

## Fifteen-year surveillance of non-typhoidal *Salmonella* bloodstream infections in a tertiary care hospital in southern Türkiye

Merve Yıldız Ergin<sup>1</sup>, Latife Mamikoğlu<sup>1</sup>, Hatice Yazısız<sup>2</sup>, Özlem Koyuncu Özyurt<sup>2</sup>, Tuncer Karpuz<sup>2</sup>, Gözde Öngüt<sup>2</sup>, Betil Özhak<sup>2</sup>, Belkis Levent<sup>3</sup>, Meral Dilara Ögünç<sup>2</sup>

<sup>1</sup> Department of Infectious Disease and Clinical Microbiology, Akdeniz University Medical Faculty, Antalya, Türkiye

<sup>2</sup> Department of Medical Microbiology, Akdeniz University Medical Faculty, Antalya, Türkiye

<sup>3</sup> National Microbiology Reference Laboratory, Turkish Public Health Institution, Ankara, Türkiye

### Abstract

**Introduction:** Nontyphoidal *Salmonella* (NTS) is an important cause of bloodstream infections (BSIs), particularly among individuals with comorbidities or immunosuppression. Long-term data on invasive NTS infections remain limited in many regions. This retrospective study aimed to describe the clinical characteristics, serotype distribution, antimicrobial resistance (AMR) patterns, and outcomes of NTS-BSIs in a tertiary care hospital in Antalya, Türkiye, between 2005 and 2019.

**Methodology:** Demographic and clinical data were obtained from hospital records. The isolates were identified using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry and serotyped at the National Public Health Laboratory. Antimicrobial susceptibility was determined by gradient diffusion. The results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing clinical breakpoints.

**Results:** Of the 58 included patients (62.1% male; median age 42.8 years), 96.4% had at least one comorbidity; most commonly solid organ malignancies (21.4%). *Salmonella* Enteritidis was the predominant serotype (82.8%), followed by *S. Infantis* (3.4%). The cases were most frequent in autumn (41.4%). The rates of resistance were 29.3% for ampicillin, 13.7% for ciprofloxacin, and 1.8% for trimethoprim-sulfamethoxazole. All the isolates were susceptible to ceftriaxone and azithromycin, while 12.0% exhibited multidrug resistance. The overall mortality was 25% (14/56), with ampicillin resistance detected in 6 fatal cases.

**Conclusions:** This long-term single-center study demonstrates that *S. Enteritidis* is the leading cause of NTS BSIs in Antalya and is associated with seasonal clustering and notable AMR. The substantial burden of comorbidities and mortality underscores the importance of continued regional AMR surveillance and appropriate empirical treatment strategies.

**Key words:** *Salmonella*; bacteremia; resistance; *S. Enteritidis*; Türkiye.

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### Introduction

Salmonellosis is a foodborne disease of major global public health importance [1]. Clinically, *Salmonella* infections are classified as typhoidal or nontyphoidal, which differ substantially in their clinical presentation. While typhoidal strains typically cause systemic illness, nontyphoidal *Salmonella* (NTS) infections most often present as self-limited gastrointestinal disease, as host defense mechanisms usually restrict bacterial dissemination beyond the intestinal tract [2]. Nevertheless, bacteremia develops in a small proportion of cases, particularly among individuals at the extremes of age or those with underlying immunosuppressive conditions [3,4].

The genus *Salmonella* consists of two species: *Salmonella enterica* and *Salmonella bongori* [3]. More than 2500 distinct *Salmonella* O:H serotypes have been identified globally. *S. enterica* subsp. *enterica*—including serotypes Typhi, Paratyphi, Typhimurium,

and Enteritidis—comprises approximately 60% of all serotypes and is responsible for over 99% of human infections [3]. NTS are widely distributed among domestic and wild animals; and human infection is most commonly acquired through the consumption of contaminated food products, including eggs, poultry, meat, and dairy products. Accordingly, serotype identification plays a key role in epidemiological surveillance, outbreak detection, and development of effective public health interventions [3].

The emergence and rapid spread of antimicrobial resistance (AMR) in *Salmonella* is a worldwide concern. Multidrug-resistant strains have been increasingly associated with treatment failure and adverse clinical outcomes, particularly in invasive infections [5]. Prompt initiation of appropriate antimicrobial therapy is essential for patients with NTS bacteremia, and empirical treatment should be guided by regional resistance patterns and adjusted according

to susceptibility results [3,6].

Despite the clinical relevance of invasive NTS infections, long-term regional data on serotype distribution, AMR patterns, and clinical outcomes remain limited. This study aimed to describe the clinical characteristics and risk factors of NTS bloodstream infections (BSIs) in a tertiary care hospital, to determine circulating serotypes, and to assess antimicrobial susceptibility patterns over a prolonged surveillance period.

## Methodology

A total of 58 NTS strains, recovered from one or more blood cultures of adult and pediatric patients between 2005 and 2019, were included in this study. These isolates had been identified as NTS and stored at the Microbiology Unit of the Central Laboratory of Akdeniz University Hospital. Demographic characteristics, underlying conditions, risk factors, antimicrobial treatments, and clinical outcomes were retrospectively collected from hospital information systems. A total of 56 patients were screened via blood cultures based on clinical suspicion of bacteremia, although clinical data were incomplete for 2 cases. Antimicrobial treatment data were recorded based on the antibiotics administered for the treatment of NTS-BSI. If patients received more than 1 antibiotic, all administered agents were included in the analysis. Recurrent isolates from the same patient were considered part of a single clinical episode and were not

included as independent cases in the primary analysis to avoid duplication bias.

## Bacterial identification and antimicrobial susceptibility test

The blood culture bottles were incubated using BACTEC 9240 or Bactec FX (Becton Dickinson, Sparks, MD, USA) devices, either until a positive signal was detected or for up to 5 days. The blood cultures were sub-cultured on Columbia blood agar, chocolate agar and MacConkey agar (BD, Heidelberg, Germany). A Bruker matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) Biotyper (Bruker Daltonik, Bremen, Germany) was used for bacterial identification. NTS serotyping was performed at the National Public Health Laboratory using antisera (Statens Serum Institute, Copenhagen, Denmark).

The gradient diffusion method (E test, bioMérieux, Marcy l'Étoile, France) was used following the manufacturer's instructions to test the *Salmonella* isolates to identify the minimum inhibitory concentrations (MIC) for 5 antimicrobial agents: ampicillin, ceftriaxone, ciprofloxacin, trimethoprim-sulfamethoxazole (TMP/SMX), and azithromycin. The antimicrobial susceptibility test results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 11.0, 2021) [7]. *Escherichia coli* ATCC 25922 was used as the quality control strain.

**Table 1.** Demographic and medical characteristics of patients with non-typhoidal *Salmonella* (NTS) growth in blood cultures.

| Variable                                      | n (%)     | Variable                                 | n (%)               |
|-----------------------------------------------|-----------|------------------------------------------|---------------------|
| <b>Gender</b>                                 | n = 58    | <b>Comorbid diseases</b>                 | n = 56              |
| Female                                        | 22 (37.9) | Solid organ cancers                      | 12 (21.4)           |
| Male                                          | 36 (62.1) | Cardiovascular diseases                  | 11 (19.6)           |
| <b>Age (years)</b>                            | n = 58    | Hematological disorders                  | 10 (17.8)           |
| < 1                                           | 2 (3.4)   | Rheumatologic diseases                   | 8 (14.3)            |
| 1–18                                          | 14 (24.1) | Solid organ transplantation              | 6 (10.7)            |
| 18–64                                         | 27 (46.6) | Chronic kidney disease                   | 5 (8.9)             |
| > 65                                          | 15 (25.9) | Inflammatory bowel disease               | 3 (5.4)             |
| <b>Serotypes</b>                              | n = 58    | Stem cell and bone marrow transplants    | 3 (5.4)             |
| <i>S. Enteritidis</i>                         | 48 (82.8) | HIV infection                            | 2 (3.4)             |
| <i>S. Infantis</i>                            | 2 (3.4)   | Selective IgA deficiency                 | 1 (1.8)             |
| Others <sup>a</sup>                           | 8 (13.8)  | Combined immunodeficiency                | 1 (1.8)             |
| <b>Clinics</b>                                | n = 57    | <b>Antimicrobial agents administered</b> | n = 42 <sup>c</sup> |
| Internal Medicine                             | 24 (42.1) | Ceftriaxone                              | 12 (28.6)           |
| Pediatrics                                    | 16 (28.1) | Piperacillin-tazobactam                  | 11 (26.2)           |
| Infectious Diseases and Clinical Microbiology | 6 (10.5)  | Meropenem                                | 10 (23.8)           |
| Others <sup>b</sup>                           | 11 (19.3) | Cefepime                                 | 3 (7.1)             |
| <b>Distribution by seasons</b>                | n = 58    | Ciprofloxacin                            | 2 (4.7)             |
| Spring                                        | 8 (13.8)  | Cefaperazone-sulbactam                   | 1 (2.4)             |
| Summer                                        | 12 (20.7) | Ertapenem                                | 1 (2.4)             |
| Autumn                                        | 24 (41.4) | Imipenem                                 | 1 (2.4)             |
| Winter                                        | 14 (24.1) | Levofloxacin                             | 1 (2.4)             |

<sup>a</sup> *S. Typhimurium*, *S. Daytona*, *S. enterica* subsp. *diarizonae*, *S. Hadar*, *S. Kasturp*, *S. Ndolo*, *S. enterica* subsp. *arizonae*, *S. enterica* subsp. *Salamae*; <sup>b</sup> Chest diseases, orthopedics and traumatology, nephrology, cardiology, thoracic surgery, pediatric nephrology, brain surgery, emergency service, intensive care unit; n: number of patients with available data included in the analyses. <sup>c</sup> n (%): number (percentage) of patients treated with each antimicrobial agent; patients may have received more than one agent.

### Statistical analyses

Descriptive data were summarized as frequencies and percentages. Associations between categorical variables were analyzed using the Pearson  $\chi^2$  test. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, USA). A *p* value of < 0.05 was considered statistically significant.

### Results

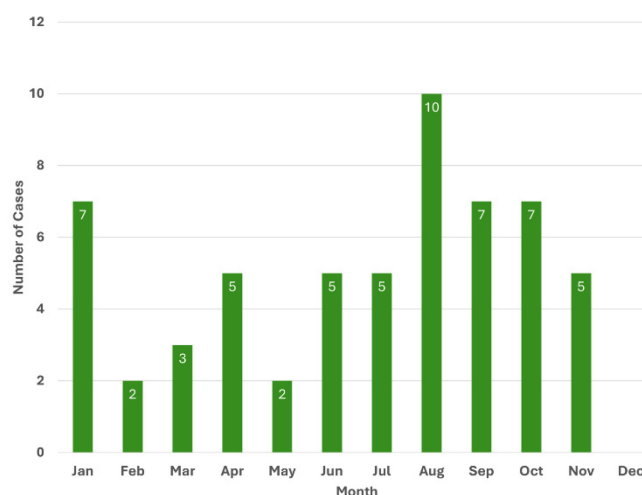
Among the 58 patients included in the study, 22 (37.9%) were female and 36 (62.1%) were male. The mean age was  $42.77 \pm 26.15$  years (range: 1–83 years). *S. Enteritidis* was the most frequently identified serotype, accounting for 48 isolates (82.8%).

Regarding departmental distribution, of the 57 patients who were evaluable, the majority were admitted to internal medicine (42.1%), followed by pediatrics (28.1%), and infectious diseases clinics (10.5%). At least 1 comorbid condition was present in 96.4% of the patients (*n* = 54/56); the most common were solid organ malignancies (21.4%), cardiovascular disease (19.6%), and hematologic disorders (17.8%). The characteristics of the patients included in the study are presented in Table 1. Seasonal distribution showed the highest proportion of cases in autumn (41.4%). However, monthly analysis demonstrated that the highest number of cases occurred in August (Figure 1).

Extraintestinal focal infections (osteomyelitis, septic arthritis, spondylodiscitis, pleurisy, and peritonitis) developed in 8 (14.2%) patients with *Salmonella* bacteremia. Eighteen patients were screened using transthoracic echocardiography and were found to be negative for infective endocarditis.

Antimicrobial susceptibility testing revealed resistance to ampicillin in 29.3% of isolates, ciprofloxacin in 13.7%, and trimethoprim-sulfamethoxazole in 1.8%. Forty isolates (69.0%) were susceptible to all tested antimicrobial agents. The MIC<sub>50</sub> and MIC<sub>90</sub> values are presented in Table 2. Resistance to 2 antimicrobial classes (ampicillin and ciprofloxacin) was observed in 6 isolates (10.3%), while 1 isolate (1.7%) exhibited resistance to 3 classes (ampicillin, ciprofloxacin, and trimethoprim-sulfamethoxazole).

**Figure 1.** Monthly distribution of nontyphoidal *Salmonella* bloodstream infection (NTS-BSI) cases (2005–2019).



No extended-spectrum beta-lactamase-producing strains were detected.

Of the 56 patients evaluated, 14 (25%) experienced a fatal outcome due to *Salmonella*-associated sepsis and related complications. No statistically significant relationship was found in the comparison of treatment outcome and causative agent type (Table 3). Ampicillin resistance was detected in 6 fatal cases, and combined resistance to ampicillin and ciprofloxacin was observed in 1.

Recurrent BSI with the same organism was observed in 4 patients. *S. Enteritidis* was isolated in 3 of these cases. One patient had newly diagnosed human immunodeficiency virus (HIV) infection and experienced recurrent bacteremia despite appropriate initial therapy, with no identifiable focal infection. The second patient was a liver transplant recipient who discontinued treatment and later re-presented with similar symptoms. The third patient was a kidney transplant recipient with underlying Crohn's disease who presented with diarrhea; repeated NTS bacteremia was documented in the absence of a localized focus. The patient recovered following ceftriaxone therapy; however, as blood cultures obtained between episodes were unavailable, reinfection could not be distinguished from persistent bacteremia. The fourth patient had rheumatoid arthritis and was receiving

**Table 2.** In vitro activity of antimicrobial agents against non-typhoidal *Salmonella* (NTS) bloodstream isolates.

| Antimicrobial agent and susceptibility breakpoints (µg/mL) | MIC range (µg/mL) | MIC <sub>50</sub> (µg/mL) | MIC <sub>90</sub> (µg/mL) | Susceptible n (%) | Resistant n (%) |
|------------------------------------------------------------|-------------------|---------------------------|---------------------------|-------------------|-----------------|
| Ampicillin (S ≤ 8/R > 8)                                   | 1–256             | 6                         | 128                       | 41 (70.7%)        | 17 (29.3%)      |
| TMP/SMX (S ≤ 2/R > 4)                                      | 0.012–32          | 0.125                     | 0.25                      | 57 (98.2%)        | 1 (1.8%)        |
| Ceftriaxone (S ≤ 1/R > 2)                                  | 0.03–0.25         | 0.125                     | 0.25                      | 58 (100%)         | 0 (0%)          |
| Ciprofloxacin (S ≤ 0.06/R > 0.06)                          | 0.012–0.38        | 0.03                      | 0.25                      | 50 (86.2%)        | 8 (13.7%)       |
| Azithromycin (S ≤ 16/R > 16)                               | 1–3               | 2                         | 2                         | 58 (100%)         | 0 (0%)          |

TMP/SMX: trimethoprim-sulfamethoxazole; MIC: minimum inhibitory concentration.

**Table 3.** Treatment outcome by pathogen type.

| Pathogen Type                                                       | Recovered n (%) | Deceased n (%) |
|---------------------------------------------------------------------|-----------------|----------------|
| Enteritidis (n: 47)                                                 | 35 (74.5)       | 12 (25.5)      |
| Non-Enteritidis (n: 9)<br>( <i>S. Kastrup</i> , <i>S. Daytona</i> ) | 7 (77.8)        | 2 (22.2)       |
| Total (n: 56)                                                       | 42 (75.0)       | 14 (25.0)      |

Chi-square ( $\chi^2$ ): 0.044; p value: 1.000.

immunosuppressive therapy with methotrexate, sulfasalazine, and etanercept. *Salmonella* Typhimurium was isolated from both blood and pleural fluid cultures. The isolate was susceptible to ciprofloxacin, and the patient achieved complete clinical recovery after a two-month course of ciprofloxacin therapy.

## Discussion

This study presents the epidemiological characteristics of NTS-BSI in Antalya Province between 2005 and 2019. The occurrence of NTS BSI has a well-known association with age and underlying medical conditions [8]. Katiyo *et al.* reported 2,484 cases of NTS bacteremia, with a higher prevalence among males. They found that neonates and older adults (aged  $\geq 65$  years) were more likely than younger adults (aged 18–44 years) to develop bacteremia. Cardiovascular disease was identified as the most common comorbidity [9]. Similarly, a tertiary care hospital in Malaysia identified 55 NTS strains, with 65.5% of patients having at least 1 serious immunosuppressive condition. The most common risk factor was underlying malignancy (23.6%), followed by HIV/AIDS [10]. A study from southern Sweden also found that patients with BSIs were more likely to be older and immunocompromised, and have comorbidities [11]. According to a recent systematic review and meta-analysis, host-related risk factors, such as HIV, malaria, and malnutrition, are particularly important in sub-Saharan Africa, where invasive NTS disease is more prevalent [12]. The present study revealed that 46.5% of patients were between 18 and 64 years of age, 62.1% were male, and the most common comorbidity was solid organ cancer.

Several studies have reported that *S. Enteritidis* and *S. Typhimurium* are the most common serotypes associated with BSI [13–17]. Certain serovars, including *S. Choleraesuis*, *S. Dublin*, *S. Heidelberg*, and *S. Virchow*, have been reported to exhibit a higher propensity for invasive disease compared to gastroenteritis-associated serovars [17,18]. Phu Huong Lan *et al.* found that *S. Enteritidis* (48%) and *S. Typhimurium* (26%) were the most identified serovars [14]. Similarly, a systematic review from Nigeria reported that among 259 invasive nontyphoidal *Salmonella* (iNTS) isolates, 103 (39.8%) were *S.*

Typhimurium, 76 (29.3%) were *S. Enteritidis*, and 80 (30.9%) were other iNTS serotypes. Additionally, *S. Typhimurium* (3.8%) was the most implicated invasive nontyphoidal serotype, followed by *S. Enteritidis* (2.8%) [19]. In the present study, *S. Enteritidis* (82.8%) was the most frequently isolated serotype, consistent with previous reports. Notably, the serotypes classically associated with higher invasiveness but uncommon in gastroenteritis were not detected, which may reflect local epidemiology or food exposure patterns.

Antimicrobial therapy remains a cornerstone in the management of NTS-BSI. International guidelines recommend testing ampicillin, fluoroquinolones, TMP/SMX, and third-generation cephalosporins for invasive isolates, with azithromycin considered in selected settings [20]. Surveillance data from the National Antimicrobial Resistance Monitoring System between 2005 and 2015 showed a decrease in ampicillin resistance (from 11.3% to 9.2%), whereas resistance increased for ciprofloxacin (2% to 10.7%), ceftriaxone (2.9% to 3.1%), and TMP/SMX (1.7% to 2.9%). Azithromycin resistance remained very low, at 0.2% in 2011 and 0.3% in 2015 [21].

A study conducted in the Netherlands from 2008 to 2018 reported resistance rates of 24.3% for ampicillin and 14.9% for fluoroquinolones in invasive *Salmonella* infections [22]. Similarly, a study conducted in the UK between 2004 and 2015 indicated a decrease in ciprofloxacin resistance levels from 27% to 17%; although this difference was not statistically significant [9].

A meta-analysis conducted in sub-Saharan Africa revealed that NTS bloodstream isolates displayed a combined resistance prevalence of 1.4% for fluoroquinolones and 1.9% for third-generation cephalosporins, and a striking 68.5% were multidrug resistant (MDR). The authors emphasized the growing public health threat posed by MDR in this region, which is already burdened by high NTS incidence and case fatality rates [23]. In the present study, no resistance to ceftriaxone or azithromycin were observed. However, the isolates showed resistance to ampicillin (29.3% of the isolates), ciprofloxacin (13.7%), and TMP/SMX (1.8%).

Among the 14 (25%) patients who died, 6 had ampicillin-resistant isolates, including 1 isolate that was

also resistant to ciprofloxacin. Notably, the presence of ampicillin resistance in fatal cases may suggest a potential association between antimicrobial resistance and poor clinical outcomes; however, no definitive conclusions can be drawn due to the limited sample size. This observation is consistent with previous evidence indicating increased mortality in antimicrobial-resistant NTS infections, particularly in the context of multidrug resistance. For example, a large Danish cohort study of 2,047 patients with *S. Typhimurium* infection demonstrated significantly higher 2-year mortality among patients infected with MDR strains compared with pan-susceptible strains, with the highest risk observed in the case of quinolone-resistant isolates [24].

Seasonal variation in salmonellosis has been well documented, with higher incidence during warmer months [25]. Previous studies have also shown strong associations between *Salmonella* transmission and environmental factors, particularly ambient temperature [22,26]. In the present study, the clustering of NTS-BSI cases during autumn is consistent with this pattern and may be influenced by regional climate, food consumption habits, and the high volume of tourism in Antalya. These factors may facilitate exposure to contaminated food products and contribute to transmission.

Several rare *Salmonella* serotypes were identified in the present study, including *S. Daytona*, *S. Hadar*, *S. Kastrup*, *S. Ndolo*, and subspecies, such as *S. enterica* subsp. *arizonae*, subsp. *salamae*, and subsp. *diarizonae*. These serotypes are reported infrequently in human BSIs and are more commonly associated with animal reservoirs or environmental sources [27–32]. Antalya's intensive agricultural activity, animal farming, and international tourism may contribute to the introduction and circulation of such uncommon strains. Türkiye's geographic position at the crossroads of multiple regions may further increase serotype diversity. These findings highlight the value of comprehensive serotyping and long-term surveillance in detecting emerging or unusual pathogens with potential clinical significance.

### Limitations

This study has several limitations. Its retrospective, single-center design may limit the generalizability of the findings. The relatively small number of cases limits the robustness of conclusions regarding seasonality and AMR patterns. Complete antimicrobial treatment records could not be retrieved for all patients due to the study's retrospective nature. Therefore, results

pertaining to treatment outcomes should be interpreted with caution.

### Conclusions

This 15-year single-center study demonstrates that NTS-BSI remains a serious infection associated with significant comorbidity, antimicrobial resistance, and mortality. Ongoing surveillance of serotype distribution and resistance patterns is essential to inform empirical treatment strategies and guide infection prevention efforts. These findings underscore the importance of rational antibiotic use and systematic surveillance to mitigate the clinical impact of iNTS infections.

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### Ethical considerations

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Ethical approval was obtained from the Clinical Research Ethics Committee of the Akdeniz University Faculty of Medicine (Approval No. 957, dated 23 October 2019).

### Corresponding author

Hatice Yazısız, MD.

Akdeniz University, Faculty of Medicine,  
Pınarbaşı, Konyaaltı, Antalya, Türkiye.

Tel: + 90 242 249 3473

Fax: + 90 242 249 69 06

Email: drhyazisiz@yahoo.com.tr

### Conflict of interest

No conflict of interest is declared.

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