Shortened IV Antibiotic Course for Uncomplicated, Late-Onset Group B Streptococcal Bacteremia

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BACKGROUND: Guidelines recommend a prolonged course (10 days) of intravenous (IV) antibiotic therapy for infants with uncomplicated, late-onset group B Streptococcus (GBS) bacteremia. Our objective was to determine the frequency with which shorter IV antibiotic courses are used and to compare rates of GBS disease recurrence between prolonged and shortened IV antibiotic courses.

METHODS: We performed a multicenter retrospective cohort study of infants aged 7 days to 4 months who were admitted to children’s hospitals in the Pediatric Health Information System database from 2000 to 2015 with GBS bacteremia. The exposure was shortened IV antibiotic therapy, defined as discharge from the index GBS visit after a length of stay of ≤8 days without a peripherally inserted central catheter charge. The primary outcome was readmission for GBS bacteremia, meningitis, or osteomyelitis in the first year of life. Outcomes were analyzed by using propensity-adjusted, inverse probability–weighted regression models.

RESULTS: Of 775 infants who were diagnosed with uncomplicated, late-onset GBS bacteremia, 612 (79%) received a prolonged IV course of antibiotic therapy, and 163 (21%) received a shortened course. Rates of treatment with shortened IV courses varied by hospital (range: 0%–67%; SD: 20%). Three patients (1.8%) in the shortened IV duration group experienced GBS recurrence, compared with 14 patients (2.3%) in the prolonged IV duration group (adjusted absolute risk difference: −0.2%; 95% confidence interval: −3.0% to 2.5%).

CONCLUSIONS: Shortened IV antibiotic courses are prescribed among infants with uncomplicated, late-onset GBS bacteremia, with low rates of disease recurrence and treatment failure.

WHAT’S KNOWN ON THIS SUBJECT: Experts recommend 10 days of intravenous (IV) antibiotic therapy for the treatment of late-onset group B Streptococcus bacteremia. Prolonged IV courses increase the risk of central line complications, including line breakage, thrombosis, and infection.

WHAT THIS STUDY ADDS: Despite recommendations to treat uncomplicated, late-onset group B Streptococcus bacteremia with prolonged IV antibiotic therapy, shortened courses are prescribed, with low rates of disease recurrence and treatment failure.
Group B Streptococcus (GBS) is a leading cause of invasive bacterial infections among infants <3 months of age. Although intrapartum antibiotic prophylaxis has substantially reduced the risk of early-onset GBS disease (infants 0–6 days of age), rates of late-onset GBS disease (infants 7–90 days of age) have not changed, affecting 1 in every 3000 infants born in the United States each year.\(^3\)

Guidelines recommend prolonged intravenous (IV) antibiotic therapy (10 days) to treat uncomplicated, late-onset GBS bacteremia; however, no studies have compared outcomes among infants who receive prolonged versus shortened durations of IV antibiotic therapy. Case reports suggest that infants who are treated with lower doses or shorter durations of IV antibiotic therapy may be prone to recurrence of disease,\(^5,6\) although more recent evidence has led to challenges to the recommendation for prolonged IV therapy.\(^7\) First, peripherally inserted central catheters (PICCs) are often necessary for these long IV antibiotic courses, but PICC complications that necessitate early line removal are common, particularly among infants.\(^8\) Second, in a prospective study published in 2007, 29 infants suffering from GBS bacteremia were successfully treated with a conversion to oral antibiotic therapy after 48 hours of IV therapy, and it was revealed that highly bactericidal concentrations were easily achieved with an enteral amoxicillin regimen.\(^9\) Third, a recurrence of GBS disease may be more related to environmental and host factors than the initial antibiotic regimen. The mucosal surfaces of infants often remain colonized with GBS after completion of antibiotic treatment,\(^10\) and breast milk may contain GBS.\(^12\) Finally, the efficacy of shortened IV antibiotic courses for other invasive pediatric infections, such as osteomyelitis,\(^13,14\) complicated pneumonia,\(^15\) and complicated appendicitis,\(^16\) has been established.

Given the existing ambiguity regarding the optimal duration of IV antibiotic therapy to treat uncomplicated, late-onset GBS bacteremia, we sought to (1) determine the frequency with which these infants are treated with IV antibiotic durations that are shorter than the guideline recommendation and (2) compare rates of GBS disease recurrence and treatment failure among infants treated with prolonged versus shortened IV antibiotic courses.

**METHODS**

**Study Design and Setting**

We identified a retrospective cohort of infants with uncomplicated, late-onset GBS bacteremia using the Pediatric Health Information System (PHIS) database. The PHIS database provides deidentified information that details hospital and patient demographic data, administrative data, such as discharge diagnosis and procedure coding, and detailed billing information, including laboratory, imaging, pharmacy, and supply charge data, for patients who are cared for at 49 US stand-alone children’s hospitals. Patients are assigned a single identifier, which allows for longitudinal linkage of all visits within a single PHIS hospital. Data for the current study were abstracted from emergency, inpatient, or observation visits. The PHIS is operated by the Children’s Hospital Association (Lenexa, KS).

**Participants**

Patients ≤4 months of age who were discharged from a PHIS hospital between January 2000 and September 2015 with an International Classification of Diseases, Ninth Revision (ICD-9) discharge diagnosis code for GBS disease and bacteremia were eligible for inclusion (see Supplemental Table 3 for ICD-9 code definitions). We did not include encounters after the implementation of International Classification of Diseases, 10th Revision coding in October 2015 because the inclusion and exposure codes that we used were validated only for ICD-9 codes. To limit the cohort to infants with uncomplicated GBS disease for whom providers would be most likely to consider shorter courses of IV antibiotics, infants were excluded if any of the following were present during their index admission: (1) a diagnosis of invasive bacterial or viral infections that might preclude transition to oral therapy (meningitis, osteomyelitis, septic joint, concomitant non-GBS bacterial infection, or herpes simplex virus infection), (2) a history of prematurity (gestational age <29 weeks or birth weight <1500 g), or (3) a complicated or severe hospital course (index hospitalization >14 days or receipt of care in an ICU). Infants ≤7 days old at the time of admission (early-onset GBS disease) were excluded. Patients who were transferred out of the PHIS hospital were excluded to mitigate outcome ascertainment bias.

**Exposure Classification**

The exposure of interest was receipt of a shortened course of IV antibiotic therapy. We defined a shortened course as IV antibiotic treatment ≤8 days, which is 2 days shorter than the guideline-recommended minimum duration.\(^4\) We subtracted 2 days from the guideline minimum to more conservatively classify a shortened course exposure because it is possible that patients could have received an additional day or 2 of parenteral antibiotics before or after their hospitalization (ie, with intramuscular ceftriaxone). The PHIS database details daily medications during hospitalization,
Accuracy of Inclusion and Exposure Codes

Using a manual medical record review of infants with blood cultures that were positive for GBS at Primary Children’s Hospital (a PHIS center) as the gold standard, we estimated the sensitivity and positive predictive values of the study’s ICD-9 inclusion codes to detect true GBS bacteremia and determined how frequently these patients received antibiotic therapy before hospital admission.

We validated our definition of PICC exposure using a PHIS data set from a previously published study of children who were hospitalized for complicated pneumonia and whose medical records were manually reviewed.15 We calculated positive and negative predictive values for PICC status in the complicated pneumonia data set according to (1) presence of a PICC by PHIS charge or procedure code (our study definition) or (2) presence of a PICC on chart review.

Outcomes

The primary study outcome was a recurrence of GBS disease, defined as a hospital revisit with a discharge diagnosis code for GBS disease and a discharge diagnosis code for bacteremia, meningitis, or osteomyelitis in a patient’s first year of life. Treatment failure, defined as a recurrence of GBS disease within 14 days of hospital discharge, was a secondary outcome. To account for the risk of misclassification of GBS disease recurrence, 1 author (E.R.C) manually reviewed all of the discharge diagnosis codes for patients who revisited the hospital in the first year of life but were not classified as suffering from a recurrence of GBS disease. Patients with ICD-9 codes for bacteremia, osteomyelitis, or meningitis but no accompanying code for GBS disease and patients with a code for GBS disease but no accompanying code for bacteremia, osteomyelitis, or meningitis were classified as possibly suffering from a recurrence. A PICC complication was defined by using a previously established set of ICD-9 codes that specified infection or mechanical complication of a vascular device (see Supplemental Table 3).17 In contrast to the original publication, we did not include ICD-9 codes for fever because we did not consider this diagnosis alone as sufficient to define a PICC complication.

To account for the possibility of readmissions for true PICC complications being misclassified as readmissions for GBS disease (falsely elevating the measured rate of recurrence among the prolonged IV therapy group), we divided the prolonged IV therapy group into 2 subgroups for further description. One subgroup received a PICC and was treated with ≤8 days of IV antibiotics as inpatients (these patients were likely discharged with their PICCs). The second subgroup did not receive a PICC and was treated with >8 days of IV antibiotics as inpatients (these patients likely completed their antibiotic treatment in the hospital).

Covariates

Covariates included sex, age (in days), race and/or ethnicity (non-Hispanic white, non-Hispanic African American, Hispanic, or other), primary insurance payer (government, commercial or self-pay, or unknown), history of a birth weight of 1500 to 2499 g or a gestational age of 29 to 36 weeks, history of a complex chronic condition, presence of a concomitant condition, presence of a concomitant urinary tract infection, hospital case mix index, and the year in which a patient was admitted to the hospital. Complex chronic conditions are defined by ICD-9 codes and derived from hospitalization patterns of children with costly illnesses and congenital defects.18 The PHIS case mix index is determined as the average cost weight after each discharge from a PHIS hospital is assigned an All-Patient–Refined Diagnosis-Related Group and severity level.

Statistical Analysis

To account for nonrandom treatment selection, we estimated the probability of each patient receiving a shortened IV course. Propensity scores were computed with a multivariable logistic regression, with the predicted probability of a shortened course as the outcome and the above covariates as predictor variables. Patients were then weighted by the inverse of their probability to receive the treatment they actually received. Inverse probability weighting maximizes patient inclusion in the model and can create more balanced comparison cohorts. Finally, the association between exposure and patient outcomes was tested by using logistic regression, with the inverse probability weights assigned to each patient. The association between receipt of a shortened IV antibiotic course and time to a GBS recurrence was measured with an inverse probability–weighted γ regression model, which is robust to nonnormally distributed outcomes. Analyses were performed by using Stata version 14 (Stata Corp, College Station, TX) and R statistical software.19

RESULTS

Study Population

We identified 1369 infants ≤4 months of age with GBS bacteremia.
After applying exclusion criteria, 775 infants with uncomplicated, late-onset GBS bacteremia remained (Fig 1), of whom 612 (79%) received prolonged IV therapy, and 163 (21%) received shortened IV therapy. Late-onset GBS bacteremia occurred at a median age of 48 days (interquartile range [IQR]: 36–68 days). Patients who received a shortened course of IV antibiotics were older, more often admitted in later years, and more likely to have a concomitant urinary tract infection (Table 1).

**Accuracy of Inclusion and Exposure Codes**

ICD-9 codes had moderate sensitivity and high positive predictive values for identifying uncomplicated GBS bacteremia. The sensitivity of our ICD-9 inclusion codes to detect true GBS bacteremia was 72%; of the 32 patients with GBS-positive blood cultures otherwise meeting inclusion criteria on chart review at Primary Children’s Hospital, 23 were captured by our ICD-9 codes in the PHIS database. The positive predictive value was 96%; of the 24 patients who were identified by ICD-9 codes in the PHIS database and cared for at Primary Children’s Hospital, 23 had verified GBS bacteremia on chart review. Among patients with verified GBS bacteremia, 22 of 23 (96%) received ≤1 additional day of antibiotic therapy before hospital admission.

The complicated pneumonia data set revealed high positive and negative predictive values for our study definition of a PICC exposure. The positive predictive value was 85%; of the 579 patients with a PICC who were identified by charges and procedure codes in the PHIS, 491 had a verified PICC on chart review. The negative predictive value was 99%; of the 1544 patients without a PICC who were identified by charges and procedure codes in the PHIS, 1522 did not have a PICC on chart review.

**Antibiotic Treatment**

The most common antibiotics that were prescribed empirically at...

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**TABLE 1** Demographics and Clinical Characteristics

| Variable                          | Shortened IV Therapy, N = 163 | Prolonged IV Therapy, N = 612 | P     |
|-----------------------------------|--------------------------------|--------------------------------|-------|
| Female sex, n (%)                 | 81 (50)                        | 289 (47)                       | .58a  |
| Age, d, n (%)                     |                                |                                | <.01b |
| 7–30                              | 13 (8)                         | 80 (13)                        |       |
| 31–90                             | 124 (76)                       | 475 (78)                       |       |
| >90                               | 26 (16)                        | 57 (9)                         |       |
| Race and/or ethnicity, n (%)      |                                |                                | .74a  |
| Non-Hispanic white                | 62 (38)                        | 215 (35)                       |       |
| Non-Hispanic African American     | 59 (36)                        | 251 (41)                       |       |
| Hispanic                          | 23 (14)                        | 81 (13)                        |       |
| Other                             | 19 (12)                        | 65 (11)                        |       |
| Primary payer, n (%)              |                                |                                | .08a  |
| Government                        | 111 (68)                       | 387 (60)                       |       |
| Commercial insurance or self-pay  | 41 (25)                        | 172 (28)                       |       |
| Unknown                           | 11 (7)                         | 73 (12)                        |       |
| History of prematurity, n (%)     | 1 (1)                          | 16 (3)                         | .12a  |
| Complex chronic condition, n (%)  | 19 (12)                        | 63 (10)                        | 62a   |
| Concomitant urinary tract infection, n (%) | 23 (14) | 32 (5) | <.01a |
| Case mix index, median (IQR)      | 1.03 (0.99–1.11)               | 1.04 (1.00–1.11)               | .52c  |
| Admission y, median (IQR)         | 2007 (04–12)                   | 2009 (05–12)                   | <.02c |

*a* χ² test.

*b* Mann–Whitney U test.

*c* t test.

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**FIGURE 1**

Study flowchart. HSV, herpes simplex virus.
hospital admission were ampicillin plus a third-generation cephalosporin (37%), third-generation cephalosporin monotherapy (28%), or third-generation cephalosporin monotherapy plus vancomycin (7%). Targeted therapy on the day of discharge was most often ampicillin (47%), penicillin (18%), or ceftriaxone (18%). Among patients in the shortened IV therapy group, 27 (16%) received an oral antibiotic on the day of discharge (23 received amoxicillin, 3 received cefdinir, and 1 received penicillin). The median duration of inpatient IV antibiotic therapy for the whole cohort was 9 days (IQR: 4–10 days); the distribution by shortened versus prolonged IV course is presented in Fig 2. Among patients who received shortened IV antibiotic courses, there are biphasic peaks at 3 and 7 days. A proportion of children in the prolonged IV antibiotic therapy group were discharged with a PICC within the first week of hospitalization, but most (67%) completed at least 9 days of inpatient IV antibiotic therapy.

The proportion of children who received a shortened IV course varied considerably by hospital (range: 0%–67%; SD: 20%; Fig 3). No patients were treated with a shortened IV course at 14 hospitals, whereas 5 hospitals treated >50% of their patients with shortened IV courses.

**GBS Recurrence**

Overall, 17 (2.2%) patients suffered from a recurrence of their GBS disease (Table 2). In all but 2 cases, the recurrence was limited to bacteremia. Rates of disease recurrence were low among patients who received shortened IV therapy and prolonged IV therapy: 3 of 163 (1.8%) compared with 14 of 612 (2.3%), respectively (adjusted absolute difference: −0.2%; 95% confidence interval [CI]: −3.0% to 2.5%). Overall, the mean time to recurrence was 25 days (SD: 17 days), and there was no difference by IV treatment duration (adjusted absolute difference: 9 days; 95% CI −13 to 31 days). None of the 27 patients in the shortened IV therapy group who received an oral antibiotic on the day of discharge suffered from a recurrence of GBS disease. The rates of GBS recurrence among patients in the prolonged IV therapy subgroups who were discharged without and with a PICC were 1.5% and 4.0%, respectively (Supplemental Table 4).
Secondary Outcomes
Treatment failure was rare (whether patients received shortened IV therapy \( n = 1 \) or prolonged IV therapy \( n = 6 \)) and did not differ by IV treatment duration (adjusted absolute difference: \(-0.3\%; 95\% \text{ CI: -1.8\% to 1.1\%}\)). Eight patients (1%) experienced PICC complications during their index admission, 7 of whom were in the prolonged IV therapy group. Three patients (all from the prolonged IV therapy group) were readmitted to the hospital with a diagnosis code for a PICC complication within 30 days of their index hospital discharge.

Possible GBS Recurrence
Sixty-one patients revisited the hospital within their first year of life but did not meet our definition of suffering from a recurrence of GBS disease. In a manual review of individual discharge diagnosis codes for these 61 patients, we identified 8 patients with a possible GBS disease recurrence: 6 patients in the prolonged IV therapy group and 2 patients in the shortened IV therapy group. Classifying these 8 patients as suffering from a GBS disease recurrence raised the overall estimate of GBS recurrence to 3.2% (25 of 775) and narrowed the difference in recurrence rates between patients who received shortened IV therapy versus prolonged IV therapy (3.3% vs 3.1%, respectively).

DISCUSSION
Among infants with uncomplicated, late-onset GBS bacteremia who were cared for at US children’s hospitals, we found that, contrary to national recommendations, shortened IV antibiotic courses are being prescribed; shortened courses were prescribed more often among older infants and those with a concomitant diagnosis of urinary tract infection. We found striking variation in IV antibiotic treatment duration by hospital and whether patients received prolonged or shortened IV courses; rates of GBS disease recurrence and treatment failure were low.

The ideal study design to use to answer the question of the effectiveness of shortened versus prolonged IV antibiotic courses for the treatment of GBS bacteremia is a randomized trial. Such a trial is unlikely given the modest prevalence of GBS disease (children’s hospitals in our study treated only 1–3 eligible patients per year) and the rarity of disease recurrence.

In lieu of a randomized trial, we conducted an observational study in which common sources of bias were addressed. First, to limit confounding by indication, we employed exclusion criteria that were used to eliminate higher-risk and sicker patients. The potential for confounding by indication is
further limited by the substantial hospital-level prescribing variation that was observed in our cohort of children with uncomplicated disease, which suggests that the local hospital culture is a major factor governing treatment duration. Second, to assess the possibility of inclusion and exposure misclassification, we validated each set of codes. The positive predictive value of our inclusion criteria was 96%, suggesting that virtually all patients who were included in the study truly had GBS bacteremia. The negative predictive value of our PICC exposure definition was 99%, suggesting that virtually all patients in the shortened IV antibiotic group truly did not receive a PICC. Nevertheless, because our PICC definition was validated among a cohort of children with complicated pneumonia, we identified a subgroup of patients for whom actual receipt of a shortened IV antibiotic course was most likely (patients given an oral antibiotic on their final day of hospitalization). None of these patients suffered a recurrence of GBS disease. A third threat to our study’s validity is outcome misclassification. Although the higher rate of disease recurrence among the prolonged IV therapy subgroup that was discharged with a PICC may be partially explained by misclassified PICC complications, the prolonged IV therapy subgroup that was discharged without a PICC experienced a similar rate of disease recurrence compared with the shortened IV therapy group. Findings were also similar after a manual review of diagnosis codes was used to augment the outcomes to include potential recurrences of GBS. Finally, we suspect that most patients who received shortened courses of IV antibiotic therapy received further treatment with high-dose oral antibiotic therapy after discharge. But because the PHIS database provides only inpatient medication charges, our study does not address the total duration of antibiotic therapy.

Infants without a history of significant prematurity who do not require intensive care for their GBS disease appear to have low rates of recurrence, whether treated with shortened or prolonged IV antibiotic courses. Beyond decreased health care costs, shortened IV antibiotic courses provide the advantage of a diminished burden for families, allowing for patients to leave the hospital sooner, making it easier to administer the antibiotic at home, and decreasing the likelihood that they would develop a treatment-related complication. On the other hand, it should be acknowledged that the CI around the adjusted absolute difference in recurrence between shortened and prolonged IV therapy that was found in the current study is fairly wide; this will warrant consideration in treatment decisions. By using the upper limit of the CI, the number needed to treat with prolonged IV therapy to prevent 1 recurrence of GBS disease would be 40. By using the point estimate, which favors shortened IV therapy, the number needed to treat would be 500. Given that the majority of GBS recurrences will be isolated bacteremia, the number needed to treat to prevent a recurrence with GBS meningitis will be much higher. These estimates may be helpful for parents and providers as they decide what IV antibiotic duration is optimal for a particular child.

**CONCLUSIONS**

A portion of infants with uncomplicated, late-onset GBS bacteremia are treated with shortened courses of IV antibiotic therapy, and they experience low rates of disease recurrence and treatment failure. Early transition to oral antibiotic therapy may be appropriate for carefully selected infants with GBS bacteremia.

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