Clarifying the Role of Adjunctive Metronidazole in the Treatment of Biliary Infections

TO THE EDITOR—Infectious diseases specialists face a challenging era highlighted by multidrug-resistant pathogens and antimicrobial resistance. These issues have fueled increasing emphasis on antimicrobial stewardship [1, 2]. Essential in antimicrobial stewardship is the practice of appropriate antibiotic use and avoidance of unnecessary antimicrobial agents. One such example is the often unnecessary double anaerobic coverage therapy [3]. In the setting of complicated intra-abdominal infections, data suggests that implementation of stewardship programs effectively reduces unnecessary antimicrobial use [4].

The Infectious Diseases Society of America (IDSA) guidelines for diagnosis and management of complicated intra-abdominal infections [5] thoroughly outline the appropriate use of antimicrobials for various diagnoses. However, some confusion arises upon further review. In Table 4 of the guidelines addressing initial empiric treatment of biliary infection in adults, except for mild-to-moderate, community-acquired cholecystitis, the recommendations for antimicrobial therapy are stated as “imipenem–cilastatin, meropenem, doripenem, piperacillin–tazobactam, ciprofloxacin, levofloxacin or cefepime, each in combination with metronidazole.” The wording suggests the invariable addition of metronidazole to every antibiotic listed, even antibiotics with significant anaerobic activity such as carbapenems and extended spectrum penicillin-beta lactamase inhibitors. Recommendation 61 in the text adds further ambiguity by stating that “anaerobic therapy is not
indicated unless a biliary-enteric anastomosis is present. (B-II)"

The IDSA guidelines specifically cite the “Tokyo Guidelines” in the Evidence Summary as references for antimicrobial therapeutic strategies that are used for cases of acute cholecystitis and cholangitis [6–9]. However, a review of the Tokyo Guidelines for specific antimicrobial therapy recommendations for acute cholecystitis reveals that adjunctive metronidazole is only recommended in moderate and severe acute cholecystitis when paired with a fluoroquinolone “when anaerobic bacteria are detected or are expected to co-exist.” The section of the Tokyo Guidelines that addresses antimicrobial therapy for acute cholangitis (which is not specifically referenced in the IDSA guidelines) lists adjunctive metronidazole as an option for moderate to severe cholangitis in combination with a third- or fourth-generation cephalosporin, aztreonam, or a fluoroquinolone. Carba-penems and “wide-spectrum penicillin/β-lactamase inhibitors” (ie, ampicillin-sulbactam and piperacillin-tazobactam) are listed as single-agent options.

Thus, in cases where anaerobic coverage is deemed appropriate, the Tokyo Guidelines seem to support a regimen consisting of a carbapenem or a beta-lactam/β-lactamase inhibitor. Either of these agents would already provide excellent anaerobic activity, and, hence, their combination with metronidazole would seem unnecessary in treating most biliary infections. In our view, the recommendations for antimicrobial therapy in the case of biliary infections in Table 4 of the IDSA guidelines may instead read as follows: “Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam OR one of the following in combination with metronidazole: ciprofloxacin, levofloxacin, or cefepime.” As we enter an age of antimicrobial stewardship where it is of the utmost importance to reduce any unnecessary antimicrobial use, we call on the authors of the IDSA guidelines to further clarify their recommendations on the role of adjunctive metronidazole in biliary infections.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Manie Beheshti,1 Christopher J. Graber,2,3 Matthew B. Goetz,2,3 and Gary L. Bluestone1**

1Division of Infectious Diseases, Department of Internal Medicine, Kaiser Permanente, Baldwin Park, 2VA Greater Los Angeles Healthcare System, and 3Division of Infectious Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California

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Correspondence: Christopher J. Graber, VA Greater Los Angeles Healthcare System and David Geffen School of Medicine at UCLA, Division of Infectious Diseases, VAGLAHS, 111F, 11301 Wilshire Blvd., Los Angeles, California 90073, USA (christopher.graber@va.gov).