- Conceptualization of Treating Infectious Diseases: A Framework to Achieve Optimal Outcomes
- The Power of the Microbiome - Can it be unlocked to break the cycle of recurrent Clostridioides difficile infection?
- Check the website later for additional opportunities

Infectious Diseases Pharmacists Day, May 22nd

MAD-ID is excited to partner with the Society of Infectious Diseases Pharmacists in celebrating the inaugural Infectious Diseases Pharmacists Day on May 22, 2021. The theme of the inaugural event is "Essential COVID-19 Healthcare Workers". SIDP and MAD-ID will share events, including a twitter storm, to highlight the important, essential work that ID pharmacists do each day. For more information, visit https://sidp.org/IDPharmacistsDay

When to go PO? A review of literature on oral step-down antimicrobial therapy for gram-negative and gram-positive bloodstream infections

Continuing Education Activity

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Disclosures: Doctors Rico, Kirwen, Yost, and Martirosov 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. Explain the risks and benefits of transitioning from intravenous to oral therapy for the treatment of bloodstream infections.
2. Identify patients who are appropriate candidates for oral step-down therapy for gram-negative or gram-positive bacteremia.
3. Select an appropriate oral antimicrobial agent for completion of treatment for gram-negative bacteremia.
4. Select an appropriate oral antimicrobial agent for completion of treatment for gram-positive bacteremia.

Introduction

A growing body of literature has been published to support the use of oral step-down antimicrobial therapy (OSAT) following initial intravenous (IV) therapy in patients with gram-negative and gram-positive bloodstream infections (BSI). Within the past ten years clinical trials have focused on identifying optimal disease states, antimicrobial agents, duration, and time of conversion to OSAT for BSI. Most available evidence is limited due to retrospective study designs, inconsistent primary outcomes, and underrepresentation of immunocompromised patients. Similarly, many of the larger studies primarily included patients with Enterobacterales bacteremia from a urinary source, limiting the generalizability to other gram-negative organisms and sources of infection. Furthermore, there is far less literature supporting the use of OSAT in gram-positive BSI.

Due of the paucity of strong clinical evidence, treatment guidelines from the Infectious Diseases Society of America and other major medical societies lack recommendations on optimal patient populations, antimicrobial selection, or timing for transition to OSAT for gram-positive or gram-negative BSI.[1,2] Despite these shortcomings, OSAT may represent a viable alternative to IV therapy, which is often associated with complications from prolonged catheter use such as subsequent catheter-associated BSI. Data suggests the

rate of catheter-associated BSI in intensive care units ranges from 1.8-5.2 cases per 1000 catheter days.[3] Additional benefits of OSAT include decreased cost, readmission rates, and incidence of adverse drug events.[4] This review will examine its utility in both gram-negative and gram-positive BSI, including evidence supporting the use of specific oral antimicrobial agents.

Gram-Negative Bacteremia

Urinary source

Urinary tract infections are one of the most common sources of BSI, representing approximately 24% of nosocomial cases.[5] Due to the high prevalence, multiple studies have evaluated OSAT in these patients. Rieger and colleagues evaluated a retrospective cohort of 241 adult patients with urine and blood cultures positive for the same Enterobacterales pathogen.[6] Patients were grouped into those who received IV therapy only (n=106) or those who received OSAT (n=135). There was no significant difference in documented treatment failure, however there was a numerically higher rate of failure in the OSAT group (3.8% IV-only versus 8.2% OSAT, p=0.19). This may have been due to the overall medical complexity of the patients included, with approximately 26% of patients requiring intensive care unit (ICU) admission and inclusion of patients with multidrug resistant organisms. The study also found that patients in the OSAT group experienced a significantly shorter hospital length of stay. These findings were replicated in a similar retrospective study of 346 patients by Thurber and colleagues, in which no difference was found in rates of treatment failure at 21 days (2.4% IV-only versus 1.5% OSAT p=0.58) as well as reduced hospital length of stay with OSAT.[7] In addition, a higher rate of IV-associated complications was found in the IV-only group, including new thrombosis, irritation at insertion site, and continued line placement beyond antimicrobial therapy. In both studies, the most common organism was *Escherichia coli,* and the most common oral antimicrobial was ciprofloxacin.

Alternative OSAT options were evaluated in two studies comparing the use of β-lactams versus fluoroquinolones (FQ) for the treatment of BSI from a urinary source with promising results. Saad and colleagues evaluated 207 patients with *E. coli* urinary tract infections and BSI who received empiric IV β-lactam therapy followed by an OSAT with a β-lactam (n=77) or FQ (n=130).[8] Patients were treated for a median of 5 days with IV therapy, 7 days with oral therapy, and 14 days in total. There was no significant difference in the primary outcome of clinical cure (98% FQ versus 94% β-lactam, p=0.13). The most commonly prescribed β-lactams were cefixime and cephalexin. In this study, only 30% of patients were male, 5% had catheter-associated urinary tract infection, and roughly 6% required intensive care unit admission, limiting generalizability in these populations. Sutton and colleagues sought to answer this question as well in a Veterans Affairs population of 4,095 patients who were transitioned to OSAT by their sixth day of IV treatment.[9] Patients were grouped into those who received a β-lactam (n=955) versus those who received FQ or trimethoprim-sulfamethoxazole [TMP-SMX] (n=3,134). There was no difference in the primary composite outcome of all-cause mortality or recurrent bacteremia at 30 days (4.4% β-lactam versus 3.0% FQ/TMP-SMX) or 90 days (10.1% β-lactam versus 7.6% FQ/TMP-SMX). The most common β-lactams included amoxicillin-clavulanate, cephalexin, and cefpodoxime.

Non-urinary source

Although most of the available literature is focused on evaluating patients with BSI from a urinary source, a limited number of studies included other sources. One of the largest studies was conducted by Tamma and colleagues, who evaluated 1,478 propensity-matched patients (n=739 in each group) from multiple centers with monomicrobial Enterobacterales BSI that were transitioned to OSAT within the first 5 days of treatment.[10] Common foci of infection included urinary (40%), followed by gastrointestinal tract

(20%), and IV catheter (18%). Patients were primarily transitioned to an oral FQ (~70%) with *E. coli* and *Klebsiella pneumoniae* comprising approximately 75% of all isolates. There was no difference in rates of all-cause mortality or recurrent bacteremia at 30 days. Additionally, patients who received continued IV therapy had significantly longer hospital length of stay (7 days IV-only versus 5 days OSAT, p<0.001).

Gram-positive Bacteremia

MRSA and MSSA Bacteremia

Until recently, most available literature focused on OSAT in gram-negative bacteremia. In 2019, Jorgensen and colleagues published a retrospective cohort study of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) BSI over ten years.[11] Patients were separated into two groups, outpatient parenteral antimicrobial therapy (OPAT) and outpatient oral antimicrobial therapy (OOAT) and compared the incidence of 90-day clinical failure. The composite outcome included MRSA BSI recurrence, deep-seated MRSA infection, and mortality. The authors utilized inverse probability of treatment weighting to adjust for differences in baseline characteristics between the treatment groups. Common foci of infection in either group included pulmonary, skin/soft tissue, and IV catheter. Of the 492 patients included in the final analysis, 422 patients completed treatment with OPAT. The authors found no statistical difference in the primary composite outcome of clinical failure between groups (adjusted HR 0.379, 95% CI [0.131-1.101]). Common agents utilized for step-down in the OOAT group included linezolid and TMP-SMX; however, there was no direct comparison of failure rates with each agent. Total duration of therapy was significantly shorter in the OOAT group (21 days versus 35 days, p=0.001).

Similarly, Perez-Rodriguez and colleagues conducted a retrospective cohort study over five years to examine the incidence of 90-day recurrence of *S. aureus* infection in patients receiving completely intravenous therapy (CIT) or oral sequential therapy (OST).[12] Of note, patients were eligible for transition to OST after 3 days of IV therapy for uncomplicated bacteremia and 14 days for complicated bacteremia. Complicated bacteremia included patients with persistent bacteremia (*S. aureus* in peripheral blood cultures after 72 hours of adequate therapy and source control), osteoarticular involvement, septic thrombophlebitis, or device involvement. Patients in the CIT group were more likely to have hospital-acquired BSI, ICU admission, and chronic renal failure while patients in the OST group were more likely to have complicated bacteremia. Multivariate analysis detected chronic kidney disease, osteoarticular source, and skin and soft tissue source as predictors of recurrence; while MRSA infection was a predictor of 90-day mortality. Common foci of infection included IV catheter sites (38%) and skin and soft tissue (19.4%); however, other/unknown foci were prevalent as well. Of the 201 patients included in the final analysis, 125 patients completed treatment with OST. There was no difference in 90-day recurrence of *S. aureus* infections between groups (6% CIT versus 3% OST, p=0.251). Common agents utilized for step-down in the OST group included TMP-SMX (66%), linezolid (9%), and levofloxacin (18%). There were no differences in clinical cure, recurrence, or mortality when comparing OST regimens.

Streptococcal Bacteremia

Intravenous β-lactam antibiotics are considered the drug of choice for streptococcal bacteremia, but more recent literature has highlighted the possibility of OSAT. In 2019, a retrospective cohort study examined the rate of clinical failure in patients who completed therapy with oral agents considered to have high-bioavailability (fluoroquinolones, linezolid, clindamycin, doxycycline) or low-bioavailability (amoxicillin, amoxicillin/clavulanate, cephalexin).[13] Only non-staphylococcal gram-positive BSI were included and approximately 75% were caused by streptococcal species. Patient groups appeared to be balanced

according to baseline demographics and concomitant disease states, except more patients had active cancer in the high bioavailability group. The majority of BSI were from pulmonary sources, while skin/soft tissue sources were common in the low bioavailability group as well. The final analysis included 77 patients in the low bioavailability group and 26 patients in the high bioavailability group. Although there was a similar incidence of clinical failure between groups (19.3% versus 23.4%, p=0.66), the study was underpowered to detect a difference. The low bioavailability group had a longer total duration of antimicrobial therapy (15 days versus 14 days, p=0.183).

Similarly, a recent retrospective cohort study examined clinical success (composite outcome of lack of all-cause mortality, recurrent infection with same organism, or infection-related readmission at 90 days) of utilizing FQ or β-lactam OSAT in 220 patients with uncomplicated streptococcal BSI.[14] The most common organisms isolated were *Streptococcus pneumoniae* (34%), *S. pyogenes* (17%), and *S. agalactiae* (16%). Patient groups were similar in terms of baseline characteristics, but the FQ group had a higher incidence of pulmonary source (62.1% versus 24.1%, p<0.001). Conversely, the β-lactam group had a higher incidence of skin/soft tissue source (45.1% versus 21.8%, p=0.0004). The primary outcome of clinical success was non-inferior when comparing β-lactams to FQ for OSAT (92% versus 93.2%, 90% CI -5.2 to 7.8, p<0.0001). Total duration of therapy was approximately 14 days in each group. The authors identified switch to oral therapy after less than 3 days of IV therapy and low dose OSAT (amoxicillin/clavulanate 500-125mg q12h, cephalexin 500mg q6h, amoxicillin 500mg q8h) were possible predictors of clinical failure in a multivariable logistic regression model (OR 5.182, 95% CI [1.211-22.162], p=0.026).

High Inoculum Infections: Infective Endocarditis

Patients with severe, high-inoculum infections, such as infective endocarditis, are often treated with at least 6 weeks of IV antibiotics. Due to the limited data examining the use of OSAT in infective endocarditis, Iversen and colleagues conducted the Partial Oral Treatment of Endocarditis (POET) trial; a multicenter, randomized, unblinded noninferiority trial.[15] Eligible patients included those receiving IV antibiotics for left-sided endocarditis (native or prosthetic valve), and had blood cultures positive for streptococcus, *Enterococcus faecalis, S. aureus,* or coagulase-negative staphylococci. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia with the primary pathogen from randomization through 6 months after the completion of antimicrobial therapy. Streptococcal species were the most common isolate in the OSAT group (45.8%), followed by *E. faecalis* (25.4%), MSSA (23.4%), and coagulase-negative staphylococci (6.5%). Selection of OSAT regimens were dependent on minimum-inhibitory concentrations (MIC) for each organism but always included high dose combination therapy with agents such as amoxicillin, linezolid, moxifloxacin, rifampin, or clindamycin. The primary composite outcome occurred in 24 patients (12.1%) in the IV group and in 18 (9.0%) in the OSAT group (OR 0.72, 95% CI 0.37-1.36), satisfying the criteria for noninferiority.

Treatment options

Bioavailability

Several trials have begun to explore various oral antimicrobial agents for OSAT, comparing them based on bioavailability. It has been hypothesized that antimicrobials with higher bioavailability will provide a better response to therapy and prevent recurrence of BSI. Kutob and colleagues completed a retrospective study to evaluate the effectiveness of oral antimicrobials with varying levels of bioavailability as OSAT for BSI.[16]

Patients were separated into groups based on bioavailability, classified as high (≥ 95%), moderate (75-94%), and low (< 75%). The most common source was urinary, and the most common isolate was *E. coli*. Rates of treatment failure were significantly lower in the high bioavailability group when compared to moderate and low bioavailability (2% high, 12% moderate, and 14% low, p=0.02). In a multivariate analysis, it was found that liver cirrhosis, immunocompromised status, and treatment with low or moderate bioavailability oral agents significantly increased risk for treatment failure. Conversely, in a subgroup analysis of a more recent study, there was no difference in mortality or recurrence of BSI when treatment was stratified into high and low bioavailability groups.[10]

When examining the available literature for OSAT in MSSA and MRSA bacteremia, antimicrobial agents with high bioavailability are commonly utilized. However, in contrast to gram-negative BSI, MSSA and MRSA BSI are more commonly associated with complicated sources of infection such as indwelling devices or skin/soft tissue infections.[4] Much of the available data does not provide direct comparisons between the antimicrobial agents utilized for OSAT, making it difficult to provide evidence-based recommendations for specific agents in MSSA and MRSA BSI. Similarly, the POET trial utilized several different antimicrobial regimens for MSSA endocarditis, including a mixture of high and low bioavailability agents and utilized higher than standard dosing regimens. Furthermore, both studies that included primarily streptococcal isolates did not find significant differences in clinical outcomes when comparing low- and high-bioavailability agents. However, the lower MICs with gram positive organisms increases the probability of attaining pharmacodynamic targets.

β-lactams vs Fluoroquinolones

Commonly, FQ are chosen for OSAT for treatment of gram-negative BSI based on their high bioavailability and the potential for improved adherence with once- or twice-daily dosing. Due to the increasing rates of FQ resistance and adverse drug reactions, there is a need to evaluate effectiveness of other antimicrobial classes, including β-lactams. In 2019, a meta-analysis was completed comparing FQ or TMP-SMX versus β-lactams for gram-negative BSI.[17] The analysis included eight retrospective cohort studies totaling 2,289 patients. Approximately 65% of these patients were treated with FQ, 8% with TMP-SMX, and 27% with β-lactams. Urinary infection was the most common cause of BSI in all studies. IV therapy was utilized for approximately 3-5 days and total duration of therapy was 14-16 days. The study did not identify a significant difference in all-cause mortality between FQ or TMP-SMX versus β-lactams. An analysis comparing β-lactams to FQ and found significantly higher rates of recurrent infection in the β-lactam group (OR 2.05, 95% CI 1.17-3.61). The authors comment that poor adherence to the β-lactam dosing regimen or the suboptimal dosing observed with the β-lactam group in the studies could have contributed to this finding.

Similarly, FQ and β-lactam agents are commonly utilized as OSAT for streptococcal BSI. As previously discussed, a direct comparison of FQ and β-lactams revealed no difference in clinical success in patients with uncomplicated streptococcal bacteremia. Common β-lactams prescribed for OSAT have typically included agents with higher bioavailability (e.g., amoxicillin-clavulanate [70-77%], cephalexin [80%], amoxicillin [70-77%]).[13]

FQ are not commonly utilized for OSAT in MSSA or MRSA BSI due to high levels of FQ resistance among staphylococcal species.[18] Most recently, Beganovic and colleagues conducted a retrospective cohort study of patients that received levofloxacin/moxifloxacin or nafcillin/cefazolin monotherapy for MSSA bacteremia. While the authors did not detect a difference in mortality, the timing for transition to OSAT was not well-described.[19]

Linezolid

Despite the Food and Drug Administration (FDA) boxed warning against the use of linezolid for catheter-related bloodstream infections, there are several studies to support the use of linezolid in gram-positive BSI. Of note, the study supporting the FDA boxed warning showed a higher mortality rate in patients with gram-negative or mixed gram-positive/gram-negative BSI together, but not with gram-positive BSI individually.[20] Shorr and colleagues conducted a pooled analysis of randomized controlled trials in 2005 to compare vancomycin and linezolid in MRSA and MSSA BSI and found similar rates of microbiological and clinical cure.[21] More recently, a retrospective cohort study compared linezolid, daptomycin, and vancomycin therapy for MRSA bacteremia. There were no differences between groups in clinical or microbiological cure rates; however, there was a higher rate of mortality in the linezolid group. This may be explained by the low number of patients receiving linezolid coupled with a higher number of patients with complicated MRSA bacteremia in the linezolid group.[22] Similarly, a propensity-matched retrospective cohort examined 90-day relapse of uncomplicated *S. aureus* BSI in patients receiving linezolid for OSAT or solely parenteral antimicrobial therapy. The median interval between appropriate antibiotic treatment initiation and oral switch to linezolid was 7 days. The authors did not find a difference in 90-day relapse or mortality when comparing the groups; however, due to the retrospective nature of the study, the parenteral therapy choices were not standardized. Patients with MSSA BSI commonly received cloxacillin (53%) or cefazolin (26%), while daptomycin (66.7%), vancomycin (16.6%), or linezolid (16.6%) were used in MRSA BSI.[23] A common theme in literature examining the use of linezolid in MRSA/MSSA bacteremia is the lack of clarification of the optimal time to switch to oral therapy. In recent literature, when linezolid was compared to other oral antimicrobial agents, it did not appear to be associated with increased mortality in patients with gram-positive BSI.[12,23]

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole is not commonly included in direct comparisons of oral agents as a part of the primary outcomes in recent studies, making it difficult to draw conclusions its utility for OSAT. Perez-Rodriguez and colleagues performed a multivariate analysis to determine predictors of 90-day mortality; TMP-SMX for OSAT was not associated with increased mortality.[12] However, an open-label, parallel-group randomized controlled trial compared TMP-SMX to vancomycin for patients with severe MRSA infections and evaluated a subset of patients with MRSA BSI. They reported higher rates of mortality in the TMP-SMX subgroup with MRSA BSI but provided no information about route or duration of therapy.[24] An older study showed similar rates of mortality when comparing TMP-SMX to vancomycin therapy in MRSA BSI; again, lacking specific information about route and duration of therapy.[25] Further studies are needed to determine TMP-SMX place in OSAT in comparison to other available oral agents.

Application to Clinical Practice

There are a variety of factors to take into consideration when evaluating whether a patient could benefit from OSAT to complete treatment for BSI. The majority of studies initiated OSAT when patients reached a point of clinician-defined stability after approximately 3-5 days of IV therapy in gram-negative BSI, but this was not well-defined in gram-positive BSI. Primarily, the ability to tolerate oral medications and remain adherent to an oral antimicrobial that may require multiple daily doses should be assessed. Additional patient-specific factors to account for include history of recurrent infection, source control (e.g., presence of indwelling devices/catheters), and degree of immunosuppression. Most studies we reviewed included primarily uncomplicated gram-negative BSI, excluding more high-risk patients (e.g., immunosuppressed, prolonged ICU admission, unattainable source control, BSI from prosthetic joint infections, endocarditis, etc.), while others only included a small percentage. Kutob and colleagues specifically found that

immunocompromised hosts were at significantly increased risk for treatment failure with OSAT.[16] Based on the current literature, it is unclear whether the benefit of OSAT in immunocompromised patients for treatment of gram-negative BSI outweighs the risk of treatment failure.

Enterobacterales are the most common organisms evaluated in the available literature with a growing body of evidence that includes favorable outcomes in MRSA, MSSA, and streptococcal BSI. Many studies chose to exclude patients with multidrug-resistant organisms; however, one study had multidrug-resistance in approximately 30% of their gram-negative isolates and found numerically higher rates of treatment failure in the OSAT group.[6] While some studies have included various sources of BSI, the most common source in gram-negative BSI is the urinary tract. Due to the smaller body of literature for OSAT in gram-positive BSI, it remains unclear which source may be most appropriate to switch to oral therapy. Careful consideration of other patient-specific factors is prudent if considering OSAT for BSI from a non-urinary or gram-positive source.

Conclusion

From our review of the literature, it appears that patients with Enterobacterales BSI from a urinary focus had favorable treatment outcomes when converted to OSAT. Traditionally, FQ have been preferred due to their high bioavailability. However, recent evidence has shown that β-lactams are also an appropriate treatment option primarily in patients with uncomplicated Enterobacterales BSI after 3-5 days of IV therapy. Gram-positive BSI presents a challenging clinical scenario due the possibility of complicated foci of infection. It may be reasonable to utilize OSAT in patients with streptococcal BSI or MRSA/MSSA BSI with a clear, modifiable source of infection such as an IV catheter. Polymicrobial, multidrug resistant BSI, and immunocompromised patients are not represented consistently in the available literature; therefore, one should exercise caution before recommending OSAT in these cases. However, future studies should focus on non-urinary gram-negative BSI, evaluate appropriate doses and duration of oral agents, and continue to assess antimicrobial classes beyond fluoroquinolones.

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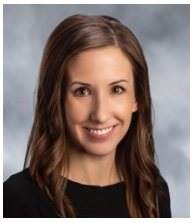

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Instructions for Obtaining CE

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; 348 Lum Crowe Road; Roswell, GA 30075. 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. Which of the following are potential benefits of transitioning from intravenous to oral therapy for the treatment of both gram-negative and gram-positive bloodstream infection?
    a. Reduced risk for catheter-related bloodstream infection
    b. Reduced cost
    c. Reduced patient adherence
    d. A and B

2. A 76-year-old male (72 kg, 67 inches) presents to the emergency department with fever, fatigue, and urinary urgency, dysuria, and retention. He is found to have a temperature of 101.1°F, blood pressure of 91/59 mmHg, and heart rate of 112 beats per minute. He is admitted to the general medical floor with urine and blood cultures that reveal pan-susceptible *Escherichia coli.* After five days of treatment with intravenous ceftriaxone, he is stable and ready for discharge. The medical team would like to discharge the patient on an oral antimicrobial. What is your recommendation?
    a. This patient is not a candidate for oral therapy
    b. Trimethoprim-sulfamethoxazole
    c. Ciprofloxacin
    d. Linezolid

3. CA is a 61-year-old female with no significant past medical history who developed a line-associated bacteremia (2/2 blood cultures) while at your institution that is attributed to methicillin-susceptible *Staphylococcus aureus* (MSSA). The treatment team determines that she no longer needs IV therapy after 7 days of IV antibiotics. Repeat blood cultures were negative, no metastatic foci of infection have been identified (including negative transesophageal echocardiogram), and she has remained afebrile. Which of the following is the most reasonable agent for step-down therapy based on the available evidence?
    a. Linezolid
    b. TMP-SMX
    c. Cefuroxime
    d. A or B

4. A 54-year-old renal transplant recipient is admitted to the hospital for a recurrent urinary tract infection. She is admitted to the intensive care unit for the first two days due to hemodynamic instability requiring vasopressor support and her urine and blood cultures grew *Enterobacter cloacae.* After 7 days of intravenous cefepime, she is stable and ready for discharge. The medical team would like to discharge the patient on an oral antimicrobial, pending susceptibility data. What is your recommendation?
    a. This patient is not a candidate for oral therapy at this time
    b. Trimethoprim-sulfamethoxazole
    c. Cefdinir
    d. Levofloxacin

5. AC is a 62-year-old male admitted with suspected community-acquired pneumonia. He has a past medical history of diabetes, hypertension, and atrial fibrillation. He begins to improve with supportive care and empiric antimicrobial therapy. The treatment team collects blood cultures and a sputum culture prior to initiating therapy that become positive on day 2. Both the sputum culture and blood cultures (2/2 sets) reveal *S. pneumoniae*. Repeat blood cultures are drawn. By day 5 of appropriate IV therapy, the team would like to consider transitioning to oral antibiotics based on his clinical improvement and repeat blood cultures remaining negative. Which of the following drug classes contain options for an appropriate oral step-down agent, if given the organism's susceptibility profile?
    a. Fluoroquinolones
    b. β-lactams
    c. Trimethoprim-sulfamethoxazole
    d. A and B

Learning Activity Assessment

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

1. What is your profession
   - ☐ Pharmacist
   - ☐ Physician
   - ☐ Nurse
   - ☐ PA
   - ☐ Other

Please indicate your degree of agreement or disagreement with the following statements regarding this learning activity by indicating strongly agree (a), generally agree (b), no opinion (c), mildly disagree (d), or strongly disagree (e):

Criteria	Strongly agree (a)	Generally agree (b)	No Opinion (c)	Mildly disagree (d)	Strongly disagree (e)
2. The speaker(s) / author(s) adequately addressed the learning objectives	a	b	c	d	e
3. The speaker(s) / author(s) used an effective learning method	a	b	c	d	e
4. The content of the activity was relevant to my practice	a	b	c	d	e
5. This activity was free of commercial bias	a	b	c	d	e
6. I will use this information to change my practice	a	b	c	d	e
7. Feel free to add any other feedback					

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