Infection and Drug Resistance

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ORIGINAL RESEARCH

Factors Associated with Multi-Drug-Resistant Non-Typhoidal *Salmonella* in the Invasive Disease, Thailand

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Purpose: Invasive non-typhoidal *Salmonella* disease, iNTS is a major global health concern, especially multi-drug resistant non-typhoidal *Salmonella*, MDR-NTS. Information about risk factors of MDR-NTS in the invasive disease patient group was limited. This study aimed to identify those risk factors.

Methods: This retrospective study examined data from patients who had non-typhoidal *Salmonella*, NTS infection, from 10 hospitals between June 2011 and June 2020. The multivariate regression analysis included demographic data, clinical data, culture reports, and antimicrobial susceptibility.

Results: A total of 166 patients were invasive salmonellosis. where the median age was 8.3 years (IQR 1.8–79). 52% were the under-15-years-old group. Most of the patient data, 64.5% (107/166), was from a tertiary hospital. The majority of cases were bacteremia 95.7% (159/166). Serogroup C was the most common serogroup (39%). MDR-NTS was present in 68.8% (95% CI 7.17–11.06) of patients. Univariate analysis showed that onset of illness >3 days PTA (p=0.11), age over 60 years old (0.014), diabetic (p=0.002), or serogroup C infection (p=0.43) were significant factors for MDR-NTS infection. Multivariate analysis showed that the onset of symptoms more than 3 days before admission (p=0.001), and age over 60 years were significant factors. The patient who had white blood cells >15,000 cells/uL (p<0.001), a peak of fever ≥39 C° (p=001), and illness for more than 3 days before admission (p=0.035) were significantly related to invasive infection by multivariate analyses.

Conclusion: The iNTS patients who were over 60 years old or had onset of illness more than 3 days before admission were associated with MDR-NTS infection. Therefore, the choice of antimicrobials selected must be appropriate for the local prevalence and epidemiology of MDR-NTS including clinical correlation.

Keywords: risk factor, multi-drug resistance, non-typhoidal *Salmonella*, invasive infection, invasive non-typhoidal *Salmonella* disease

Introduction

Non-typhoidal *Salmonella* (NTS) is a common cause of infectious diarrhea. It causes invasive diseases, including bacteremia, meningitis, and other focal infections, which result in hospitalization, morbidity, and mortality.[1] Some of the diseases caused by NTS which are not typically related to diarrhea are non-specific febrile illnesses with symptoms that are clinically inseparable from other febrile illnesses, which complicates diagnosis and treatment.

Previous studies have shown that malnourished infants, elderly people, sickle-cell disease, HIV, acute or recent malaria, and antimicrobial-resistant NTS are risk factors for invasive diseases, especially MDR-NTS.[1–3] MDR-NTS is associated with poorer clinical outcomes and higher case fatality.[4] The extended-spectrum ß-lactamases (ESBL), and AmpC ß-lactamases (AmpC) were major mechanisms of cephalosporine resistance. The mutations of the DNA gyrase enzyme are important mechanisms which are resistance to fluoroquinolone. The organisms also have gene transfers of

Received: 1 September 2022
Accepted: 29 October 2022
Published: 10 November 2022

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point mutations between them, which affected to increase of MDR-NTS from more reported worldwide.[4–13] Studies about risk factors associated with MDR-NTS in invasive diseases are limited, particularly in Asia. Previous studies in Africa show children younger than 5 years, elderly people (aged ≥70 years), people with HIV infection, and patients who are infected with *Salmonella* serogroups B (*S*. Typhimurium, *S*. Heidelberg), and D (*S*. Enteritidis, *S*. Dublin,) had more invasive infection with MDR-NTS.[1,2] The studies in Thi-Qar Governorate Iraq found that children from households with domestic animals supplied with pipe water had a higher risk compared to households without them.[13] In Bangladesh children under five years of age with severe malnutrition who presented with a duration of fever ≥ 5 days were at risk. However, those studies differed from Southeast Asia in population, living conditions, economic characteristics, and access to health systems. This study was conducted to determine the risk factors of MDR-NTS in invasive diseases in Thailand. This study is a continuation of a previous study of the prevalence and trend of antimicrobial susceptibility patterns of multidrug-resistant non-typhoid salmonella in the central region, 2012–2019, which is the same researcher.[14]

Materials and Method

Methods

This study was conducted retrospectively, by collecting patient data from ten hospitals: six district hospitals, three private hospitals, and one tertiary hospital, with permission from the hospital directors. Patients who were diagnosed with *Salmonella* infections based on ICD-10[15] between June 2011 and June 2020 were included. The research includes patients who had invasive diseases (bacteremia, meningitis, and severe focal infections). Demographic data including age, gender, lab investigation, culture (blood, stool and/or other body fluid), and clinical, and antimicrobial susceptibility testing reports were reviewed. The patients without serogroup and/or antimicrobial sensitivity testing results were excluded.

Microbial Definition

The study reported *Salmonella* culture by using O antigen to classify them as serogroups A, B, C, D, and E, based on the Kauffman-White classification.[15] Antimicrobial susceptibility testing was performed using the agar disk diffusion method. The antimicrobial susceptibility was interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI),[16] which is under control standards set by the Department of Medical Sciences in the Ministry of Public Health.[17] CLSI defines drug resistance non-typhoidal *Salmonella* (DR-NTS) as NTS resistant to at least one class of antimicrobials. MDR-NTS was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[18]

Statistical Methods

Descriptive statistics were used to analyze demographic data and prevalence. The differentiation between groups was analysed by Pearson's Chi-square and 95% confidence interval. The quantitative data analyses use multivariate. SPSS version 21 was used as the analysis tool.

Results

The Prevalence and Characteristics of Invasive Disease

A total of 166 (38.3%) from 433 NTS were diagnosed with invasive disease. The median age of these patients was 8.3 years, IQR (1.8–47). The patients with invasive diseases were subdivided into three age groups: <15 years 52.4% (n= 87/166), 15–60 years 25.3% (n=42/166), >60 years 22.2% (n= 37/166). 55.4% (n= 92/166) of the patients were male and 44.6% (n= 74/166) were female. The patient data came from a tertiary hospital 64.5% (n=107/166), district hospitals 11.4% (n= 19/166) and private hospitals 24.1% (n=40/166). The invasive diseases encountered were 159 bacteremias,1 meningitis, 1 meningitis with brain abscess, 2 osteomyelitis, 2 arthritis, and 1 urinary tract infection with bacteremia. The patients infected with non-drug resistant non-typhoidal *Salmonella* (NDR-NTS) were 9.6% (n=16) (95% CI 1.08–4.62). Twenty percent (n=20/166) (95% CI 9.85–23.19) had NTS resistant to one class of antimicrobial (1-DR-NTS). 17.5% (n=29/166) (95% CI 8.20–53.07) were resistant to two classes of antimicrobial (2-DR-NTS), and 68.8% (n=101/166)

(95% CI 7.17–11.06) were resistant to at least one agent in three or more antimicrobial categories (MDR-NTS). Serogroup C was the main serogroup at 39% (n=66/166) (95% CI 2.00–9.87). The most common underlying diseases were metabolic diseases 24.6% (n=41/166) (16 diabetes, 5 diabetes with hypertension, 4 diabetes with hyperlipidemia, 8 diabetes with other), hematologic disorders 15% (n=25/166) (7 thalassemias with regular blood transfusion, 6 thalassemias with non-regular blood transfusion, 8 Iron deficiency anemia, 1 G6PD, 3 other), and hyperlipidemia 2.4% (n=4/166). The 5 Immunological disorders were all HIV-infected patients. 59% (n=98/166) patients had white blood cells >15,000 cells/uL with a median concentration of 21,000 cells/uL (IQR 2200–35,000 cells/uL), and 59% (n=99/166) of patients had anemia (hemoglobin <12 g/dl). Almost all patients came with a high-grade fever of more than 39 C° (95.2% (n=158/166). Of the 91/166 invasive disease patients for which date of onset was known, 84% (n=77/91) of patients had symptoms of illness more than 3 days before admission, with a median of 1.5, IQR (1–5) (Table 1).

Antimicrobial-resistant patterns in invasive disease

Overall, the NTS resistance to ampicillin was 72.3% (n=120/166), norfloxacin was 53.6% (n=89/166), sulfamethoxazole/trimethoprim was 59% (n=98/166), tetracycline was 39% (n=66/166), amoxicillin-clavulanic acid was 46.3% (n=77/166), ciprofloxacin was 41% (n=68/166), ceftriaxone was 33.7% (n=56/166), cefotaxime was 27.1% (n=45/166), amikacin was 10.8% (n=18/166), gentamicin was 6% (n=11/166), ampicillin/sulbactam was 6% (n=10/166), ceftazidime was 1.2% (n=2/166), piperacillin/tazobactam was 0.6% (n=1/166), meropenem was 0.6% (n=1/166).

Risk Factors Associated with MDR-NTS in the iNTS

This study found onset time of symptoms before admission ≥3 days (p=0.011), age >60 years (p=0.014), and diabetes (p=0.022) were significantly associated with MDR infection in the univariate analysis (Table 1).

Patients with symptoms more than three days before hospitalization (p=0.001) and patients older than 60 years were the main predisposing factors to infection by MDR-NTS in a multivariate analysis (Table 1).

Risk Factors Related to Invasive Infection in NTS Patients

The univariate logistic regression analysis showed that white blood cells ≥15.000 cells/uL (p<0.001), haemoglobin less than 12 g/dl (p=0.001), the peak of fever ≥39 C° (p<001), and onset of illness more than 3 days PTA (p=0.009) were the factors significantly associated with invasive infection in all NTS patients (n=433) (Table 2).

The multivariate analysis showed that white blood cells >15,000 cells/uL (p<0.001), the peak of fever ≥ 39 C° (p=001), and illness for more than 3 days before admission (p=0.035) were the factors significantly associated with invasive infection in all NTS patient groups (Table 2).

Risk Factors Related to MDT-NTS Infections in NTS Patients

Diabetes patients (p=0.014), Invasive diseases (p=0.023), and serogroup C were significantly associated with MDR infection in the univariate analysis. Invasive infection patients (p=0.024), and serogroup C (p=0.046) were significantly associated with MDR-NTS infection and with ceftriaxone and ciprofloxacin resistance in the multivariate logistic regression analysis (Table 3).

Discussion

The increase of MDR-NTS is a worldwide threat to public health. The MDR-NTS causes both invasive diseases and diarrhea. For enteritis, healthy patients can self-recover without the use of antibiotics, but not for invasive infection. The MDR-NTS-related invasive disease affects the failure of treatment.

This study found an Invasive infection rate of 38.4% (166/433), similar to a study in Africa at 39% (1966–2014),[19] and higher than a previous systematic review of scientific databases (1990–2017) in Thailand (10–24.9%),[1] Australia (2–4.9%), and Taiwan 6.9% (in children).[20] However, this incidence may be inflated; it is possible that some patients with diarrhea did not confirm the diagnosis. This study supported that MDR-NTS is associated with invasive disease, and our MDR-NTS rate of 69% was a little higher than a study which compared all NTS patients in Thailand (62.3%)[14] but lower than a study in Africa (50–75%).[1,21]

Table 1 The Binary Logistic Regression Analysis of the Risk Factors Associated with MDR-NTS in Invasive Patients (n=166).

Characteristic	Non-MDR-NTS** (n=65)	MDR-NTS (n=101)	Statistics	*p*-value	Univariate Analysis	Multivariate Analysis		
	n(%)	n(%)			p-value	Adjusted OR	95% CI[β]	p-value
Sex			0.007a	0.933				
Male (n=92)	37(40.2)	55(59.7)			0.933			
Female (n=74)	28(37.8)	46(62.1)						
Age group			0.005b	0.014	0.014			
<15 yr. (n=87)	42(72)	45(44.5)				6.7	0.324–14.789	0.002*
15–60yr. (n=42)	19(45.2)	23(54.8)				Ref.	0.981–015.984	
>60 yr. (n=37)	4(10)	33(89)				2.5	1.223–9.892	
Type of hospital			1.137a	0.566	0.954			
Tertiary hospital (n=107)	41(38.3)	66(61.7)						
District hospital (n=19)	8(42.1)	11(57.9)						
Private hospital (n=40)	15(37.5)	25(62.5)						
***Salmonella* serogroup**			0.22a	0.143	0.408			
Salmonella serogroup A (n=5)	2(40)	3(60)						
Salmonella serogroup B (n=46)	16(34.7)	30(65.2)						
Salmonella serogroup C (n=66)	22(33.3)	44(66.7)						
Salmonella serogroup D (n=32)	18(56.3)	14(43.7)						
Salmonella serogroup E (n=17)	7(41.2)	10(58.8)						
Underlying disease(n=66)								
Hematologic (n=25)	17(68)	8(32)	1.735a	0.188	0.199	4.8	0.885–6.556	
Gastrointestinal (n=12)	7(58.3)	5(41.7)	0.166b	0.09	0.111	8.5	0.691–9.586	
Immunological (n=5)	3(60)	2(40)	0.029b	0.864	0.866	3.3	0.908–9.656	
Neurological (n=9)	6(66.7)	3(33.3)	0.075b	0.417	0.436	5.3	0.660–2.056	
Cardiovascular disease(n=9)	7(77.8)	2(22.2)	−0.002b	0.978	0.978	1.1	0.181–4.660	
Dyslipidemia (n=8)	5(62.5)	3(37.5)	0.094b	0.291	0.317	3.4	0.4501–7.656	
Diabetes mellitus (33)	7(16.2)	26(83.8)	0.038b	0.022*	0.047	2.1	1.811–9.656	0.051
Other (n=5)	2(40)	3(60)	−0.021b	0.587	0.473	Ref.		
Complete Blood Counts					0.375			
White Blood Cell: WBC								
<5000 cells/uL(n=39)	15(38.5)	24(61.5)	1.965a	0.374				
5000–15,000 cells/uL(n=29)	11(72.4)	8(27.6)						
>15,000 cells/uL(n=98)	57(58.2)	41(41.8)						

(*Continued*)

Table 1 (Continued).

Characteristic	Non-MDR-NTS** (n=65)	MDR-NTS (n=101)	Statistics	*p*-value	Univariate Analysis	Multivariate Analysis		
	n(%)	n(%)			p-value	Adjusted OR	95% CI[β]	p-value
Neutrophil			2.103a	0.349	0.359			
<40% (n=27)	18(66.6)	9(33.3)						
40–70%(n=45)	17(37.7)	28(62)						
>70%(n=94)	30(31.9)	64(68.1)						
Lymphocyte			0.797a	0.671	0.666			
<20% (n=58)	27(46.6)	31(53.4)						
20–50%(n=38)	10(26.4)	26(68.4)						
>50%(n=70)	26(37.1)	44(62.9)						
Monocyte			−0.04b	0.113	0.186			
<4%(n=56)	29(51.8)	27(48.2)				Ref.		
4–13%(n=67)	27(40.3)	40(59.7)				2.5	0.801–7.656	0.115
>13%(n=43)	9(20.9)	34(79)				6.6	0.727–60.741	0.093
Haemoglobin			1.277a	0.258	0.256			
<12 g/dl (n=99)	33(33.3)	66(66.6)						
12–17 g/dl (n=67)	32(47.7)	35(52.2)						
Platelet Count			0.016b	0.182	0.255			
<150,000 cells/uL(n=39)	26(66.6)	13(33.3)						
150,000–400,000 cells/uL(n=84)	24(28.6)	60(71.4)						
>400,000 cells/uL (n=43)	15(34.2)	28(65.1)						
Stool examination(n=98)					0.982			
Colour								
Yellow (n=36)	15(46.7)	21(58.3)						
Green (n=44)	19(43.2)	25(56.8)						
Brown (n=18)	9(50)	9(50)						
White Blood Cell: WBC			0.04b	0.764	0.728			
< 5 cells (n=25)	13(52)	12(48)						
5–20 cells (n=35)	21(60)	14(40)						
≥ 20 cells (n=38)	21(55.3)	17(44.7)						
Red Blood Cell: RBC			0.105a	0.473	0.481			
< 5 cells (n=35)	27(77.1)	8(22.9)						
>5 cells (n=12)	8(66.7)	4(33.3)						

(*Continued*)

Table 1 (Continued).

Characteristic	Non-MDR-NTS** (n=65)	MDR-NTS (n=101)	Statistics	*p*-value	Univariate Analysis	Multivariate Analysis		
	n(%)	n(%)			p-value	Adjusted OR	95% CI$^{\beta}$	p-value
Occult Blood(n=21)			−0.102b	0.459	0.436			
Positive (n=8)	3(37.5)	5(62.5)						
Negative (n=13)	8(61.1)	5(38.4)						
The peak of fever								
≥ 39.0 C° (n=152)	47(31)	105(69)	1.49a	0.222	0.225	2.4	0.87–6.678	0.34
< 39.0 C° (n=18)	5(27.8)	13(72.2)				Ref.		
Onset time symptoms before admission								
≥3 day (n=77)	13(16.8)	64(83.2)	1.68a	0.011*	0.048	3.1	1.01–9.459	0.001*
<3 day (n=22)	12(54.5)	10(45.5)			0.032	Ref.		

Notes: [a]Pearson Chi-square test. [b]Chi-square test for independence. [β]Statistically significant (95% CI does not include 1.0). *p < 0.05 is statistically significant. **Non-MDR-NTS included non-DR-NTS and NTS which had drug-resistant less than 3 classes of antimicrobials.

Table 2 The Binary Logistic Regression Study of the Factors Related to Invasive Patients in All NST Patients (n=433).

Characteristic	Non-Invasive (n=267)	Invasive (n=166)	Statistics	*p*-value	Univariate Analysis	Multivariate Analysis		p-value
	n(%)	n(%)			p-value	Adjusted OR	95% CI$^{\beta}$	
Sex			0.556a	0.456				
Male (n=195)	71(59.7)	48(40.3)			0.453			
Female (n=238)	(69(64.5)	38(35.5)						
Age group			0.463a	0.977	0.941			
6–15 yr (n=232)	30(63.8)	17(36.2)						
16 −60 yr. (n=106)	36(60)	24(40)						
>60 yr. (n=95)	33(62.3)	20(37.7)						
Type of hospital			19.212a	0.456	0.456			
Tertiary hospital (n=207)	44(45.4)	53(54.6)				2	0.869to5.084	0.099
District hospital (n=135)	72(75)	24(25)				0.6	0.277to1.642	0.386
Private hospital (n=91)	35(68.6)	16(31.4)				Ref.		
***Salmonella* serogroup**			3.730a	0.444	0.438			
Salmonella serogroup A (n=52)	46(88.5)	6(37.5)						
Salmonella serogroup B (n=108)	83(73.2)	25(23.1)						
Salmonella serogroup C (n=124)	24(19.3)	100(80.6)						
Salmonella serogroup D (n=95)	70(73.7)	25(26.3)						
Salmonella serogroup E (n=54)	41(81.4)	10(18.5)						

(*Continued*)

Table 2 (Continued).

Characteristic	Non-Invasive (n=267)	Invasive (n=166)	Statistics	*p*-value	Univariate Analysis	Multivariate Analysis		p-value
	n(%)	n(%)			p-value	Adjusted OR	95% CI[β]	
Underlying disease(n=143)								
Hematologic (n=36)	28(52.8)	25(47.2)	2.354a	0.125	0.128			
Gastrointestinal (n=24)	10(45.5)	12(54.5)	2.768a	0.096	0.101			
Immunological (n=14)	5(38.5)	8(61.5)	3.194b	0.07	0.079	2.7	0.707to10.326	0.146
Neurological (n=12)	7(43.8)	9(56.3)	2.387a	0.122	0.129			
Cardiovascular disease(n=8)	3(37.5)	5(62.5)	0.004a	0.948	0.948			
Dyslipidemia (n=27)	14(63.6)	8(36.4)	0.031a	0.859	0.859			
Diabetes mellitus (46)	17(60.7)	11(39.3)	0.018a	0.982	0.892			
Other (n=12)	7(87.5)	1(12.5)	2.301a	0.129	0.101			
Complete Blood Counts(n=249)								
White Blood Cell: WBC			30.96a	<0.001*	<0.001*			
<5000 cells/uL (n=64)	25(39.1)	39(60.9)				4.2	1.534to11.541	0.005*
5000–15,000 cells/uL (n=77)	48(62.3)	29(37.6)				Ref.		
>15,000 cells/uL (n=108)	10(9.3)	98(90.7)				4.7	2.296to9.686	<0.001*
Neutrophil					0.47			
<40% (n=58)	31(53.4)	27(46.6)	5.524a	0.47				
40–70% (n=80)	35(43.7)	45(56.3)						
>70% (n=111)	17(15.3)	94(84.7)						
Lymphocyte			1.999a	0.149	0.051			
<15% (n=96)	38(39.6)	58(60.4)				1.1	0.535to2.066	0.885
15–50% (n=65)	27(41.5)	38(58.5)				Ref.		
>50% (n=88)	18(20.4)	70(79.6)				1.7	0.608to4.979	0.302
Monocyte					0.163			
<5% (n=89)	33(37)	56(63)						
5–15% (n=99)	32(32.3)	67(67.6)						
>15% (n=61)	18(29.5)	43(70.5)						
Hemoglobin			10.065a	0.001*	0.001*			
<12 g/dl (n=115)	16(13.9)	99(86.1)				3.2	0.987to23.876	0.085
≥12 g/dl (n=134)	67(50)	67(50)						

(*Continued*)

Table 2 (Continued).

Characteristic	Non-Invasive (n=267)	Invasive (n=166)	Statistics	*p*-value	Univariate Analysis	Multivariate Analysis		p-value
	n(%)	n(%)			p-value	Adjusted OR	95% CI[β]	
Platelet Count			1.018b	0.081	0.081			
<150,000 cells/uL (n=39)	0(0)	39(100)						
150,000–400,000 cells/uL (n=151)	67(44.3)	84(55.7)				Ref.		
>400,000 cells/uL (n=59)	16(27.1)	43(72.9)				3.2	1.175to8.866	0.123
Stool examination (n=362)								
Colour			0.05a	0.975	0.975			
Yellow (n=135)	99(73.4)	36(26.6)						
Green (n=177)	133(75.2)	44(24.8)						
Brown (n=50)	32(64)	18(36)						
White Blood Cell: WBC			2.472a	0.291	0.281			
< 5 cells (n=65)	40(61.5)	25(38.4)						
5–20 cells (n=203)	168(82.7)	35(17.3)						
> 20 cells (n=94)	56(59.6)	38(40.4)						
Red Blood Cell: RBC			0.029b	0.689	0.506			
<5 cells (n=136)	101(78.5)	35(21.4)						
> 5 cells (n=199)	136(68.3)	63(31.7)						
Occult Blood			2.19a	0.139	0.126			
Positive (n=14)	6(42.9)	8(57.1)						
Negative (n=42)	29(69)	13(31)						
The peak of fever					<0.001*			0.001
< 39 C° (n=225)	217(87.6)	28(2.4)						
≥ 39 C° (n=198)	50(25.3)	148(74.7)	1.498a	<0.001*		1.56	2.657to12.895	
Onset time symptoms before admission (>3 day) (n=92)								
< 3 days (n=45)	22(48.8)	23(51.1)						
≥3 days (n=92)	15(16.3)	77(83.6)	3.079a	0.009*	0.009*	1.9	1.974to4.806	0.035*

Notes: [a]Pearson Chi-square test. [b]Chi-square test for independence. [β]Statistically significant (95% CI does not include 1.0). *p < 0.05 is statistically significant.

The risk factor related to MDR-NTS infection in iNTS cases in this study, onset time of symptoms ≥3 days before admission (p=0.011), was similar to a study in the French West Indies[22] that showed a delay between onset of symptoms and hospital admission >5 days (P = 0.01) was significantly associated with MDR-NTS in a multivariate analysis, but the different duration may be due to differences in access to treatment and public health systems. This study found the median time of onset before treatment was only 1.5 days in all NST cases. The study in the French West Indies also identified vomiting (P = 0.001) and increased respiratory rate (P = 0.001)[22] as risk factors, which this study did not.

Table 3 Binary Logistic Regression Analysis of the Factor Associated with MDR-NTS Compared to Non-MDR-NTS

	MDR-NTS		Univariate Analysis	Multivariate Analysis		p-value
	Non-MDR** (n=204)	MDR (n=229)	p-value	Adjusted OR	95% CI$^{\beta}$	
	n(%)	n(%)				
Sex			0.605			
Male (n=195)	97(81.5)	22(18.5)				
Female (n=238)	90(84.1)	17(15.9)				
Age group			0.218			
6–15 yr (n=232)	43(91.5)	4(8.5)				
16 −60 yr. (n=106)	47(78.3)	13(21.7)				
>60 yr. (n=95)	47(88.7)	6(11.3)				
Type of hospital			0.141			
Tertiary hospital (n=207)	78(37.7)	129(62.3)		Ref		
District hospital (n=135)	87(64.5)	48(35.5)		0.5	0204–1.207	0.122
Private hospital (n=91)	39(42.9)	52(57.1)		1.5	0.648–3.606	0.33
Type of infection			0.023*			
Non-invasive (n=267)	139(52.1)	128(47.9)		Ref		
Invasive (n=166)	65(39.1)	101(60.8)		0.6	0.745–3.33	0.024*
***Salmonella* serogroup**						
Salmonella serogroup A (n=52)	29(55.8)	23(44.2)	0.459	Ref		
Salmonella serogroup B (n=108)	67(62)	41(38)	0.087			
Salmonella serogroup C (n=124)	34(27.4)	90(72.6)	0.038*	0.5	0.9875–32.651	0.046*
Salmonella serogroup D (n=95)	39(56)	56(55)	0.753			
Salmonella serogroup E (n=54)	35(64.8)	19(35.2)	0.098			
Underlying disease (n=143)						
Hematologic (n=69)	41(77.4)	36(22.6)	0.178			
Gastrointestinal (n=24)	17(77.3)	15(22.7)	0.419			
Immunological (n=14)	7(50)	7(50)	0.522			
Neurological (n=25)	18(72)	7(28)	0.796			
Cardiovascular disease (n=8)	3(37.5)	5(20.8)	0.548			
Dyslipidemia (n=27)	12(44.4)	15(55.6)	0.419			
Diabetes mellitus (46)	9(19.5)	37(80.5)	0.014*	0.9	0.987–21.879	0.119
Other (n=12)	5(41.6)	7(58.3)	0.528	Ref		

(*Continued*)

Table 3 (Continued).

	MDR-NTS		Univariate Analysis	Multivariate Analysis		p-value
	Non-MDR** (n=204)	MDR (n=229)	p-value	Adjusted OR	95% CI[β]	
	n(%)	n(%)				
Complete Blood Counts						
White Blood Cell: WBC			0.214			
<5000 cells/uL (n=64)	23(35.9)	41(64.1)				
5000–15,000 cells/uL (n=77)	33(42.9)	44(57.1)				
>15,000 cells/uL(n=108)	70(64.8)	38(35.2)				
Neutrophil			0.943			
<40% (n=58)	19(32.8)	38(67.2)				
40–70% (n=80)	35(43.7)	45(56.3)				
>70% (n=111)	78(70.2)	33(29.8)				
Lymphocyte			0.765			
<15% (n=96)	73(76)	23(4)				
15–50% (n=65)	28(43)	37(57)				
>50% (n=88)	34(38.6)	54(61.4)				
Monocyte			0.248			
<5% (n=89)	66(74.1)	23(25.9)				
5–15% (n=99)	73(73.7)	26(26.2)				
>15% (n=61)	39(64)	22(36)				
Hemoglobin			0.409			
<12 g/dl (n=115)	84(73.1)	31(26.9)				
≥12 g/dl (n=134)	78(58.2)	56(41.7)				
Platelet Count			0.082*			
<150,000 cells/uL(n=39)	24(61.5)	15(38.4)		0.7	0.277–1.544	0.654
150,000–400,000 cells/uL(n=151)	99(66.66)	52(33.4)		0.3	0.124–0.848	0.325
>400,000 cells/uL (n=59)	36(61)	23(39)				
Stool examination (n=362)			0.537			
Color						
Yellow (n=135)	45(33.4)	90(66.6)				
Green (n=177)	77(43.5)	100(56.5)				
Brown (n=50)	31(62)	19(38)				

(*Continued*)

Table 3 (Continued).

	MDR-NTS		Univariate Analysis	Multivariate Analysis		p-value
	Non-MDR** (n=204)	MDR (n=229)	p-value	Adjusted OR	95% CI$^{\beta}$	
	n(%)	n(%)				
White Blood Cell: WBC			0.133			
< 5 cells (n=65)	33(50.8)	32(49.3)				
5–20 cells (n=203)	133(65.5)	70(34.5)				
> 20 cells (n=94)	27(28.7)	67(71.3)				
Red Blood Cell: RBC			0.705			
< 5 cells (n=136)	78(57.3)	58(42.6)				
5–20 cells (n=199)	129(64.8)	70(35.1)				
>20 cells (n=2)	1(50)	1(50)				
Occult Blood				0.842		
Positive (n=14)	5(35.7)	9(64.3)				
Negative (n=42)	23(54.7)	19(45.2)				
The peak of fever						
< 39 C° (n=235)	151(64.3)	84(35.7)	0.708			
≥ **39 C° (n=198)**	53((26.7)	145(73.3)	0.053	0.9	0.897–9.786	0.065
Onset time symptoms before admission (>3 day) (n=92)						
< 3 days (n=45)	34(75.5)	11(24.4)	0.86			
≥3 days (n=92)	10(10.9)	82(89.1)	0.12	1.3	0.67–21.908	0.861

Notes: $^{\beta}$Statistically significant (95% CI does not include 1.0). *p < 0.05 is statistically significant. **Non-MDR-NTS included non-DR-NTS and NTS which ant less than 3 classes of antimicrobials.

The patients who were over 60 years old (p=0.014) were significantly associated with MDR-NTS in this study, which was similar to a systematic research review in a high-income county group that showed elderly people (51·2% among those aged ≥70 years)[1] were associated with iNTS. There are also studies relating young patients to MDR-NTS in iNTS,[1,23,24] which this study did not find.

Information from WHO found the proportion of the world's population over 60 years old will nearly double from 12% to 22% between 2015 and 2050. The number of people aged 60 years and older will outnumber children younger than 5 years. And in 2050, 80% of older people will be living in low- and middle-income countries. This demographic shift is a major challenge for all countries to encounter, so they must make health policies to ensure their health.[25]

The univariate analysis for this research also showed diabetic patients related to MDR-NTS (p=0.022). Many studies have found a relationship between diabetic mellitus (DM) patients and MDR-NST infection. Other multidrug-resistant pathogens also have complications and co-infection[26–29,30–35] similar to this study. In general, patients with DM have infections more often than those without DM. Some studies found decreased cellular responses in vitro. No disturbances in adaptive immunity in diabetic patients have been described, and disturbances to release of complement factor 4, and decreased cytokine response after the infection have been noted. Important cellular innate immunity is impaired; most

studies show decreased functions [chemotaxis, phagocytosis, and killing of diabetic polymorphonuclear cells and diabetic monocytes/macrophages] compared to cells of controls. Another mechanism which can lead to the increased prevalence of infections in diabetic patients is an increased adherence of microorganisms to diabetes compared to nondiabetic cells. Furthermore, some microorganisms become more virulent in a high glucose environment.[30,31] However, diabetes is a dominant underlying disease in this study, that may affect sampling bias, which requires further study. Many past studies present a burden of NTS infection that included iNTS and MDR-NTS among HIV-infected individuals.[1,24,32–34] A past study in Thailand (1992–2004)[35] showed similar results, but this study did not. This study found only 4 HIV-infected cases, and all of them got treatment and had CD4 >200 cell/cu.mm. However, this research was retrospective, so the number of cases may be under-reported; therefore, randomization bias requires further study.

For all NTS (n=433), the patients who had WBC ≥ 15,000 cell/uL, Hb less than 12 g/dL, or high-grade fever ≥39°C were more frequently found to have iNTS than patients without those symptoms. This is consistent with other studies.[1,19,23,36] Delay of more than three days between the onset of symptoms and treatment was significantly associated with iNTS.

iNTS was significantly associated with MDR in all NTS patients (n=433) in this study, which was similar to many past research studies.[1,24,32] The study also showed that serogroup C was significantly related to iNTS, while other studies commonly showed D.[1,24,35]

Other factors may be related to infection with DR-NST, particularly the history of previous antibiotic consumption, including type, frequency, quantity, and duration of antibiotic. Occupations, nutritional status, and frequency of previous diarrhea may also be related to other factors. This needs further study.

The principle of prevention of MDT-NTS infections, whether iNTS or not, is good food, hygiene, and good immunity and controlling MDR-NTS in the environment is essential. Thailand had the Antibiotic Smart Use programs started in 2007.[37] They are effective in reducing drug-resistant strains; however, some conditions, such as the easy access to over-the-counter antibiotics without a doctor's prescription, and antibiotic stewardship[38] campaigns include encouraging using the practice guidelines to increase the confidence of doctors and patients. And also includes controlling the use of antibiotics in livestock. This requires government policies that consider the appropriate benefits and risks.

Limitations

This research is a retrospective study, so data for comparison was limited. In addition, the hospitals had different kinds of information, for example, types of antimicrobial tests and sources of specimens (blood, urine, stool, etc.). The data of MIC and serotype of *Salmonella* classification were limited because these tests are not routinely performed in general hospitals, limiting our data. Lastly, this study's findings cannot be generalized to a general population, so further studies are needed.

Conclusion

The invasive infection NTS patients who were older than 60 years and had onset of illness >3 days before admission were associated with MDR-NTS infection. The MDR-NTS was related to iNTS. The factors associated with iNTS were WBC ≥ 15,000 cell/uL, hemoglobin <12 g/dL, and the peak of fever ≥39 C°. Therefore, patients with these factors may be infected with MDR-NTS. However, the choice of antimicrobial selected must be appropriate for the local prevalence and epidemiology of MDR-NTS and correlate with the clinical responsiveness.

Ethical Approval

The study protocol was approved by the research ethics committee of Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University. All information was anonymized to maintain patients' privacy, Declaration of Helsinki. Considering the retrospective and anonymous nature of the study, the Ethics Committee did not require written informed consent provided by patients.

Acknowledgments

The authors thank all patients, health practitioners and directors of all hospitals authorized to collect research data.

Funding

Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University, supported this research.

Disclosure

The authors report no conflicts of interest in relation to this work and declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in the research.

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