

Changing trend of antibiotic susceptibility pattern of Enteric Fever: What is Next?

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Abstract:

Enteric fever continues to be a major global public health problem, predominantly in the developing countries, including Bangladesh. Mortality rates due to enteric fever can be reduced from 30% to <1% by providing effective antimicrobial therapy which is facing challenges due to emerging antimicrobial resistance. The changing trend of antibiotic susceptibility pattern of Enteric fever from pre-antibiotic era through susceptible antibiotics, then multidrug resistance (MDREF) followed by re-emergence of sensitivity to some older resistant antibiotics pose therapeutic challenges for the physicians. The purpose of this review article is to compare the antibiogram of Salmonella isolates of different recent studies and analyzing the changing trend of antibiotic resistance pattern for further successful management. This may also enable planning of antibiotic recycling wherever feasible.

Keywords: Enteric fever, antibiotic, changing trend of antibiotic, susceptibility pattern of antibiotic.



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Introduction:

Nothing is constant in Medical Science- with time, the knowledge and experience is always changing. One antibiotic may be drug of choice now; but with time, it may gain resistance and become outdated. This ultimately necessitates the invention of newer drugs and newer researches. This is what actually happened in case of Enteric fever. The changing trend of antibiotic susceptibility pattern of Enteric fever from pre-antibiotic era through susceptible antibiotics, then multidrug resistance (MDREF) followed by re-emergence of sensitivity to some older resistant antibiotics pose therapeutic challenges for the physicians. The purpose of this review article is to compare the antibiogram of Salmonella isolates of different recent studies and analyzing the changing trend of antibiotic resistance pattern for further successful management. This may also enable planning of antibiotic recycling wherever feasible.

Enteric fever is an acute multi-system febrile illness transmitted by faeco-oral route, caused primarily by *Salmonella enterica serotype Typhi* (S. Typhi) and *Paratyphi A* which infect only humans. Enteric fever is one of the major

public health problems in developing countries including Bangladesh, where safe drinking water and sanitation not properly ensured yet.

Worldwide, enteric fever is most prevalent in areas that are overcrowded with poor access to sanitation. Incidence estimates suggest that south-central Asia, Southeast Asia, and southern Africa are regions with high incidence of S. Typhi infection (more than 100 cases per 100,000 person-years).¹ In 2000, it was estimated that over 21.6 million (incidence of 3.6 per 1,000 population) of typhoid occurrences worldwide, resulting in 216,000 deaths and that more than 90% of this morbidity and mortality occurred in Asia.² In an urban slum in Dhaka, the incidence of Salmonella typhi (S. typhi) was found to be 390/100,000 population.³ Outbreaks are more common in summer season⁴ due to scarcity and contamination of drinking water. Infected and healthy carriers are the source of infection and “five Fs” (food, fingers, flies, fomites and faeces) play an important role in the spread of the disease.⁵

Mortality rates due to enteric fever can be reduced from 30% to <1% by providing effective antimicrobial therapy which is facing challenges due to emerging antimicrobial resistance.⁶ Indiscriminate and injudicious use of antibiotics in undiagnosed febrile illness, sometimes by unqualified practitioners, often without laboratory support in antibiotic sensitivity test of organisms is responsible for diagnostic difficulties and antibiotic resistance. So, typhoid fever is not only a problem for patients, but also for treating physicians.

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The history of antibiotic resistance:

Antibiotic resistance is a moving target. The history of antibiotic resistance of Enteric fever can be summarized as follows:

Chloramphenicol was used universally to treat typhoid fever from 1948 until the 1970s.

Widespread resistance to Chloramphenicol occurred during 1970.

Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMZ) (co-trimoxazole) then became treatments of choice.

In the late 1980s, some *S typhi* and *S paratyphi* strains developed simultaneous plasmid-mediated resistance to all three of these agents (multidrug resistant [MDR] *S typhi* or *S paratyphi*).

This led to the use of fluoroquinolones in the management of enteric fever.

Afterwards, subsequent emergence of nalidixic acid resistance (NaR) and decreased susceptibility to fluoroquinolones and eventually full resistance to fluoroquinolones (Lynch 2009) occurred.

In fluoroquinolone resistant isolates, a third generation cephalosporin, frequently ceftriaxone, is often the drug of choice (Basnyat 2007) (high cost & parenteral route of administration limit the use of Ceftriaxone).

However, sporadic cases of third generation cephalosporin resistance have been reported⁷. An isolate of *S.typhi* from Bangladesh with high-level resistance to ceftriaxone has already been reported.⁸

If resistance develops against even the third generation cephalosporins, the treatment options available would be; fourth generation cephalosporins, penems, tigecycline or combination antibiotic therapy which will make treatment expensive.

However, due to restricted use of first line drugs leading to withdrawal of selective pressure, recent studies have shown that strains previously resistant to the first line drugs are showing very low or no resistance at all.⁹ Therefore reuse of first line drugs can be considered for management of enteric fever.¹⁰

Comparison of studies:

The antibiotic sensitivity pattern for the commonly used antibiotics was analyzed from different recent studies to detect the variations in the sensitivity pattern.

Antibiotic susceptibility pattern of Salmonella isolates:

Study done by	Reza IB et al ¹¹	Sharvani R et al ¹²	Singh CL et al ¹³	Chaudhary et al ¹⁴	Prajapati B et al ¹⁵	Lynch et al ¹⁶	Ahasan et al ¹⁷
Place of study	Dhaka, Bangladesh	India (multicenter)	India	Southern India	Nepal	USA	Khulna Bangladesh
Year of study	2018	2013	2012-2014	2009-2011	2007-2008	1999-2006	1991-1992
Study Period	6 months	1 year	27 months	2 years	1 year	7 years	1 year
Number of culture	139	167	46	322	235	2016	48%
Positive cases of Salmonella							
ANTIBIOTIC							
Ampicillin	69%	94.6%	91.30%	90.68%	66.7%	86.5%	10.6%
Co-trimoxazole	75%	95.8%	91.30%	95.03%	93.5%	86.5%	2.1%
Nalidixic Acid	52%	9.5%	50%	8.07%	62.4%	
Ciprofloxacin	68%	62.2%	76.8%	54.34%	86.6%	63.59%	100%
3 rd generation Cephalosporin	100%	97%	93.47%	100%	98.9%	66.6%
Chloramphenicol	80%	95.2%	100%	93.2%	86.5%	19.5%
Imipenem	100%				
MDREF	30%					13%	

Discussion:

Enteric fever continues to be a major global public health problem, predominantly in the developing countries, including Bangladesh. In the pre-antibiotic era, the case fatality rate due to Typhoid fever approached 20%. However, after 1948, the situation changed abruptly with the discovery of powerful antibiotic Chloramphenicol. Treatment with effective antimicrobial agents - ampicillin, chloramphenicol, cotrimoxazole and later ciprofloxacin - has reduced the case fatality rate to less than 1%.¹⁸ The ensuing 7 decades have chronicled an epic thrust-and-parry duel between the appearance of powerful new antibiotics and a wily bacterial foe's stepwise acquisition of resistance to them- now a days, this drug resistance of enteric fever is major concern rather than the disease itself.

The first multidrug-resistant strain (i.e., resistant to all the three first-line recommended drugs for treatment, i.e., chloramphenicol, ampicillin, and co-trimoxazole) emerged in Southeast Asia in the late 1980s and have since spread throughout the region. A study conducted in ICDDR,B in 2005 among 428 culture positive cases, the prevalence of MDRTF was found to be 91.4%.¹⁹ Interestingly, several recent studies have found that strains previously resistant to the first-line drugs (chloramphenicol, ampicillin and co-trimoxazole) are now showing decreasing resistance. Thus, Variations in the sensitivity patterns reported for *Salmonella* isolates, stress the significance of continuous monitoring of antibiotic susceptibility pattern of locally prevalent strains.

In the present paper, we have compared 6 recent studies of different countries (including Bangladesh) regarding antibiotic susceptibility pattern of *Salmonella* isolates. All the studies, revealed increasing sensitivity of *Salmonella* isolates to the first line drugs (chloramphenicol, Co-trimoxazole & Ampicillin) more than ciprofloxacin. The sensitivity of Chloramphenicol & co-trimoxazole is almost similar to the sensitivity of 3rd generation cephalosporin (>95% in some studies). The withdrawal of selective pressure has probably resulted in the re-emergence of sensitivity to these first-line drugs.²⁰

In all the studies, rates of nalidixic acid resistance are of particular concern. Although this older antibacterial is rarely used for treatment, resistance to nalidixic acid can be a marker for decreased susceptibility to fluoroquinolones. Nalidixic Acid Resistance (NAR) indicates low level resistance to ciprofloxacin and results in treatment failure. In all the studies, sensitivity of Nalidixic acid and ciprofloxacin is less than the first line drugs. Hence ciprofloxacin can no longer be the keystone for treatment.

In all the studies, susceptibility to third generation cephalosporins is >95%, sometimes 100% (Reza IB et al¹¹ Chaudhary et al¹⁴). A small percentage of isolates showed resistance to third generation cephalosporins (2.9% *S. typhi* in Sharvani R et al¹²), similar to study done by Jain et al., in Delhi (2% of *Salmonella* enteric strains). Therefore, cephalosporins continue to be a good option for treatment of MDR and NAR cases. The cost and parenteral route of administration, however, make ceftriaxone less suitable for patient treatment in low and middle-income countries, particularly as 60%–90% of enteric fever patients are treated as outpatients. An alternative would be the oral, third-generation cephalosporin cefixime.

Study across five endemic Asian countries- China, India, Indonesia, Pakistan and Vietnam in the year 2008 showed 7-65% prevalence of MDR *salmonella* isolates.²¹ In the study of Sharvani R et al¹², MDR was observed in 1.7% of *S. typhi* isolates, similar to studies reported by Indian Network for Surveillance, Gopal Muthu et al., in Madras, Shaik Mohammed et al., in Bangalore, World Health Organization, Jain et al., in Delhi.²² The low proportion of MDR may be due to restricted use of first line drugs leading to withdrawal of selective pressure, therefore reuse of first line drugs can be considered for management of enteric fever.

Conclusion:

There is shifting of antimicrobial susceptibility profile. Increasing resistance to quinolones is alarming so it is necessary to determine MIC levels for ciprofloxacin to avoid treatment failures. Third generation cephalosporins still remain as a drug of choice for treatment of MDR enteric fever cases. Reuse of the first line antibiotics can be considered for treating enteric fever cases. Their cheaper cost and availability in developing countries, in addition to their well-established clinical efficiency, are among the benefits of re-using chloramphenicol or ampicillin. Thus constant surveillance and vigorous audits of antibiotic sensitivity testing results are needed to determine whether the reintegration of these first-line drugs can be applied to a particular region.

Conflict of interest: None.

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