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TITLE

A ROLE OF WIDAL TEST IN PYREXIA SUSPECTED PATIENTS – A SYSTEMATIC REVIEW

SUBMITTED

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DEPARTMENT OF MICROBIOLOGY

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A ROLE OF WIDAL TEST IN PYREXIA SUSPECTED PATIENTS- A SYSTEMATIC REVIEW

A

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Submitted to

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In partial fulfillment of the requirements for the award of degree of

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In

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By

PEEYUSH

ENROLLMENT NO: - 1900104269

Guide:

Dr. TASNEEM SIDDIQUI (MBBS, MD)

Assistant professor
Dept.of Microbiology

Co-Guide:

Dr. AUSAF AHMAD(PHD)

Associate professor
Department of Comm. Medicine

INTEGRAL INSTITUTE OF MEDICAL SCIENCE AND RESEARCH, KURSI ROAD, LUCKNOW,226026

INTEGRAL UNIVERSITY

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State Legislation
Approved by University Grants Commission
Phone No.: +91 (0552) 2890812, 2890730,
3296117, 6451039

Fax No.: 0522-2890809

Kursi Road, Lucknow-226026, Uttar Pradesh
(INDIA)

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I hereby declare that this dissertation entitled **"A ROLE OF WIDAL TEST IN PYREXIA SUSPECTED PATIENTS A SYSTEMATIC REVIEW***"* is bonafide and genuine research work carried out by me under the guidance of **Dr. Tasneem Siddiqui** Assistant Professor, Department of Microbiology and Co-guide **Dr. Ausaf Ahmad** Associate Professor, Department of Community Medicine, Integral Institute of Medical Sciences and Research, Lucknow.

DATE: 15-07-2022 PEEYUSH
PLACE: LUCKNOW

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Fax No.: 0522-2890809

Kursi Road, Lucknow-226026, Uttar Pradesh (INDIA)

ENDORSEMENT BY THE HOD

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DATE: 15/07/2022

PLACE: LUCKNOW

Dr. NOOR JAHAN

PROFESSOR AND HEAD,

DEPT. OFMICROBIOLOGY,
IIMS&R

INTEGRAL UNIVERSITY

Established Under U.P. Act No 09 of 2004 by
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Approved by University Grants Commission
Phone No.: +91 (0552) 2890812, 2890730,
3296117, 6451039

Fax No.: 0522-2890809 Kursi Road, Lucknow-226026, Uttar Pradesh (INDIA)

CERTIFICATE BY THE GUIDE & CO-GUIDE

This is to certify that the dissertation entitled **"A ROLE OF WIDAL TEST IN PYREXIA SUSPECTED PATIENTS A SYSTEMATIC REVIEW "**is a bonafide and genuine research work done by **Peeyush** in partial fulfilment of the necessity for the degree of Masters of Science in Medical Microbiology.

The research methods and procedures described are done by the candidate and results are observed by the guide periodically.

DATE:15-07-2022

PLACE:LUCKNOW

Dr. TASNEEM SIDDIQUI

Assistant professor (MBBS, MD)

Dept. of Microbiology
Medicine IIMS&R, LUCKNOW

Dr. AUSAF AHMAD

Associate professor

Department of Community
IIMS&R, LUCKNOW

INTEGRAL UNIVERSITY

Established Under U.P. Act No 09 of 2004 by State Legislation
Approved by University Grants Commission
Phone No.: +91 (0552) 2890812, 2890730, 3296117, 6451039

Fax No.: 0522-2890809

Kursi Road, Lucknow-226026, Uttar Pradesh (INDIA)

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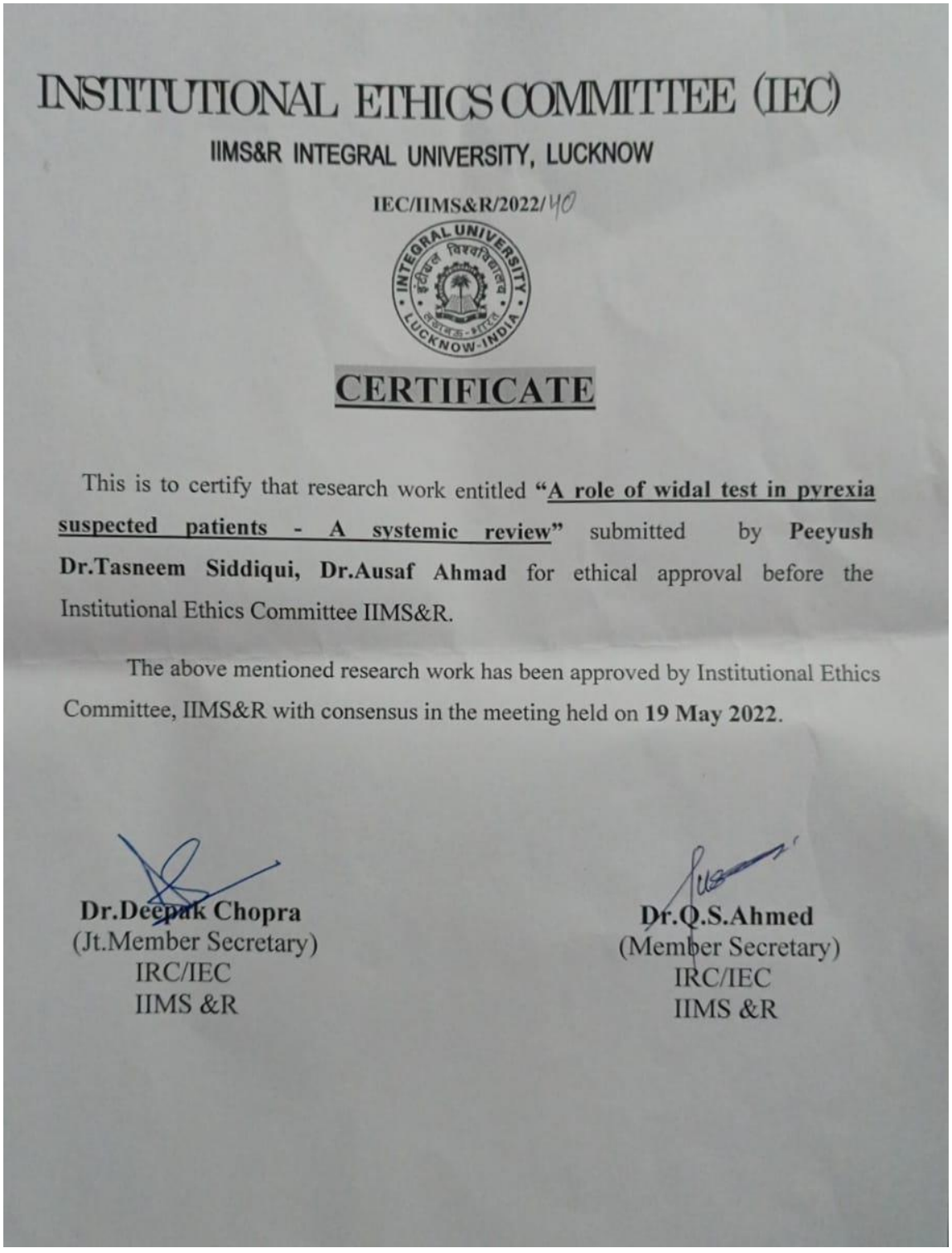

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Dr.Deepak Chopra
(Jt.Member Secretary)
IRC/IEC
IIMS &R

Dr.Q.S.Ahmed
(Member Secretary)
IRC/IEC
IIMS &R

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DEDICATED TO

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&

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CONTENTS

INTRODUCTION

PYREXIA

Pyrexia is also known as fever. Fever is the endogenous elevation of at least one measured body temperature to ≥38°C, regardless of activity level, meals, time of day, anatomical site, type of thermometer, age or environmental conditions during measurement.[1] Fever is a morning temperature ≥37.2°C or a temperature ≥37.8°C at any time of the day when taken orally or >38.3°C when measured rectally[2].

Fever often occurs in response to infection, inflammation, trauma. This view of fever, however, is only an oversimplification, as growing evidence suggests that fever represents a complex host adaptive response to various immune challenges, infectious or non-infectious. Although elevated body temperature is an essential part of the febrile response, it is not synonymous with fever.It is generally accepted that fever is a regulated rise in body temperature, above normal diurnal fluctuations, that occurs in conjunction with a high thermoregulatory setpoint [3].

The Commission of Thermal Physiology of the International Union of Physiological Sciences defined fever in 2001 as a state of elevated core temperature that is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to material intrusion alive (micro-organism) or inanimate. invaded by host recognized as pathogenic or foreign [4]Fever is thought to be induced by production of prostaglandin E2 and cyclooxygenase 2 stimulated by endogenous interleukin (IL)-1 and tumor necrosis factor (TNF)-α produced in response to external stimuli (5). Therefore, fever is an important indicator that suggests the presence of an infection.

In a multicentre observational study (FACE study), approximately 63% of patients with a body temperature of 38.5°C or higher were diagnosed with sepsis. However, fever is also a physiological response to non-infectious conditions (6), including surgery, blood transfusion, drug administration, acute rejection, acute

myocardial infarction, cerebral infarction, cerebral hemorrhage, acute pancreatitis, malignancy and other conditions.

Based on guidelines for the management of febrile illnesses provided by agencies such as the World Health Organization (WHO) and the Society of Critical Care Medicine and the Infectious Disease Society of America (IDSA) [7].

Temperature equivalent rectal temperatures of ≥38◦C(100.4◦F) or axillary temperatures ≥37.5°C (99.5◦F) indicate fever in adults and children. However, compared to older children and adults, infants and young children have higher and longer fevers, faster temperature rises, and greater temperature swings.

Physiological effects of fever-

Fever can have adverse effects such as B. causing discomfort, increasing minute ventilation and oxygen consumption, and worsening neurological findings. In a post-hoc analysis to assess the independent association of fever with ventilation-free days in critically ill patients requiring mechanical ventilation, a significant association between fever and ventilatio days was found in all included subjects [8].

Laupland et al. conducted a large epidemiological study on critically ill patients and showed that increased mortality in the intensive care unit (ICU) is not associated with the presence of fever (≥38.3°C) but high fever (≥39.5°C) [9]in case of fever, thermal equilibrium point is reset to a higher level, so that normal peripheral and central body temperatures are now detected ascoldtemperaturesignalsbythermoregulatory circuits [10]. Thus, fever is distinct from heat stroke and hyperthermia, in which the body temperature is elevated without a corresponding increase in the thermal equilibrium point.The different biological molecules involved in generating the febrile response and the pathways involved in these responses are discussed in the next section.

Fever: the role of pyrogens and cryogens-

The initiation, manifestation and regulation of the febrile response depend on the pyrogenic and antipyretic properties of various exogenous and endogenous substances [11]. While pyrogens directly or indirectly cause fever, cryogens prevent excessive temperature rise. It is the balance in the interactions between pyrogens and cryogens that determines the height and duration of the febrile response to any immune challenge.

Pyrogens-

Pyrogens are classified into exogenous (produced outside the host) and endogenous (produced inside the host) pyrogens based on their production location. Exogenous pyrogens are essentially partial or whole microorganisms or products of microorganisms such as toxins. The gram-negative component of the cell wall - lipopolysaccharide (LPS), remains the most studied exogenous pyrogen and most of the current data on the febrile response is based on studies using LPS as a pyrogenic agent.

Other clinically significant endogenous pyrogens include muramyl dipeptidase, a component of cell wall microorganisms, and enterotoxins of Staphylococcus aureus and group A and B streptococcus, collectively referred to as superantigens [12]. Endogenous pyrogens are mainly pyrogenic cytokines, including interleukins (IL) 6, IL-1, interferon gamma (INF-) and ciliary neurotropic factor (CNTF) and tumor necrosis factor (TNF), among others [12]. However, TNF has both pyrogenic and antipyretic actions depending on the experimental conditions. Endogenous pyrogens are produced by immune cells such as neutrophils, macrophages and lymphocytes, as well as by endothelial cells, astrocytes and glial cells in response to exposure to exogenous pyrogens. However, some endogenous substances such as antigen-antibody complexes, inflammatory

bile acids, complements and various lymphocyte-derived molecules can act as pyrogens without induction by exogenous pyrogens [13]

Cryogens-

Cryogens include anti-inflammatory cytokines (e.g. IL-10), hormones (e.g. melanocyte stimulating hormone, corticotropin and corticotropin releasing hormone) and many other neuroendocrine products (e.g. neuropeptide Y, bombesin and tyroliberin), cytochrome P-450 (P - 450), among others [11]. They exert their antipyretic effects by inhibiting the synthesis of pyrogenic cytokines (e.g. glucocorticoids), blocking cytokine receptors (e.g. IL-1 receptor antagonist) and increasing heat loss through the sensitivity of heat-sensitive neurons (e.g. bombesin) [13].] Increase. other mechanisms. These endogenous antipyretic systems protect the host from the destructive effects of uncontrolled fever.

Classification, types and patterns of fever-

Fever can be arbitrarily classified into acute, subacute and chronic fever based on duration. Acute fevers (lasting 2 weeks) are typical of chronic bacterial infections such as tuberculosis, viral infections such as HIV, cancers and connective tissue disorders [14]. However, any cause of acute fever can become persistent or chronic if left untreated.Based on the height of the body temperature, fever can also be classified into low grade, moderately severe, high grade and hyperpyrexia [15]. The increase in body temperature may have some diagnostic and prognostic implications. Some studies have attributed high fevers in infants to serious bacterial infections, although others have also shown that children with high fevers are also at high risk for serious bacterial infections and viral illnesses [16].Three main types of fever have been described, namely persistent/continuous fever, intermittent fever and relapsing fever.

Continuous or persistent fever is defined as fever that does not vary by more than about 1°C (1.5°F) in 24 hours, but never returns to normal [17]. Continuous fever is characteristic of lobar and Gram-negative pneumonia, typhoid fever, acute bacterial meningitis, urinary tract infections, among others. A fever characterized by a slow, gradual increase in temperature and a high plateau is typical of typhoid. However, in clinical practice, this febrile pattern is only reported in about 12% of cases [18], possibly because most febrile patients self-medicate with antibiotics before seeing a physician.

Intermittent fever is defined as a fever that is present for only several hours a day. This fever pattern can be seen in malaria, pyogenic infections, tuberculosis (TB), schistosomiasis, lymphoma, leptospira, borrelia, kala-azar, or blood poisoning. Sources of continuous, intermittent, or transient bacteremia can lead to continuous, intermittent, or transient fever. In malaria, fever can occur with a periodicity of 24 h (everyday due to Plasmodium falciparum), 48 h (Tertian-Plasmodium ovale and vivax) or 72h (Quartan– Plasmodium malariae), depending on the type of parasite. Pel-Epstein fever is a low-grade intermittent fever characterized by 3-10 days of fever with subsequent 3-10 day febrile periods [19]. It is thought to be a typical but rare manifestation of Hodgkin's lymphoma.

Remitting fever is defined as a fever with daily fluctuations greater than 2 ° C but never becomes normal. Remitting fever is often associated with infectious diseases such as infective endocarditis, rickettsial infections, and brucellosis. Recurrent fever refers to recurrent fevers separated by periods of mild fever or no fever. Periodic or recurrent fever is observed in malaria, lymphoma, borrelia, cyclic neutropenia, and rat bite. Fever associated with night sweats has been described in infectious diseases such as tuberculosis, nocardia, brucellosis, liver or lung abscesses and subacute infectious endocarditis, as well as in non-infectious diseases such as polyarteritis nodosa and cancers such as lymphomas [20]

Pyrexia of unknown origin-

Petersdorf and Beeson defined pyrexia of unknown origin (PUO) in 1961 [21]. It is defined as:

-Several times a temperature above 38.3 ° C.

-Accompanied by more than three weeks of illness.

Failure to reach a diagnosis after one week of clinical examination.

This timing allowed for the exclusion of patients with long-term but self-limiting viral diseases, allowing time to complete studies. This has now been amended to include patients diagnosed after two 0outpatient visits or three days in hospital. Common causes of fever of unknown origin[22].In most cases, these are rather unusual presentations of widespread diseases - e.g. B. tuberculosis, endocarditis, gallbladder disease and HIV infection - only to rare or exotic diseases.In adults, infections and cancer (25-40% of cases each) are responsible for most PUO. Autoimmune diseases represent 10 to 20% of cases. In children, infectious diseases (37.6%) are the main cause of PUO, followed by malignant diseases (17.2%), miscellaneous diseases (16.1%) and collagen vascular diseases (14, 0%).

Healthcare-related PUO-

Common causes include drug-induced fever, postoperative complications (e.g. occult abscesses), septic thrombophlebitis, recurrent pulmonary embolism, myocardial infarction / Dressler's syndrome, stroke, transfusion reactions and Clostridium difficile colitis bacterial.

Abscesses: There should be no localizing symptoms.

Previous abdominal or pelvic surgery, trauma, or a history of diverticulosis or peritonitis increase the likelihood of an occult intra-abdominal abscess.

They are usually found in the subphrenic space, liver, right lower quadrant, retroperitoneal space, or pelvis in women.

Tuberculosis - when dissemination has occurred (e.g. in immunocompromised patients), the initial presentation will be constitutional symptoms rather than localized signs. CXR may be normal.

Urinary tract infections (UTIs) - these are rare causes. Perinephric abscesses sometimes do not communicate with the urinary system, resulting in a normal urinalysis.

Endocarditis : Culture-negative endocarditis is reported in 5-10% of endocarditis cases.

The HACEK group is responsible for 5-10% of cases of infective endocarditis and is the most common cause of gram-negative endocarditis in people who do not abuse intravenous drugs: it is a group of Gram-negative bacilli - Haemophilus spp., (H. parainfluenzae, H. aphrophilus and H. paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens and Kingella spp. They are part of the normal oropharyngeal flora, grow slowly and prefer an atmosphere enriched with carbon dioxide. Due to their demanding growth requirements, they have been a common cause of culture-negative endocarditis. Previous antibiotic therapy is the most common reason for negative

blood cultures. Hepatobiliary infections (eg, cholangitis) - these may occur without local signs and with mildly elevated or normal LFTs, particularly in the elderly.

Osteomyelitis - This usually causes at least sporadic localized pain or discomfort. Brucellosis - this should be considered in patients with persistent fever and a history of exposure to cattle, pigs, goats or sheep, or in patients consuming raw dairy products.

Borrelia recurrentis - transmitted by ticks. It is responsible for relapsing fever. Other spirochetal diseases that can cause PuO - these include Spirillum minor (rat bite fever), Borrelia burgdorferi (Lyme disease) and Treponema pallidum (syphilis).

viral

Herpes viruses (eg cytomegalovirus (CMV) and Epstein-Barr virus (EBV) - these can cause persistent febrile illnesses with constitutional symptoms and no pronounced organic manifestations, especially in the elderly.

HIV: Prolonged episodes of fever are common in patients with advanced HIV infection. Most cases are infectious in nature. The rest are mostly due to lymphoma, and a small portion of them are due to HIV itself. Patients with AIDS and lymphoma often have extranodal involvement, particularly the CNS, gastrointestinal tract, liver, and bone marrow. A patient with low CD4 counts presenting with progressive dyspnoea, non-productive cough, and hypoxia should be evaluated for pneumocystis pneumonia (PCP).

A patient with fever, loose stools, abdominal pain, and recent antimicrobial therapy should be evaluated for C. difficile colitis. If non-infectious, consider malignancy, drug reactions (eg, antiretrovirals) and autoimmune diseases (sometimes with HIV). Mushrooms

Immunosuppression, use of broad-spectrum antibiotics, presence of intravascu-

lar devices, and total parenteral nutrition predispose people to disseminated fungal infections parasites.

Toxoplasmosis - This should be considered in febrile patients with enlarged lymph nodes.

Trypanosoma, Leishmania and Amoeba species - these can rarely cause PUO.

Malaria is the most common cause of fever in returning travellers.

Classification

It can mainly be classified into four categories-

1. Classic:

The classic category includes patients who meet the original FUO criteria, with a new emphasis on outpatient evaluation of these previously healthy patients. The revised criteria require an assessment of at least three days in the hospital, three outpatient visits, or a week of logical, intensive outpatient examination without elucidation of the cause of the fever. The most common causes of classical FUO are infections, malignant tumors and vascular collagen diseases.

2. Nosocomial

Nosocomial FUO is defined as multiple relapse of fever in a patient who has been hospitalized for at least 24 hours and who has not shown an apparent source of infection that may have been present prior to admission. To make this diagnosis, it takes at least three days of evaluation without determining the cause of the fever. Conditions that cause nosocomial FUO include septic thrombophlebitis, pulmonary embolism, Clostridium difficile enterocolitis, and drug-induced fever. In patients with nasogastric or nasotracheal tubes, sinusitis may also be a cause.

3. Immunodeficiency

Immunodeficient FUO, also known as neutropenic FUO, is defined as a recurrent fever in a patient whose neutrophil count is 500 per mm2 or less and who has been examined for three days without the fever's etiology being established. In

most of these cases, the fever is caused by opportunistic bacterial infections. These patients are usually treated with broad-spectrum antibiotics to cover the most likely pathogens. Occult fungal infections such as hepatosplenic candidiasis and aspergillosis should be considered. Less commonly, the herpes simplex virus may be the causative organism, but this infection tends to present with characteristic skin signs.

4. Associated with HIV

HIV-associated FUO is defined as a recurrent fever lasting four weeks in an outpatient or three days in an HIV-infected hospitalized patient. Although acute HIV infection remains an important cause of classic FUO, the virus also predisposes patients to opportunistic infections. The differential diagnosis of FUO in HIV-positive patients includes infectious etiologies such as Mycobacterium avium-intracellulare complex, Pneumocystis carinii pneumonia, and cytomegalovirus. Geographical considerations are particularly important in determining the etiology of FUO in HIV-infected patients. For example, an HIV-positive patient living in the southwestern United States is more susceptible to coccidioidomycosis. In HIV-infected patients, noninfectious causes of FUO are less common and include lymphoma, Kaposi's sarcoma, and drug-induced fever.[23]

TYPHOID FEVER

Typhoid is also called enteric fever. It is a prospective, multisystemic disease that constitutes a public health problem, particularly in developing countries. It is caused by Salmonella typhi and Salmonella paratyphi.[24]

Enteric fever is a collective term that describes both typhoid fever and paratyphoid fever. Paratyphoid is clinically indistinguishable from typhoid fever; therefore, enteric and typhoid fever are used interchangeably. Typhoid fever is a leading cause of mortality and morbidity in overcrowded and unsanitary areas, although extensive research and public health interventions have reduced its inci-

dence.The course of the disease ranges from early gastrointestinal disturbances to nonspecific systemic diseases, but can ultimately lead to multiple complications. Salmonella is said to spread through the "four Fs" (flies, fingers, feces, fomites). Fever typically presents in a gradual (i.e. alternating up and down) pattern followed by headache and abdominal pain. Each year, approximately 16 million new cases of typhoid fever with 600,000 deaths occur worldwide due to the Salmonella enterica Typhi (S. Typhi) serotype, with the highest incidence (1,000 cases per 100,000 people per year) in Southeast Asia. The incidence of typhoid fever in the Asia-Pacific region is estimated at more than 100 cases / 100,000 population per year. The highest burden of disease was observed in children [25].

ETIOLOGY

The main causative agent of typhoid fever is Salmonella typhi and Salmonella paratyphi, both belonging to the Enterobacteriaceae family. Salmonella is a genus [26] that has classified two species Salmonella enterica serovar and enteritidis through a comprehensive multiplex quantitative polymerase chain reaction (PCR) assay. Both Salmonella typhi and Salmonella paratyphi (A, B, C) are serotypes of Salmonella enterica. Non-typhoid salmonella (NTS) is more common in children and is usually limited to gastroenteritis.

Salmonella is transmitted by the fecal-oral route through contaminated water, undercooked food, fomites from infected patients and is more common in areas of overcrowding, social chaos and poor sanitation. It is only transmitted from one infected person to another person because humans are its only host. The main sources of salmonella are poultry, eggs and rarely turtles.
In a study of the prevalence of Salmonella isolates by whole genome sequencing in chicken slaughterhouses in China, 57% of samples were positive.[28]

The normal intestinal flora protects against infections. The use of antibiotics like streptomycin destroys the normal flora, which increases its invasion.

Malnutrition reduces normal gut flora and therefore also increases susceptibility to this infection.[29] Therefore, the use of broad-spectrum antibiotics and poor diet increase the incidence of typhoid.

PHYSIOPATHOLOGY

The pathogenesis of typhoid depends on a number of factors, including the infecting species, virulence, host immunity, and infectious dose. The larger the infectious dose, the shorter the incubation period and the higher the attack rate. Typhoid fever is common in debilitated and immunocompromised patients, such as B. HIV-infected patients (mainly paratyphoid), patients on corticosteroid therapy, and patients with impaired phagocytic function (i.e. patients with malaria and sickle cell anemia), more severe.

Salmonella is an acid-sensitive bacterium, except for a few resistant strains, so it is usually destroyed in the stomach by stomach acid unless a large dose is ingested.[30] In patients with achlorhydria, taking antacids and antihistamines, salmonella colonization occurs even at low doses. Foods and drinks also act as a buffer against stomach acid, making it easier for bacteria to reach the small intestine.[29]

The virulence of Salmonella is determined by typhoid toxin, Vi antigen (polysaccharide capsule), liposaccharide O antigen and flagellar H antigen. Vi antigen-positive strains have twice the attack rate of Vi-negative strains, even with the same dose of microorganisms. One of the main differences between Salmonella typhi and non-typhoid salmonella (NTS) is the presence of the Vi antigen in Salmonella typhi but not in NTS. The main role of the Vi antigen is to act as an antiphagocyte, preventing the action of macrophages and thus protecting the O antigen from antibodies that confer serum resistance. Flagellar H antigen ensures bacterial motility and adhesion to the intestinal wall mucosa.

The invasion of the intestinal wall is mediated by flagella and the type III secretion system is able to secrete bacterial proteins into enterocytes and M cells (specialized epithelial cells that serve as antigen-presenting cells in the intestinal mucosa or lymphoid tissue) or by direct invasion of mucosa to be transferred. Bacteria attached to M cells are taken up by pinched cytoplasm containing bacteria and extruded into the luminal space. M cells are damaged and the basal lamina exposed. It provides easy access to pathogens for invasion, making the situation worse.[31]

The cystic fibrosis transmembrane conductance regulator (CFTR) is believed to be important in Salmonella intake; Thus, patients with abnormal CFTR protein are resistant to typhoid fever.[32] The transferred proteins activate the host cell's Rho-GTPases, which trigger actin rearrangement, allowing uptake of bacterial proteins into phagosomes, where bacteria can grow. This special property of bacteria helps them to remain viable in a host immunity pool. Salmonella also produces a molecule that stimulates epithelial release of the chemoattractant eicosanoid, which sequesters neutrophils in the lumen and potentiates mucosal damage. Bacteria induce the proliferation of Payer's plaques via the recruitment of lymphocytes and mononuclear cells and induce necrosis and eventually ulceration, complicating symptoms. Pathogens reach the reticuloendothelial system through the lymphatic system and the circulatory system, including other multiple organs, most commonly the gallbladder in almost all cases. The early bacteremic phase (24 to 72 hours) is asymptomatic and transient because these bacteria are phagocytosed by macrophages and monocytes of the reticuloendothelial system, called primary bacteremia.

The ability of pathogens to grow in these immune cells makes them distinctive, and the intracellular proliferation of bacteria in the reticuloendothelial sys-

tem forces them to re-enter the bloodstream, causing continuous bacteremia over days and weeks, called secondary bacteremia. Secondary bacteremia is the phase in which symptoms of the disease manifest.[29]

As with other gram-negative bacteria, an endotoxin plays an important role in pathogenesis. Lipopolysaccharide triggers the shock-like response and endotoxemia results in vascular hyperactivity and release of catecholamines, resulting in focal necrosis and hemorrhage.[33]

DIAGNOSIS

Diagnosis is difficult in the first week, but various laboratory tests help establish the diagnosis.[34]

Blood culture: Blood culture remains the main mechanism for confirming a diagnosis of typhoid fever. It is widely used and the most commonly performed test because it is neither expensive nor technically difficult. Blood culture efficiency is increased when large sample volumes are collected. Blood cultures obtained during secondary bacteremia (i.e. clinical manifestations) are more reliable, although 30% to 50% of cultures may be false negative depending on technique and time series.[35]

Stool culture: Stool culture is less effective in the bacteremic phase of the disease. stoolculture is diagnostic at the second and third week. It was estimated that it resulted in a positive outcome in only 37% of patients on antibiotic therapy.[36] The sensitivity of stool culture depends on the amount of stool sample taken and the duration of the disease. Chronic carriers transmit pathogens intermittently in feces over a long period of time, so multiple samples should be taken. Other metabolite biomarkers are currently being investigated.[37]

Bone marrow: Bone marrow culture is the gold standard for typhoid diagnosis.[38] The aspirated bone marrow sample is cultured in special agar media. Due to the greater number of microorganisms in the bone marrow, it is more sensitive

than blood cultures. Bone marrow culture is very sensitive (about 90%) and even remains positive in more than 50% of cases despite antibiotic therapy for several days.[36] However, the test is very invasive and expensive, so it is not routinely used to diagnose and treat typhoid.

Widal test: The Widal test is a serological test for intestinal fever, which detects antibodies to the O (surface) and H (flagellar) antigens. An antibody titer greater than 1: 160 and greater than 1:80 for anti-H antigen and anti-O antigen, respectively, are considered cut-off values to predict recent typhoid fever infection in an area. endemic. [38] However, these borders depend on the geographic area. When the recovery titer is four times higher than the acute titer, the test is considered positive. Endemic areas will require higher titers to make the diagnosis and are still limited as they may represent a previous infection. Widal's test is unreliable due to its frequent false negative and false positive results, poor concurrence with blood culture, and poor performance

Skin incision test: punch biopsies of characteristic pink spots may be culture positive in up to 63% of positive cases with prior therapeutic antibiotic treatment.[36]

Polymerase chain reaction (PCR) test: Polymerase chain reaction (PCR) can provide DNA-based genetic identification of multiple serotypes such as H antigen gene and O antigen gene .[38] However, susceptibilities may be low due to low bacterial concentrations during bacteremia. These tests are also expensive in many low-resource environments.

Enzyme-Linked Immunosorbent Assay (ELISA): ELISA identifies antibodies to Vi capsular polysaccharide antigens, which may be useful in identifying carriers but are rarely useful in acute disease.[39]

Other: Urine cultures and cultures of duodenal contents via suture capsules are not done routinely, but can detect Salmonella typhi. Leukopenia and neutropenia

are present in 15-25% of cases, but leukocytosis can also be observed, especially in children. Liver function tests may show a pattern of viral hepatitis, although nonspecific C-reactive protein may be elevated. Upon receipt, CSF studies may show slight pleocytosis (less than 35 cells), although most are unremarkable.[40] Electrocardiogram, ultrasound, liver enzymes and functional tests, urinalysis, X-ray to assess air under the diaphragm are additional tests that may be helpful in diagnosing other complications of the disease .

Collection sample:-

A 2ml blood sample is taken aseptically after venipuncture into a clean clot activator vial and the blood is allowed to stand for 30 minutes to generate clots. When the blood has clotted, the sample is centrifuged at 3500 rpm for 15 minutes to separate the serum.

Widal test procedure-

SLIDE TEST

1. Place a drop of Positive Control on a reaction circle on the slide.
2. Pipette a drop of isotonic saline solution onto the next reaction circle. (control -ve).
3. Pipette one drop of the patient serum to be tested onto the remaining four reaction circles.
4. Add a drop of Widal Test Antigen Suspension 'H' to the first two reaction circles. (PC and NC).
5. Add one drop each of O, H, AH, and BH antigens to the remaining four reaction circles.
6. Using separate stirrers, mix the contents of each circle evenly throughout the circle.
7. Gently shake the slide and macroscopically observe the agglutination within one minute.

STANDARD TUBE TEST METHOD

1. Take 4 sets of 8 Dreyer tubes/Felix tubes and label them 1-8 for detection of O, H, AH and BH antibodies.
2. Pipette 1.9 ml of isotonic saline solution into tube 1 of each set.
3. To each of the remaining tubes (2 to 8) add 1.0 ml of isotonic saline.
4. To test tube no. 1, add 0.1ml of the serum sample to be tested in each row and mix well.
5. Transfer 1.0 ml of diluted serum from tube 1 to test tube no. 2 and mix well.
6. Transfer 1.0 ml of the diluted sample from tube 2 to test tube no. 3 and mix well. Continue this serial dilution to tube 7 in each set.
7. Discard 1.0 ml of diluted serum from tube 7 of each set.
8. Test tube no. 8 in all kits acts as a saline solution. Now the dilution of the serum sample obtained in each set is as follows: Tube number: 1 2 3 4 5 6 7 8 (control) Dilutions 1:20 1:40 1:80 1: 160 1: 320 1: 640 1: 1280.
9. To all tubes (1 to 8) of each set, add one drop of the respective Widal Test antigen suspension (O, H, AH and BH) from the reagent vials and mix well.
10. Cover the tubes and incubate at 37°C overnight (approximately 18 hours).
11. Carefully dislodge the sedimented button and observe clumping.

Interpretation of the Widal test

: The titer of patient serum using Widal test antigen suspensions is the highest dilution of the serum sample that gives visible agglutination. : Specimen that has a titer of 1:100 or more for O agglutinations and 1:200 or more for H agglutinations should be considered clinically significant (active infection).

REVIEW OF LITERATURE

In a study by Buddha Basnyat et.al (2021)

Enteric fever, also known as typhoid fever, is a common infectious disease in low- and middle-income countries.1 It is the most common bacterial cause of fever among returning travelers and migrants from these areas.2 3 About 14 million people are affected annually with 136,000 deaths, mainly in low- and middle-income countries, according to estimates by the Global Burden of Disease Study in 2017. [42]

Enteric fever includes typhoid fever, caused by infection with the bacterium Salmonella Typhi (S Typhi), and paratyphoid fever, caused by Salmonella Paratyphi A and B. S Typhi causes approximately 76% of intestinal fever worldwide. Paratyphus is found mainly in parts of South Asia and China. Ingestion of food or water contaminated with contaminated human feces causes infections. [43]

Poor access to safe water and inadequate sanitation and sanitation increase the risk of transmission.Bowel fever is more common in South Asia (incidence> 500 per 100,000 population); Southeast Asia, Sub-Saharan Africa and Oceania (> 100 per 100,000 inhabitants); and Latin America and the Caribbean (1-10 per 100,000 population) . Children and young adults are most commonly affected.8-10 Among travellers [44], intestinal fever is more common in adults after visiting endemic areas. According to a systematic review, taking proton pump inhibitors increases susceptibility to intestinal fever by decreasing stomach acid. The role of HIV infection as a risk factor is unclear, but it may contribute to disease severity.12 A case series has reported neonatal sepsis due to S typhi and paratyphi in babies born to infected mothers.[45]

Abdominal pain such as diarrhea, nausea, vomiting, and abdominal pain are common according to a systematic review of the clinical profile of enteric fever (see Supplementary Table 1 at bmj.com).9 Abdominal pain is diffuse and

poorly localized, but sometimes intense. to the right iliac fossa, mimicking appendicitis. Patients may also experience headaches, coughing, and malaise. Children under 5 often have only fever and the diagnosis may go unrecognized unless complications arise.[46] Symptoms begin 7-14 days after exposure (range 3-60 days). Paratyphoid has a shorter incubation period (4-5 days) but the symptoms are indistinguishable from those of typhoid.

The mean mortality rate for enteric fever is 2.49% (95% CI 1.65% to 3.75%) and 4.45% (2.85% to 6.88%) in hospitalized patients according to a recent systematic review (44 studies, 41,723 patients).

In a study by Pooja Chaubey (2018)

Typhoid is treated with antibiotics that kill Salmonella bacteria. With antibiotics and supportive care, mortality was reduced to 1–2%. With appropriate antibiotic therapy, improvement usually occurs within one to two days and recovery within seven to ten days. Vaccines are now available for those traveling to risk areas.[47].The sensitivity and specificity of the Widal titer of anti-TO 1:80 and above in this study were approximately 71.4% and 74.1%, and 28.6% and 86.3%, respectively, for anti-TH titers of 1:160 and above. The overall titer sensitivity of positive Widal tests was approximately 71.4%, similar to the anti-TO titer as there was not a single anti-TH titer that demonstrated cultured typhoid fever. The situation is similar with the study by Olsen et al. Another study in Kenya found that Widal serum tests performed in the acute phase of patients suspected of having typhoid fever had limited diagnostic capabilities due to its low sensitivity, with only 26% of all typhus cases having a diagnostic titre.

while the O and H titers were less than 1:40 With the cut-off of anti TO ≥1: 80 and anti-TH ≥ 1: 160 Widal titre in this study, the Widal test had relatively good NPV, but the PPV was very low Positive predictive value is more important than other clinical diagnostic method measures because it pro-

vides the percentage of patients with positive test results who are correctly diagnosed, but is strongly influenced by a prevalence of the disease [48]

In a study by Akili Mawazo et.al (2018)

Typhoid fever is an infectious disease caused by Salmonella typhi. Less commonly, non-typhoid strains of salmonella commonly cause intestinal infections accompanied by diarrhea, fever, and abdominal cramps that often last for 1 week or less. Non-typhotic salmonella can cause extraintestinal infections such as bacteremia and urinary tract infections [49]

Accurate early diagnosis of typhoid fever at an early stage aims to identify etiological agents and carriers that can serve as a source of transmission during an outbreak [50]. Culture of blood, bone marrow, and stool are the most reliable diagnostic methods, as bone marrow culture is the gold standard for typhoid fever. Definitive diagnosis of typhus requires isolation of S. typhi from blood or stool [51]

Sensitivity of blood / stool culture ranges from 40 to 97% if the patient has not taken antibiotics. Blood cultures and feces are less commonly used in developing countries due to cost and need for highly trained professionals [52]

Widal's test has been associated with some controversies, including inherent variabilities of the test, difficulty in determining a baseline steady-state titer for the population, repeated exposure to S. typhi in endemic regions, cross-reactivity with other non-Salmonella organisms, and lack of reproducibility of the test result [53]. The test is also based on detecting an increasing antibody titer in paired samples 10 to 14 days apart.[54]. In typhoid, it is so difficult to detect such an increase even in patients who have had blood cultures [55]. It is also impractical because patients cannot be kept on hold without starting treatment and a second return to hospital is costly and impractical in developing countries [56]. Widal's test is influenced by other factors, including cross-reactivity of

other Salmonella subspecies which are not the direct cause of fever and may also become positive in malaria infection [57]. In developed countries, the Widal test is no longer used due to the low prevalence of typhoid, access to clean water, better laboratory techniques to isolate bacteria, and poor performance of the test for Widal [58]. In contrast, the Widal test continues to be used to diagnose typhoid in most developing countries, including Tanzania, and is the second required test after malaria screening [59].

In a study by Godwin Terver Jombo (2016)

In a study of 270 patients with fever in a hospital in Ethiopia, Widal's test was found to have low sensitivity, specificity, and positive predictive values (PPV), but good negative predictive values (NPV). On the other hand, a related study in Tanzania of 1680 children with fever found that 1% (n=16) of them had a positive Widal test.

The test was 75% sensitive, 98% specific, 100% NPV and only 26% PPV.Also in Benin City, astudy of 271 feverish patients showed: 45.76% had a positive Widal agglutination test, 22.10% of blood samples cultivated Salmonella species. The study found a sensitivity of 35%, a specificity of 51%, a PPV of 17% and a NPV of 73% with an overall disqualification of the Widal test procedure as a valid tool for the diagnosis of typhoid.[60]

In a study by Hylemariam Mihiretie Mengis et.al (2015)

A systematic review of published articles on the diagnostic value of the Widal test to exclude typhoid fever was performed. Published articles were identified from PubMed, Google Scholar, HINARI and other sources. The mean, median, percentile and standard deviation of the sensitivity, specificity, NPV and PPV of the articles reviewed were calculated using SPSS version 24 software. A total of 16 articles were was included in the systematic review, with the oldest publication dating from 1994 and the most recent from 2015. The mean sensitivity,

specificity, positive predictive value (PPV) and negative predictive value (NPV) of the Widal test was 73 .5%, 75.7%, 60% and 75.2% respectively.

Sensitivity is the probability that a truly infected person will test positive, while specificity is the probability that a truly uninfected person will test negative. The positive predictive value (PPV) is the probability that those who test positive are really infected and the negative predictive value (NPV) is the probability that those who test negative are not really infected. The mean Widal sensitivity test is 73.5 ± 12.6 (95% CI: 60.9-86.1). The probability that a true patient with typhus is positive on the Widal test ranges from 60.9% to 86.1%. Therefore, 13.9% to 39.1% of true typhus patients will be false negative on the Widal test. The lowest sensitivity of the Widal test was 45.2% and the highest is 98%. The average ability of the Widal test to declare negative febrile patients not infected with salmonella varies from 55.5% to 95.9%. This indicates that 4.1% to 44.5% of true negative test results are false positives using this method compared to blood/stool culture methods. The lowest specificity of the Widal test was 13.8% and the highest 98%. Mean Widal test PPV is 60% ± 29% (95% CI: 31% to 89%) and mean Widal test NPV is 75.2% ± 24.8% (95% CI : 50.4% to 100%).

In a study by Indu Sharma et.al (2014)

The most likely cases have been seen in regions such as India, South and Central America, and Africa with rapid population growth, increased urbanization, and limited clean water, infrastructure, and health systems. . Although definitive diagnosis of disease requires isolation of Salmonella typhi from bone marrow or blood, feces, urine, or other bodily fluids, isolation and culture facilities are often not readily available in developing countries, especially in small hospitals, clinics and diagnostic centers. .[61] Often, the diagnosis is usually based on the clinical features of the disease and the detection of agglutinating antibodies against S.

typhi (Widal's test). Although Widal's test has been used as an aid in the diagnosis of typhoid for more than a century (6,18), it is widely used in modern times and still remains one of the practical diagnostic investigative tools. and specific ones used in the serodiagnosis of typhoid are available.[62]

In this study, elevated levels of agglutinin were found in patients with various other bacteremic diseases, including those caused by other Salmonella spp., E. coli, Klebsiella spp. and S. aureus. In general, the level of O antibodies was higher than that of H antibodies in these patients. The elevated levels may be due to cross-reacting antigens or an anamnestic response. There are over 40 cross-reacting antigens between S. typhi and other Enterobacteriaceae [63].

In a study by Tarique Aziz et.al. (2012)

The Widal test has been widely used in the serodiagnosis of typhoid[64]. individual and outpatient patients attending the laboratory departments of Rajendra Institute of Medical Sciences (RIMS) Ranchi and Indira Gandhi Institute of Medical Sciences (IGIMS) Patna, India for treatment. Fresh blood was placed in a vial containing ethylenediaminetetraacetic acid (EDTA). In addition, patients were provided with sterile, dry, leak-proof, wide-neck universal laboratory bottles for collecting median urine for culture.

The results of the corrugated tube agglutination test are shown in Table 1. Titer values of 1:80 and above were considered significant and therefore positive for the Salmonella antigen. A total of 50 (62.5%) of 80 children had significant agglutination titer values (O titer ≥ 1:80, H titer ≥ 1:80) and were therefore considered positive.

In a study by P.C. Somerville et al. (1980)

Analyzed the results of the Widal test in the north and east of the Trans-

vaal on bacteriologically confirmed cases of typhoid fever, patients with suspected disease, febrile patients without typhoid fever and healthy subjects. Titers of 1:200 or higher for agglutinins H or 0 were recorded in 75.2% of patients with bacteriologically proven typhoid fever, in 4.6% of healthy subjects living in an endemic area, and in 7.5% of patients with non-typhoid fever. Age, sex and region were found to affect the percentage of positive tests recorded. Apart from these. Due to shortcomings, the Widal test has proven itself in the diagnosis of typhoid. The concept of a diagnostic titer has been considered unreliable, but when combined with the clinical picture, o- or H-agglutinin titers of 1:200 or greater can be considered strong presumptive evidence of typhoid fever.[65]The Widal test was carried out on 4 different groups of patients in the Transvaal.

Group A - A random selection of 74 households was made in Rita village, Lebowa. On a population of 647 subjects, 204 subjects were tested, of which 46 between the ages of 0 and 5, 47 between the ages of 6 and 10, 45 between the ages of II and 15, 18 between the ages of 16 and 20 years old, 8 between the ages of 21 and 25 and 40 were over 26 years old. Another 78 people, workers from a nearby citrus grove, were also tested. Their ages ranged from 18 to 60 years. During the test they had no complaints and, as far as could be ascertained, they had not been vaccinated in the last 2 years. The Widal tests were conducted by the South African Institute for Medical Research in Pietersburg and Duiwelskloof. The institute's standard H and O agglutination suspensions, prepared by the central laboratory in Johannesburg, were used.

Group B - This group consisted of 67 patients with febrile illnesses without typhoid fever at Letaba Hospital, Gazankulu, 15 km from Rita village. These patients were examined from April to August 1979. Widal tests were carried out at least twice, at least 6 days apart, at the National Laboratory of the Institute of Tropical Diseases, Tzaneen. Agglutination suspensions manufactured by Wellcome Laboratories were used.

Group C - This group consisted of 330 patients with bacteriologically proven typhoid fever. Of these, 275 were presented to Themba Hospital between December 1974 and December 1978. The Widal test was performed either at the Themba Hospital laboratory using Wellcome reagents or at the SAIMR laboratory in Nelspruit using the Institute's own reagents. The test was performed on admission and repeated in most cases after 7-10 days. Only the highest agglutinin titer was recorded in the results. The remaining 55 patients were presented to the other hospitals (listed in group D) and the Widal test was performed only on admission

Group D - The last group consisted of 763 patients with clinically suspected typhoid fever. Presentarion was in various hospitals in the northern Transvaal between December 1974 and March 1979 (Themba Hospital near Nelspruit, Donald Fraser Hospital in Venda, Elim Hospital near Pietersburg, Blouberg and Helene Franz Hospitals in Lebowa, and Pietersburg Hospital). the SAIMR laboratories in Pietersburg and Nelspruit and the hospital laboratories in Themba and Elim.

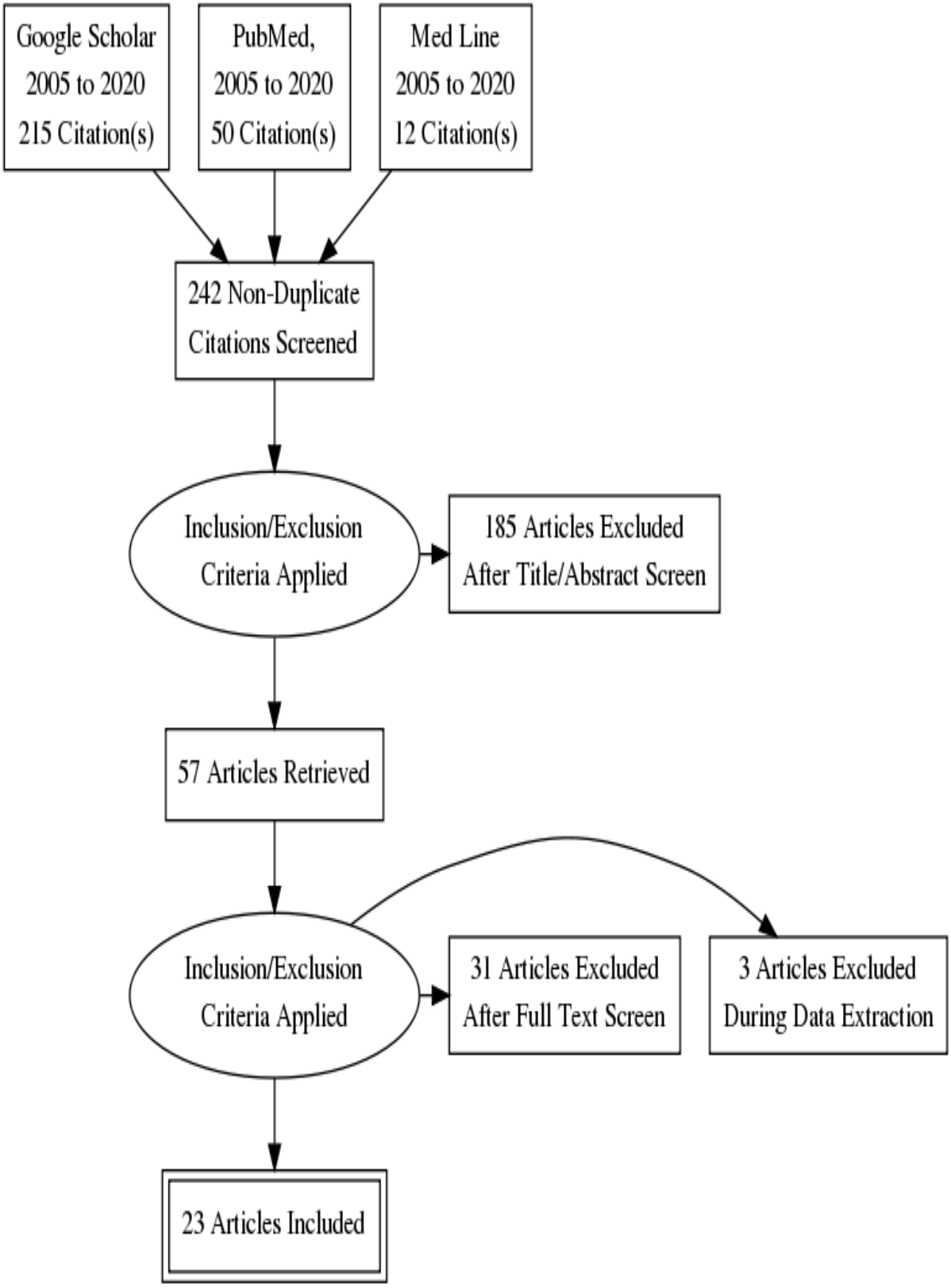
AIM AND OBJECTIVES:-

AIM- To find the role of widal test in pyrexia suspected patients.

OBJECTIVES- To determine widal test in pyrexia suspected patients.

Methodology

Study design and data source Systematic review of the published literature of observational studies was conducted. Original studies providing data on the diagnostic value of Widal test were identified through a computerized search using databases of **Medline/PubMed, Google Scholar, HINARI (Health Inter Network Access to Research Initiative) and manual search** with detailed search-strategy and cross-checking of reference lists. The search terms used to search the database were diagnostic value, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and test efficiency of Widal test.


Google Scholar
2005 to 2020
215 Citation(s)
PubMed,
2005 to 2020
50 Citation(s)
Med Line
2005 to 2020
12 Citation(s)
242 Non-Duplicate
Citations Screened
Inclusion/Exclusion
Criteria Applied
185 Articles Excluded
After Title/Abstract Screen
57 Articles Retrieved
Inclusion/Exclusion
Criteria Applied
31 Articles Excluded
After Full Text Screen
3 Articles Excluded
During Data Extraction
23 Articles Included

RESULT AND OBSERVATIONS

S.NO	AUTHOR	YEAR	PLACE	FINDINGS
1.	Buddha Basnyat et.al	2021	China	About 14 million people are affected annually with 136 000 deaths The Typhidot test had an average sensitivity of 66% (59% to 73%) with a specificity of 81%
2.	Pooja chaubey	2018	Bhopal	10 participants were females and 22 were males in blood culture and 20 were positive, 12 were negative. Total 62 cases of S. typhi were identified with the total prevalence of typhoid fever. The total number of patients who have indicative of recent infection by either of O and H antigens.
3.	Akili Mawazo et.al	2018	Tanzania	158 patients participated in the study, 128 (81%) tested positive for the Widal test and 17 (11%) patients were stool culture positive. Widal test recorded 81.5% sensitivity, 18.3% specificity, 10.1% positive predictive value and 89.7%.

4.	Godwin Terver Jombo et.al	2016	Nigeria	the 389 patients suspected patients to have typhoid fever, 61.2% (238) were males and 38.8% (51) females; the age range was four and 72 years with a median age of 56 and bimodal ages of 41 and 52 years.
5.	Hylemarian Mihiritie mengist et.al	2015	Ethiopia	A total of 16 articles were included in the systematic review with the oldest publication in the year 1994 and the recent in 2015. The reviewed articles included 50 sample size with the smallest and 1735 samples with the largest.
6.	Indu Sharma et.al	2014	Assam	Highest agglutination for the overall data for the positive cases were found to be in H antigen with a titre of 1:80 in 56 patients followed by 1:640 titre in 54 patients, 1:160 titre in 33 patients and in 1:320 titre in 31 patients. Highest titre was observed that in O antigen in 34 patients followed by 1:640 titre in 32 patients, 1:160 titre in

				33 patients and 1:320 titre in 27 patient
7.	Tarique Aziz et.al	2012	India	A total of 16 articles were included in the systematic review with the oldest publication in the year 1994 and the recent in 2015. The reviewed articles included 50 sample size with the smallest and 1735 samples with the largest.
8.	P C Somerville	1980	Petersburg	Highest agglutination for the overall data for the positive cases were found to be in H antigen with a titre of 1:80 in 56 patients followed by 1:640 titre in 54 patients, 1:160 titre in 33 patients and in 1:320 titre in 31 patients. Highest titre was observed that in O antigen in 34 patients followed by 1:640 titre in 32 patients, 1:160 titre in 33 patients and 1:320 titre in 27 patient Titer values from 1:80 and above were regarded as significant and therefore positive for the Salmonella antigen. A total of 50 (62.5% approx) out

				of the 80 children had significant (O titre ≥ 1:80, H titre ≥ 1:80) slide agglutination titer values and therefore were regarded as positive. Titres of 1:200 or greater for either H or 0 agglutinins were recorded for 75,2% of patients with bacteriologically proven typhoid fever, 4,6% of healthy subjects residing in an endemic area and 7,5% of patients presenting with non-typhoid fevers.

DISCUSSION

Typhoid fever is a major public health problem associated with significant morbidity and mortality in many countries[9].Blood culture has remained the gold standard test in diagnosis of typhoid fever, but its utility in early diagnosis is limited in early phase of illness thereby making the isolation of the organism difficult. Although the Widal test at this cut-off titer performed relatively well in terms of sensitivity, specificity and NPV, its PPV was low. It has been argued that PPV is the most important measure of a clinical diagnostic method since it represents the proportion of patients with positive test results that are correctly diagnosed[10]. The PPV is not intrinsic to the test; it is affected by prevalence of the disease. There are several difficulties associated with evaluation of the Widal test.

Firstly, levels of agglutinins detectable in the non-infected populations of different areas vary considerably by time and place depending on the endemicity of the disease, which affects test performance. For example, the sensitivity and specificity of a Widal test. Widal positivity is more of an epidemiological evaluation rather than clinical because a rising titer repeated after two weeks duration should be demonstrated before it is of clinical significance, although this has also been under serious criticism in recent years. Sharing of O and H antigens by other Salmonella serotypes and other members of Enterobacteriaceae makes the role of widal test even more controversial in diagnosing typhoid fever

As the world continue fighting against antimicrobial resistance, correct, rapid and accurate di- agnosis is needed toward archiving the goal. In Tanzania, febrile pre- senting diseases such ty- phoid fever are among the disease which are commonly diagnosed [10]. Therefore an experi- ment was done to evaluate the diagnostic accuracy of the commonly performed Widal test and stool culture while keeping blood culture as a golden standard.

The overall sensitivity of titer positive Widal test was about 71.4%, similar with anti TO titer be- cause there was no only anti TH titer positive culture proven typhoid fever identified. because there was no only anti TH titer positive culture proven typhoid fever identified

Widal testing done on acute phase serum of patients suspected to has typhoid fever had limited diagnostic capability given its low sensitivity in which among all typhoid cases only 26% had diagnostic titer while 53.6% had O and H titer less than 1:40

, the definitive diagnosis of typhoid fever can be a problem to clinicians because as a clinical entiry it differs in many respects from the description in textbooks based mainly on experience in developed countries. The protean features which may be encountered have been well described by Wicks and others; in Rhodesia. The traditional views that agglutinin titres only become positive towards the end

of the second week ofthe illness, rising through the third week, and that H agglutinin titres are ofvery limited value, do not appear to be generally true in this region.

Wicks er al. 5 and Senewiratne6 both found that high agglutinin titres could be demonstrated at an early stage in the illness, often during the first week. This suggests that, in an endemic area with frequent exposure to S. typhi and antigenically related salmonellae, the immune response may often not be a primary one

Conclusion

- The systematic review results show that the reliability of Widal test is comparatively poor. Therefore, Widal test should not be used as a diagnostic tool to rule out typhoid fever unless supported by invasive clinical pictures and other confirmatory tests.
- Both O and H agglutinin titres of 1/200 are recommended as being considered of diagnostic significance; also the Widal test being easy to perform, inexpensive, and relatively non-invasive test can be of diagnostic value in situations where blood cultures cannot be obtained.
- It is concluded, that even today, the Widal test remains one of the best, easily accessible, cheap and simple method in comparison to other molecular and biochemical test for the diagnosis of typhoid fever.
- The Widal test still has an important role to play in the diagnosis of typhoid fever in this region. A titre of 1:200 of either H or 0 agglutinin in a patient suspected on clinical grounds of having typhoid fever is a significant indicator of active infection, but a rising titre muse be looked for. Apart from bacteriological isolation of S. typhi (which also is not full proof, since a carrier state may exist) a fourfold rising agglutinin titre IS the most definitive evidence for a current attack of typhoid fever. Blood cultures should always be examined early in the disease and the Widal test must be repeated after a period of at least 7 - 10 days. The effect of chloramphenicol on depressing the antibody titre must also be borne in mind.
- Total 62 cases of S. Typhi or paratyphi were identify with the total prevalence of typhoid fever. Widal test is 30 patients were observed and blood culture were observed 32 patients.

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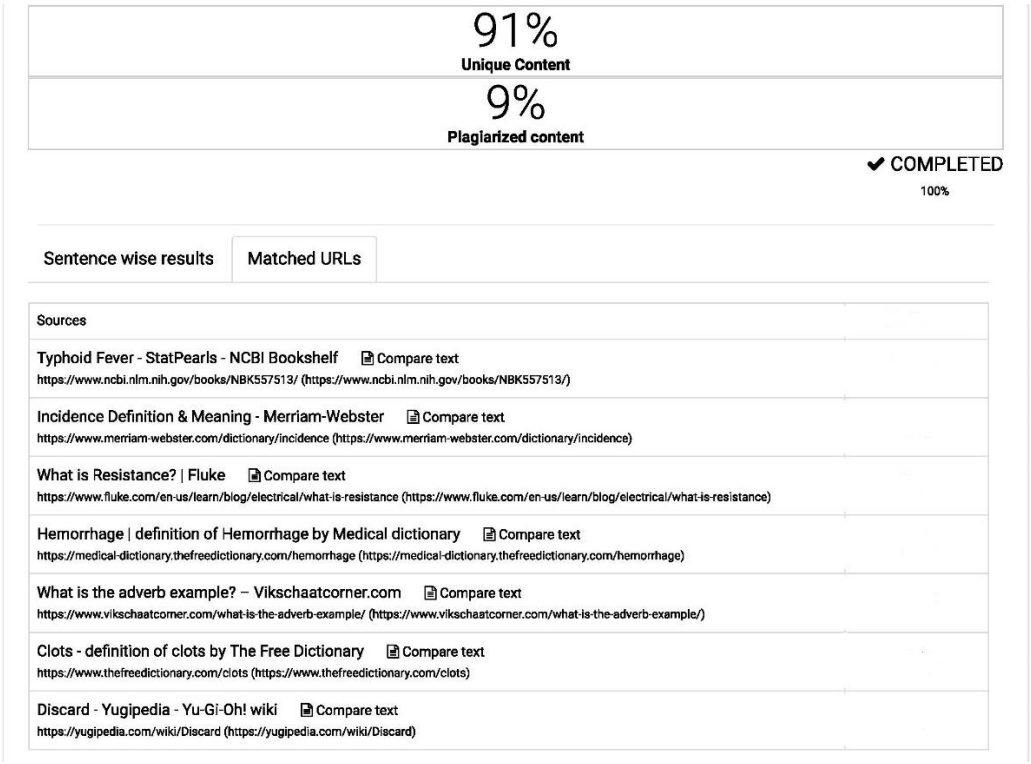

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