Open Forum Infectious Diseases

MAJOR ARTICLE

Practice Patterns of Infectious Diseases Physicians in Transitioning From Intravenous to Oral Therapy in Patients With Bacteremia

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Background. Bacteremia in adult patients has traditionally been treated with extended courses of intravenous antibiotics. Data on the use of (or rapid transition to) oral therapy are limited.

Methods. Adult infectious disease physicians participating in the Infectious Diseases Society of America Emerging Infections Network (EIN) were surveyed regarding their use of oral antibiotics in patients with bacteremia. Respondents were asked to assume that patients were hemodynamically stable, recovered bacteria were susceptible to potential antibiotics, adequate source control had been achieved, and patients had adequate gastrointestinal absorption. Variables of specific bacteria, oral agent, and associated infection were included.

Results. A total of 655 (50%) of 1321 EIN participants responded. Under certain conditions, 88% would transition patients with Gram-negative bacteremia to complete a course of therapy with oral antibiotics; 71% would transition patients with Gram-positive bacteremia to oral agents. Only 78 (12%) respondents would not treat any bacteremic patient with oral agents. Most respondents (≥75%) were comfortable treating infections secondary to Enterobacteriaceae, *Salmonella*, *Pseudomonas*, *Stenotrophomonas*, *Streptococcus pneumoniae*, and β-hemolytic streptococci with oral agents. Fewer than 20% endorsed use of oral antibiotics for *Staphylococcus aureus* or in cases of endocarditis. Fluoroquinolones and trimethoprim-sulfamethoxazole were the preferred agents in Gram-negative bacteremia; linezolid and β-lactams were the preferred agents in Gram-positive bacteremia.

Conclusions. In select circumstances, the majority of respondents would transition patients to oral antibiotics, in both Gram-negative and Gram-positive bacteremia. Most agreed with the use of oral agents in Gram-negative bacteremia caused by Enterobacteriaceae, but they would not use oral agents for Gram-positive bacteremia caused by *S aureus* or in endocarditis.

Keywords. bacteremia; oral antibiotics; oral antimicrobial agents.

Infections complicated by bacteremia have traditionally been treated with intravenous (IV) antimicrobial agents. Data supporting the use of (or rapid transition to) oral antimicrobial agents in these infections are quite limited. Intravenously infused antibiotics carry multiple advantages, including high blood levels, delivered to the site of infection, with assurance that patients are receiving adequate therapy, through avoidance of potential issues with drug absorption, distribution, and adherence. Once the patient's infection is controlled and the cause (pathogen, antimicrobial susceptibility of the pathogen, source, etc) is known, continued treatment with IV antibiotics may not be the most beneficial choice. In addition to the cost of these agents and the expense of placement and maintenance of IV access, catheter-related infections and thrombosis are untoward effects of continued IV therapy. Oral treatment, when possible, obviates these negative impacts. Multiple factors influence the efficacy of transitioning to oral antimicrobial agents in these serious infections, including bioavailability of the agent and whether therapeutic levels of drug are achievable at the site of infection. Additional concerns include patient adherence to treatment plans.

The Infectious Disease Society of America (IDSA) Emerging Infections Network (EIN) is a provider-based emerging infections sentinel network that includes infectious disease (ID) specialist physicians from across the United States [1]. We conducted a survey to assess the practice patterns of these ID specialists in transitioning patients to oral antibiotics in the treatment of bacteremia. Our survey examined which bacterial pathogens our respondents felt comfortable treating with oral agents and with which antibiotics. We also included the source of infection as a variable in these questions.

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METHODS

A 10-question multiple choice/open comment survey was developed by the authors, with input and pilot testing by ID physicians with additional content expertise. On September 18, 2018, we distributed the survey by e-mailed link or by facsimile to all 1441 IDSA EIN IDs physician members in active adult-based practice. Two reminders were sent to nonrespondents and the survey remained open until October 14, 2018.

The survey included 2 clinical vignettes. The first case was a patient with Gram-negative bacteremia secondary to acute pyelonephritis. The second was the case of a patient with Gram-positive, central-line associated bloodstream infection (see Supplementary Appendix A). Questions associated with each vignette asked respondents to select oral antibiotics/antibiotic classes, specific organisms/organism group, and infectious sources of bacteremia for which they would be comfortable transitioning patients to oral therapy. For both clinical vignettes, the survey included a note stating, "For all questions assume a hemodynamically stable patient with known susceptible bacteria, adequate source control, and presumed adequate gastrointestinal absorption." An open-text field was provided following each answer to allow survey respondents to comment on the choices.

Practice characteristics for participants, including employment, geographic location, and years of practice were imported from the EIN database. Similar to previous EIN surveys, the response rate was calculated from EIN members who had ever responded to a survey [1]. Descriptive statistics were calculated as percentages for each response category. Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

RESULTS

Participants

Of 1321 adult ID physician IDSA EIN participants who had ever responded to an EIN survey, 655 (50%) responded to this survey (Table 1). This included physicians from all regions of the United States, ranging in experience from fellows-in-training to those with at least 25 years of IDs experience. Hospital types represented by respondents included community, nonuniversity teaching, university, Veterans' Affairs or other federal (eg, military), and city/county.

Gram-Negative Bacteremia

A total of 575 of 655 (88%) of participants responded yes to the question, "In your clinical practice, are there scenarios in which you transition patients with gram-negative bacteremia to oral antibiotics to complete a course of therapy?" In a clinical vignette describing a 36-year-old woman with acute pyelonephritis and *Escherichia coli* bacteremia, more than 50% of the 575 respondents felt comfortable transitioning this patient to an oral fluoroquinolone, trimethoprim/sulfamethoxazole, or beta-lactam antibiotics (Figure 1A). When queried about duration of total therapy for Gram-negative bacteremia, 64 of 557 reported treating for ≤7 days (11%), 234 reported treating from 8 to 13 days (42%), 254 reported treating for 14 days (46%), and 5 reported treating for more than 14 days (0.9%).

Respondents were asked if their willingness to use an oral agent would change if the bacterial pathogen were altered. More than 60% of participants felt comfortable with oral antibiotic therapy in patients bacteremic with other Enterobacteriaceae, *Salmonella*, *Pseudomonas*, *Stenotrophomonas*, multidrug-resistant *E coli*, and *Acinetobacter* (Figure 1B). When queried about other sources of Gram-negative bacteremia, more than 80% of participants felt comfortable using oral agents in bacteremias from gastrointestinal sources, without abscess or with drained abscess, pulmonary sources, and catheter-related infections (line removed) (Figure 1C). Only 34% felt comfortable using oral agents in gastrointestinal sources with undrained abscesses; 15% reported they would feel comfortable using oral agents in Gram-negative endocarditis.

Gram-Positive Bacteremia

In response to the general question, "In your clinical practice, are there scenarios in which you transition patients with gram-positive bacteremia to oral antibiotics to complete a course of therapy?", 71% (466 of 655) of participants responded in the affirmative. When provided with a scenario in which a 50-year-old man presented with group B *Streptococcus* bacteremia that was associated with a central venous catheter infection, more than 60% of participants felt comfortable transitioning this patient to oral linezolid or a beta-lactam antibiotic (Figure 2A). When queried how their practice would change in response to other Gram-positive bacteria, more than 80% indicated that they would feel comfortable treating with oral agents if the Gram-positive bacteria were *Streptococcus pneumoniae* or other beta-hemolytic streptococci. This declined to 50% or more feeling comfortable if non-*aureus Staphylococcus* or *Enterococcus* (including vancomycin-resistant enterococci) were recovered. Less than 20% felt comfortable using oral antibiotics to treat *Staphylococcus aureus* bacteremia (Figure 2B). Most participants (more than 90%) would use oral antibiotics in the treatment of Gram-positive bacteremia when the source was skin and skin structure infection without abscess or with abscess drained (Figure 2C). Greater than 80% would use oral antibiotics in bacteremias with a pulmonary source. Only 12% reported they would use oral antibiotics in the setting of endocarditis.

DISCUSSION

Based on our results, the majority of ID physicians in the United States seem to be comfortable transitioning patients with both Gram-negative and Gram-positive bacteremia from IV to oral

Table 1. Practice Characteristics for Infectious Diseases (ID) Physician Respondents (N = 655) Categorized by Whether There Were Scenarios in Which They Would Transition Patients With Gram-Negative and Gram-Positive Bacteremias to Oral Antibiotics to Complete a Course of Therapy

Variable	Would Use Oral Antibiotics in Gram-Negative Bacteremia	Would Use Oral Antibiotics in Gram-Positive Bacteremia	Total
Total number (%)	575 (87.8)	466 (71.2)	655 (100)
US Census Bureau Region			
South	163 (84.9)	128 (66.7)	192
Midwest	153 (90.0)	121 (71.2)	170
Northeast	122 (87.8)	104 (74.8)	139
West	133 (88.7)	109 (72.7)	150
Canada and Puerto Rico	4 (100)	4 (100)	4
Years of ID Experience			
<5 years	118 (89.4)	93 (70.5)	132
5–14 years	202 (91.0)	164 (73.9)	222
15–24 years	91 (87.5)	69 (66.4)	104
≥25 years	164 (83.3)	140 (71.1)	197
Primary Hospital Type			
Community	160 (89.9)	120 (67.4)	178
Nonuniversity teaching	162 (90.5)	134 (74.9)	179
University	181 (83.8)	155 (71.8)	216
Veterans' Affairs or other Federal	44 (88.0)	35 (70.0)	50
City/county	28 (87.5)	22 (68.8)	32
Primary Hospital Bed Size			
<200	58 (80.6)	43 (59.7)	72
200–350	135 (90.6)	113 (75.8)	149
351–450	90 (84.9)	71 (67.0)	106
451–600	124 (90.5)	100 (73.0)	137
>600	168 (88.0)	139 (72.8)	191

antibiotics under many clinical scenarios. Whether and when to use oral antibiotics in the treatment of patients with infections complicated by bacteremia has not been clearly defined by randomized clinical trials. Thus, clinicians who choose to transition to oral therapy in treatment of bacteremia are forced to select the best oral antimicrobial agent and to decide when to transition patients away from IV therapy, all without the benefit of robust data from randomized controlled trials. What data exist are chiefly from retrospective studies, small randomized trials, and data extracted (ie, subanalysis) for bacteremic patients identified in larger randomized studies. Most data are from urinary tract infections secondary to Enterobacteriaceae, community-acquired pneumonias secondary to *S pneumoniae*, and endocarditis secondary to Gram-positive bacteria. Timing of transition to oral agents and total length of therapy varies greatly amongst these reports.

Gram-Negative Bacteremia

The greatest quantity of data currently exists for oral stepdown therapy in patients with Enterobacteriaceae bacteremia. The majority of these data are from pyelonephritis/complicated urinary tract infections, but the literature does include data from gastrointestinal infections and, less commonly, from central line-associated, pulmonary and skin and skin structure infections [2–10]. Only the study by Mombelli et al [10] directly compares oral and IV therapy in a randomized fashion—comparing oral and IV ciprofloxacin as initial empirical therapy in severe pyelonephritis or complicated urinary tract infection. In this study of 163 patients, 83 received oral therapy. Bacteremia was noted in 53 participating patients, and outcomes were noted to be similar in bacteremic patients with oral or IV ciprofloxacin. Another randomized clinical trial reported the use of early oral antibiotics (after 6 days of IV therapy) in the treatment of acute cholangitis with bacteremia [7]. This small study of 59 patients found noninferiority in the orally transitioned patient group when compared with those who received all IV therapy. Comparison of the available retrospective data is also made difficult by varying times of transition to oral antimicrobials (ranging from 3 to 6 days). This interpretation is further confounded by emerging data on the use (ie, efficacy) of shorter course antimicrobial therapy in Enterobacteriaceae bacteremia (6–10 days versus 11–16 days) [11]. In our survey, courses of therapy from 8 to 14 days were preferred by most ID physicians. Courses of 7 days or less were acceptable to only 11% of respondents. Therefore, if shortened courses of antibiotic therapy are ultimately proven to be effective, a transition to oral antibiotics after 6 or more days may become irrelevant.

Gram-Positive Bacteremia

Current data available to inform use of oral antimicrobials in the treatment of Gram-positive infections with bacteremia are also limited. Virtually no data on using initial oral therapy in

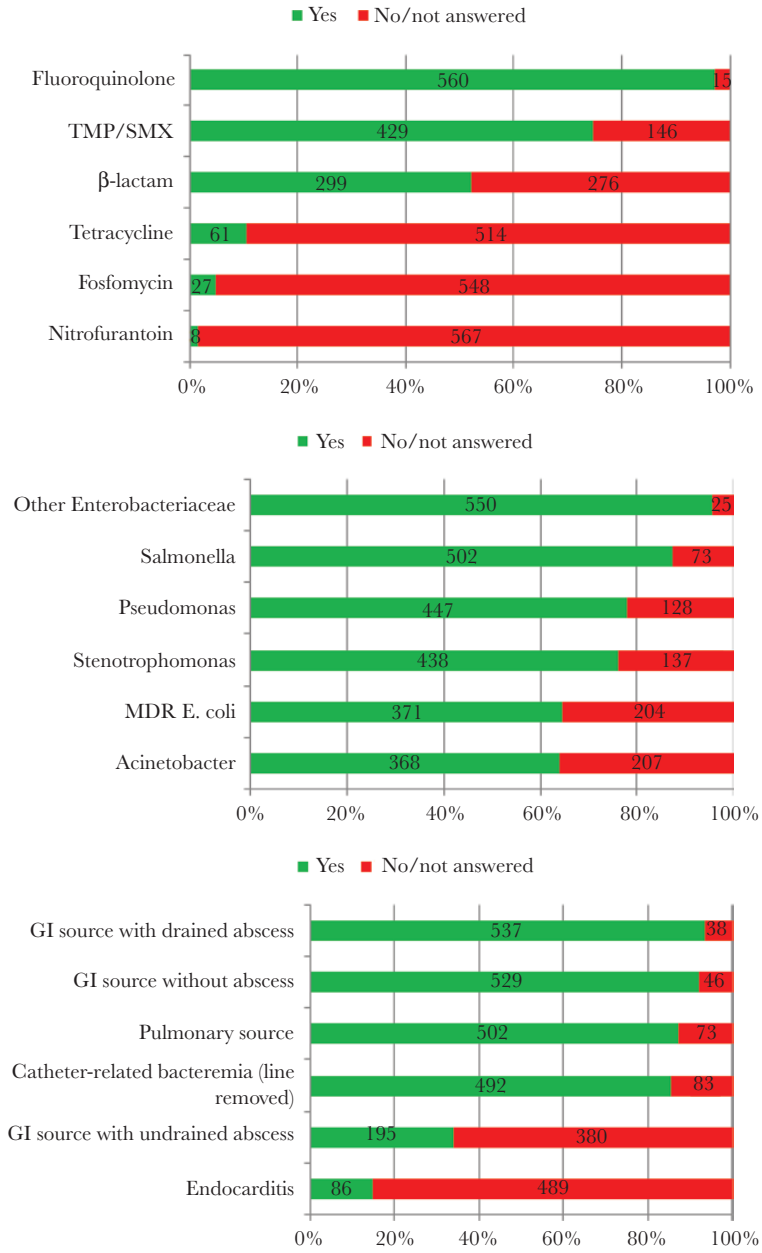

Figure 1. Patient vignette of a 36-year-old woman who presented with symptoms of acute pyelonephritis, who responded to initial intravenous antibiotics, and had *Escherichia coli* recovered in both blood and urine cultures, susceptible to all listed agents; N = 575. (A) Which of the listed oral agents would respondents feel comfortable transitioning to. (B) Would respondents be willing to use an oral antibiotic if the organism was not an *E coli*, but rather _____? (C) Would respondents feel comfortable using an oral agent given the following sources of the Gram-negative bacteremia? MDR, multidrug-resistant; TMP/SMX, trimethoprim/sulfamethoxazole.

Gram-positive bacteremia exists. Agreement on transition to oral therapy in Gram-positive bacteremia appears most consistent in pneumonia (with bacteremia) caused by *S pneumoniae*. Based on small retrospective studies and a single randomized controlled trial, clinical practice guidelines for community-acquired pneumonia currently suggest that a "patient should be switched from intravenous to oral therapy when they are hemodynamically stable and improving clinically" [12–14]. In a recent study, a randomized clinical trial supporting transition to oral antibiotics in endocarditis was published. This study of 400 subjects included follow-up on oral therapy in patients with Gram-positive endocarditis after receiving at least 10 days of IV therapy [15]. The authors found that transition to oral was noninferior to continued IV therapy. In another large study, 214 patients were switched to oral therapies after a median 21 days of IV therapy [16]. Similar results were reported in another retrospective cohort study, which required only 3 days of IV therapy before change [17], and a recent single-center retrospective review of outpatient therapy of methicillin-resistant *S aureus* bacteremia [18]. Older data also support the use of

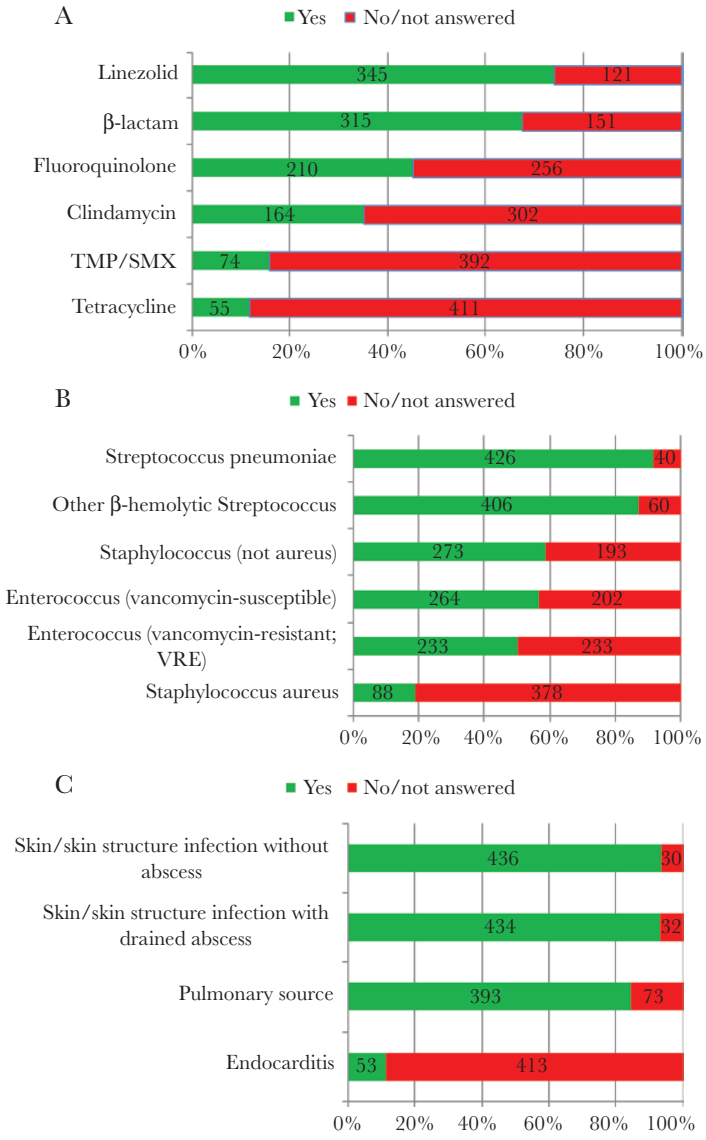

Figure 2. Patient vignette of a 50-year-old man admitted with fevers, chills, and leukocytosis correlated with central venous catheter infusions. He is started in intravenous vancomycin and the catheter is removed. Symptoms and leukocytosis resolve; blood cultures recovered group B *Streptococcus*, susceptible to all listed antibiotics. Follow-up blood cultures are negative; N = 466. (A) Which of the listed oral agents respondents would feeling comfortable transitioning to. (B) Would respondents be willing to use an oral antibiotic if the organism was not a group B *Streptococcus*, but rather _____? (C) Would respondents feel comfortable using an oral agent given the following sources of the Gram-positive bacteremia? TMP/SMX, trimethoprim/sulfamethoxazole.

combination oral antibiotic regimens in the treatment of right-sided endocarditis secondary to *Staphylococcus* [19–21]. Use of IV linezolid in the treatment of *S aureus* and enterococcal bacteremia is the subject of several studies [22–25]. Although the use of oral linezolid has not been included in these, the approximately 100% bioavailability of the oral formulation of this drug has been interpreted by many as supportive of oral linezolid use in these infections. In a recent subanalysis of a nonrandomized, noncontrolled *S aureus* bacteremia study, Willekens et al [26] identified 45 patients transitioned to oral linezolid between 3 and 9 days of therapy. Compared with a propensity score-matched group of 90 patients who received standard parenteral therapy (both groups treated for a median of 15 days), there was no difference in 30-day all-cause mortality or 90-day relapse, and median length of hospital stay was 11 days less.

The overall burden of bloodstream infections in the United States has been estimated to be 536–628 000 per year, with 70–85 000 deaths per year in the United States [27]. Management of these infections in the safest, most effective and cost-efficient manner is imperative. In addition to preventing unnecessary central line-associated infections and thromboses, antimicrobial stewardship programs also promote early transition to oral antimicrobials as a cost-saving measure [28]. Unfortunately, no data from randomized clinical trials inform clinicians' decisions

to select the best oral antimicrobial agent and decide when to transition patients away from IV therapy. Selection of when to transition, and which agents to transition to, is based on many factors including bioavailability of drugs, source of patient's bacteremia, patient's ability to absorb antimicrobial agents, perceived adherence, and other underlying comorbidities. Previous reviews and surveys (including of European ID specialists) have examined this issue in recent years [29–31].

Our study has 4 major limitations. First, we recruited a convenience sample of ID physicians, so the opinions of respondents may not be generalizable to other IDs physicians. Second, we relied on self-report, and individual responses to questions may be subject to recall bias. For example, we did not do chart reviews to validate expressed treatment approaches. Third, we limited the number of questions for this query to minimize response fatigue; however, this approach also limited the number of different antimicrobial-prescribing scenarios considered, limiting the overall scope of inquiry. Finally, although our 50% physician response rate was relatively high, a response bias may still exist. Respondents may have been more likely to transition to oral therapy than the general IDs physician population.

CONCLUSIONS

Despite the limitations listed above, our findings indicate that the vast majority of respondents would transition patients with Gram-negative bacteremia from IV to oral antibiotics, and a majority of respondents would transition patients with some Gram-positive bacteremias, provided that source control is achieved. In contrast, most respondents would not use oral agents for Gram-positive bacteremia caused by *S aureus* or for patients with endocarditis. Our results clearly indicate the need for future randomized controlled trials to inform optimal treatment choices for patients with bacteremia. Without guidance from randomized clinical trials, expert assistance by an ID physician and IDs pharmacists in managing many or most of these cases is warranted.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author

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