

PITFALL IN THE DIAGNOSIS AND MANAGEMENT OF TYPHOID FEVER

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Introduction

- Enteric fever also known as typhoid fever
 - is a common cause of febrile illness in the developing countries where sanitary condition is poor and
 - is a sporadic disease in the developed countries occurring mainly in travelers returning from endemic areas or with occasional point source epidemic

Introduction

- It affects roughly 21.6 million people and kills an estimated 200,000 people every year

Introduction

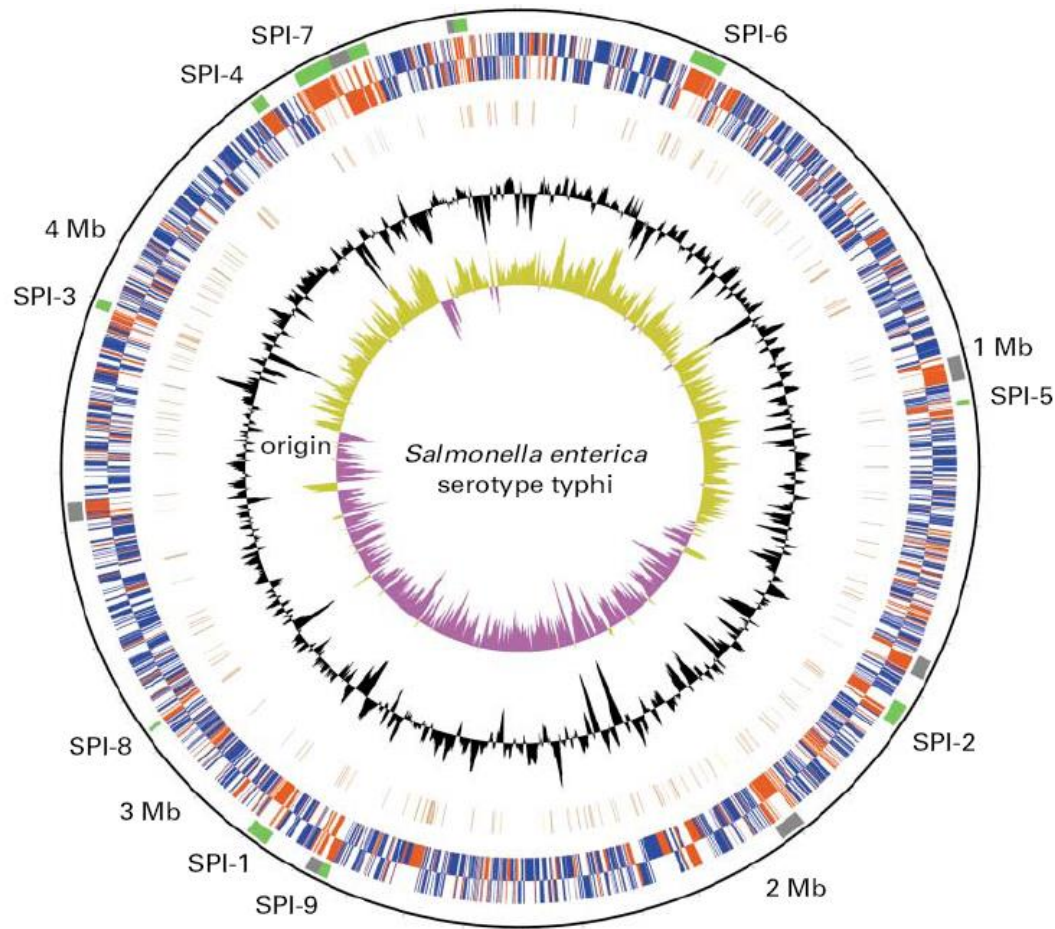
- There are lots of pitfalls in the diagnosis and management of the disease which have been complicated by the development drug resistance

Disease

Bacteriology

- Etiologic agents of enteric fever—*S. Typhi* and *S. Paratyphi* serotypes A, B, and C
- *S. Paratyphi* A is thought to cause milder disease than *S. Typhi*, with predominantly gastrointestinal symptoms
- Don't have hosts other than humans

Genetic constitution: *S. typhi*



Epidemiology

- Most commonly, food or water borne transmission results from fecal contamination by ill or asymptomatic chronic carriers

Epidemiology

Incidence is

- Highest (>100 cases /100,000 population / yr.)
 - South-central and Southeast Asia
- Medium (10–100 cases/100,000)
 - Rest of Asia, Africa, Latin America, and Oceania (excluding Australia and New Zealand) and
- Low
 - other parts of the world

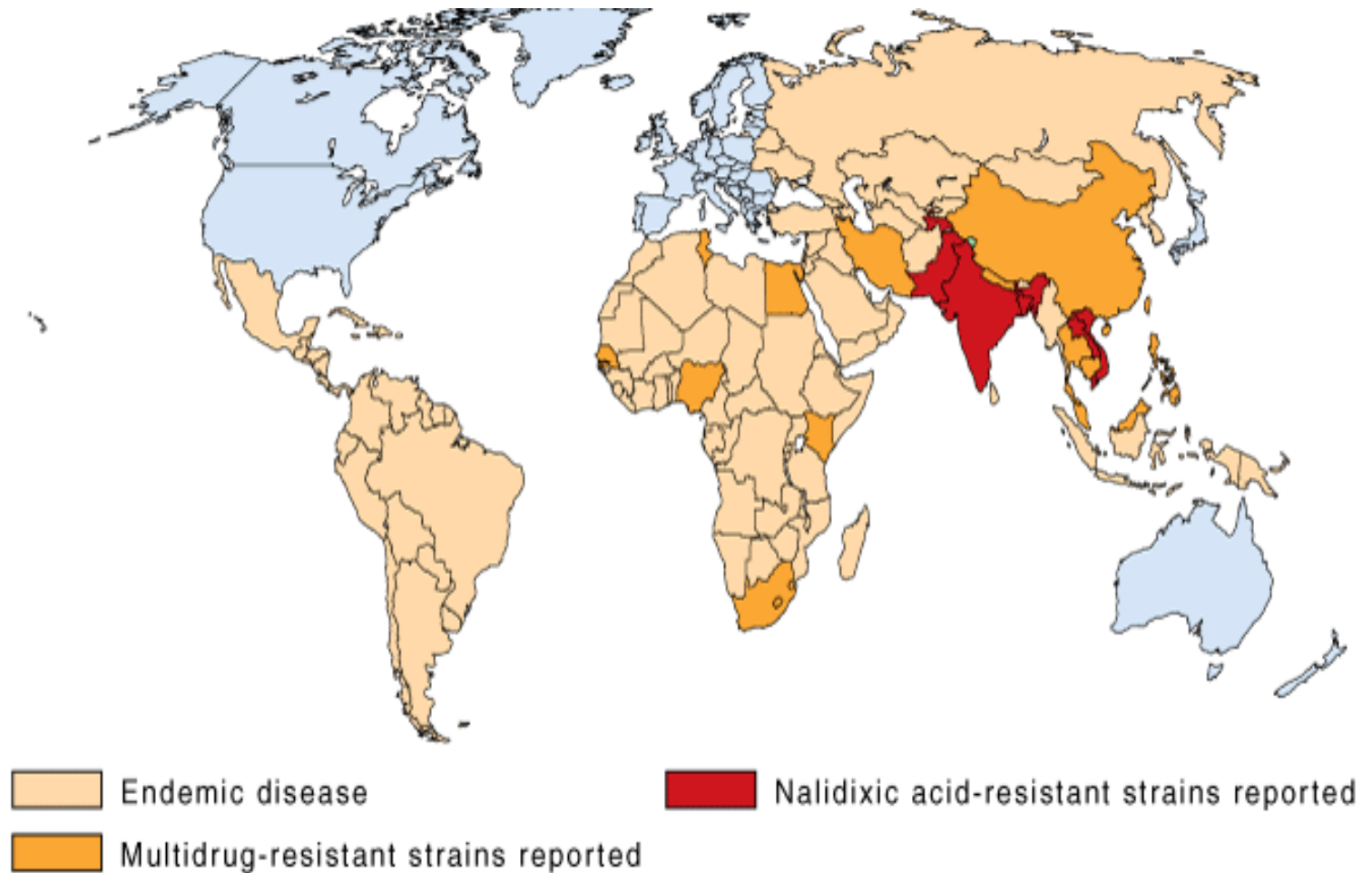
Epidemiology

- Higher incidence correlates with poor sanitation and lack of access to safe drinking water
- In endemic regions, the disease is more common in urban than rural areas and among young children and adolescents

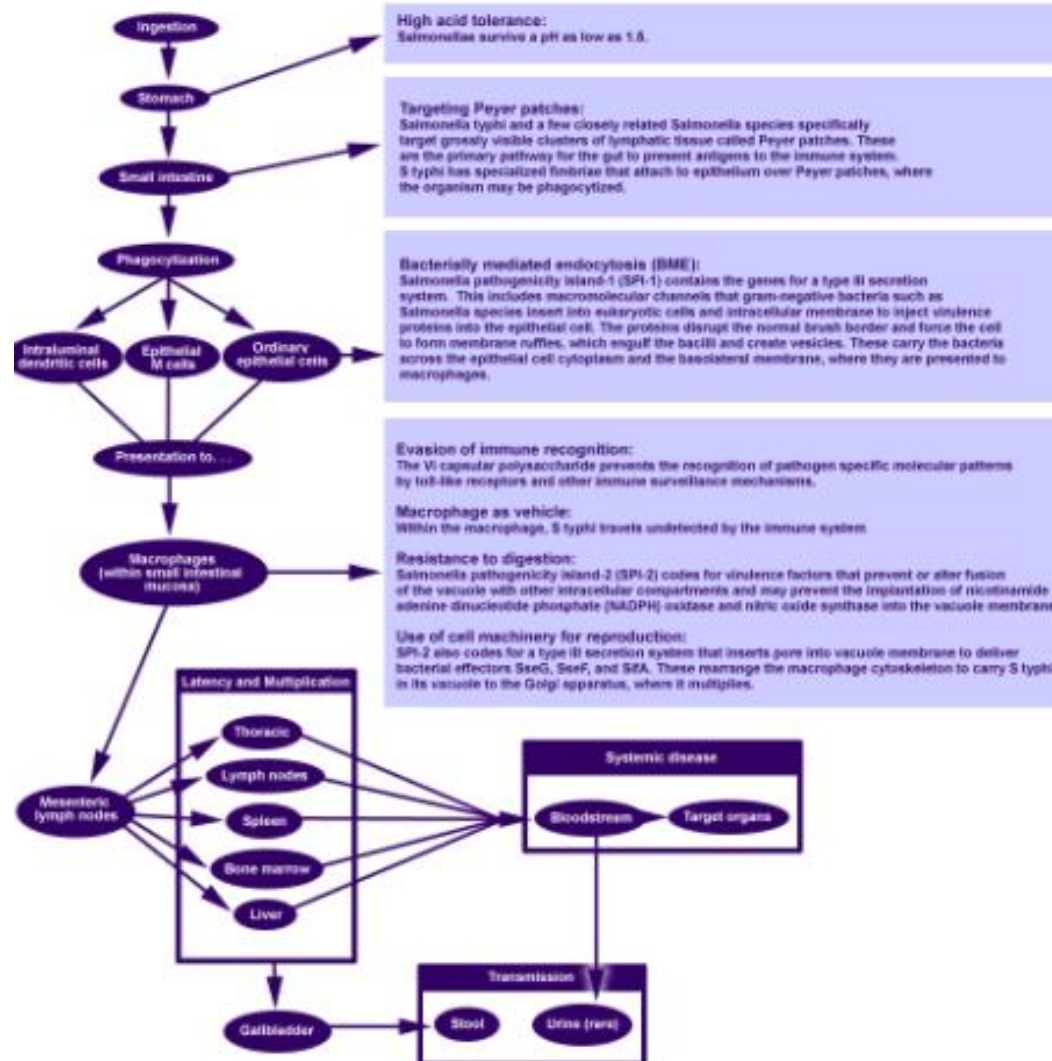
Epidemiology

- Multidrug-resistant (MDR) strains of *S. Typhi* emerged in 1989 in China and Southeast Asia and have since disseminated widely
- These strains contain plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim—antibiotics long used to treat enteric fever
- With the increased use of fluoroquinolones to treat MDR enteric fever, strains of *S. Typhi* and *S. Paratyphi* with reduced susceptibility to ciprofloxacin have emerged in India and Vietnam and have been associated with clinical treatment failure

Global distribution of disease & multidrug resistance *S. typhi*



Pathogenesis and pathology of T. Fever



Diagnosis

Clinical features

- Classic disease
- Atypical manifestations
- Complications
- Asymptomatic carrier

Clinical features

- *Enteric fever* is a misnomer, in that the hallmark features of this disease—fever and abdominal pain—are variable
- While fever is documented at presentation in >75% of cases, abdominal pain is reported in only 30–40%. Thus, a high index of suspicion is necessary when a person presents with fever in endemic area or having a history of recent travel there

Clinical features

- The incubation period averages 10–14 days (3 to 21 days)
- Most prominent symptom fever (>75%), headache (80%), chills (35–45%), cough (30%), sweating (20–25%), myalgias (20%), malaise (10%), and arthralgia (2–4%), anorexia (55%), abdominal pain (30–40%), nausea (18–24%), vomiting (18%), diarrhea (22–28%) and constipation (13–16%)

Clinical features

- Physical findings include coated tongue (51–56%), splenomegaly (5–6%), and abdominal tenderness (4–5%), rash ("rose spots"), hepatosplenomegaly (3–6%), epistaxis, and relative bradycardia at the peak of high fever

Rose spot rash: typhoid fever



Symptoms in 2095 children with suspected typhoid fever in Nigeria

Symptoms	No. of cases	(%) of total
Fever e	2775	95.51
Head ache	1950	67.1
Abdominal pain	1720	59.2
Diarrhoea	1450	49.9
Convulsion	955	34.3
Vomiting	648	22.3
Anorexia	436	15.0
Constipation	348	11.9
Abnormal behaviour	160	5.5

Clinical signs in 2095 children with suspected typhoid fever in Nigeria

Signs	No. of cases	(%) of total
Pyrexia	2745	94.5
Abdominal tenderness	1698	58.6
Dehydration	1102	37.9
Hepatomegaly	978	33.7
Jaundice	64	22.1
unconsciousness	15	0.5

Common clinical features of typhoid fever in childhood in hospital and community setting in Karachi Pakistan. Values are number (percentage)

	Hospital based patients (n=1158)	Community based cohort (n=340)
High grade fever	1044 (95)	238 (99)
Anorexia	811 (70)	11 (3)
Vomiting	451 (39)	43 (13)
Hepatomegaly	471 (41)	68 (20)
Diarrhoea	406 (35)	26 (8)
Toxicity	377 (33)	1 (0.3)
Abdominal pain	320 (28)	65 (19)
Splenomegaly	226 (20)	17 (5)
Constipation	127 (11)	1 (0.3)

Common clinical features of typhoid fever in childhood in hospital and community setting in Karachi, Pakistan. Values are number (percentage)

	Hospital based patients (n=1158)	Community based cohort (n=340)
Head ache	138 (12)	26 (8)
Jaundice	23 (2)	00
Obtundation	23 (2)	1 (0.3)
Ileus	12 (1)	1 (0.3)
Intestinal perforation	58 (5.0)	1 (0.3)
Myalgia	174 (15)	15 (4.4)

Atypical manifestation

Atypical manifestations of typhoid fever include

- isolated severe headaches that may mimic [meningitis](#)
- acute lobar pneumonia
- isolated arthralgias
- urinary symptoms
- severe jaundice
- fever alone

Atypical manifestation

- Some patients, especially in India and Africa, present primarily with
 - neurologic manifestations such as [delirium](#) or
 - in extremely rare cases
 - parkinsonian symptoms or
 - Guillain-Barré syndrome

Atypical manifestation

- Other unusual complications include
 - [pancreatitis](#)
 - Meningitis
 - [Orchitis](#)
 - osteomyelitis, and
 - abscesses anywhere on the body.²

Case definition

- Confirmed case of typhoid fever
 - A person with fever (38°C and above) that has lasted at least for 3 days with a laboratory positive culture (blood, bone marrow, bowel fluid) of *S. typhi*
- Probable case of typhoid fever
 - A person with fever (38°C and above) that has lasted at least for 3 days with a positive serodiagnosis or antigen detection test but without *S. typhi* isolation

Case definition

- Chronic carrier
 - Excretion of *S. typhi* with stool or urine (or repeated positive bile or duodenal string culture) for longer than 1 year after the onset of acute typhoid fever

Complications

- Gastro intestinal
- Hepatobiliary
- Neurologic al
- Renal
- Cardiovasculr

Laboratory diagnosis

- Microbiological tests
- Serological tests
- Molecular diagnostics
- Others

Laboratory diagnosis of typhoid fever

Diagnostic test	Sensitivity range (%)	Specificity range (%)
Microbiological tests		
Blood culture	40-80	NA
Bone marrow culture	55-67	30
Urine culture	0-58	NA
Stool culture	30	NA

Laboratory diagnosis of typhoid fever

Diagnostic test	Sensitivity range (%)	Specificity range (%)
Serological diagnosis		
Widal test (Tube and slide agglutination)	47.77	50-92
Typhidot	66-88	75-91
Typhidot -M	73-95	68-95
Tubex	65-88	63-89

Laboratory diagnosis of typhoid fever

Diagnostic test	Sensitivity range (%)	Specificity range (%)
Molecular diagnostics		
Polymerase chain reaction	100	100
Nested chain reaction	100	100
Others		
Urine antigen detection	65-95	NA

Causes of negative Widal agglutination tests

- Absence of infection by *S. typhi*
- The carrier state an inadequate inoculum of bacterial antigen in the host to induce antibody production
- Technical error in the performance of the test
- Previous antibiotic treatment
- Variability in the preparation of commercial antigens

Causes of positive Widal agglutination tests

- The patient being tested has typhoid fever
- Previous immunization with salmonella antigen
- Cross reaction with non typhoidal salmonella
- Variability and poorly standardized commercial antigen preparation
- Infection with malaria or other enterobacteriaceae
- Other disease such dengue

Distribution of O and H antibody titers (1/160) and sensitivity of Widal test among culture confirmed TF cases (n=254) by times since onset of symptoms

Widal values for O and H antibody titers	1 st week (n=182)	2 nd week (n=54)	3 rd week (n=18)
Positive O titer only	31(17%)	12(22%)	2(11%)
Positive H titer only	20(11%)	13(24%)	7(39%)
Positive O and H	82(45%)	23(43%)	7(39%)
Total positive	133(73%)	48(89%)	16(89%)
Sensitivity	73%	89%	89%

Sensitivity and specificity of Widal test done in developing countries endemic for typhoid fever.

Country	Agglutination	Cut off titre	Sensitivity	Specificity	Reference
Tube agglutination					
Philippine	O	1:20	61	88	Aquino
Philippine	O	1:80	64	100	Buck et al
Hongkong	O and H	1:50	84	99	Chow et al
Jordan	O and H	1:160	92	-	Shehabi
Peru	O	1:160	58	-	Levine
	H	1:160	82	-	
Ceylon	O and H	1:160	85.7	88	Seneratne

Sensitivity and specificity of Widal test done in developing countries endemic for typhoid fever

Country	Agglutination	Cut off titre	Sensitivity	Specificity	Reference
Slide agglutination test					
Phipplines	O	1:160	72.5	57.5	Roxas et al
		1:320	57.5	100	
Jakarta	O and H	1:20	53	98	Hoffmann et al
Ethiopia	O and H	1:160	82	-	Abraham et al
South Africa	O and H	1:200	75	92.5	Somerville et al

Widal agglutination titers in Nigerian patients with or without positive malaria smear

Groups	Positive	1:40	1:80	1;160
POSITIVE MALARIA SMEAR	45	85%	12%	3%
NEGATIVE MALARIA SMEAR	69	45%	15%	10%

Managements

General principles of management

- Rapid diagnosis and appropriate antibiotic treatment
- Adequate rest, hydration and correction of fluid and electrolyte balance
- Antipyretic therapy as required
- Adequate nutrition: soft easily digestible diet unless the patient has abdominal distension or ileus

General principles of management

- Close attention to the hand washing and limitation of close contact with susceptible person during acute infection
- Regular follow up and monitoring for complications and clinical relapse

Antibiotic Therapy for Enteric Fever in Adults

Indication	Agent	Dosage (Route)	Duration, Days
Empirical Treatment			
	Ceftriaxone ^a	1–2 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
Fully Susceptible			
	Ciprofloxacin ^b (first line)	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Amoxicillin (second line)	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO or IV)	14–21
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	14

Antibiotic Therapy for Enteric Fever in Adults

Indication	Agent	Dosage (Route)	Duration, Days
Multidrug-Resistant			
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Ceftriaxone	2–3 g/d (IV)	7–14
	Azithromycin	1 g/d (PO) ^c	5
Nalidixic Acid-Resistant			
	Ceftriaxone	1–2 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
	High-dose ciprofloxacin	750 mg bid (PO) or 400 mg q8h (IV)	10–14

Treatment of uncomplicated typhoid fever

	Optimal therapy			Alternative effective drugs		
Susceptibility	Antibiotic	Daily dose mg/kg	Days	Antibiotic	Daily dose mg/kg	Days
Fully sensitive	fluroquinolone e.g. ofloxacin or ciprofloxacin	15	5-7	Chloramphenicol	50-75 75-100	14-21
				Amoxicillin		14
				TMP-SMX	8-40	14
Multi drug resistant	Fluroquinolone or cefixime	15 15-20	5-7 7-14	Azithromycin or cefixime	8-10 15-20	7 7-14
Quinolone resistant	Azithromycin or ceftriaxone	8-10 75	7 10-14	Cefixime	20	7-14

Treatment of severe typhoid fever

Optimal parenteral drug				Alternative effective parenteral drug		
Susceptibility	Antibiotic	Daily dose mg/kg	Days	Antibiotic	Daily dose mg/kg	Days
Fully sensitive	fluroquinolone e.g. ofloxacin	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	14
				TMP-SMX	6-40	14
Multi drug resistant	fluroquinolone	15	10-14	Ceftriaxone or cefotaxime	60 80	10-14
Oinolone resistant	Ceftriaxone or cefotaxime	60 80	10-14	fluroquinolone	20	7-14

Prevention of typhoid fever

- In endemic countries:
 - Institution of public health measure to ensure safe drinking water and sanitary disposal of excreta
- Other world:
 - Travelers to endemic countries should avoid raw unpeeled fruits or vegetables
 - Should drink only boiled water

Vaccines

- In endemic areas mass immunization with typhoid vaccine at regular interval
- Vaccines are not recommended for children under 2 years of age
- Travelers to endemic areas should vaccinated at one week prior to arrival
- In pregnancy vaccines are studied

Vaccine

- Vi capsular polysaccharide antigen vaccine (ViCPS)
 - Primary vaccination: single parenteral dose of 0.5ml
 - Booster dose : every two years
 - Efficacy 55% (95% CI, 30-70%)
- Ty21a oral vaccine (enteric coated capsule)
 - 1 cap daily for 4 days
 - Booster with same dose every 5 years interval
 - Not recommended in children under 6 years
 - Cumulative efficacy 51%(95% CI, 36-62%)

Vaccine

- Acetone inactivated parenteral vaccine
 - Used for US army
 - Efficacy 75-94%
 - Booster every 3 years

PITFALLS

Pitfall: Clinical diagnosis

- Clinical manifestation is protean
- Community based studies in endemic areas indicate that patients with typhoid fever particularly the children under 5 years may have nonspecific illness that is not recognized clinically as typhoid fever
- 60-90% of patient with typhoid fever don't receive medical attention or are treated as out patients

Pitfall: Clinical diagnosis

- Sensitivity and specificity of individual presenting manifestation are not appropriately evaluated or very low
- Significant level of relapse or development of carrier state
- Diagnosis made on clinical ground poses problems as it may mimic many other febrile illness without localizing signs in endemic areas like- malaria and viral fevers

Pitfalls: Study comments - 1

- Enteric fever: Diagnostic value of clinical features
- Neopane A, Poudel M, Prodhan B, Dhakal Rand Karki B.
- KUMJ. 2006 Jul-Sep'4(3):307-15
- Objectives: to evaluate the diagnostic value of clinical symptoms and signs in enteric fever and to propose a diagnostic criteria
- Study design: Prospective observational

Pitfalls: Some study comments - 1

Results:

- 64% of the clinically diagnosed cases had blood/bone marrow culture positive
 - the diagnostic accuracy of the various symptoms and signs excluding fever was between 42-75.5%
 - Majority of the symptoms and signs did not have very high independent diagnostic accuracy
 - After combining symptoms and with diagnostic accuracy of >50% final diagnostic criteria was proposed having an accuracy of 66%
- Conclusion: None of clinical symptoms and signs have very high diagnostic accuracy.

Pitfalls: Some study comments - 2

- Title: Value of clinical features in the diagnosis of enteric fever
- Author: Haq SA, Alam MN, Hossain SM, Ahmed T, and Tahir M. Department of Medicine Institute of post graduate Medicine and Research, Dhaka. Bangladesh Med Res Counc Bull. 1997 Aug;23(2):42-6.
- Objective: assess the value of some clinical and simple laboratory features in the diagnosis of enteric fever

Pitfalls: Some study comments - 2

- Study design: descriptive prospective study
- Results:
 - 106 patient and 170 febrile control
 - Stepladder rise of temperature, loose motion, relative bradycardia, and coated tongue had very high specificity (100%, 94.71%, 94.71, and 94.12% respectively), positive and negative predictive values
 - Headache, hepatomegaly and splenomegaly were moderately powerful
 - ESR and WBC count appeared to have little value

Pitfalls: Some study comments - 2

- Conclusion:
 - Elucidation of the power of these markers in distinguishing enteric fever from other febrile illness with the help of better designed prospective studies would lessen dependence on expensive and time consuming laboratory investigation

Pitfall: laboratory diagnosis

- Specific diagnosis dependent on isolation of *S. typhi* from different body fluids by culture
- Bone marrow is gold standard
 - Not easily available
 - Time consuming
 - difficult procedure
 - Results depend on different factors
 - Duration of illness
 - Specimen used
 - Prior antibiotic used
 - Severity of infection

Pitfall: laboratory diagnosis

- Low sensitivity and specificity
- Costly procedure
- Not well accepted to patients and physicians

Pitfall: serologic procedures

- Most widely practiced test is Widal test-100 years old
- Lacks sensitivity and specificity
- Other serologic tests lacks criteria/s of ideal laboratory tests

Comment: Serologic tests on - 13

- Olopoenia LA and King AL
- Widal agglutination test – 100 years later: still plagued by controversy (Review)
- Postgrad Med J 2000;76:80-84
- Objectives: review the significance of the Widal agglutination test in the diagnosis of typhoid fever

Comment: serologic tests - 13

- Conclusion
 - Widal can't be expected to give reliable results in the endemic regions.
 - The use of widal test should't be encouraged
 - As cultures are more time consuming , increased efforts should be made to find a better more rapid sensitive and specific test (such as antigen screening) to supplement clinical and culture data

Comment: serologic tests - 10

- Adeleke SI and Nwokedi EE. Department of Pediatrics, Faculty of Medicine Bayero University, Nigeria
- African scientist vol. 9, No.1 March31, 2008
- Diagnostic value of widal test in febrile children
- Retrospective study to determine the utilization and validity of the Widal test in febrile children

Comment: serologic tests - 10

- Results: 2,905 children with febrile illness, single widal test was positive in 1,803(62.1%) but only 304(10.5%) were confirmed by blood culture
- Conclusion: there is no justification for a widal to be under taken in a considerable number of febrile children

Comment: Serologic tests - 12

- Telma ET, Roxanne LA, Myrna TM, Carmelita UT and Somsak L.
- Phil J Microbiol Infect Dis 1991, 20(1):23-26
- Clinical application of Widal test : sensitivity and specificity of widal test done at developing countries endemic for typhoid fever
- Results:
 - from sensitivity and specificity data, it is clear that some culture proven cases of typhoid fever may be associated with a “negative” Widal test particularly if done early in the course of illness so that the predictive value of “negative” Widal test is limited

Comment: Serologic tests - 12

- Result
 - Conversely a positive Widal test may be seen in non typhoidal patients and healthy controls from endemic areas
- Conclusion:
 - Culture isolation of *S. typhi* from blood and bone marrow should be considered the standard diagnostic test to confirm typhoid fever

Conclusion

- Typhoid fever is one of the common causes of febrile illness in the developing countries which faces lots of pitfalls in diagnosis and managements
- Most of the patients diagnosis and management are done on suspicion
- So the mortality, morbidity and development of chronic carrier remains very high.
- So to overcome pitfalls remains the corner stone to reduce the incidence of the disease in endemic countries