AAC Journals.ASM.org

Reply to "Are There Reasons To Prefer Tetracyclines to Macrolides in Older Patients with Community-Acquired Pneumonia?"

Kevin A. Brown,[a] Nagham Khanafer,[b] Nick Daneman,[c] David N. Fisman[a]

Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada[a]; Laboratoire de Biométrie et de Biologie Évolutive, Université de Lyon, Lyon, France[b]; Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada[c]

We thank S. Di Bella et al. for their comments regarding the potential of tetracyclines to improve the treatment of community-acquired pneumonia (CAP) in elderly patients at risk of *Clostridium difficile* infection (CDI) (1). Prescribing for CAP is a major driver of seasonal trends in antibiotic use in temperate countries, where wintertime antibiotic prescribing increases by almost one-third relative to summer levels (2). These differences in antibiotic prescribing in elderly patients may be at least partially responsible for the increased wintertime risk of CDI in North America (3, 4).

As S. Di Bella et al. note, the low risk profile of the use of tetracyclines for treatment of CDI in observational epidemiologic studies of hospital- and community-acquired CDI suggests that they may have advantages as a class of agents for patients with CAP at risk of CDI. Doxycycline, for example, which has activity against susceptible pneumococci and atypical pneumonic pathogens, has been shown to have only a moderate effect on total counts of gut anaerobic bacteria (5).

We caution that increased prescribing of tetracyclines for CAP could help select antimicrobial-resistant *Clostridium difficile* pathogens, and so tetracycline-associated CDI risks have the potential to change over time (6), such that ongoing monitoring of this relationship is necessary (7). It is also important to note other drawbacks of this class of antimicrobials, including their contraindication in children and pregnant women.

REFERENCES

1. **Di Bella S, Taglietti F, Petrosillo N.** 2013. Are there reasons to prefer tetracyclines to macrolides in older patients with community-acquired pneumonia? Antimicrob. Agents Chemother. **57:**4093.
2. **Daneman N, Stukel TA, Ma X, Vermeulen M, Guttmann A.** 2012. Reduction in Clostridium difficile infection rates after mandatory hospital public reporting: findings from a longitudinal cohort study in Canada. PloS Med. **9:**e1001268. doi:10.1371/journal.pmed.1001268.
3. **Polgreen PM, Yang M, Bohnett LC, Cavanaugh JE.** 2010. A time-series analysis of clostridium difficile and its seasonal association with influenza. Infect. Control Hosp. Epidemiol. **31:**382–387.
4. **Gilca R, Fortin E, Frenette C, Longtin Y, Gourdeau M.** 2012. Seasonal variations in Clostridium difficile infections are associated with influenza and respiratory syncytial virus activity independently of antibiotic prescriptions: a time series analysis in Quebec, Canada. Antimicrob. Agents Chemother. **56:**639–646.
5. **Nord CE, Kager L, Heimdahl A.** 1984. Impact of antimicrobial agents on the gastrointestinal microflora and the risk of infections. Am. J. Med. **76:**99–106.
6. **Baxter R, Ray GT, Fireman BH.** 2008. Case-control study of antibiotic use and subsequent Clostridium difficile-associated diarrhea in hospitalized patients. Infect. Control Hosp. Epidemiol. **29:**44–50.
7. **Doernberg SB, Winston LG, Deck DH, Chambers HF.** 2012. Does doxycycline protect against development of Clostridium difficile infection? Clin. Infect. Dis. 55:615–620.

Address correspondence to Kevin A. Brown, kevin.brown@mail.utoronto.ca.

This is a response to a letter by Di Bella et al. (doi:10.1128/AAC.00828-13).

doi:10.1128/AAC.00864-13

AAC Journals.ASM.org

Are There Reasons To Prefer Tetracyclines to Macrolides in Older Patients with Community-Acquired Pneumonia?

S. Di Bella, F. Taglietti, N. Petrosillo

National Institute for Infectious Diseases L. Spallanzani, Rome, Italy

In a recent meta-analysis, Brown et al. investigated the association between antibiotic class and the risk of community-associated *Clostridium difficile* infection (CDI). The results demonstrated that the risk of CDI in patients treated with macrolides was more than twice that in patients with no antibiotic exposure (odds ratio [OR], 2.65; 95% confidence interval [CI], 1.92 to 3.64), and yet in those patients receiving tetracyclines, no increased risk was observed (OR, 0.92; 95% CI, 0.61 to 1.40) (1). In another recent study on 3,305 patients exposed to ceftriaxone (24% with pneumonia on admission), the incidence of CDI was 1.67 cases per 10,000 patient-days in those receiving doxycycline compared to 8.11 per 10,000 patient-days in those who did not receive doxycycline (2). In the same study, the hazard ratio for development of CDI in a patient receiving a 5-day course of doxycycline plus ceftriaxone compared to a 5-day course of a macrolide plus ceftriaxone was 0.15 (95% CI, 0.03 to 0.77) (2). Community-acquired pneumonia (CAP) is the third-commonest hospital diagnosis among patients aged ≥65 years and the sixth leading cause of death in developed countries. The mortality rate is 10% to 25% and is particularly high in the elderly population (3). It is estimated that, every year, 4 million people in the United States develop CAP. Of these, 80% are managed in the outpatient setting, whereas the remaining 20% are admitted to hospitals (4). The Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) published guidelines on the management of CAP in adults in 2007 (5). According to these guidelines, for outpatient treatment of CAP, tetracyclines can be used instead of macrolides as monotherapy in previously healthy patients and can also be used as part of combination therapy (e.g., with beta-lactam antibiotics) in patients with comorbidities. However, regarding doxycycline, the strength of recommendation is weaker because a strong evidence base supporting its use is lacking. Treatment decisions should always involve a risk-benefit analysis for each patient and all antibiotics associated with adverse events. *Clostridium difficile* infection is one such risk factor to consider prior to starting therapy. Recent trends show an increasing incidence in community-onset and community-associated CDI. In a recent large population cohort study, 41% of CDI cases were community acquired (6). Furthermore, although the mean age of patients with community-associated CDI is lower that of those with health care-associated CDI, it still exceeds 65 years (7, 8). Morbidity and mortality associated with community-associated CDI are increasingly reported and are perhaps underestimated (9). As discussed above, patients treated with macrolides may be at higher risk of developing CDI. In addition, a large cohort study reported an increase in cardiovascular deaths (which were most pronounced among patients with a high baseline risk of cardiovascular disease) during azithromycin therapy (10). Given these premises, the risk-benefit analysis for treating CAP may favor doxycycline, especially in patients over 65 years who would be receiving outpatient treatment.

REFERENCES

1. **Brown KA, Khanafer N, Daneman N, Fisman DN.** 2013. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob. Agents Chemother. **57:**2326–2332.
2. **Doernberg SB, Winston LG, Deck DH, Chambers HF.** 2012. Does doxycycline protect against development of Clostridium difficile infection? Clin. Infect. Dis. **55:**615–620.
3. **Fernández-Sabé N, Carratalà J, Rosón B, Dorca J, Verdaguer R, Manresa F, Gudiol F.** 2003. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. Medicine (Baltimore) **82:**159–169.
4. **Welte T, Kohnlein T.** 2009. Global and local epidemiology of community-acquired pneumonia: the experience of the CAPNETZ Network. Semin. Respir. Crit. Care Med. **30:**127–135.
5. **Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM, Jr, Musher DM, Niederman MS, Torres A, Whitney CG.** 2007. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin. Infect. Dis. **44**(Suppl. 2):S27–S72.
6. **Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, Harmsen WS, Zinsmeister AR.** 2012. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. Am. J. Gastroenterol. **107:**89–95.
7. **Dumyati G, Stevens V, Hannett GE, Thompson AD, Long C, Maccannell D, Limbago B.** 2012. Community-associated Clostridium difficile infections, Monroe County, New York, USA. Emerg. Infect. Dis. **18:**392–400.
8. **Dial S, Kezouh A, Dascal A, Barkun A, Suissa S.** 2008. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. CMAJ **179:**767–772.
9. **Khanna S, Pardi DS.** 2010. The growing incidence and severity of Clostridium difficile infection in inpatient and outpatient settings. Expert Rev. Gastroenterol. Hepatol. **4:**409–416.
10. **Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM.** 2012. Azithromycin and the risk of cardiovascular death. N. Engl. J. Med. 366:1881–1890.

Address correspondence to S. Di Bella, stefano932@gmail.com.

For the author reply, see doi:10.1128/AAC.00864-13.

doi:10.1128/AAC.00828-13