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Typhoid: Diagnosis and Treatment

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Abstract: Typhoid fever is most prevalent in the Asian part of the world especially in the developing countries of Asia like Pakistan and India, caused by a Gram-negative bacterium Salmonella enterica servar typhi. It is an orally transmitted communicable disease caused by consuming contaminated food and impure water. The incubation period of the disease is 7 to 14 days. Symptoms include high fever, rash, weakness, abdominal pain constipation, headache, and poor appetite. Antibiotic resistance is a major problem to treat it effectively. First line drugs are mostly not used to treat typhoid and the resistance is emerging in fluoroquinolones. The only choice of drug remaining is ceftriaxone and azithromycin. A counteractive action of typhoid fever is chiefly by individual and household cleanliness. The provision of clean

water and safe disposal of faeces should be implemented to eradicate S. typhi. Good surveillance, better diagnostics, more sensible use of antibiotics and efficient vaccine will be significant to reduce the burden of disease caused by S. typhi.

Typhoid: An Introduction

Typhoid is an extreme, infectious and dangerous malady related with fever [1]. It is caused by *Salmonella enterica* serovars *typhi*, *paratyphi A*, *paratyphi B*, and *paratyphi C* can be collectively categorized as typhoidal *Salmonella*, though some are gathered as Non Typhoidal Salmonella [NTS][2,3,4]. Typhoid strains are human host-confined life forms that reason typhoid fever and paratyphoid fever, together alluded to as enteric fever [5,6]. In some Asian nations, *S.* serovar *Paratyphi A* has represented a developing extent of enteric fever [7,8]. Typhoidal Salmonella transmit dominatingly via water or sustenance polluted with the feces of human. The hazard of disease is high in underdeveloped nations where typhoidal Salmonella is endemic and there is poor hygiene and sanitation and non-availability of safe sustenance and water. An ongoing report on worldwide weight of typhoid fever announced 27 million diseases and 200,000 to 600,000 passing every year because of typhoid fever[9,10]. The International Vaccine Institute reported 11.9 million typhoid fever ailments and 129,000 passing in low-and center pay nations in 2010. Typhoid is endemic in the greater part of the creating nations like Pakistan. The most recent two decades have seen the development and spread of multidrug opposition against the ordinary antityphoid drugs (chloramphenicol, co-trimoxazole, fluoroquinolones and ampicillin) among the typhoid salmonellae, particularly in South and Southeast Asia A bout 200 times ago, one of the major causes of morbidity and mortality in the western world was typhoid fever or for that matter enteric fever[11,12]. Because of advancements in sanitation and overall health situations, the conditions have greatly bettered now and the deadly complaint of yester times is veritably scarce now in the USA and the Europe. still, typhoid fever is still a deadly complaint in developing countries, particularly in India[13,14]. An ongoing report on worldwide weight of typhoid fever blazoned 27 million conditions and,000 to,000 passing every time because of typhoid fever. [15,16] The International Vaccine Institute reported11.9 million typhoid fever affections and,000 expirations in low- and center pay nations in 2010 [17,18,19,20].

Aim of the study

The present review targeted the main headlines related to Typhoid prevalence and epidemiology.

Epidemiology

Epidemiology As indicated by the worldwide gauge, every year around 27 million new instances of typhoid happen with mortality in around 200,000[21]. The most noteworthy dismalness and mortality are noted in South Central and Southeast Asia. In total, taking all these standardized studies, typhoid epidemiology data were abstracted from 47 countries across the entire global regions[22]. Data were also obtained from population-based and prospective vaccine studies for 13 countries. The remaining incidence data were collected by typhoid fever surveillance systems in the several developed regions where regular and systematic national-level surveillance was in vogue. Paratyphoid fever incidence data were available for only 9 countries of which the USA, despite having an advanced and regular surveillance system, did not have even a single case of paratyphoid fever during the entire period of their study. The incidence of typhoid was high (>100 cases per

100,000 population per year) in Asia (excepting Japan) and Southern Africa. It is medium (10-100 cases per100,000 population per year) in North Africa, Latin America, Caribbean islands and Oceania[23].

The incidence of typhoid fever was estimated to be low in Europe, North America, Australia and New Zealand (<10 cases per 100,000 population per year).previous typhoid fever incidence rates (IR) reported in Egypt during various vaccine trials varied from 209/100,000 in 1972-73 to 48/100,000 person in 1978-81 In one of the investigation led in matta, swat predominance of enteric fever was discovered 13.5%[24].

A serological diagnosis of *S. typhi* in District Hospital Quarter of Charsadda was performed and indicated 22% of prevalence. Typhoid is found to be a seasonal disease; in the monsoon itself there is occurrence of 45% of the total annual reported cases. In South Asia the disease occurrence is highest during July to October because of heavy rainfall during that period [25].

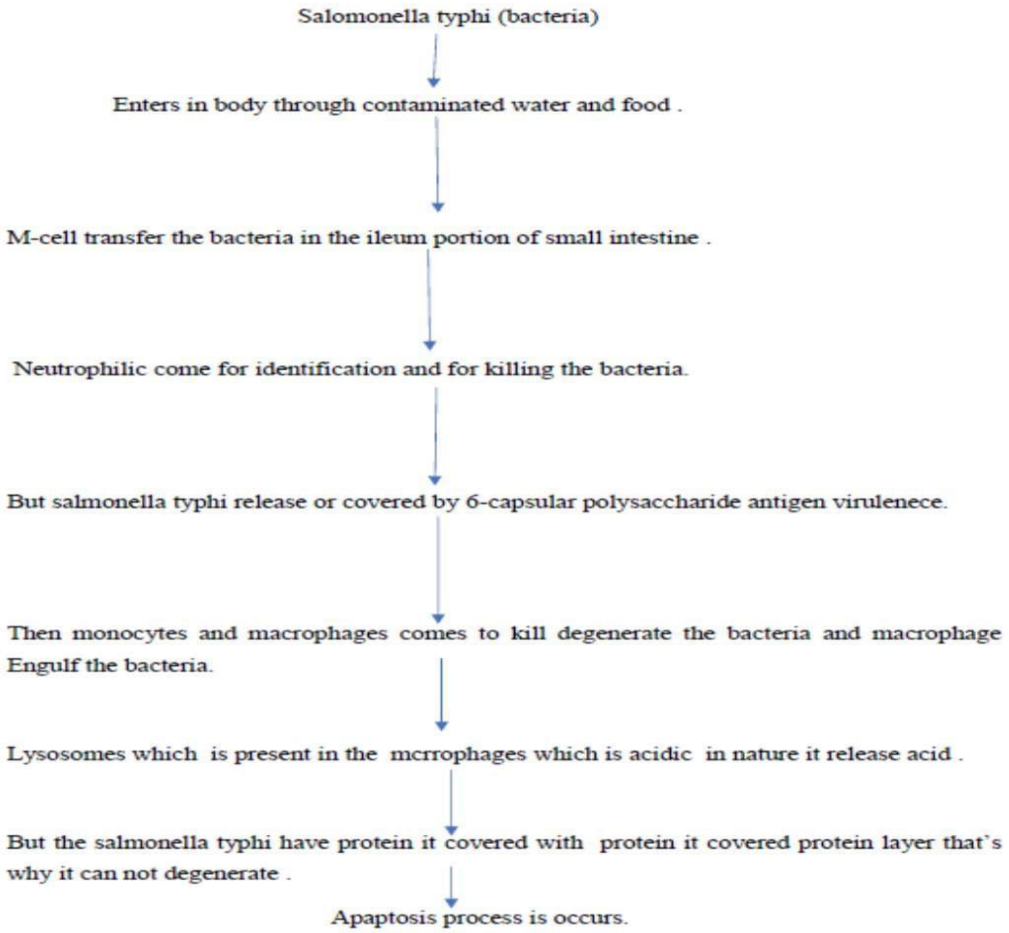
Aetiology:

The complaint typhoid fever is an orally transmitted contagious complaint caused by the bacteria *S. typhi*. It's generally caused by consuming unpurified water and defiled food. As *S. typhi* bacteria can survive in water for days, impurity of face water similar as sewage, fresh water and ground water acts as major etiological agent of typhoid. Defecation in open places is another notable cause of typhoid transmission. Amidst food, cut fruits kept uncovered for some time are an important cause of impurity in utmost developing countries. Papaya has a neutral pH and its cut face can support the growth of colorful microorganisms. It was observed by Hosoglu *et al* in a Turkish study that eating cut papaya, lettuce salad and some traditional raw foods in Turkey (e.g. cig kofte) was an important causative factor[26].

Pathogenesis

Between 1000 and 1 million organisms are required to create the disease typhoid in a human being, which therefore is said tobe the infectious dose of *S. enterica* serotype *typhi*[27,28]. Obviously, *S. typhi* Vi-positive strains are more infectious and more virulent than Vi-negative strains of *S. enterica* serotype *typhi*. High gastric acidity is one important barrier against invasion of *S. typhi and* a low gastric pH is therefore an important defence mechanism [29,30]. Aging, gastrectomy, proton-pump inhibitors or antacids leads to achlorhydria and facilitates typhoid infection. In the small intestine, the bacteria first adhere to mucosal cells and then invade the mucosa following which they rapidly penetrate the mucosal epithelium via either microfold cells or enterocytes and arrive in the lamina propria, where they rapidly elicit an influx of macrophage that ingest the bacilli but do not generally kill them. Some bacilli remain within the macrophage of the small intestinal lymphoid tissue and some microorganisms translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes and by which they enter the thoracic duct and the general circulation [31] 7 to 14 days is usually the incubation period of typhoid. After that there is an interaction between host immunologic mediator and bacterial factors leading ultimately to the necrosis of Peyer’s patches. Interestingly, in Africa the disease is often due to non-typhoidal salmonellae such as *typhimurium*. In contrast to the Asian situation; however, the two are clinically indistinguishable [32, 33, 34].

Flow Chart of Typhoid (Pathogenesis)



The World Health Organization (WHO) assess for yearly worldwide rate of typhoid fever, around 21 million cases, is likely a disparage in view of poor diagnostics. A few choices exist for diagnosing enteric fever: clinical signs and side effects; serological markers; bacterial culture; antigen discovery; and DNA intensification. None is totally acceptable. The clinical conclusion of typhoid fever is troublesome in light of the fact that the indications of the ailment are differing and there are numerous reasons for delayed fever in typhoid endemic areas [19].

Diagnosis

World Health Organization (WHO) assess for yearly worldwide rate of typhoid fever, around 21 million cases, is likely a disparage in view of poor diagnostics. A few choices exist for diagnosing enteric fever: clinical signs and side effects; serological markers; bacterial culture; antigen discovery; and DNA intensification. None is totally acceptable. The clinical conclusion of typhoid fever is troublesome in light of the fact that the indications of the ailment are differing and there are numerous reasons for delayed fever in typhoid endemic areas [2,8].

Diagnosis by culture: WHO appraise for yearly worldwide frequency of typhoid fever, around 21 million cases, is likely a disparage as a result of poor diagnostics. A few alternatives exist for diagnosing enteric fever: clinical signs and manifestations; serological markers; bacterial culture; antigen recognition; and DNA enhancement. None is totally palatable. The clinical determination of typhoid fever is troublesome in light of the fact that the indications of the sickness are different and there are numerous reasons for delayed fever in typhoid endemic areas. Lab determination of enteric fever in creating nations is essentially accomplished either by blood culture or bone marrow suction culture which are highest quality level for diagnosis. In creating nations affectability of blood culture is brought due down to silly utilization of anti-infection agents. Bone marrow culture

is touchier at that point blood culture in view of high bacterial focus in bone marrow and are generally unaffected by anti-toxins . Stool culture is likewise an essential aide for finding; it might be certain when blood culture is negative and it is additionally vital for the observing of carriage of *S. typhi* after clear clinical fix, a hazard factor for the groups of cases . Advancement media containing selenite are utilized to disconnect *S. typhi* from stool due to expansive quantities of contending microorganisms, particularly *Escherichia coli* [35].

Serological Diagnosis: Because of obtrusiveness and specialized trouble of the technique, one needs to depend on serological finding [36,37,38,39].

The Widal test, Agglutinating antibodies are measured against LPS (O) and flagellar (H) antigens of Salmonella serovar typhi in the sera of people with suspected enteric fever. Albeit normally disheartened because of error, it is basic and cheap to perform is still broadly utilized as a part of a few nations [40,41].

Tubex TF Tubex, TF depends on a restraint response between tolerant antibodies (IgM) and monoclonal antibodies incorporated into the test that predicament to a *S. typhi* particular O9 lipopolysaccharide. A perceptibly noticeable de-colorization of serum of patient in test reagent arrangement via attractive molecule detachment demonstrates a positive outcome . Execution of TUBEX® TF in the analysis of enteric fever in private tertiary care Hospital Peshawar, Pakistan was checked and affectability of TUBEX® TF was discovered 41.86% while specificity was 95.97% [42,43].

Typhidot, Conversely the typhidot depends on a subjective dab smudge catalyst connected immunosorbent measure that independently identifies the nearness of IgM and IgG in persistent sera against a *S. typhi*[44,45].

Molecular diagnosis: The sub-atomic technique for conclusion of typhoid fever has been advanced to conquer the impediments of societies and serologic tests. Numerous creators have investigated the utilization of Polymerase Chain Reaction (PCR) for distinguishing particular DNA succession of the creatures introduces in clinical examples. The PCR as an indicative methodology for typhoid fever was first assessed in 1993, Song et al., effectively intensified the flagellin quality of *S. typhi* in all instances of culture demonstrated typhoid fever and from none of the solid controls. By utilizing two sets of preliminaries assessed in the examination by Song et al, enhancement of the flagellin quality of *S. typhi* affirmed the nearness of the life form in the patient's blood. In Pakistan, 55 instances of suspected typhoid fever and a control gathering of 20 sound people were analyzed by PCR from blood tests and blood culture. The PCR and blood culture gave 58.2% and 14.5% energy, individually demonstrating fundamentally better outcomes by PCR . Again in Pakistan, a multiplex PCR focusing on five unique qualities for differential conclusion of typhoidal pathogens has been created for utilize specifically on clinical blood tests. Of 42 multiplex PCR-positive blood tests, 35 were sure for *S. typhi*. In view of the absence of the accessibility of good symptomatic apparatuses, especially that are field based, rectify analysis of typhoid fevers remains a hazy area. So the analysts in the creating nations should accentuation the exploration on the advancement of more current and simple indicative [36,42,46].

For a definitive diagnosis of typhoid fever, the (WHO) recommends bacterial isolation from blood or bone marrow. The gold standard is bone marrow culture, obtained through aspiration of the iliac crest or sternum and has a suggested sensitivity of 90% after 4 days of culture. However, due to the invasive nature of bone marrow biopsies, the diagnosis typically depends on blood culture or the Widal test. According to the WHO, the criteria for establishing a diagnosis of Typhoid Fever have three modalities: Suspected Case. Confirmed Carrier and Chronic Carrier[47,48]. A suspected patient has a fever for at least three successive days in an endemic region or after travelling from an endemic zone. During this timescale, the acute phase of the infection is detectable with rapid tests such as TUBEX and Typhidot, and serological testing such as the Widal test, albeit the Widal test is currently not clinically accepted. A confirmed case is a patient whose laboratory findings or molecular techniques for recognising *S. typhi* confirm the bacterial presence. In this phase, the

patient presents with compatible typhoid-like symptoms such as persistent high-grade fever, fatigue, headache, nausea, abdominal pain, and diarrhoea or constipation. At this stage of the disease, a blood culture or bone marrow culture is used to confirm the diagnosis. Thus, it has been recommended to have clinicians with a firm grasp on the clinical presentation of typhoid fever, laboratory testing, and ruling out other causes of fever to suspect and confirm typhoid fever cases in Africa. Lastly, a chronic carrier is a person who still excretes the bacteria causing typhoid for up to months or more[49,50,51].

The patient here presents gall bladder pathology in conjunction with cholecystitis, cholelithiasis, gall bladder cancer and other pathologies at anatomical sites where the bacteria localise and grow. Although the (PCR) was adopted to diagnose the chronic carrier status in Africa, still stool culture is the investigation of choice during this stage. Diagnosing Typhoid fever in Africa is hindered by the resource and personnel limitations within the continent. When developed nations had adopted blood or bone marrow culture as the diagnostic investigations of choice when trying to confirm the enteric fever, almost all of the countries in Africa were still reliant upon serology or agglutination tests especially the widal test as the investigation of choice [52,53].

The future of typhoid diagnostics

While a variety of techniques are currently in use for the diagnosis of typhoid, no single technique satisfies the requirement for sensitivity and specificity while being rapid and cost effective. This was again confirmed in the most recent data generated by find and partners, and the need for innovations was once again made obvious [54]. However, future innovation for typhoid diagnosis should not only focus on disease diagnosis for immediate treatment purposes but also disease surveillance and the detection of carriers, to support public health interventions [55].

Ultimately both aspects are different sides of the same coin and need to be advanced simultaneously to accelerate disease elimination as a whole. RDTs using selected antigens such as the protein HlyE and sugars in the lipopolysaccharide are under investigation and exhibit some potential. Furthermore, studies using metabolomic platforms have sought to identify biomarkers specific to typhoid. Identifying a single or a combination of metabolites S18 • OFID 2023:10 (Suppl 1) • Sapkota et al during the course of typhoid illness could provide several promising biomarkers [56]. Polymerase chain reaction (PCR)– based detection of typhoid in the blood generally shows poor sensitivity. Conventional to real-time PCR and nested and multiplex PCR using different targets have been used to diagnose typhoid with sensitivity ranges of 40%– 100% . However, a more recent study using machine-learning algorithms to identify expression signatures of host-associated genes showed some promise. This study identified the transcripts of 5 key genes (STAT1, SLAMF8, PSME2, WARS, and ALDH1A1) that can differentiate enteric fever from other febrile illness; this approach may have some traction for a multipathogen diagnostic approach. The latter 2 approaches might provide better value and may aid in identifying the cause of undifferentiated febrile disease (including typhoid) in resource-limited LMICs for better patient management. At this point, however, this is not yet the case as none of the existing tools meet the needs of resource-poor settings, both in terms of cost and performance. A tool would have to be cheap and simple to use (akin to the GeneXpert) to really make it suitable for hospitals in lowerresource settings. While simple molecular tools to be used at the POC level were scarce pre-2020, after the scientific advancements and investments made linked to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic it might be more feasible to think about a workable POC device that can be used to identify a magnitude of possible fever causes. Given the complexities of typhoid diagnosis in patients or carriers using simply accessible samples, public health agencies might have to resort to identifying the pathogens in the environment as a proxy for patients. Molecular approaches look promising to detect S. Typhi in environmental samples. These methods are not meant as tools for healthcare workers to inform patient management so will not advance this area, yet they might open up a more promising area for public health surveillance, similar to cholera. When thinking about and envisioning the next generation of diagnostic tools, it is critical that we do not confuse the different use cases and that we make sure the future Target Product Profiles

account for all[57,58]. As of now, the ideal approach unfortunately remains elusive as it needs to be low-cost and simple to use even when deployed for environmental surveillance. Looking toward a future with increased focus on typhoid, the most likely scenario is a combined approach where more hightech approaches are developed by research and public health authorities and individual patient management remains to be guided by culture as well as improved RDTs[59,60].

Treatment

Treatment Typhoid fever is a noteworthy wellbeing worry in the creating World. Most recently In last two decades there is development And spread of multidrug obstruction against customary Antityphoid drugs (chloramphenicol, co-trimoxazole, and Ampicillin) among the typhoid salmonellae, particularly in South and Southeast Asia, including Pakistan [61]. The rise of medication safe typhoid has been another stressing Improvement. After sporadic flare-ups of chloramphenicol safe Typhoid in the vicinity of 1970 and 1985, numerous strains of *S. typhi* created plasmid interceded multidrug protection from the Three essential antimicrobials utilized (ampicillin, Chloramphenicol, and Co-trimoxazole). This was countered by the coming of oral quinolones, yet chromosomally procured quinolone obstruction in *S. typhi* and *S. paratyphi* has been as of late depicted in different parts of Asia, perhaps identified with the broad and aimless utilization Of quinolones [62, 63, 64]. Antimicrobial powerlessness, dictated by Kirby-Bauer plate dispersion strategy, demonstrated that 54% of the *S. typhi* separates were completely defenseless to Ciprofloxacin/ofloxacin.

Already, a few emotional changing Patterns in anti-infection agent's opposition are examined for Typhoid salmonellae in Islamabad. From 1996 to 2000, no Confines were observed to be impervious to fluoroquinolones like ciprofloxacin in an examination led In Armed Forces Institute of Pathology, Rawalpindi however in session, 2003-2001a portion of the ciprofloxacin safe detaches were Achieved from local populace [65]. In the 1980s, ciprofloxacin turned into main line medication For treatment *S.* typhi diseases after the majority of the Customary medications ended up inadequate . Notwithstanding, protection from ciprofloxacin was seen in the Clinical disconnects of *S. typhi* disconnected from Faisalabad District are demonstrating expanding ciprofloxacin opposition As showed by increment in nalidixic corrosive safe confines. In Any case, more up to date fluoroquinolones like ofloxacin and Gatifloxacin are still extremely viable[66,67]. Among third era Cephalosporins, ceftriaxone demonstrated promising outcomes yet rising obstruction was apparent. Recently settled CLSI Rules for azithromycin circle dispersion and MIC Interpretive Criteria for *Salmonella* serovar *typhi* were distributed In CLSI Report in 2015[67,68,69,70,71].

Azithromycin in a cure of 500 mg(10mg/ kg) given formerly daily for seven days has proven Effective in the treatment of typhoid fever in some grown-ups and children. A cure of 1g per Day for five days was also set up to be more effective in utmost grownups. Of the third Generation cephalosporins, oral Cefixime (15- 20 mg per kg per day, for grown-ups, 100- 200 Mg doubly daily) has been extensively used in children in a variety of geographical settings And set up to be satisfactory. Still, in some trials Cefixime showed advanced rates of failure and relapse than fluoroquinolones. But antibiotic perceptivity pattern in BSMMU showed advanced perceptivity around 78.8. Intravenous third generation cephalosporins(ceftriaxone, Cefixime, cefotaxime) are effective with low relapse (3 to 6) and fecal carriage(< 3) rates. Ceftriaxone is effective at a cure of 2-4gm diurnal in single or two disunited boluses. Typhoid fever cases by age group from 2004-2014[72,73]. The dark blue bars show the proportion of Typhoid fever cases in children younger than 5 years. The navy blue bars represent the number Of typhoid fever cases in children aged 5-14 years. The pale blue bars indicate the cases of Typhoid fever in individuals aged 15-44 years.The sky blue bars show typhoid fever cases in Adults aged 45-64 years.The gray-blue bars represent typhoid fever cases in those aged 65 years and order [74,75]..

Prevention

Since the early acknowledgment of the part of water in the transmission of typhoid fever, it has been shown that upgrades In access to clean water and enhanced sanitation result in Emotional decreases

in typhoid fever-related passing rates in numerous settings. Moreover, safe drinking water and Sanitation have been announced a human rights issue by the Worldwide network, because of their significance in human Wellbeing[75]. Unmistakably as access to safe water and enhanced Sanitation are being produced, this ought to drastically decrease The introduction to *S. typhi* and *S. Paratyphi* microorganisms In nature and, accordingly, enteric fever ailment. Be that as it May, worldwide advance toward widespread access to both Safe water and enhanced sanitation at the family unit level Where the medical advantages are ideal are lacking, and are Likely aggravated by a few variables incorporating disparity in Scope[76,77], where the most defenseless populaces have the poorest Access; expanding urbanization; and expanding water shortage In numerous districts. There has been enthusiasm for typhoid fever immunization for A very long while, and despite the fact that there has likewise Been advance in creating control answers for typhoid, this Advance has been to some degree stilted in numerous locales. The main antibody, an inactivated entire cell immunization, Was being used for >100 years, for the most part in British and US military populaces, yet was esteemed too react genic for Proceeded with utilize. Presently, 2 typhoid antibodies are Universally authorized and have been appeared to be sheltered And adequate in people >2 years old[78]. A 2-measurement VirEPA conjugate antibody was produced by the US National Institutes of Health, where Vi-PS is conjugated to a novel Bearer protein comprising of recombinant exotoxin of *Pseudomonas aeruginosa* and showed 91.5% defensive Viability among preschool youngsters matured 2-5 years in Vietnam; however this immunization has not yet been Authorized universally[79].

Typhoid in Iraq

Typhoid in Balad City

One thousand nine hundred and twenty individuals admitted to the General Teaching Hospital in Balad City, suffer from abdominal pain, fever, a headache and nausea. Acute and chronic Typhoid-patients caused by *S.typhi* were diagnosed according to positive blood and stool culture respectively, and using serological test IgG/ IgM. Out of total 1920 individuals, we documented 312 typhoid patients caused by *S.typhi*; 209(67%) in urban and 103(33%) in rural region and there were 263(84%) acute cases and 49(16%) chronic. The results recorded 180(57.7%) male and 132(42.3%) female and the age group 31-40 was the most infected with 130 cases (41.7%). In conclusion: There was high prevalence of typhoid fever in urban than rural in Balad City and acute infections were dominant. The most cases were in middle age groups in hot seasons [80].

Typhoid in four selected sites Al-Haweeja, Al-Hay, Al- Majar, and North Najaf

In a cross-sectional observational study conducted in four districts in Iraq which has a population ranging from 170 000 to 431 000. A consecutive sample of (757) patients attended the outpatient or admitted to hospitals with any Widal positive case, probable typhoid case and suspected typhoid case were included in the study. A questionnaire including demographic, clinical, laboratory and exposure data was filled for each suspected case. Confirmation of the diagnosis of typhoid fever was done by serological examination and culture (blood, urine or feces) for each patient included in the study. The occurrence of typhoid fever (per 100 000 population) was 34, 9.4, 3.5, 0 in AlHaweeja, Al-Hay, Al-Majar, and North Najaf districts, respectively. This occurrence was lower in three study districts when compared with the same period of 2010 and 2011. The mean of the age of cases was 25.8 years ±16.03 and the male to female ratio of confirmed cases was 0.7:1. Also, this study showed that the sensitivity of the Widal test was 16.7% and the specificity was 36.2% when compared with culture results [81].

Typhoid in Diyala city

In a study included the collection of 120 blood samples, with 59.16% (71) and female patients (40.83%), 49 years of age (60-1 years), 24.16% of patients in hospital and 75.83% Patients who are not in hospital.

The samples were initially identified using the Widal test as a traditional method of diagnosis and the rate was 75 positive and 45 negative, 20 blood samples were isolated from the suspected disease with typhoid fever, and the diagnosis of bacterial isolates was 17 Widal test (85% (P> 0.01). The isolates studied under the Polymerase Chain Reaction were detected as carriers of the Flic gene and 16.7%. Based on the emergence of a 599 bp package, a base pair of Nasted PCR was the size of 360 bp base pair [82].

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