INTRODUCTION
Sometimes even the simplest problem throws the toughest challenge. A young girl aged 17 years was suffering from fever with headache for 3 weeks. Despite treatment by several physicians with recent well known antibiotics she continued to suffer from high fever all the same. Many other investigations were done which did not suggest otherwise. Incidentally, her blood culture and drug sensitivity test was not done because of expenses and feasibility problems. Meanwhile, a senior erudite Professor of Medicine examined her and empirically prescribed her Azithromycin at a dose of 1 gm per day. She was cured with total alleviation of symptoms in 4 days.

So, even in 2016, that is, 132 years after the isolation of the bacterium by the German Scientist Gaffky, it is sad to say that typhoid fever is still an enigma. Every year throughout the world there are still around 15 million cases of typhoid out of which some 600,000 succumb to death. Interestingly, more than 80% of all cases of typhoid fever belong to Asia and Africa. However, it is not uncommon in western countries either, like in the UK about 1 out of 1,00,000 populations suffer from typhoid every year.

Added to these problems, the treatment of typhoid fever has been even more challenging because of the emerging trends of resistant strains. Microbial resistance regarding Salmonella Typhi is basically of two types, viz., Quinolone Resistant Salmonella Typhi (QRST), and multidrug resistant (MDR) type. There is also a strain which is known as DCS (decreased ciprofloxacin susceptibility) strain of S. typhi causing typhoid fever.

A study on knowledge, attitude and practice of general practitioners (GP) regarding treatment of typhoid fever by Paul et al in January, 2016 has shown that the antibiotics used by GPs for treatment of typhoid are : Azithromycin (42%), Fluoroquinolones (32%), Cefixime(16%), Amoxycillin (6%) and Choramphenicol (4%). A combination of antibiotics is preferred by 38% of GPs and the preferred combinations of antibiotics are Cefixime + Azithromycin (26%) and Ciprofloxacin + Azithromycin (12%). Parenteral antibiotic is preferred in most cases when the patient is unable to consume orally usually due to excessive vomiting.

Thus, a new plan and expanded thinking is now required regarding present and future management of typhoid fever.
Ingestion

Widespread dissemination

Fig 1: Pathogenesis of typhoid fever

**S. typhi**

Intestine

Enterocytes lining the terminal ileum

Peyer patch and resident macrophages

Mesenteric Lymph node

Blood Stream

Primary Bacteremia

Secondary Bacteremia

Onset of clinical symptoms of typhoid fever like Fever, headache, myalgia, constipation...

Peyer patches re-exposed to S. typhi via bile

Liver

Spleen

Bone Marrow

S. typhi is disseminated throughout the body and colonize the organs of Reticulo endothelial system, where they may replicate within macrophage

Usually asymptomatic and blood culture results are frequently negative

**Laboratory diagnosis of typhoid fever**

Isolation of organism

Detection of typhoid antigen

Titration of antibody against S. typhi

Detection of typhoid antigen

**Fig. 2: Laboratory Diagnosis**

was found in a study performed in Central India. Hence clinical utility is controversial, with divergent views on the test’s utility in various areas of endemicity. Usually, O antibodies appear on days 6-8 and H antibodies on days 10-12 after the onset of the disease.

Recent advances include the IDL Tubex® which detects IgM antibodies, Typhidot®, a dot enzyme immunoassay, Typhidot-M® and typhoid IgM dipstick assay for the sero-diagnosis of typhoid fever. However, most of the GPs do not prefer to use these modalities in their day to day practice.

**SUPPORTIVE MANAGEMENT**

With early diagnosis, majority of the patients with typhoid fever can be managed at home with oral antibiotics and antipyretics. Proper nutrition and hydration should be maintained.

**EMERGING RESISTANCE**

Emergence of extended spectrum cephalosporinase producing strains of S. typhi have been reported from Bangladesh, Egypt, India, Kuwait, Iraq, Pakistan, Philippines and the UAE. Confirmed cases reported from
India (bla<sub>CTs-M-15</sub>) and Philippines (bla<sub>SHV-12</sub>). The first case of AmpC producing S. typhi was isolated from an Indian child in 2009.

ANTIMICROBIALS WITH PROMISING EFFECT AGAINST S. TYPHI

The treatment of enteric fever is given in Table 1. Fourth generation fluoroquinolones have good effect against S. typhi but presence of drug related toxicity limits its use.

Fig. 3: Antibiotic therapy for enteric fever in adults

<table>
<thead>
<tr>
<th>OPD Cases</th>
<th>Indoor Cases</th>
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<tbody>
<tr>
<td>Oral Cefixime 20 mg/kg/day for 14 days</td>
<td>Inj Ceftriaxone 100 mg/kg/day and shift to oral Cefixime once fever resolves</td>
</tr>
<tr>
<td>Azithromycin 10-20 mg/kg/day for 7-10 days</td>
<td>Second line</td>
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<td>• Ofloxacin 15 mg/kg/day in 2 divided doses for 10 to 14 days.</td>
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<td></td>
<td>• Chloramphenicol 50-75 mg/kg/day orally for 14 days</td>
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<td></td>
<td>• TMP-SMX 8 mg/kg/day orally for 14 days</td>
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(Gatifloxacin was banned by the Indian Government in 2011). Carbapenems and Tigecycline show good in-vitro activity against S. typhi.

TREATMENT OF CARRIERS

An individual is considered to be a chronic carrier if he or she is asymptomatic and continues to have positive stool or rectal swab cultures for S. typhi a year following recovery from acute illness and can be treated for 4-6 weeks with an appropriate antibiotic. Treatment with oral amoxicillin, TMP-SMX, ciprofloxacin, or norfloxacin is effective. However, in cases of biliary or kidney stones, eradication often requires both antibiotic therapy and surgical correction.

CONCLUSIONS

Lack of reliable rapid diagnostic test create a problem in confirmation of diagnosis of typhoid fever. Emergence of antimicrobial resistant strains of typhoid bacilli creates a great challenge for a treating physician. However, safe drinking water supply, proper sanitation, early diagnosis and treatment and effective vaccination will help to control typhoid fever (Table 2).

REFERENCES


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