BRIEF REPORT

# IV Antibiotic Durations for Nontyphoidal *Salmonella* Bacteremia

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ABSTRACT

**OBJECTIVES:** The objective was to determine if shorter intravenous (IV) antibiotic (<7 days) for nontyphoidal *Salmonella* bacteremia (NTS-B) is noninferior to longer (≥7 days) in terms of 30-day emergency department (ER) or rehospitalization in healthy children.

**METHODS:** A retrospective observational study of otherwise healthy children admitted to a children's hospital in the United States from 2006 to 2017 with NTS-B was conducted.

**RESULTS:** Of 231 patients reviewed, 51 patients had NTS-B. Median IV duration for all patients was 5 days (range 2–17 days). The short-duration group (SDG) (<7 days; $N = 32$) had a median of 4 days (range 2–6 days) of IV antibiotics versus a median of 9 days (range 7–17 days) in the long-duration group (LDG) (≥7 days; $N = 19$). The hospital length of stay in the SDG was 3.5 days versus 7 days in the LDG ($P < .001$). The SDG was significantly noninferior to the LDG in terms of ER visits or hospital readmissions within 30 days (absolute risk difference 5.3%; 95% confidence interval −16% to −5%), with only 1 child in the LDG returning to the ER.

**CONCLUSIONS:** IV antibiotic durations for NTS-B in otherwise healthy children were variable within our study group. Shorter courses (<7 days) of IV antibiotics were noninferior to longer courses in healthy children and reduced hospital stay. ER visits and readmissions were rare, and there was no association between IV treatment duration and risk of relapse. Prospective studies are needed to study the safety of shorter courses, but given the absence of evidence favoring longer courses, shorter courses can be considered.

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Deidentified individual participant data will not be made available.

Drs Hess and Dutta designed the data collection instrument, completed data collection, conceptualized and designed the study, and drafted and critically reviewed the initial manuscript; Ms Burdick contributed to the conceptualization of the data collection instrument, completed data collection, and contributed to the manuscript drafting; Dr Minard conducted the analysis and reviewed the final manuscript; and all authors approved the final manuscript as submitted.

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*Salmonella* is a Gram-negative bacilli that causes an estimated 3.4 billion illnesses worldwide and is a major cause of death globally.[1] In 2015, *Salmonella* species (not *Salmonella typhi*) was the most common pathogen isolated from blood cultures in the United States with >7000 infections, of which 37% were in children.[2]

Antibiotics are not recommended for nontyphoidal *Salmonella* gastroenteritis (NTS-GE) because they do not decrease the number of days of symptoms and can prolong shedding.[3,4] Experts do recommend treatment of invasive disease, including bacteremia (nontyphoidal *Salmonella* bacteremia [NTS-B]), but there is limited evidence to support the ideal route and/or duration of therapy.[5] Before the 2018 update, the American Academy of Pediatrics *Red Book: Report of the Committee on Infectious Diseases* recommended that patients with NTS-B receive 10 to 14 days of treatment but did not specify the route. In 2018, their updated recommendations stated that patients confirmed to have NTS-B should receive intravenous (IV) treatment until clearance of bacteremia and then transition to oral therapy to complete 7 to 10 days.[6] These recommendations came from studies done outside the United States that showed that shorter courses of IV antibiotics (3–5 days) are noninferior to ≥10 IV courses and did not increase the risk of readmission to the hospital.[7–9]

Our primary aim in this study was to determine if shorter durations of IV courses (<7 days; short-duration group [SDG]) were noninferior to longer courses (≥7 days; long-duration group [LDG]) in preventing complications and readmissions related to NTS-B in healthy children (aged ≥3 months–18 years) in the United States.

## METHODS

### Study Design and Setting

We conducted a retrospective review of pediatric (≥3 months–18 years old) patients admitted to a large (>500-bed, freestanding) tertiary-care hospital in the United States, from 2007 to 2016. The study was approved by the hospital's institutional review board.

### Study Population

Patients were identified within the electronic medical record by using International Classification of Diseases, Ninth Revision (ICD-9) or International Classification of Diseases, 10th Revision (ICD-10) codes for *Salmonella* infections. Admitted patients aged ≥3 months to 18 years with NTS-GE were included if they had blood cultures obtained. Patients with NTS-B were defined as patients with blood culture results that were positive for nontyphoidal *Salmonella* (NTS) with or without positive stool culture results for NTS, and persistent bacteremia was defined as ≥2 positive culture results.

Exclusion criteria included the following: immunodeficiencies, history of transplant, hemoglobinopathies, or focal extraintestinal infection present on admission.

Clinical information collected included demographics, clinical manifestations, exposures, laboratory and microbiologic results, treatment regimens, antimicrobial susceptibility, and NTS serotypes.

Follow-up data to evaluate treatment outcomes included the following: repeat blood cultures, complications during the hospital stay, and emergency department (ER) visits and/or readmissions within the 30-day period.

### Statistical Analysis

Statistical analyses were performed with SAS for Windows version 9.4 technical support level 1M3 (SAS Institute, Inc, Cary, NC). Noninferiority testing was done by looking at return ER visits within 30 days between the SDG and LDG. The noninferiority test assumed a 0.10 margin of noninferiority, and statistical significance was assessed at the 1-sided 0.05 level. We did not adjust for predictors of IV treatment duration because the primary outcome of return ER visit and/or readmission was rare ($n = 1$).

Baseline patient demographics and clinical characteristics were summarized by medians with minimum and maximum values or frequencies with percentages.

## RESULTS

### Patient Demographics and Clinical Presentation

A total of 231 charts were reviewed with ICD-9 or ICD-10 diagnoses related to *Salmonella* infections, and 51 patients (22%) were found to have NTS-B (Fig 1). Of the 51 patients with NTS-B reviewed, 24 (47%) were of male sex and the mean age at presentation was 3.84 years (range 0.25–16 years; SD 4.6). The most common species was *Salmonella* group C ($N = 29$; 57%), followed by group D ($N = 7$; 14%) and group B ($N = 4$; 8%; Table 1). The most common clinical manifestation was fever ($N = 50$; 98%) and diarrhea ($N = 40$; 78%; Table 1). All patients received cefotaxime or ceftriaxone (CTX) empirically, with 3 patients receiving other empirical antibiotics. Forty-eight (94%) NTS isolates from blood were pansusceptible, and all isolates were susceptible to CTX. Of the 3 isolates that had resistance, 1 group D isolate was resistant to multiple antibiotics but was susceptible to CTX (recent history of international travel to Mexico). Oral antibiotic choices at discharge included amoxicillin ($N = 19$; 37%), third-generation cephalosporin ($N = 14$; 27%), trimethoprim-sulfamethoxazole ($N = 7$; 14%), or ciprofloxacin ($N = 5$; 9.8%), with all others completing 10 days of IV treatment.

### Comparison of Long Versus Short Duration of IV Antibiotics

We compared the demographics, clinical features, exposures, and laboratory values of children in the SDG versus LDG (Table 1). There was no significant difference in age, exposure, NTS serotype, or clinical presentations, including number of boluses required, between the 2 groups.

Of the 51 patients with NTS-B, 32 (63%) were in the SDG and 19 (37%) were in the LDG. Median IV duration for all patients was 5 days (range 2–17 days), and median total duration was 14 days (range 7–18 days), which was not different between the groups ($P = .22$). The SDG had a median of 4 days (range 2–6 days; SD 1.15) of IV antibiotic versus 9 days (range 7–17 days; SD 3.2) in the LDG ($P < .001$). The LDG had a lower white blood cell count on presentation (SDG



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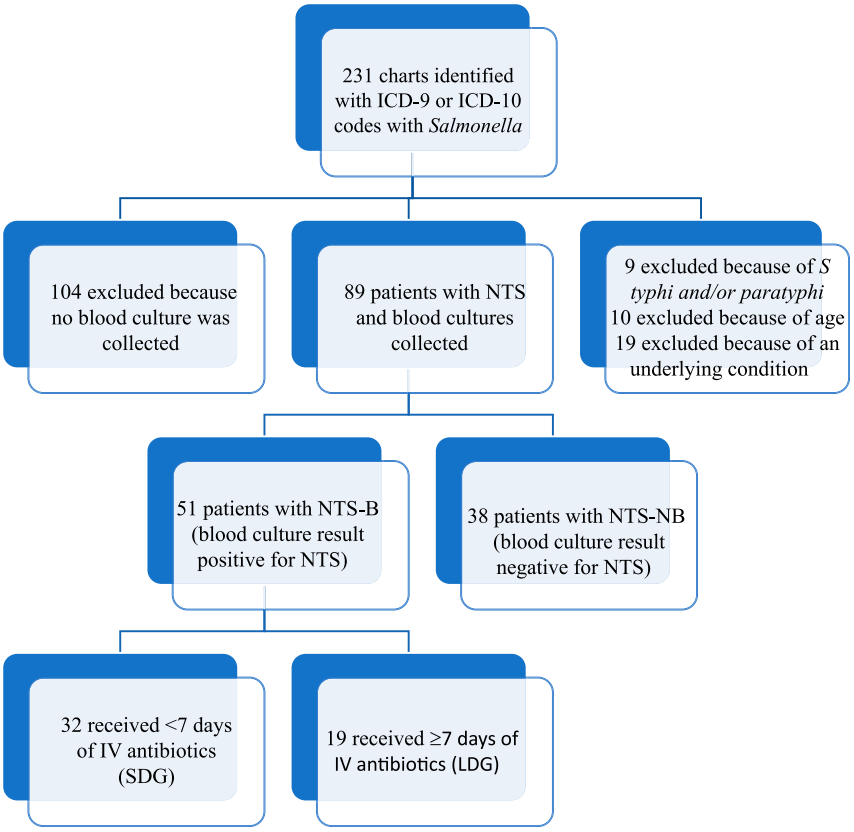


**FIGURE 1** Study population. NTS-NB, nontyphoidal *Salmonella* gastroenteritis without bacteremia.

12 [$10^3$ per $\mu$L] versus LGD 9; $P = .007$), but there was no difference in percent bands or neutrophils. Persistent bacteremia was found in 51% of all patients: 17 (53%) in the SDG and 9 (47%) in the LDG ($P = .06$). Hospital length of stay (LOS) had a median of 3.5 days (range 1–7 days) for the SDG and 7 days (range 4–11 days) for the LDG ($P < .001$). Comparing charges between the LDG and SDG, the difference in LOS translated to a >$15 000 decrease in hospital cost per patient.

The risk of 30-day ER visit or readmission was 0% (95% confidence interval [CI] 0% to 11%) in the SDG and 5.3% (95% CI 1.3% to 26%) in the LDG. The SDG was significantly noninferior to the LDG for 30-day ER visits (1-sided $P = .009$; margin of noninferiority = 0.10). The absolute risk difference was 5.3% (95% CI −16% to −5%). The 1 patient who returned to the ER was in the LDG, received 7 days of IV treatment, and had persistent diarrhea related to NTS-GE but was well appearing and did not require hospitalization.

## DISCUSSION

To our knowledge, this is the largest pediatric study done in the United States to address the implications of shorter IV antibiotic courses in NTS-B in otherwise healthy children. Our study demonstrates that there was significant variability in the duration of IV antibiotic use and revealed that revisits and rehospitalization were rare and did not appear to be associated with IV treatment duration. Consistent with other large pediatric studies, we did not find any adverse outcomes when patients were transitioned to oral antibiotic in <7 days.[10]

Although there are no randomized controlled trials to evaluate the minimum adequate therapy among children with NTS-B, a study in Vietnam done among patients with *Salmonella typhi* infections revealed that a 3-day course of oral ofloxacin was effective in treatment of typhoid fever.[11]

Similarly, another study found shorter courses (3–5 days IV) of antibiotics in children with NTS-B did not increase the risk of complications or readmissions to the hospital.[9] Our study supports the American Academy of Pediatrics *Red Book* updated recommendation of shorter IV antibiotic course followed by oral antibiotic for NTS-B after bacteremia clears.[6]

The choice of antimicrobial treatment is critical in the management of NTS-B. Growing antibiotic resistance among *Salmonella* species is a problem worldwide, with recent reports of NTS showing CTX resistance.[12–14] Current recommendations suggest empirical CTX therapy followed by oral antibiotics to be appropriate management.[6] The universal susceptibility to CTX noted in our study supports the recommendation to use this as a first-line agent in NTS-B. Oral antibiotic choice, as long as susceptible, did not affect the treatment outcome in our study.

It has been shown that 41% of patients with NTS-B have persistent bacteremia, and 2.5% developed a focal complication.[15] Our study had 51% of children with persistent bacteremia, but none developed focal complications. This is potentially related to the fact that all our children were previously healthy with no risk factors for invasive diseases.

Not surprisingly, our study showed that patients in the SDG have shorter hospital LOS, which translates to lower cost and may prevent some of the morbidities associated with hospitalization.

There are several limitations to our study. Firstly, this is a retrospective study; thus, symptom duration may have been subjective. Secondly, patients who did not have blood cultures drawn or were treated as outpatients were excluded, which could lead to a selection bias, potentially toward sicker patients. Another limitation was our small sample size. Although we were likely underpowered to detect small but still potentially meaningful differences in outcomes between the groups, our findings that poor outcomes were rare, regardless of IV treatment duration, should help inform future treatment decisions. Finally, this was a single-institution study; hence, findings



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**TABLE 1** Comparison of SDG versus LDG

| Variables | Total | Short IV (<7 d, SDG) | Long IV (≥7 d, LDG) | *P* |
|---|---|---|---|---|
| | *N* = 51 | *n* = 32 | *n* = 19 | |
| Age at infection, y, mean (SD) | 3.84 (4.59) | 3.39 (4.48) | 4.59 (4.81) | .85 |
| Sex, *n* (%) | | | | >.99 |
| Male | 24 (47.1) | 15 (46.9) | 9 (47.4) | |
| Female | 27 (52.9) | 17 (53.1) | 10 (52.6) | |
| Race, *n* (%) | | | | .004 |
| White | 41 (80.4) | 26 (81.3) | 15 (78.9) | |
| African American | 6 (11.8) | 6 (18.8) | 0 (0) | |
| Asian American | 4 (7.8) | 0 (0) | 4 (21.1) | |
| Ethnicity | | | | >.99 |
| Hispanic, *n* (%) | 18 (36.7) | 11 (36.7) | 7 (36.8) | |
| Non-Hispanic, *n* (%) | 31 (63.3) | 19 (63.3) | 12 (63.2) | |
| Missing | 2 | 2 | 0 | |
| Clinical presentation, *n* (%) | | | | |
| Fever | 50 (98) | 31 (96.9) | 19 (100) | >.99 |
| Diarrhea | 40 (78.4) | 27 (84.4) | 13 (68.4) | .29 |
| Bloody stools | 21 (41.2) | 14 (43.8) | 7 (36.8) | .77 |
| Nausea and/or vomiting | 17 (33.3) | 10 (31.3) | 7 (36.8) | .76 |
| Abdominal pain | 14 (28) | 25 (78.1) | 11 (61.1) | .32 |
| Previous antibiotics within 7 d | 12 (23.5) | 7 (21.9) | 5 (26.3) | .74 |
| Acuity at presentation, ≥2 boluses | 10 (19.6) | 6 (18.8) | 4 (21.1) | >.99 |
| Exposure, *n* (%) | | | | |
| Pets | 7 (13.7) | 3 (9.4) | 4 (21.1) | .40 |
| Travel | 11 (21.6) | 6 (18.8) | 5 (26.3) | .73 |
| Sick contacts | 16 (31.4) | 11 (34.4) | 5 (26.3) | .76 |
| Food | 7 (13.7) | 5 (15.6) | 2 (10.5) | .70 |
| Laboratory values | | | | .007 |
| Initial WBC count, *n* | 50 | 31 | 19 | |
| Days, mean (SD) | 11 (5.1) | 12.19 (4.51) | 9.06 (5.51) | .22 |
| Initial band count percent, *n* | 46 | 29 | 17 | |
| Days, mean (SD) | 20 (13.4) | 18.01 (12.93) | 23.4 (13.9) | .53 |
| Neutrophil percent, *N* | 50 | 31 | 19 | |
| Days, mean (SD) | 26.6 (17.7) | 28.3 (19.02) | 23.8 (15.3) | |
| Positive blood culture results, *n* (%) | | | | .06 |
| 1 | 25 (49) | 15 (46.9) | 10 (52.6) | |
| 2 | 23 (45) | 17 (53.1) | 6 (31.6) | |
| 3 | 2 (3.9) | 0 | 2 (10.5) | |
| 4 | 1 (2) | 0 | 1 (5.3) | |
| Species, group, *n* (%) | | | | .13 |
| A | 1 (2) | 0 | 1 (5.3) | |
| B | 4 (7.8) | 4 (12.5) | 0 (0) | |
| C | 29 (56.9) | 15 (46.9) | 14 (73.7) | |
| D | 7 (13.7) | 5 (15.6) | 2 (10.5) | |
| Other | 10 (19.6) | 8 (25) | 2 (10.5) | |
| Days of fever in hospital, median (range) | 1.0 (0–7) | 1 (0–5) | 2 (0–7) | .047 |

WBC, white blood cell.



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may not be generalizable to other institutional practices.

## CONCLUSIONS

Our study demonstrates that a strategy of shorter IV duration (<7 days; SDG) is noninferior to longer IV duration (≥7 days; LDG) for treatment of NTS-B and can lead to shorter LOS and overall costs and supports the updated guidelines. Overall complications and return to ER and/or admissions were rare in these patients.


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