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EDITORIAL COMMENTARY

Trimethoprim-Sulfamethoxazole for *Staphylococcus Aureus* Bacteremia Prophylaxis in Patients on Hemodialysis: A Future Tool for the "Swiss Army Knife" of Antibiotics?

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Staphylococcus aureus bacteremia (SAB) is one of the most common and morbid conditions faced by infectious diseases clinicians worldwide, with an in-hospital mortality rate of 18% [1, 2]. Patients receiving long-term hemodialysis are at exceptionally high risk and bear a disproportionate burden of SAB. Recent surveillance data from the Centers for Disease Control and Prevention Emerging Infections Program found the SAB rate to be 100 times higher among patients receiving hemodialysis than adults not on hemodialysis between 2017 and 2020 [3]. Given an estimated 3.9 million persons receiving kidney replacement therapy worldwide, 69% of whom receive hemodialysis, this is a significant public health dilemma [4].

A variety of strategies have been attempted to reduce the rates of *S aureus* infections, ranging from nasal decolonization to prophylactic antibiotics in certain situations and even candidate vaccines, with varied success [5]. Perhaps the most influential interventions have focused on increased awareness, standardized care bundles, and adequate catheter maintenance to prevent catheter-related bloodstream infections (CRBSI) [6, 7], Despite modest gains, SAB remains problematic and further interventions are needed.

In this issue of *Open Forum Infectious Diseases*, Bryce et al utilized their unique setting in Northern Australia, where trimethoprim-sulfamethoxazole (TMP-SMX) 160 mg/800 mg is administered three times weekly after hemodialysis for the purposes of melioidosis prophylaxis during the wet season (November–April), to explore differences in the incidence of SAB between wet and dry seasons [8]. This retrospective, single-center cohort study from 2017–2022 included 1145 patients receiving hemodialysis, of which 52 (17%) developed SAB. The SAB population consisted of 65% females and 75% Aboriginal Australians, with 46% having CRBSI. One third of these *S aureus* isolates had TMP-SMX resistance, whereas the TMP-SMX resistance per the local antibiogram was only 8%.

The key observation was a 56% decrease in the estimated incidence of SAB among patients receiving hemodialysis during the wet compared to dry season (1528/100,000 person years vs 3438/100,000 person years; incident rate ratio, 0.44; 95% confidence interval, 0.23–0.82). Comparatively, patients with SAB not receiving hemodialysis had no seasonal difference in incidence, consistent with Far North Queensland data demonstrating no SAB seasonality [9]. Interestingly, one quarter of the patients who acquired SAB during the wet season were not receiving TMP-SMX prophylaxis, and 29% of all SABs occurred in those receiving TMP-SMX, with nearly half of those isolates retaining TMP-SMX susceptibility.

Important limitations of this study include its single-center, retrospective design that subjects it to potential confounding and a small sample size that may overestimate the effect size. Additionally, the geographically limited practice of periodically administering TMP-SMX makes external validity and replication more challenging. Another consideration is whether hemodialysis-related infection prevention practices (e.g., dressings, antibiotic locks, chlorhexidine use, alcohol-impregnated caps) were optimized; notably, this center has implemented prior antisepsis interventions [10].

TMP-SMX's spectrum of activity includes a broad array of bacteria, fungi, and parasites, serving as a sort of anti-infective "Swiss Army knife," with prior literature demonstrating off-target reductions in different infections, including *S aureus*, when utilized as prophylaxis for another indication. In people with advanced HIV in the 1990s, TMP-SMX

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prophylaxis for *Pneumocystis jirovecii* pneumonia was associated with a 40% risk reduction in *S aureus* infections in addition to decreased infections from *Haemophilus*, *Salmonella*, and *Toxoplasma* [11]. In a randomized controlled trial (RCT) of people with HIV in Côte d'Ivoire, TMP-SMX prophylaxis significantly reduced rates of bacterial pneumonia, *Cystoisospora*, and malaria [12]. TMP-SMX/heparin lock solution decreased rates of CRBSIs compared to heparin control in an RCT of patients receiving hemodialysis via tunneled catheters [12]. In Northern Australia, wet season TMP-SMX melioidosis prophylaxis was associated with a similar temporal decrease in invasive group A streptococcal infections [13]. In this context, Bryce et al add further evidence for TMP-SMX's versatility to prevent infections in vulnerable populations [8].

The results of this study generate a fascinating question for future research: should TMP-SMX be employed as a prophylactic agent against SAB among patients receiving hemodialysis (or more broadly to other populations at highest risk of SAB)? Evaluating a large population-based infection prevention measure should include a careful assessment of the relative benefits versus potential harms, and lessons can be drawn from other population-level anti-infective interventions.

Despite TMP-SMX's broad utility, adverse drug effects (ADEs) are numerous, and intolerance is frequently encountered in clinical practice. Although renal toxicities (e.g., hyperkalemia, elevated creatinine) may be less consequential in patients receiving hemodialysis, ADEs include hematologic abnormalities, hepatitis, neuropsychiatric effects, and, rarely, life-threatening allergic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis [14]. In clinical trials of TMP-SMX used for *P jirovecii* pneumonia prophylaxis for people with HIV, rates of ADE were relatively frequent and increased with the dosage used [15–17]. For example, in Northern Australia, ~30% of patients did not receive TMP-SMX prophylaxis on hemodialysis because of allergy, intolerance, and logistics [8, 18].

Beyond individual patient-level ADEs, implementing a large-scale antimicrobial prophylactic measure raises concerns about increasing antimicrobial resistance amongst *S aureus* and other bacteria. Although TMP-SMX is not a first-line agent in the treatment of SAB, it is an important oral agent for *S aureus* infections, especially methicillin-resistant isolates. Bryce et al found a concerning signal for increased TMP-SMX resistance in patients on hemodialysis compared to the local population, but it is not clear if this is due to TMP-SMX exposure or other baseline differences in comorbidities and antibiotic exposure between populations. Similarly, TMP-SMX prophylaxis in PLWH has been associated with higher rates of TMP-SMX resistant *S aureus* infections and colonization, as well as concerns for increased resistance to other antibiotic classes among non-*S aureus* pathogens, including higher rates of extended-spectrum beta-lactamase Enterobacterales [19, 20]. Evidence for this latter concern appears mixed, however, because a prior systematic review found a signal that TMP-SMX prophylaxis may be protective against resistance to other antibiotics (perhaps via decreasing colonization and infection rates), although the number of studies included was small [21].

Because a definitive answer to the proposed question of whether TMP-SMX *should* be employed for SAB prophylaxis in patients receiving hemodialysis or at otherwise high risk is challenging without further study, we currently urge caution in implementing these findings in clinical practice yet remain intrigued. A low-cost intervention that may substantially reduce the risk of a highly mortal infection in a vulnerable population is tempting to adopt zealously because the potential adverse events and risk of antibiotic resistance is likely acceptable if a mortality reduction is demonstrated; however, before implementation, this intervention deserves rigorous scientific investigation via a proper RCT to weigh the risks and benefits, given that this intervention has the risk of worsening outcomes. Further studies should evaluate whether nonsystemic antimicrobial prophylactic techniques offer similar or additional benefits to catheter-care bundles (e.g., antibiotic locks, chlorhexidine/mupirocin decolonization), the optimal prophylactic dose and frequency, and further risk stratification to determine if the benefit is limited to select patients receiving hemodialysis (e.g., only hemodialysis catheters vs arteriovenous grafts/fistulas). While awaiting further data, close attention to evidence-based infection prevention measures remains essential.

As a derivative of 1 of the primordial antimicrobials and having perhaps the most impressive spectrum of anti-infective activity in our field spanning multiple biological kingdoms, TMP-SMX has saved innumerable lives preventing and treating numerous common pathogens. Given the burden of SAB, it seems worth considering whether its use could be extended to prophylaxis against SAB in certain high-risk populations. Doing so, however, may have unforeseen consequences, as adding another tool could potentially overburden TMP-SMX's utility as an invaluable "Swiss Army knife."

Notes

Patient Consent Statement. This manuscript does not include factors necessitating patient consent.

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