Antimicrobial Stewardship News
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Duration of Therapy for Gram-Negative Bloodstream Infections

Introduction

The optimal duration of treatment of Gram-negative bloodstream infections (GNBSI) has been a long-standing unresolved question. Shortly after the discovery of penicillin, experts reported success using treatment durations ranging from 6 to 46 days.[1,2] However, until recently, no well-constructed studies were done to determine the optimal duration of treatment. Current IDSA guidelines remain unhelpful in answering this important question. A recent survey of infectious diseases specialist's practice patterns concluded that most specialists prescribe at least 14 days of antibiotics for their patients with BSI due to Gram-negative bacilli.[3]

This DASON newsletter will focus upon the results of recent studies addressing the duration of antibiotic therapy, the efficacy and optimal timing of oral step-down therapy, and the impact of antimicrobial stewardship programs in the treatment of uncomplicated GNBSIs.

Duration of Therapy

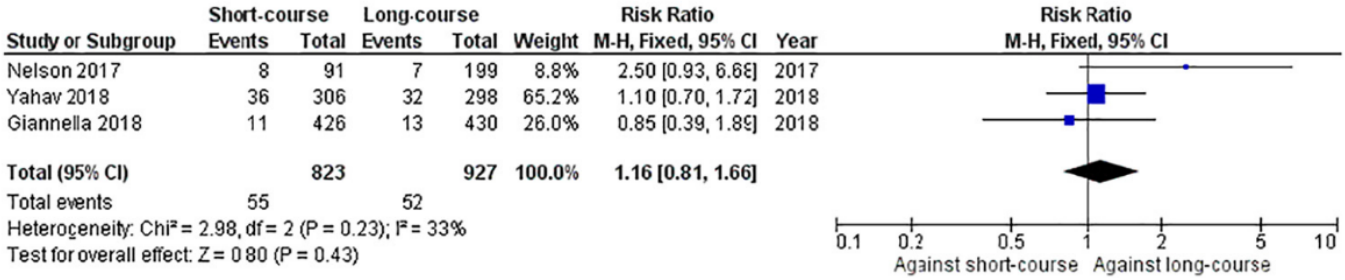
Chotiprasitsakul and colleagues performed a retrospective, propensity-score matched analysis of 770 patients with *Enterobacteriaceae* GNBSI across three large, academic medical centers.[4] Patients were dichotomized into two cohorts: short antibiotic duration (6-10 days, median 8 days) and long antibiotic therapy (11-16 days, median 15 days). After propensity adjustment, there was no difference in 30-day all-cause mortality (9.6% vs 10.1%, respectively). Rates of recurrent infection, *Clostridioides* infection, and MDR GN carriage at 30 days were also similar between groups. In a subanalysis, no risk reduction was seen for each additional day of antibiotic therapy. Of note, *E. coli* and *Klebsiella* species comprised the majority of infections. Importantly, most patients included in this study (over 99%) underwent adequate source control within 7 days of diagnosis.

Giannella et al. evaluated 856 Italian patients with GNBSI who received short (≤ 10 days, median 8 days) or long (> 10 days, median 15 days) courses of antibiotic therapy for *E. coli* bacteremia.[5] No differences in mortality (4.9% vs. 6.0%) or rates of relapse (5.4% vs. 4.4%) were observed between the short and long duration cohorts. However, immunosuppression and end-stage liver diseases were independent risk factors for relapse.

Nelson et al. reviewed 411 patients with GNBSI and found that 90-day mortality was higher (8.2% vs. 3.3%) in patients who were given short (7-10 days, median 8 days) durations of therapy when compared to patients treated with longer (>10 days, median 13 days) regimens. However, a substantial number of patients (121) were lost to follow-up and censored in this study.

To avoid biases inherent in retrospective analyses, Yahav and investigators conducted a randomized, open-label, non-inferiority trial of the duration of therapy for GNBSI at two Israeli and one Italian hospitals.[6] Six-hundred and four patients with GNBSI were randomized to receive 7 or 14 days of antibiotics. Patients were required to be afebrile and hemodynamically stable for 48 hours at the time of randomization.

Figure 1. Forest plot from meta-analysis of 90-day all-cause mortality among patients receiving ≤ 10 days versus > 10 days of antibiotics.



The primary outcome of the study was a composite of 90-day all-cause mortality, relapse, hospital readmission, or prolonged hospitalization greater than 14 days. In both intention-to-treat and per protocol analyses, the 7-day duration arm was non-inferior to the 14-day duration in arm with respect to the primary outcome.

Finally, Tansarli published a meta-analysis comprised of the studies performed by Yahav, Giannella, Chotiprasitsakul, and Nelson, along with another retrospective analysis from Mercuro.[7,8] In pooled analyses, cure rates, 30- and 90-day mortality rates were not statistically or clinically different in patients who received short or long antibiotic courses (**Figure 1**).

In summary, a growing body of evidence suggests that 10-day (and probably 7-day) antibiotic courses are sufficient for treatment of uncomplicated (i.e, source control attained), Gram-negative bacteremia caused by Enterobacteriaceae. Further studies are needed to determine treatment of other GNBSIs, such as *Pseudomonas* and *Acinetobacter*.

Oral Stepdown Therapy

Many patients with GNBSI are initially treated with IV antibiotics, and then "stepdown" oral therapy is substituted following clinical improvement. However, the efficacy and optimal timing of conversion to oral antibiotics are important unresolved questions.

Tamma and her colleagues evaluated the efficacy of oral stepdown therapy in patients with GNBSI in a retrospective study with propensity score matching at two university hospitals.[9] Outcomes of patients who completed a 7-15-day course of intravenous antibiotic therapy were compared to patients who were transitioned to oral antibiotics within 5 days of antibiotic initiation. After propensity matching, there were no differences in 30-day all-cause mortality (13.1% vs. 13.9%, PO vs IV group). Patients transitioned to oral therapy spent two fewer days hospitalized (5 days vs. 7 days). This study was not sufficiently powered to detect differences in outcomes among various oral stepdown regimens (e.g. fluoroquinolones vs. beta-lactams).

Mercuro and colleagues retrospectively evaluated the outcomes of 305 patients with GNBSI due to an Enterobacteriaceae species who received stepdown oral therapy for Enterobacteriaceae GNBSI with either a beta-lactam or a fluoroquinolone.[8] The most commonly used beta-lactams were amoxicillin-clavulanate, cephalexin, and cefdinir. After adjustment, beta-lactams were non-inferior to fluoroquinolones with respect to all-cause mortality; however, the all-cause mortality was extraordinarily low— (1%) in the entire study cohort.

Punjabi comprised a meta-analysis of 8 retrospective studies and 2289 patients with GNBSI who received step down oral therapy.[10] All-cause mortality did not differ between fluoroquinolone and beta-lactam cohorts; however, risk of relapse was significantly higher in patients treated with beta-lactam therapy (1.98% v. 5.46%). The authors could not determine if this difference was due to intrinsic differences between fluoroquinolones and beta-lactams, or simple under-dosing of beta-lactams.

Antimicrobial Stewardship Strategies

How can this information be implemented at the local hospital level? Is such implementation feasible and is it safe?

Erickson et al. recently published a retrospective study of outcomes before and after adoption of an antibiotic stewardship "bundle" designed for patients with GNBSIs.[11] An ID physician and pharmacist reviewed all cases of GNBSI and provided guidance on the total duration of therapy, the optimal timing and choice of oral step-down therapy, the appropriateness of follow-up diagnostic testing, and 7-day treatment durations, as appropriate. Patients were excluded from review if they had received a hematopoietic or solid organ transplant, or if source control could not be achieved. Following implementation of this protocol, duration of therapy decreased from a median of 14 days (10-16 days, IQR) to a median of 10 days (7-14 days, IQR). LOS decreased by one day, and a cost savings of $3,800 per case was calculated. While 30-day mortality increased from 0% pre-intervention to 2.3% post-intervention, this was not statistically significant and represented only two deaths in the post-intervention phase.

These findings offer an encouraging framework for the creation of tailored bundles to combat GNBSI at local community institutions.

Key Points

- Uncomplicated GNBSI caused by Enterobacteriaceae can be effectively treated with 7-10 days of antibiotics if patients rapidly improve after starting effective treatment and source control is achieved.
- Transition to oral antibiotic stepdown therapy can be performed within 5 days of antibiotic initiation if the patient is clinically improving.
- More investigation is needed to determine the optimal regimen for oral stepdown therapy. However, oral regimens consisting of a beta-lactam or a fluoroquinolone agent are usually effective if they are active against the causative pathogen, if they are properly dosed, and if patient compliance occurs.
- Bundles similar to the one described above may be an effective tool in managing patients with uncomplicated GNBSI due to Enterobacteriaceae at institutions with stewardship programs staffed with personnel with the expertise and resources to provide timely clinical reviews and effective communication with treating clinicians.
- Immunosuppressed patients and those with end-stage liver disease are at higher risk of relapse with shorter durations of antibiotic therapy. In these patients a longer duration (10-14 days) may be warranted.

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