

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%), Amoxicillin (6%) and Chloramphenicol (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.

CLINICAL MANIFESTATIONS

In the first week of typhoid fever, the features are non specific with headache (80%), malaise and a rising remittent fever. Patient may have constipation (16%) or diarrhoea (28%). Constipation is more common in cases of adults whereas, diarrhoea is more prominent in cases of children. Rose spots is a faint, salmon-colored, blanching, maculo-papular rash located primarily on the trunk and chest, evident in 30% of patients at the end of the first week and resolves after 2–5 days (difficult to detect in dark skinned person). Patients can have two or three crops of lesions, and Salmonella can be cultured from punch biopsies of these lesions.

During the second week of the disease, the patient looks more toxic with sustained temperature, abdominal distension and splenomegaly may be found. In the third week, development of continuous high fever and a delirious confusional state with pronounced abdominal distension, ileus, or diarrhoea may occur, with liquid, foul green–yellow stools. The patient is likely to become obtunded and hypotensive and crackles may develop over the lung bases. Death may occur at this stage from overwhelming toxemia, myocarditis, intestinal hemorrhage or perforation.

The diagnosis of typhoid fever is usually made on clinical grounds. The symptoms sometimes mimic other common illnesses, such as malaria, sepsis with other bacterial pathogens, tuberculosis, brucellosis, tularemia, leptospirosis and rickettsial disease. Viral infections such as dengue, acute hepatitis and infectious mononucleosis are also included in the differential diagnosis.

Positive blood culture confirms diagnosis of typhoid fever. In 15 -25% of cases, leucopenia and neutropenia can be detected. Leukocytosis is more common among children, during the first 10 days of illness and in cases complicated by intestinal perforation or secondary infection.

Blood cultures are the standard diagnostic method, and the results can be positive in 60 – 80 % of patients, provided that a large volume of blood (typically 15 ml for adults) is cultured. Culture of the infectious agent may also be obtained from stool, urine, bone marrow or bile. Bone marrow is the most sensitive source (80-95 %), but is not practical.

Widal test is commonly used. A fourfold or greater increase in titer (when paired acute and convalescent samples are compared) is considered positive. However, seropositivity (8 – 14%) amongst healthy blood donors

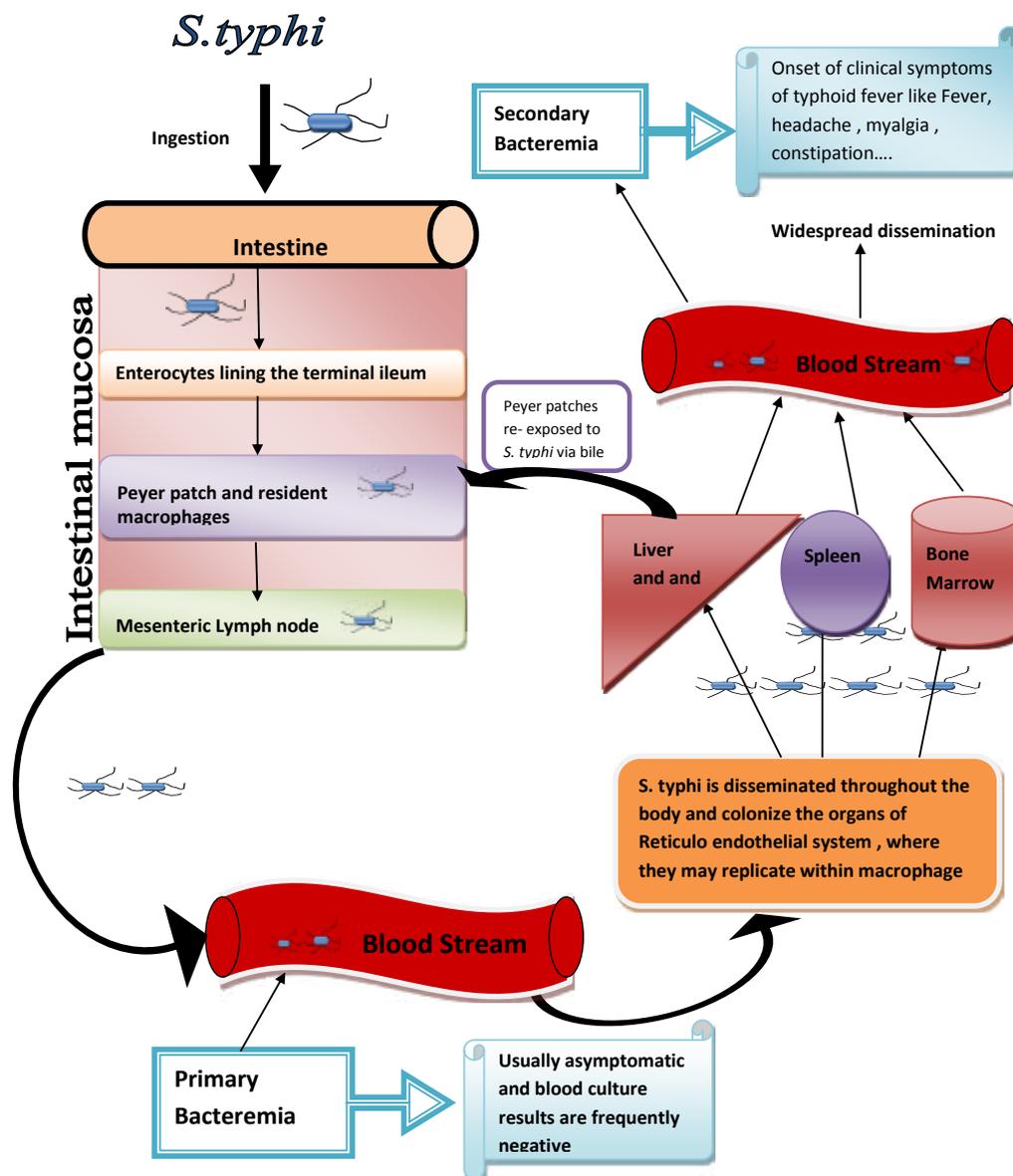


Fig 1: Pathogenesis of typhoid fever

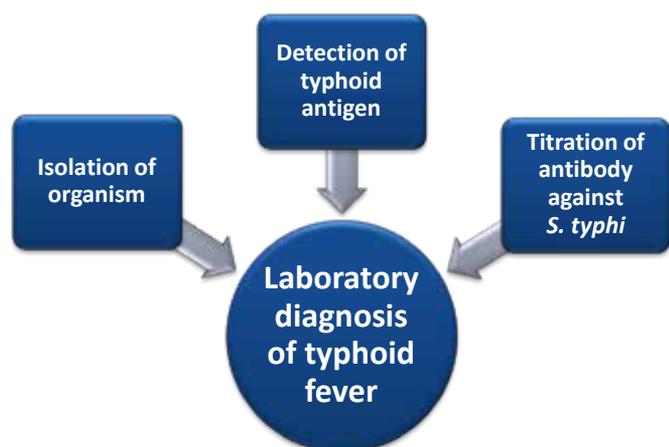


Fig. 2: Laboratory Diagnosis

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 immuno-assay, 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

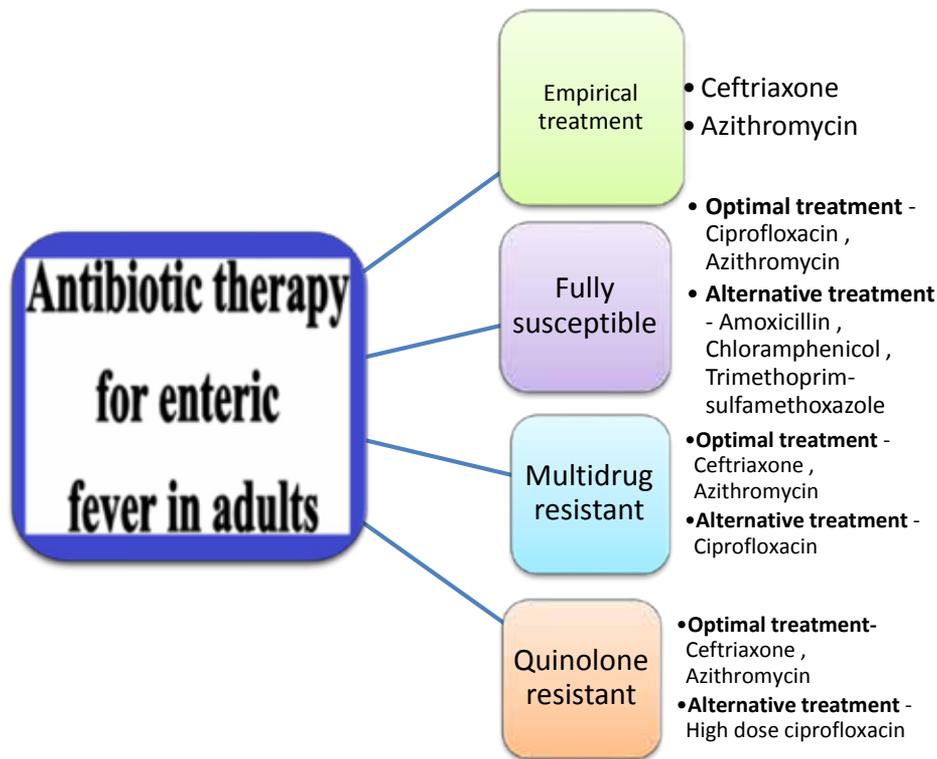


Fig. 3: Antibiotic therapy for enteric fever in adults

India ($bla_{CTS-M-15}$) and Philippines (bla_{SHV-12}). 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

Table 1 : Treatment of Enteric fever	
OPD Cases	Indoor Cases
Oral Cefixime 20 mg/kg/day for 14 days Azithromycin 10-20 mg/kg/day for 7-10 days	Inj Ceftriaxone 100 mg/kg/day and shift to oral Cefixime once fever resolves Second line <ul style="list-style-type: none"> • Ofloxacin 15 mg/kg/day in 2 divided doses for 10 to 14 days. • Chloramphenicol 50-75 mg/kg/day orally for 14 days • TMP-SMX 8 mg/kg/day orally for 14 days

(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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Table 2: Vaccines for Typhoid Fever				
Vaccine	Age (years)	Route	Dosage	Revaccination (years)
Vi CPS	2	subcutaneous	0.5 ml, single dose	2
Ty21 a, live	6	oral	1 capsule given on days 1,3, 5, and 7 days	5

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