

## Pattern of Anti-Microbial Sensitivity and Resistance against Salmonella Species in a Tertiary Hospital in Dhaka

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Received: May 31, 2014 Accepted: March 28, 2015

doi: <http://dx.doi.org/10.3329/jemc.v5i2.23378>

### Abstract

**Background:** Drug resistant *Salmonella* spp. continues to remain a health problem as last two decades have witnessed the emergence and spread of multidrug resistance against conventional anti-typhoid drugs. Multidrug resistant (MDR) typhoid is now a serious problem in many developing countries including Bangladesh. **Objectives:** To find out antimicrobial sensitivity and resistance patterns of different types of *Salmonella* spp. in patients with enteric fever and to find out the epidemiological strains (e.g. resistant strain, epidemic strain, MDR strain) in patients with enteric fever. **Materials and Methods:** This cross-sectional study was done during October 2009–November 2010 and January–December 2012 at United Hospital Limited, Dhaka. Laboratory reports of blood culture were collected from those patients who were investigated as suspected cases of enteric fever. Both the indoor and outdoor patients were enrolled in the study. *Salmonella* species resistant to one or more of the first line drugs were divided into resistant strain, epidemic strain and multi-drug resistant strain. **Results:** During the period October 2009–November 2010, total 210 subjects were enrolled. Among the participants, 122 were male and 88 were female. *S. typhi* were found in 133 samples whereas 76 were *S. paratyphi* A and only 1 *S. paratyphi* B. Sensitivity was found 77% for ampicillin, 91.4% for cotrimoxazole, 78.6% for chloramphenicol, 87.6% for ciprofloxacin, 96.6% for cefixime, 98% for ceftriaxone and only 22.1% for azithromycin (77.9% resistant). Total 91 (43.3%) cases were found having resistant strain, 6 (2.8%) epidemic strain and 8 (3.8%) MDR strain *Salmonella* spp. The sensitivity of azithromycin was analyzed among different categories of strains and revealed that 52.7% showed resistance in resistant strain, 100% in epidemic strain and 87.5% in MDR strain. During the period between January–December 2012, total 139 subjects were enrolled. Among the participants 68 were male and 71 were female with a ratio of 1:1.04. *S. typhi* were found in 84 cases whereas 55 were *S. paratyphi* A and no *S. paratyphi* B. Sensitivity was found 62.7% for ampicillin, 82% for cotrimoxazole, 83% for chloramphenicol, 45.2% for azithromycin, 95% for ciprofloxacin, 99.3% for cefixime and 100% for ceftriaxone. Total 55 (39.6%) cases were found having resistant strain, 3 (2.1%) epidemic strain and 17 (12.2%) MDR strain *Salmonella* spp. Against azithromycin 67.3% showed resistance in resistant strain, 33.3% in epidemic strain and 29.4% in MDR strain. **Conclusion:** The policy of empirical treatment of enteric fever needs to be rationalized and newer generation antibiotics should be restricted only for multi-resistant cases of enteric fever.

**Key words:** Enteric fever; *Salmonella* species; Resistance and sensitivity patterns; Multiresistant cases

J Enam Med Col 2015; 5(2): 88–92

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## Introduction

Enteric fever is a global health problem. Around 21.6 million people are affected (incidence of 3.6 per 1000 population) with enteric fever which kills an estimated 200,000 people every year. The disease is endemic in Indian subcontinent, Southeast Asia, South and Central America and Africa.<sup>1</sup> Bangladesh being in this region and a country with poor sanitary infrastructure is endemic for enteric fever as other South Asian countries.

Enteric fever has been reported from almost every part of Bangladesh. It is a common cause of febrile illness among the patients presenting to medical facilities and also happens to be the major reason for seeking health service by the general population. Studies conducted in Bangladesh by ICDDR,B showed an incidence of approximately 2000 per 100 000 per year.<sup>2</sup>

Chloramphenicol became the standard antibiotic for treating typhoid in 1948.<sup>3</sup> But in 1972, chloramphenicol-resistant typhoid fever became a major problem.<sup>4</sup> Several outbreaks occurred in Mexico, India, Vietnam, Thailand, Korea and Peru.<sup>4</sup> *S. enterica* serotype typhi strains were also resistant to sulfonamides, tetracycline and streptomycin, but initially amoxicillin and trimethoprim-sulfamethoxazole remained effective alternative drugs. At the end of 1980s and 1990s, *S. enterica* serotype typhi developed resistance simultaneously to all the first-line drugs (chloramphenicol, trimethoprim, sulfamethoxazole and ampicillin).<sup>4</sup> Outbreaks of infections with these strains occurred in India, Pakistan, Bangladesh, Vietnam, the Middle East and Africa.<sup>5</sup>

Third generation cephalosporins are now the mainstay of treatment of enteric fever. Isolation of *S. typhi* resistant to ceftriaxone from Bangladeshi population and reports of clinical strains with higher minimum inhibitory concentration (MIC) from India are increasing. Thus treatment options are getting limited.<sup>6,7</sup> This situation highlights the need of continued surveillance for changing antibiotic sensitivity and resistance profile of *Salmonella spp.* over time so that physicians can choose the right antibiotic and prevent misuse of valuable drugs.

This study was conducted to identify the recent epidemiological pattern of *Salmonella species* in the capital of Bangladesh as well as to analyze the recent trend of antimicrobial sensitivity and resistance against it.

## Materials and Methods

This cross-sectional study was done in the department of Medicine of United Hospital Limited, Dhaka during October 2009–November 2010 and January–December 2012. Laboratory reports of blood culture were collected from those patients who were investigated as suspected cases of enteric fever. Both the indoor and outdoor patients were enrolled in the study. Data were processed and analyzed by rate, ratio and percentage.

*Salmonella species* resistant to one or more of the first line drugs (chloramphenicol, cotrimoxazole and ampicillin) were divided into resistant strain, epidemic strain and multi-drug resistant strain.<sup>8</sup> Resistant strains of *Salmonella* were resistant to at least one of the first line drugs. Epidemic strains of *Salmonella* were resistant to chloramphenicol and cotrimoxazole but susceptible to ampicillin. Multidrug-resistant *S. typhi* (MDRST) is mainly reserved for strains resistant to all three first-line antityphoidal antimicrobial agents, namely ampicillin, chloramphenicol and cotrimoxazole.<sup>9</sup>

## Results

During the period October 2009–November 2010, total 210 subjects were enrolled. Among the participants, 122 were male and 88 were female with a ratio of 1.3:1. During the period January–December 2012, total 139 subjects were enrolled. Among the participants 68 were male and 71 were female with a ratio of 1:1.04. Age distribution of culture positive enteric fever subjects is shown in Fig 1. *S. typhi* was found in 133 cases followed by 76 cases of *S. paratyphi A* and only 1 *S. paratyphi B* in the period of October 2009–November 2010 (Fig 2). *S. typhi* was found in 84 cases followed by 55 cases of *S. paratyphi A* and no *S. paratyphi B* in the period of January–December 2012 (Fig 2).

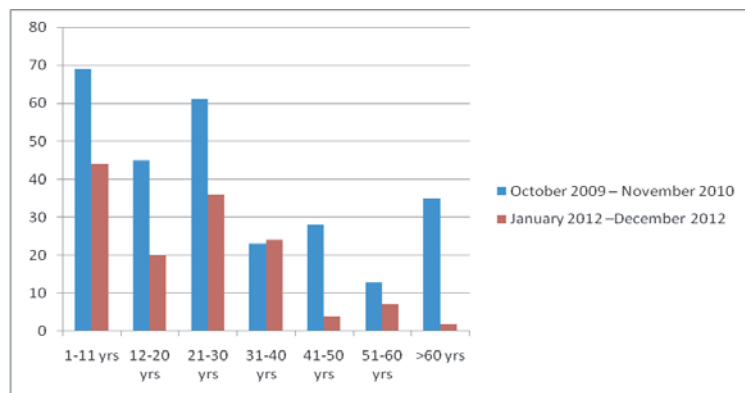


Fig 1. Age distribution of culture positive enteric fever subjects

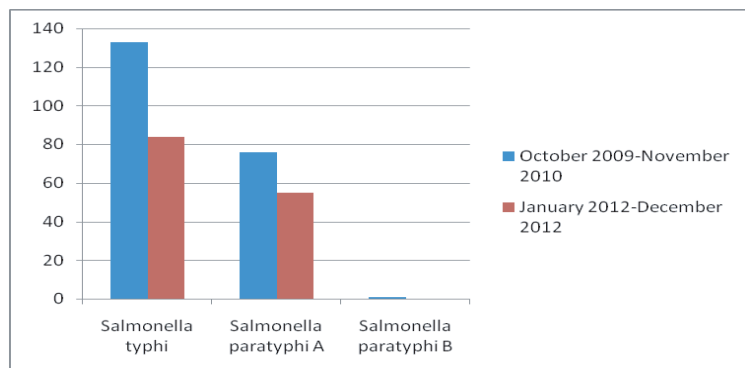


Fig 2. Distribution of isolated organisms

During the period October 2009–November 2010, sensitivity was found 77% for ampicillin, 91.4% for cotrimoxazole, 78.6% for chloramphenicol, 87.6% for ciprofloxacin, 96.6% for cefixime, 98% for ceftriaxone and only 22.1% for azithromycin (77.9% resistant) (Table I). During this period 91 (43.3%) cases were found having resistant strain, 6 (2.8%) epidemic strain and 8 (3.8%) MDR strain *Salmonella spp.* (Table II). During the period January–December 2012, sensitivity was found 62.7% for ampicillin, 82% for cotrimoxazole, 83% for chloramphenicol, 45.2% for azithromycin, 95% for ciprofloxacin, 99.3% for cefixime and 100% for ceftriaxone (Table I). During this period, there were 55 (39.6%) resistant strain, 3 (2.1%) epidemic strain and 17 (12.2%) MDR strain *Salmonella spp.* (Table II).

Table I: Antimicrobial sensitivity pattern in enteric fever

October 2009–November 2010			January 2012–December 2012		
Drugs	Sensitive (%)	Resistant (%)	Drugs	Sensitive (%)	Resistant (%)
Ciprofloxacin (n=209)	183 (87.6)	26 (12.4)	Ciprofloxacin (n=139)	132 (95)	7 (5)
Cotrimoxazole (n=209)	191 (91.4)	18 (8.6)	Cotrimoxazole (n=139)	114 (82)	25 (18)
Chloramphenicol (n=206)	162 (78.6)	44 (21.4)	Chloramphenicol (n=135)	112 (83)	23 (17)
Cefixime (n=203)	196 (96.6)	7 (3.4)	Cefixime (n=139)	138 (99.3)	1 (0.7)
Ampicillin (n=200)	154 (77)	46 (23)	Ampicillin (n=134)	84 (62.7)	50 (37.3)
Azithromycin (n=204)	45 (22.1)	159 (77.9)	Azithromycin (n=135)	61 (45.2)	74 (54.8)
Ceftriaxone (n=205)	201 (98)	4 (2)	Ceftriaxone (n=139)	139 (100)	0 (0)

Table II: Epidemiologic resistant strain pattern in enteric fever

Epidemiologic strains	Oct 2009–Nov 2010		Jan–Dec 2012	
	Frequency	Percentage	Frequency	Percentage
Resistant strain	91	43.3	55	39.6
Epidemic strain	6	2.8	3	2.1
Multi-drug resistant strain	8	3.8	17	12.2

Table III: Pattern of azithromycin resistance among various epidemiological strains

October 2009–November 2010			January–December 2012		
Epidemiologic strains	Frequency	%	Epidemiologic strains	Frequency	%
Resistant (n=91)	48	52.7	Resistant (n=55)	37	67.3
Epidemic (n=6)	6	100	Epidemic (n=3)	1	33.3
Multidrug resistant (n=8)	7	87.5	Multidrug resistant (n=17)	5	29.4

The sensitivity to azithromycin was analyzed among different strains. During the period between October 2009–November 2010, 52.7% showed resistance in resistant strain, 100% in epidemic strain and 87.5% in MDR strain (Table III). During the period between January–December 2012, 67.3% showed resistance in resistant strain, 33.3% in epidemic strain and 29.4% in MDR strain (Table III).

## Discussion

Typhoid fever is highly endemic in developing countries like Bangladesh and is an important cause of health problem involving huge health care costs, high morbidity and economic loss. Children are affected mostly between 5–12 years.<sup>10</sup> Atypical presentation of typhoid fever may be misdiagnosed in pre-school age group due to an underdeveloped reticuloendothelial system.<sup>11</sup>

In our study causative organisms of enteric fever were predominantly *S. typhi* followed by *S. paratyphi*. Shirakawa et al found *S. paratyphi* as the commonest cause of typhoid fever.<sup>12</sup>

In this study *Salmonella spp.* remained sensitive to chloramphenicol, ampicillin, and cotrimoxazole over both study periods. The re-emergence of increased sensitivity of cotrimoxazole and chloramphenicol to *Salmonella* should be considered in using it as first line therapy. High susceptibility to chloramphenicol, cotrimoxazole, and ampicillin were also reported from several parts of India such as Bangaluru, Chennai, Chandigarh, central west, and northern India.<sup>13</sup> A study done by Chand et al<sup>14</sup> revealed re-emergence of susceptibility to ampicillin, chloramphenicol and cotrimoxazole in great proportion.

Patients in Indian subcontinent or with the history of travel to the Indian subcontinent were suggested to

receive ciprofloxacin as first line therapy.<sup>15</sup> But *S. typhi* isolates resistant to ciprofloxacin and ceftriaxone have been reported. *S. typhi* strains with reduced susceptibility to fluoroquinolones have become a major problem in Asia and other parts of the world.<sup>16</sup> In this study, sensitivity to ciprofloxacin increased from the first study period (87.6%) to the second (95%).

Optimal antimicrobial treatment of patients with enteric fever depends on an understanding of local patterns of antimicrobial resistance and is enhanced by the results of antimicrobial susceptibility testing of the *Salmonella* isolated from the individual patient. Third-generation cephalosporins such as ceftriaxone may be used. However, the cost and route of administration make ceftriaxone less suitable for treatment in some low- and middle-income countries, and the oral third-generation cephalosporin cefixime appears to be inferior to other oral agents both in terms of fever clearance time and treatment failure.<sup>17</sup> In this study, sensitivity to ceftriaxone was high in both periods. All the 139 isolates of January–December 2012 were sensitive to ceftriaxone which correlates with the study of Arora et al.<sup>18</sup> This underlies the importance of the drug for treating MDR and ciprofloxacin resistant enteric fever cases. Emphasis has to be laid on the sparing use of the drug to prevent the occurrence of resistance to ceftriaxone.

WHO recommends the fluoroquinolones or cefixime for the treatment of MDR typhoid fever and azithromycin, the third-generation cephalosporins, or a 10–14 day course of high-dose older generation fluoroquinolones for the treatment of nalidixic acid resistant typhoid (NART). But in this study resistance of different strains of *Salmonella* to azithromycin is very high.

Antibiotics are unnecessarily prescribed for infections such as the common cold, cough and diarrhea which are usually of viral etiology and can be resolved by the immune system. Emphasis is placed on treatment instead of finding the causative organism and reaching a proper diagnosis. This leads to patients being treated with broad spectrum antibiotics, which results in the emergence of MDR organisms.<sup>15</sup>

A limitation of our study was that clinical outcomes were not analyzed. Quinolones may remain effective despite in vitro resistance and ceftriaxone may be associated with prolonged time to fever resolution despite in vitro sensitivity.

The policy of empirical treatment of enteric fever needs to be rationalized and newer generation antibiotics should be used only for multi-resistant cases of enteric fever. Consistent surveillance and antibiotic susceptibility testing is required in different parts of the country to know the sensitivity pattern among enteric fever pathogens, which will be helpful for clinicians for rational prescribing.

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