ETIOLOGICAL PROFILE OF FEVER OF UNKNOWN ORIGIN IN CHILDREN BETWEEN 1 MONTH TO 12 YEARS ADMITTED IN AN URBAN REFERRAL CENTRE

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CERTIFICATE

Certified that this dissertation entitled

"ETIOLOGICAL PROFILE OF FEVER OF UNKNOWN ORIGIN IN CHILDREN BETWEEN 1 MONTH TO 12 YEARS ADMITTED IN AN URBAN REFERRAL CENTRE"

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has been conducted by me at the Institute of Child Health and Hospital for Children, under the guidance and supervision of my unit Chief **Prof.Dr.C.D. Natarajan, MD., DCH.** It is submitted in part of fulfillment of the award of the degree of M.D (Pediatrics) for the September 2006 examination, to be held under the Tamil Nadu Dr.M.G.R Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma.

(DR. N.THIAGARAJAN)

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INTRODUCTION

"Fever is the mighty engine which mother nature brings in to the world for the conquest of her enemies" - Dr.Sydhenam (1960).

DEFINITION

Fever has been defined[1] as "a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host".

Most fevers are both brief and self limited and do not require extensive diagnostic investigation or specific therapy. Some fevers are manifestations of more serious illnesses, most of which can be readily diagnosed and effectively treated. A small but important subgroup of fevers are both persistent and difficult to diagnose. Such perplexing subgroup of fevers can be conveniently termed as fever of unknown origin so that it warrants a particular systematic approach to diagnostic evaluation and management.

Fever in children may be categorized as[2]

1. Fever with localising signs for which diagnosis can be established by clinical history ,physical examination with or without laboratory tests.

2. Fever without localising signs, usually of acute onset and present for less than a week.

3. Fever of unknown origin (FUO) is best reserved for children with a fever documented by a health care provider and for which the cause could not be identified after 3 wks of evaluation as an outpatient or after 1 wk of evaluation in hospital. Patients with fever not meeting these criteria, and specifically those admitted to the hospital with neither an apparent site of infection nor a noninfectious diagnosis, may be considered to have fever without localising signs

Most fever of unknown origin result from common disease that may be atypical in the presentation. In some cases the presentation of fever of unknown origin is typical of the diseases (Juvenile rheumatoid arthritis) but an explicit diagnosis can be established only after prolonged observation because there are no associated findings on physical examination and all laboratory results are negative or normal.

PATHOGENESIS[3]

Mechanism of fever from disease is complex, but by a brief sort of definition is produced by action of certain substances (probably produced by disease process from the tissues or WBC of the host) acting on thermoregulatory centers in the hypothalamus. The normal balance between the anterior center (concerned with heat dissipation by vasodilation and sweating related to parasympathetic activity)and the posterior center (concerned with conserving heat by vasoconstriction and shivering and related to sympathetic activity) is upset to produce a positive heat balance and raise the body temperature above normal. Fever may be provoked by many stimuli. Most often, they are bacteria and their endotoxins, viruses, yeasts, spirochetes,

protozoa, immune reactions, several hormones, medications, and synthetic polynucleotides. These substances are commonly called exogenic pyrogens. Cells stimulated by exogenic pyrogens form and produce cytokines called endogenic pyrogens. Endogenic pyrogens centrally affect the thermosensitive neurons in the preoptic area of the hypothalamus increase the production of heat and decrease the heat loss. The body temperature increases until it reaches the set point. This information is transferred by temperature of blood that flows around the hypothalamus. The decrease of temperature is controlled by activation of mechanisms regulating increased outcome of heat to the surrounding area. Increased outcome continues in favourable case until the new equilibrium is achieved. The most important endogenic pyrogens are IL-1, IL-6 and cachectin also called the tumour necrosis factor (TNF).In the hypothalamus, IL-1 and TNF trigger the synthesis of prostaglandins of group E from the arachidonic acid of cytoplasmic membranes of target cells. Precise mechanism by which prostaglandin PGE reset the central thermostat, is not known.

In the process of fever, IL-1 and TNF play the central role. Except introduced activity in fever, they interfere with many mechanisms in an organism. Some of their effects are executed with the participation of metabolites of arachidonic acid. IL-1 and TNF affect myelopoiesis, release of neutrophils and enhancement of their functions. They cause vasodilatation and increase in the adhesivity of cells, increase the production of PAF and thrombomodulin by endothelial cells, proteolysis and glycogenolysis in muscles, mobilisation of lipids from adipocytes, proteosynthesis and glycogenolysis in the liver, induce proliferation of fibroblasts, activate

osteoclasts and the release of collagenase from chondrocytes, induce slow wave sleeping activity in the brain, the release of ACTH, beta endorpins, growth hormone and vasopressin, the release of insulin, cortisol, and catecholamines. TNF and partially also IL-1 in longlasting operation may cause cachexia mainly by decreasing the appetite. It is so in chronic infections, inflammatory processes, and in neoplastic processes.

Besides that, TNF and IL-1 significantly increase the immune response by activation of T-cells and stimulation of IL-2 production. IL-1 enhances B-cells proliferation. It is interesting that these processes have the temperature optimum at 39.5^{o}C. It follows that the fever can be supposed as a positive factor. Fever and specific effects of IL-1 and TNF form together highly integrated processes that are involved in the response to infection and acute inflammatory processes.

Interferons, and especially IFN-a (formed by T lymphocytes and NK cells) may enhance this response. Several parts of this complex response have protective and the others may have malignant consequences. Septicemia, or septic shock is an overshot response of the organism. In this complicated reaction of the organism, it is not easy to decide whether fever should be treated by antipyretics or not. By antipyretics the symptoms of fever may be suppressed but it is uncertain if it is reasonable to suppress also the positive effects of fever and everything that is connected with it. This complex process (fever) mobilises not only the immune system but also those processes that improve the nutrition of cells and have protective importance on their activity.

NORMAL BODY TEMPERATURE[4]

The commonly accepted value of 98.6^{o}F (37.0^{o}C) orally, and 99.6^{o}F (37.7^{o}C) rectally is only a generally accepted average with a range reported in the literature from 97.2^{o}F to 99. 9^{o}F for oral values. It slightly increases during the day since morning (from 6:00 a.m.). The peak is reached at 6:00p.m to 10:00 p.m. The lowest temperature is between 2:00 and 4:00 a.m. Diurnal variation depends on the activity throughout the day. Such a diurnal variation is also kept when fever occurs. Fever reaches the peak in evening, and in morning even a very sick patient may have almost normal temperature.

Mechanism for temperature regulation: Is via the blood flow through the skin and subcutaneous area. Vasoconstriction allows the increased accumulation of heat and vasodilatation secures its quick loss. Changes in temperature up to 3^{o}C don't cause an interruption of physiological functions. Spasms may occur during high fever in children. If the body temperature is increased over 42.2^{o} C, irreversible changes in the brain occur.

RECORDING OF TEMPERATURE[5]

In clinical practice, temperatures are commonly recorded orally, rectally, in the axillae, and more rarely in the groin, and of recently voided urine. More rarely, or for special studies, temperature can be recorded for various parts of the skin or other parts of the body (e.g. , the ear, esophagus, etc.) Oral and rectal temperatures are, in a sense, "spot" or "local" readings. However, for practical purposes, the oral or rectal temperatures are used in clinical practice as indicative or reflective of body temperature. The tympanic membrane

temperature comes closer to reflecting the body temperature in the thermoregulating centers of the brain.

Oral Temperature: This type is most commonly used in practice and, if correctly taken, may be more indicative of fluctuations of body temperature than rectal readings. Oral readings of temperature are easily falsely lowered by mouth breathing, drinking or eating cold substances, and in shock, are falsely elevated by hot food or drink, chewing (activity of muscles of mastication), smoking and increased salivary gland activity (as after a meal or with chewing).

Rectal Temperature: 0.5^{o}F -1.0^{o}F higher than oral temperature, but this relationship is not constant. This reading is used especially in sick children, in adults with suspected shock, or where oral reading is not valid for reasons given above.

Axillary Temperature: In children this approximates oral temperature; time taken for measurement is five minutes.

Tympanic Membrane: Increasingly, tympanic thermometry is being utilised. The readings are more reliable than oral or rectal recordings. They are consistent with esophageal readings which, while valuable, are impractical to utilise for routine clinical activities. They are only 0.2^{o}C lower than the esophageal temperature. Tympanic recordings more accurately reflect the central temperature in man than oral, skin or rectal temperatures. This technique has been especially helpful for continuous recording of body temperature during surgical operations while the patient is under anesthesia.

FEVER PATTERN[6]

Some diseases are characterized by certain stereotypic consequence of temperature changes. According to the temperature curve, we may distinguish several types of fever.

Hyperpyrexia or Hyperthermia – this refers to body temperature higher than 105.8^{o}F.

Intermittent (or Quotidian) Fever – here the daily fever peak is followed by a fall to normal temperature level.

Hectic (or Septic) Fever - an intermittent fever with large daily swings in body temperature, usually accompanied by chills and sweats.

Remittent Fever - significant variations in temperature level more than 2^{o}C with in 24 hrs without a drop to normal level of temperature. Some examples are: acute-rheumatic fever, pulmonary tuberculosis, etc.

Continuous (or Sustained) Fever - fever sustained at a high level in which daily diurnal variations are less than 1^{o}C (1.5^{o}F). Some examples are pneumococcal lobar pneumonia before treatment, rickettsial diseases, certain types of drug fever, etc.

In most infections or inflammatory processes, the characteristics of fever pattern are of little diagnostic importance[7]. With the use of antibiotics and antipyretics these classical types of fever are not often seen.

REVIEW OF LITERATURE

In 1961, Petersdorf and Beeson[8] published their classic article on fever of unknown origin (FUO) and established criteria that have effectively delineated this entity:(1) an illness of at least 3 weeks duration, (2) with fever (temperature >38.3°C on several occasions), and (3) no established diagnosis after 1 week of hospital investigation. This time-honoured definition has enabled research on the topic and comparisons over time and between regions of the diseases and diagnostic categories that make up the FUO spectrum. The first 2 criteria allow elimination of most acute, self-limited, frequent viral diseases and habitual hyperthermia, respectively. This study was done in 100 adult patients and in the study infections lead the group by 39%, followed by neoplasms in 21%, niid(non infectious inflammatory diseases) in 19%, unknown causes 1%, and 20% were grouped under miscellaneous.

Dechovitz et al[9] found it useful to define FUO as fever lasting for more than 2 weeks, in which no diagnosis could be made. This was studied in 155 children where infections lead the group by 45%, niid (4%), malignancy (2%). No cause was attributed in 35%. Fever was not recognized after hospital admission in 14%. In infections, respiratory tract infections were commonest. In his study he has not defined either inpatient or outpatient evaluations in the criteria.

In 1975 Mcclung[10] defined fever of unknown origin as defined by Petersdorf and Beeson, and found that infection constituted 28%, niid 14%, malignancy 11%, miscellaneous 16%, no diagnosis established in 11% and resolved during investigations 20%.

Pizzo[11] et al 1975 studied one hundred children admitted to a hospital over a six-year period with temperatures over 38.5°C for longer than two weeks and of undetermined etiology . Fifty-two were infections (21 presumed viral), 20 collagen-inflammatory disorders, 6 malignancies, 10 miscellaneous, and 12 discharged undiagnosed. Children less than 6 years were more likely to have an infectious etiology while 80% of collagen-inflammatory disease occurred in the group older than 6. The overall mortality (9%) was not age-related. Careful history and physical examinations were helpful but the usual laboratory data (CBC, urinalysis, X-ray) were notably disappointing; however, sedimentation rates and serum protein electrophoresis were often reliable screening tests. Biopsy and laparotomy were less frequently done but when performed yielded productive information. He concluded that unusual presentations of common diseases comprised the majority of childhood fevers.

In 1978 Cruz Guerrero G[12] et al studied 79 children from zero to seven years of age admitted to hospital with fever of unknown origin of more than two weeks duration. Children in whom fever was not clinically observed after one week of hospitalization were not included. In 50 cases (63.2%), it was possible to establish a definitive diagnosis within the first fortnight of admission. The most frequent cause of fever was that of infection, found in 51 children (64.5%), tuberculosis and urinary infections predominating with ten cases each. In another ten children neoplastic disease was diagnosed (mostly leukemia), and there was collagen diseases in seven cases (8.8%). In another seven children, the etiology was not established. Mortality rate was 7.5%. Clinical history and exploration were of main importance in the orientation of the diagnoses. The findings of this study suggest that in all children presenting

F.U.O., apart from hospitalization of at least one week, a very thorough history and clinical exploration are most important in establishing the diagnosis, along with a more or less aggressive approach to the problem according to the findings.

In 1984 Barboda[13] fj et al analysed one hundred and thirty-three patients with fever of unknown origin ,an etiologic diagnosis had been made in 105 patients: 41 patients had an infection, 24 had a neoplasm, 17 had a connective tissue disease, and 23 had various diseases grouped under miscellaneous. FUO was self-limiting in 25 of the remaining patients. Invasive procedures (arteriography, biopsy, laparoscopy, laprotomy) were necessary to establish a diagnosis in 67 patients, non-invasive tests (sero-immunologic, bacteriologic, conventional radiologic tests, clinical course and treatment response) were sufficient in 27 patients. In 11 patients, the cause of FUO was determined in necropsy Seventeen patients died of FUO, 6 patients with a neoplasm, 4 with a connective tissue disease, and 7 with diseases termed miscellaneous.

In 1992, Gamboa Marruffo[14] et al reported on a series of 180 children with fever more than 3 weeks, he found that infections lead the cause. Among infections typhoid fever and UTI were the most frequent. In more than 29%,cause of fever could not been established.

In 1992, Gartner[15] et al defined FUO as fever lasting for more than 2 weeks in which infections lead the causes of fever of unknown origin. He concluded that among infection in the infants respiratory focus lead the cause, and most FUO are uncommon manifestations of common diseases.

In 1992, Kazanjian[16] PH et al described FUO in 86 patients, infectious diseases remain the most common category of illnesses causing FUO; He pointed out that noninvasive approach established the diagnosis in many instances.

In 1992, Sharma BK, Kumari S, Varma SC, Sagar S, Singh S[17] made a prospective study for five years along with a retrospective analysis of all patients admitted over 10 years with the diagnosis of prolonged undiagnosed fever was carried out in a referral hospital of North India to determine the specific disorders responsible for it. One hundred and fifty patients (80 prospective and 70 retrospective) were included in the study. Infections, especially tuberculosis, was the most dominant cause (50%), followed by lymphoreticular and haematological disorders (21.32%), collagen vascular disorders and neoplasms (8.67%) each. Miscellaneous causes were responsible in 6.67% and in 14.67% the cause of fever remained unknown.

In 1994, Chantada et al[18] studied medical records of 113 children who had undiagnosed fever for at least 3 weeks. Infection (N = 41) was the most frequent cause of fever of unknown origin. Respiratory tract infections were the most common cause in infants and endocarditis and tuberculosis were more frequent in older children. Neoplastic disorders (N = 11) occurred in children older than one year. Juvenile rheumatoid arthritis (N = 9) was the most common collagen-vascular disorder (N = 15). Miscellaneous disorders and factitious fever occurred in 21 and 4 cases, respectively. Twenty-two patients remained undiagnosed. History and physical examination led to a final diagnosis in 81% of cases. Abdominal ultrasonography was performed in 71

patients (61%) and was helpful for diagnosis in 15%. Children with life-threatening or chronic disorders (N = 58) were older than those with self-limiting conditions .Cardiovascular and articular signs and symptoms were more frequent in the former group .

In 1996, Handa R, Singh S, Singh N, Wali JP[19] et al studied prospectively,one hundred and twenty-one cases of FUO presenting to a large teaching hospital in northern India over a period of 2 years. Infections were the commonest cause accounting for 43.8% cases of FUO, with tuberculosis (TB) being the commonest infection encountered. Collagen vascular diseases and tumours accounted for 15.7% and 8.3% cases, respectively, 14% were grouped under miscellaneous. No cause could be found out in a substantial number of cases (19%) even after invasive investigations

In 1996, Chien ch et al [20], studied 86 children with fever lasting for at least 6 days without diagnosis at admission after initial physical examination and preliminary laboratory tests in a retrospective analysis. Bacterial infections occurred in 19 patients (22%), viral infections in 17 (20%), mycoplasmal infections in 3% and malaria in 1%. Collagen vascular diseases were diagnosed in 13 children (15%), including 7 juvenile rheumatoid arthritis and 5 systemic lupus erythematosus. Thirteen children (15%) had neoplastic or hematological diseases, including leukemia, lymphoma, myelodysplastic syndrome and neuroblastoma. The fevers of the other 14 patients (16%) were attributed to miscellaneous.

In 1996 Haq[21] et al ,in their prospective study conducted in the Institute of Postgraduate Medicine & Research (IPGMR), Dhaka, 212 patients with

prolonged pyrexia were thoroughly evaluated clinically and with the help of laboratory investigations with a view to reaching the diagnosis. Their clinical and laboratory data were recorded. Clinical features pertaining to a particular organ gave appropriate clue in 52% cases. Imaging techniques were instrumental in 24%, microbiological or serological investigations in 35%, invasive procedures were diagnostic in 42%, laprotomy had to be resorted to in five cases. Infectious diseases were the commonest causes of prolonged pyrexia accounting for about 63.21% of cases followed by neoplasms (12.74%) and connective tissue disorders (10.85%). Tuberculosis was the most common infection (24.53% of all cases) followed by enteric fever (12.74%) and visceral leishmaniasis (9.43%). Pleura was the commonest seat for tuberculosis followed by lymph nodes and abdomen. Leukemias were the commonest neoplasm and SLE the commonest connective tissue disorder presenting with prolonged fever.

In 1998 Sarala Rajajee[22] et al in a retrospective study and prospective study of 75 children with FUO in Chennai from 1996 to 1998,documented that 78.1%was due to infections, 9.3% malignancy, 9.3%, vasculitis, and drug fever 2.7%. Common cause of infections were typhoid fever (26%), followed leptospirosis (14.6%),tuberculosis (10.6%) and malaria (8%).

Between 1995-2002 Ciftci[23] et al analysed 102 children fitting with classical FUO. Infections, collagen vascular disorders, malignancy and miscellaneous conditions constituted 44.2%, 6.8%, 11.7% and 24.5% of cases, respectively, while 12.8% of the cases remained undiagnosed. Enteric fever, brucellosis and respiratory tract infections were the most commonly

encountered infections, whereas familial Mediterranean fever was the commonest non-infectious disorder. Biopsy, aspiration, serology, bacteriology, radiology and observation of the clinical course were the most useful diagnostic procedures.

1n 2002 Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S[24] made a prospective study of 100 cases.Infections, especially tuberculosis was the most dominant cause (53%), followed by neoplasms (17%), and collagen vascular disorders (11%) Miscellaneous causes were responsible in 5% cases and in 14% the cause of fever remained undiagnosed.

CAUSES OF FEVER OF UNKNOWN ORIGIN[2]

	Salmonella
Infections	Tuberculosis
Bacteria	Yersiniosis
Caused by specific organism	Localized infections
Actinomycosis	Abscesses: abdominal, brain, dental, hepatic, pelvic, perinephric, rectal, subphrenic
Bartonella henselae (cat-scratch disease)	Cholangitis
Brucellosis	Infective endocarditis
Campylobacter	Mastoiditis
Francisella tularensis (Tularemia)	Osteomyelitis
Listeria monocytogenes (Listeriosis)	Pneumonia
Meningococcemia (chronic)	Pyelonephritis
Mycoplasma pneumoniae	Sinusitis
Rat-bite fever (Streptobacillus moniliformis; streptobacillary form of rat-bite fever)	

SPIROCHETES

Borrelia burgdorferi (Lyme disease)

Relapsing fever (Borrelia recurrentis)

Syphilis

Leptospirosis

Rat-bite fever (Spirillum minus; spirillary form of rat-bite fever)

PARASITIC DISEASES

Amebiasis

Babesiosis

Giardiasis

Malaria

Toxoplasmosis

Trichinosis

Trypanosomiasis

Visceral larva migrans (Toxocara)

FUNGAL DISEASES

Blastomycosis (extrapulmonary)

Coccidioidomycosis (disseminated)

Histoplasmosis (disseminated)

RICKETTSIA

Lymphogranuloma venereum

Psittacosis

Chlamydia

Ehrlichia canis

Q fever

Rocky Mountain spotted fever

Tick-borne typhus

VIRUSES

Cytomegalovirus

Hepatitis viruses

HIV

Infectious mononucleosis (Epstein-Barr virus)

RHEUMATOLOGIC DISEASES

Behçet's disease

Juvenile dermatomyositis

Juvenile rheumatoid arthritis

Rheumatic fever

Systemic lupus erythematosus

HYPERSENSITIVITY DISEASES

Drug fever

Hypersensitivity pneumonitis

Pancreatitis

Serum sickness

Weber-Christian disease

NEOPLASMS

Atrial myxoma

Cholesterol granuloma

Hodgkin's disease

Inflammatory pseudotumor

Leukemia

Lymphoma

Neuroblastoma

Wilms' tumor

GRANULOMATOUS DISEASES

Crohn's disease

Granulomatous hepatitis

Sarcoidosis

Familial-hereditary diseases

Anhidrotic ectodermal dysplasia

Fabry's disease

Familial dysautonomia

Familial Mediterranean fever

Hypertriglyceridemia

Ichthyosis

Sickle cell crisis

MISCELLANEOUS

Chronic active hepatitis

Diabetes insipidus (non-nephrogenic and nephrogenic)

Factitious fever

Hypothalamic-central fever

Infantile cortical hyperostosis

Inflammatory bowel disease

Kawasaki disease

Kikuchi-Fujimoto disease

Pancreatitis

Periodic fever

Poisoning

Pulmonary embolism

Thrombophlebitis

Thyrotoxicosis

Recurrent or relapsing fever

UNDIAGNOSED FEVER

Persistent

Recurrent

Resolved

STUDY JUSTIFICATION

Etiology of fever of unknown origin varies from region to region, and also with age. Although the relative frequencies are some what different, the three most commonly identified causes of fever of unknown origin in children are: Infectious diseases, Rheumatological disorders and Malignancies. The adage that a fever of unknown origin is more likely to be caused by an unusual manifestation of a common disorder than by a common manifestation of a rare disorder is true in pediatrics .

Early identification of exact etiology will help in better management of similar cases in future.

Hence to know the exact etiology of fever of unknown in children between 1 month - 12 years, in this region this study has been planned.

OBJECTIVE OF THE STUDY

1 To study the etiological profile, of fever of unknown origin in children between 1 month to 12 years.

2. To utilize the outcome of the present study in the management of similar cases in future so as to shorten the delay .

MATERIALS AND METHODS

METHODOLOGY

Study design

Descriptive study

Study place

Institute of child health and hospital for children, Egmore, Chennai.

Study period

August 2004 to March 2006.

Sample Size

n - 182 cases

Case definition[2]

Children with a fever documented by a health care provider and for which the cause could not be identified after 3 wks of evaluation as an outpatient or after 1 wk of evaluation in hospital

Inclusion criteria[37]

1. Fever

   A. A documented fever of more than 38^{o}C which is present at least twice weekly for longer than three weeks for outpatients.

   Or

   B. A child with fever more than 38^{o}C with no apparent diagnosis even after one week of inpatient investigations.

   All children who are satisfying above criteria are included.

Exclusion criteria[38]

1. Immunocompromised children as defined by;

   a. Neutropenia: (WBC count <1000 per microlitre and or neutrophil count <500 per microlitre)

   b. Known HIV patient.

   c An intake of immunosuppressive drugs or prednisolone more than 2mg/kg/day at least for 2 weeks/>20mg if weight >10kg.

2. Nosocomial FUO, is a hospital-associated disorder in which patients first manifest fever after having been hospitalized for at least 24hours, not present or incubating on admission

3. All children with insufficient basic work up on admission.

4. Etiologic diagnosis already established by referring physician.

MANOUVERE

1. All children who were admitted and who fullfill the inclusion criteria were included. Detailed history of present illness, past history, treatment history, socio-economic history, immunization status ,and recorded in the proforma (annexure)from the reliable informant.

2. Nutritional status and vital signs were recorded.

3. A thorough clinical examination was done. Positive findings and relevant negative findings in general examination, cardio-vascular system, respiratory system, gastro-intestinal system, and central nervous system were noted in the proforma.

INVESTIGATIONAL APPROACH

1. INITIAL SCREENING INVESTIGATIONS FOR ALL THE CASES.

a. Complete blood count, differential count, haemoglobin, erythrocyte sedimentation rate, peripheral smear, thick and thin smear for malaria parasite, QBC, mantoux, and urine microscopic examination for the presence of pus cells .

b. Venous blood was drawn from the patient and sent for culture of

   1. Nonenteric organisms

   2. Enteric organisms

c. Mid stream clean catch urine sent for culture and sensitivity on three consecutive days for children in infants suprapubic aspiration was done.

d. Serology

1 Blood Widal test using tube agglutination test for H and O agglutinins.

2. In children with pattoc stain slide agglutination test positive for leptospirosis or dark field microscopy positive in urine or blood for leptospirosis, or with clinical suspicion of leptospirosis, blood was sent for microscopic agglutination test (MAT) and repeated after two weeks if the first titer was 100 or more for rise in titer

3. Brucella slide agglutination test.

e. Liver function test , renal function test, and serum uric acid.

f. Screening with ELISA for HIV 1 and 2 were done for all cases with consent obtained from the informant.

g. USG abdomen.

h. Chest x-ray

2. OTHER INVESTIGATIONS IN RELEVANT CASES.

a. Xray sinus, or Xray of relevant bone.

b. Hepatitis B surface antigen and IgM anti - Hbc if Hepatitis Ag positive.

c. Resting gastric juice contents in suspected tuberculosis patient, the material examined by Ziehl Neelson technique for AFB.

d. CSF analysis was done for children with convulsions,or altered sensorium or signs for meningeal irritation. CSF cell count biochemical analysis, culture and sensitivity were sent

e. ECHO for patients with suspicion of infective endocarditis.

f. Children were evaluated for connective - tissue disorders in suspected cases in the Rheumatology clinic, Madras Medical College where ASO titer, CRP, rheumatoid factor and anti-nuclear antibodies were done for all suspected patients.

g. In children with suspicion of SLE ds-dna was done in a reliable institute nearby.

h. Bonemarrow aspiration in relevant cases.

i. Barium meal study in appropriate cases.

j. CT scan abdomen.

k. Laprotomy and biopsy in relevant cases.

After informed consent, children were included in the FUO protocol. In the present study the choice of investigations was made from potentially diagnostic clues which are defined as all localising signs, symptoms or abnormalities potentially pointing towards possible diagnosis. The causes of FUO included four categories- infections, malignancies, connective tissue diseases, and undiagnosed cases. FUO was classified as undiagnosed if no evidence of the cause of fever was obtained and if there was complete spontaneous recovery even though the fever had persisted for several weeks or fever resolved during investigation.

DIAGNOSTIC CRITERIA

1. Malaria : either of the following or both

    a. Peripheral smear positive for malarial parasite

    b. QBC positive for malarial parasite.

2. Typhoid fever : any one of the following or both

    a. Blood culture positive for Salmonella typhi.

    b. Blood Widal “O” titer greater than 1:200 dilution positive or four fold rise in titer.

3. URINARY TRACT INFECTION[2]

Method of collection	Colony count	Probability of infection(%)
Suprapubic aspiration	Urinary pathogen in any numbers	99%
Urethral catheterization	10^3 cfu/ml	95%
Midstream clean catch	$\geq 10^5$ cfu/ml	90-95%

Cultures of urine specimens collected from a bag applied to the perineum have unacceptably high false positive rates, and are not recommended. Bag specimens are, however, a useful indicator of the absence of infection if no growth or a very scanty growth of usual urinary pathogens is found .

A urine culture should be repeated in case contamination is suspected, e.g., mixed growth of two or more pathogens, or growth of organisms that normally constitute the periurethral flora (lactobacilli in healthy girls and enterococci in infants and toddlers.). The cultures also repeated in situations where UTI is strongly suspected but colony counts are equivocal.

4. SYSTEMIC LUPUS ERYTHEMATOSUS

American College of Rheumatology 1997 revised diagnostic criteria for systemic lupus erythematosus

The presence of four or more criteria is required for systemic lupus erythematosus classification. All other reasonable diagnoses (eg, infectious syndromes, malignancy) should be excluded.

Criterion	Definition
1. Malar (butterfly) rash	Fixed erythema, flat or raised, over malar eminences and sparing nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as result of unusual reaction to sunlight, determined by history taking or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	**a.** Pleuritis: convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion OR **b.** Pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	**a.** Persistent proteinuria: >0.5 g/day or >3+ if quantification not performed OR **b.** Cellular casts: red cell, hemoglobin, granular, tubular, or mixed

8. Neurologic disorder	**a.** Seizures: in absence of offending drugs or known metabolic derangements (eg, uremia, ketoacidosis, electrolyte imbalance) OR **b.** Psychosis: in absence of offending drugs or known metabolic derangements (eg, uremia, ketoacidosis, electrolyte imbalance)
9. Hematologic disorder	**a.** Hemolytic anemia with reticulocytosis OR **b.** Leukopenia: <4.0 X 10^3/microliter total on two or more occasions OR **c.** Lymphopenia: <1,500/microliter on two or more occasions OR **d.** Thrombocytopenia: <100 X 10^3/microliter in absence of offending drugs
10. Immunologic disorder	**a.** Anti-DNA: antibody to native DNA in abnormal titer OR **b.** Anti-Sm: antibody to Sm nuclear antigen OR **c.** Positive finding of antiphospholipid antibodies based on (1) abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) positive test result for lupus anticoagulant using standard method, or (3) false-positive test result for syphilis for ≥6 mo and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	Abnormal titer of antinuclear antibody by immunofluorescence or equivalent assay at any point and in absence of drug

5. CRITERIA FOR THE CLASSIFICATION OF JUVENILE RHEUMATOID ARTHRITIS[2]

a. Age at onset <16 yrs.

b. Arthritis (swelling or effusion, and presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased heat) in one or more joints

c. Duration of disease 6 wks or longer

d. Onset type defined by type of disease in first 6 months

Polyarthritis: 5 or more inflamed joints

Oligoarthritis: <5 inflamed joints

Systemic: arthritis with characteristic fever

e. Exclusion of other forms of juvenile arthritis

Other rheumatic diseases

Infectious diseases

Childhood malignancies

Nonrheumatic conditions of bones and joints

Miscellaneous conditions

6. KAWASAKI SYNDROME[2]

Fever, daily for more than 5 days, high spiking and intermittent, with four of the five following clinical features:

1. Bulbar conjunctival injection, generally nonpurulent

2. Changes in the oral mucosa, consisting of:

a. Red, fissured lips

b. Redness of the mouth

c. Strawberry tongue

3. Changes in the hands and feet, consisting of:

    a. Redness of the palms and soles

    b. Swelling of the hands and feet

    c. Peripheral desquamation in the subacute stage of illness

4. Rash, erythematous and polymorphous but nonvesicular

    Maculopapular

    Erythema multiforme–like

    Scarlatiniform

5. Cervical lymphadenopathy, greater than 1.5 cm in diameter.

7. TUBERCULOSIS[39]

Any one Criteria

a. AFB positive either in sputum or other body fluids.

b. Histopathological evidence of tuberculosis in biopsied specimen.

c. Mantoux postivity with compatible clinical features, and response to anti tuberculous treatment.

8. LEPTOSPIROSIS[2].

Any one criteria

a. Microscopic agglutination test showing four fold rise in titer in paired sera taken two weeks apart.

b. Microscopic agglutination test showing a titer of 1:100 or greater in two or more specimens in correlation with clinical symptoms and response to treatment.

9. MALIGNANCY

a. Blood picture and bone marrow aspiration show evidence of leukemia.

b. Histopathological evidence of malignancy in biopsy of lymphnode or specific organ.

10. VIRAL HEPATITIS[2]

Icterus with altered liver function with no evidence of other causes of hepatitis and Positive IgM anti-HBcAg in children with Australia antigen(Hbs Ag) positivity.

11. INFECTIVE ENDOCARDITIS[2]

The Duke criteria help in the diagnosis of endocarditis.

1. Major criteria include

(a) Positive blood cultures (two separate cultures for a usual pathogen, two or more for less typical pathogens)

(b) Evidence of endocarditis on echocardiography (intracardiac mass on a valve or other site, regurgitant flow near a prosthesis,

abscess, partial dehiscence of prosthetic valves, or new valve regurgitant flow)

2. Minor criteria include predisposing conditions, fever, embolic-vascular signs, immune complex phenomena (glomerulonephritis, arthritis, rheumatoid factor, Osler nodes, Roth spots), a single positive blood culture or serologic evidence of infection, and echocardiographic signs not meeting the major criteria.

Two major criteria, one major and three minor, or five minor criteria suggest definite endocarditis.

12. BRUCELLOSIS[2] : any one of the following or both

1. Slide agglutination test, a single titer of more than 1:160.

2. Four fold increase in titer taken 2 weeks apart

OBSERVATIONS

182 children in the age group of 1month-12 years were studied.

TABLE - 1

DISTRIBUTION BY AGE AND GENDER

Age (In years)	Total	Male		Female	
	n	n	%	n	%
0-1	13	9	69.2	4	30.8
>1-3	35	24	68.6	11	31.4
>3-6	49	30	61.2	19	38.8
>6-9	41	25	61	16	39
>9-12	44	18	40.9	26	59.1
Total	182	106	58	76	42

* The male to female ratio was 1.3:1.

* Children in the age group of 3-6 years constitute the majority of the study population.

TABLE - 2

CAUSES OF FEVER OF UNKNOWN ORIGIN ACCORDING TO AGE GROUP

Total number of cases with diagnosis-n=152.

Total number cases remain undiagnosed-n=30.

Age group	Infections	Malignancy	Non-infectious inflammatory diseases	Undiagnosed
0-1 (n=13)	9(69.2%)	4(30.7%)	0	0
>1-3(n=35)	6(17.14%)	18(51.4%)	5(14.28%)	6(17.1%)
>3-6(n=49)	22(44.9%)	11(22.4%)	8(16.3%)	8(16.3%)
>6-9(n=41)	21(51.2%)	5(12.1%)	6(14.6%)	9(21.9%)
>9-12(n=44)	0	6(13.6%)	21(47.7%)	7(15.9%)
Total	68 (37.4%)	44 (24.2%)	40 (22%)	30 (16.5%)

* In infancy infections remain the commonest cause of fever of unknown origin, and no case in this age group remain undiagnosed.

* Between 1-3years malignancy (especially acute lymphoblastic leukemia) was the commonest cause.

* Between 3-6 years infections are the commonest cause of fever of unknown origin.

* After 9 years non-infective inflammatory disease dominates causes of FUO.

TABLE - 3

CAUSES OF FEVER OF UNKNOWN ORIGIN

Causes of FUO	n	%
Infections	**68**	**37.4**
Tuberculosis	22	32.4
UTI	12	17.6
Enteric Fever	12	17.6
Brucellosis	6	8.8
Malaria	2	2.9
Hepatitis B	3	4.4
Endocarditis	3	4.4
Leptospirosis	2	2.9
Bone & joint infections*	3	4.4
Other bacterial infections#	3	4.4
Malignancy	**44**	**24.2**
ALL	29	65.9
AML	7	15.9
Hodgkins Lymphoma	4	9.1
Non-Hodgkins Lymphoma	1	2.3
Hisitocytosis	2	4.5
Myelo Dysplastic Syndrome(refractory anemia with excess blast)	1	2.3
Non-infectious Inflammatory disease	**40**	**22**
Juvenile Rheumatoid Arthritis	25	62.5
SLE	10	25.0
Vasculitis	4	2.5
Kawasaki disease	1	10.0
Undiagnosed	**30**	**16.5**
Death	1	3.3

* Two cases of osteomyelitis,one case of mastoiditis

\# Splenic abscess ,liver abscess ,cholangitis.

TABLE - 4

DISTRIBUTION OF INFECTIONS BY AGE GROUP

Diagnosis	Age group (in years)									
	0-1 (n=13)		>1-3 (n=35)		>3-6 (n=49)		>6-9 (n=41)		>9-12 (n=44)	
	n	%	n	%	n	%	n	%	n	%
Tuberculosis	1	7.7	3	8.6	6	12.2	8	19.5	4	9.1
UTI	4	30.8	-	-	3	6.1	3	7.3	2	4.5
Typhoid fever	1	7.7	-	-	5	10.2	5	12.2	1	2.3
Brucellosis	-	-	-	-	5	10.2	1	2.4	-	-
Malaria	-	-	-	-	-	-	1	2.4	1	2.3
Hepatitis B	-	-	-	-	1	2.0	1	2.4	1	2.3
Endocarditis	-	-	1	2.9	-	-	1	2.4	1	2.3
Leprospirosis	-	-	-	-	1	2.0	1	2.4	-	-
Bone + joint infections	2	15.4	-	-	1	2.0	-	-	-	-
Other bacterial infections	1	7.7	1	2.9	-	-	1	2.4	-	-

* In infancy - UTI was the commonest infection in FUO

* Between 1 - 12 years - Tuberculosis was the commonest infection presenting as FUO

TABLE - 5

DISTRIBUTION OF MALIGNANCY BY AGE GROUP

Diagnosis	Age group (in years)									
	0-1 (n=13)		>1-3 (n=35)		>3-6(n=49)		>6-9 (n=41)		>9-12 (n=44)	
	n	%	n	%	n	%	n	%	n	%
ALL	2	15.4	11	31.4	9	18.4	2	4.9	5	11.4
AML	1	7.7	3	8.6	1	2.0	2	4.9	-	-
Hodgkins Lymphoma	-	-	2	5.7	-	-	1	2.4	1	2.3
Non-hodgkins Lymphoma	-	-	-	-	1	2.0	-	-	-	-
Hisitocytosis	-	-	2	5.7	-	-	-	-	-	-
Myelodysplastic Syndrome	1	7.7	-	-	-	-	-	-	-	-

* In all the age groups ALL was the commonest malignancy presenting as FUO.

TABLE - 6

DISTRIBUTION OF NON-INFECTIOUS INFLAMMATORY DISEASES BY AGE GROUP

Diagnosis	Age group (in years)									
	0-1 (n=13)		>1-3 (n=35)		>3-6 (n=49)		>6-9 (n=41)		>9-12 (N=44)	
	n	%	n	%	n	%	n	%	N	%
Juvenile Rheumatoid Arthritis	-	-	3	8.6	4	8.2	4	9.8	14	31.8
SLE	-	-	1	2.9	-	-	2	4.9	7	15.9
Non-specific vasculits	-	-	-	-	4	8.2	-	-	-	-
Kawasaki Diseases	-	-	1	2.9	-	-	-	-	-	-

* In older children between 9 - 12 years, NIID was the commonest cause of FUO

* Among NIID JRA was the commonest cause of FUO in all age groups.

TABLE- 7

DISTRUBUTION OF UNDIAGNOSED FUO BY AGE GROUP

Diagnosis	Age Group (in years)				
	0-1 (n-13)	**>1-3 (n-35)**	**>3-6 (n-49)**	**>6-9 (n-41)**	**>9-12 (n-44)**
RESOLVED	-	6 (17%)	8 (16.4%)	8 (19.6%)	7 (15.9%)
DEATH	-	1(2.9%)	-	-	-

Fever resolved spontaneously in 19 children before results of first line investigations were available and diagnosis could not be made with the first line investigations.

Fever remained undiagnosed in the remaining children even after appropriate investigations were done and these children were discharged as FUO .

TABLE - 8

COMMON CAUSES OF FEVER OF UNKNOWN ORIGIN

CAUSES	n	%
1.Undiagnosed	30	16.5
2.Acute lymphoblastic leukemia	29	16
3.Juvenile rheumatoid arthritis	25	13.7
4.Tuberculosis	22	12.1
5.Urinary tract infections	12	6.6
6. Typhoid fever	12	6.6
7.Systemic lupus erthymatosus	10	5.5
8.Acute myeloid leukemia	7	3.8
9.Brucellosis	6	3.3
10.Hodgkins lymphoma	4	2.2
11.Nonspecific vasculitis	4	2.2
12.Infective endocarditis	3	1.6
13.Bone and joint infections	3	1.6
14.Hepatitis B	3	1.6
15.Leptospirosis	2	1.1
16.Malaria	2	1.1
17.Kawasaki disease	1	0.5
18.Other bacterial infections	3	1.6
19.Other malignancy	4	2.2

Infections (37.4%) were the commonest cause of FUO, followed by Malignancy (24.2%) and NIID (22%). Among individual causes, after undiagnosed group, acute lymphoblastic leukemia, followed by Juvenile rheumatoid arthritis, tuberculosis urinary tract infections, enteric fever, systemic lupus erthymatosus constitute the bulk of the cases.

TABLE - 9

CAUSES OF FEVER OF UNKNOWN ORIGIN BY TIMING OF DIAGNOSIS.

Diagnosis	All pateints with diagnosis (n=152)	Early diagnosis (<7 days) (n=62)	Intermediate diagnosis (7-14 days) (n=64)	Late diagnosis (> 14 days) (n=26)
INFECTIONS	**68(44.7%)**	**26(36.1%)**	**32(50%)**	**10(38.4%)**
Tuberculosis	22	7	12	3
Urinary tract infections	12	5	6	1
Enteric fever	12	5	6	1
Brucellosis	6	1	2	3
Infective endocarditis	3	1	-	2
Hepatitis B	3	1	2	-
Leptospirosis	2	-	2	-
Malaria	2	2	-	-
Bone & joint infections	3	3	-	-
Other bacterial infections	3	1	2	-
MALIGNANCY	**44(28.9%)**	**26(36.1%)**	**18(28.1%)**	**-**
Acute lymphatic leukemia	29	19	10	-
Acute myeloid leukemia	7	5	2	-
Hodgkins lymphoma	4	2	2	-
Non-hodgkins lymphoma	1	-	1	-
Histiocytosis	2	-	2	-
Myelodysplastic syndrome(raeb)	1	-	1	-
NON-INFECTIOUS INFLAMMATORY DISEASES	**40 (26.3%)**	**10 (13.9%)**	**14 (21.8%)**	**16 (61.1%)**
Juvenile rheumatoid arthritis	25	7	6	12
Systemic lupus erythematousus	10	1	7	2
Non-specific vasculitis	4	2	1	1
Kawaski disease	1	-	-	1

Table 9 lists the final diagnosis and the diagnostic categories in the 152 children with diagnosis, subdivided according to the timing of diagnosis.

In the group with late diagnosis, noninfectious inflammatory disease constituted the most prevalent diagnostic category.

In the group with early diagnosis, infection & malignancy were the most common diagnosis.

TABLE - 10

DECISIVE METHOD OF DIAGNOSIS

Diagnostic Method	All patients with diagnosis (n-152)	Early diagnosis (<7 days) (n-62)	Intermediate diagnosis(7-14days) (n-64)	Late diagnosis (>14 days) (n-26)
	n	n	n	n
History and evolution	25 (16.4%)	7 (28%)	6 (24%)	12 (48%)
Culture	14 (9%)	9 (64%)	5 (35%)	-
Infections serology	21 (14%)	3 (14%)	13 (61%)	5 (23.8%)
Standard radiology	2 (1.3%)	2 (100%)	-	-
Abdominal USG	1 (0.6%)	1 (100%)	-	-
ECHO	3 (1.9%)	1 (33%)	-	2 (67%)
CTScan	3 (1.9%)	1 (33%)	2 (67%)	-
Bone marrow aspiration	37 (24%)	24 (64%)	13 (36%)	-
Biopsy	17 (12%)	4 (23%)	13 (76.4%)	-
Others / Combination	20 (19%)	10 (34%)	12 (41%)	7 (24%)

Table 10 gives the decisive method of diagnosis in whom a diagnosis was obtained. Bone marrow aspiration was the most rewarding technique, especially in the groups with early or intermediate diagnosis. Microbiological analysis (culture and serology) also had reasonable diagnostic yield (35%). History and evolution of disease made a significant contribution in late group. Imaging techniques (Radiological, Echo, CT Scan, Usg) although infrequently leading in isolation to definite diagnosis, were often contributory.

TABLE - 11

OUTCOME

A. FINAL DIAGNOSIS

Final diagnosis	All patients with diagnosis (n=62)	Early diagnosis (< 7 days) (n=62)	Intermediate diagnosis (7 - 14 days) (n=64)	Late diagnosis (> 14 days) (n=26)
	n	n	n	n
Infections	68	26 (38%)	32 (47%)	10 (15%)
Malignancy	44	26 (59%)	18 (40.9%)	-
Non infectious inflammatory diseases	40	10 (25%)	14 (35%)	16 (40%)

B. OUTCOME BY AGE GROUPS

Age Group	All patients (n = 182)		Diagnosed (n=152)		Undiagnosed (n=30)		Death (n=9)		Lost to Followup (n=8)	
	n	%	n	%	n	%	n	%	n	%
< 1 year	13	7.1	11	84.6	-	-	2	15.4		
>1 – 3 years	35	19.2	26	74.3	6	17.1	2	5.7	1	2.9
>3 – 6 years	49	26.9	36	73.5	8	16.4	-	-	5	10.2
>6 – 9 years	41	22.5	30	73.2	8	19.5	3	7.3	-	-
>9 – 12 years	44	24.2	33	75.0	7	15.9	2	4.5	2	4.5

C. OUTCOME RELATED TO TIME OF DIAGNOSIS

Outcome	All patients (n = 182)		Early Diagnosis (n = 62)		Intermediate Diagnosis (n = 64)		Late Diagnosis (n = 26)		No Diagnosis (n = 30)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alive	165	90.6%	54	87.0%	58	90.6	24	92.3	29	96.7
Dead	9	4.9	3	4.8	4	6.2	1	3.8	1	3.3
Related to febrile illness	7	3.8	3	4.8	4	6.2	-	-	-	-
Unrelated to febrile illness	2	1.1	-	-	-	-	1	3.8	1	3.3
Lost to followup	8	4.4	5	8.0	2	3.1	1	3.8	-	-

Nine children died during the index admission. In two cases death was unrelated to the febrile illness (died of aspiration). Four deaths occured among malignancy(three cases of acute lymphatic leukemia, one case of histiocytosis).A twelve year female child diagnosed to have splenic abscess died due to rupture, two children diagnosed as systemic lupus erythematosus died of acute renal failure.

While hematological malignancies constitute 24.1% of cases of fever of unknown origin, they were responsible for 4(57.1%) of the 7 fatalities related to the febrile illness.

TABLE - 12

TUBERCULOSIS

Category	n - 22 (%)
1. Abdominal tuberculosis	14 (63%)
a. Intestinal tuberculosis	6 (27%)
b. Peritoneal form	4 (18%)
c. Mesentric adenopathy	4 (18%)
2. Endobronchial tuberculosis	2 (9%)
3. Tuberculosis lymphadenopathy	2 (9%)
4. Pleural tuberculosis	2 (9%)
5. Meningeal tuberculosis	1 (4.5%)
6. Disseminated tuberculosis	1 (4.5%)

* Among 22 children,12(55%) were male and 10(45%) were female.

* Commonest age group was between 6-9 years.

* Contact history was positive only in 5(27%).

* Mantoux positivity was as high as 18(81%)

* BCG scar was seen in 14 children.

* There was predominance of non-specific symptoms like anorexia, weight loss and low grade intermittent fever.

* Barium meal series helped in diagnosis in all children with intestinal tuberculosis. Findings in barium meal series were pulled up caecum, malabsorbtion pattern, hypersegmentation or thickened mucosal folds.

* Laprotomy with biopsy was needed to confirm tuberculosis in children with ileocecal tuberculosis and adenopathy form.

* In 2 cases endobronchial tuberculosis was diagnosed by flexible fibrooptic bronchoscopy.

* Of 4 cases of peritoneal tuberculosis, AFB was positive in one case, ADA levels helped in diagnosis in one. Remaning were diagnosed with exudative ascites, mantoux positivity and response to antituberculosis therapy.

* Two children presented with generalised lymphadenopathy and anemia diagnosed by lymph node biopsy.

* Among 22 children, malnutrition was present in 90%,and hypoalbuminemia in 45% of cases.

TYPHIOD FEVER

* Commonest age group was between 3-9years.

* Salmonella typhi was grown in culture in 2(16%)

* 9(75%) children showed “o” agglutinin titre of 200 and above, in 3(25%) children there was four fold rise in titers one week apart.

* There was no characteristic type of fever, continuous high grade fever occurred in 6(50%).

* GIT symptoms were more common in typhoid fever, diarrhoea was more common than constipation.

* In 4(33%) respiratory symptoms was predominant presenting feature, nonproductive cough

* 3(25%) children presented like acute encephalopathy.

* Thrombocytopenia was present in 6(50%) cases

* Though elevated liver enzymes was present in 8(66%), hepatitis like presenting feature observed in only one.

URINARY TRACT INFECTIONS

TABLE - 13

ETIOLOGIC AGENTS

Organisms	n(%)
1.E.coli	6(50%)
2.klebsiella	4(33%)
3.pseudomonas	1(8%)
4.proteus	1(8%)

* In infancy there was predominance of UTI in male children as compared to female children ratio being 3:1.

* In infancy UTI was the most common cause of FUO

* There was predominance of non-specific signs like vomiting, loose stools & lethargy.

* Vesicoureteral reflex was observed in two children. Phimosis was seen in one.

* Out of 12 culture positive UTI cases, 4 were observed to have normal routine urine analysis.

* Microcytic hypochromic anemia was seen in three children, and normochromic normocytic anemia in five children.

BRUCELLOSIS

TABLE - 14

ETIOLOGICAL AGENTS

Species	**n - 6**
B.Melitensis	4 (66%)
B. Abortus	2 (33%)

* The triad of fever, arthralgia / arthritis, and hepatosplenomegaly was observed in all six cases.

* Nonspecific signs dominated the clinical features in all the six cases

* All six cases were diagnosed most probably as brucellosis with SAT >1 :160, along with negative tests for other diseases.

ACUTE LEUKEMIA

TABLE - 15

SUB TYPES OF ALL CASES

Types	No of Cases n=29
L1	16 (80%)
L2	3 (7.8%)
L3	1 (5%)

* Among acute leukemia, acute lymphoblastic leukemia constituted twenty cases, acute myeloid leukemia in seven cases.

* Males constitute 61% cases, females 39%

* Fever, anemia and bone tenderness were the principal presenting symptoms in pediatric age group.

* In the age group between one to three years, acute leukemias were the commonest cause of fever of unknown origin.

* Total count was normal in 9(25%) children with leukemia. Among seven children who present with total count in leucopenic range five children (13.8%) did not show blast cells in the peripheral smear.

* Death in two children was due to intra cranial haemorrhage, in one case due to profound sepsis.

JUVENILE RHEUMATOID ARTHRITIS

TABLE - 16

SUBGROUPS OF JRA

Subgroups	n-25
1. Systemic onset	19(76%)
2. Polyarticular	6(24%)
a. Rheumatoid factor positive	5(83%)
b. Rheumatoid factor negative	1(7%)

* Commonest joint involved was knee 21(84%), followed by ankle 19(76%) and wrist 12(48%).

* Symmetrical joint involvement in 16(64%) and asymmetrical joint involvement in 9(36%) children.

* Maculopapular rash which characteristically occurs in systemic onset was only observed in nine cases (36%).

* Other causes of arthritis were ruled out before making a diagnosis of juvenile rheumatoid arthritis, history and evolution of the disease was the decisive method of diagnosis.

* No cases of pauciarticular onset of JRA presented as FUO.

SYSTEMIC LUPUS ERYTHEMATOSUS

* Out of 10 children,7(70%) were between 9-12 years, youngest age observed was 3 years

* Female children constitute 8(80%),male children 2(20%).

* Though skin manifestation was the predominant clinical feature, typical skin manifestation like malar rash was present in only 3(30%)

* Small joints of the hands were the commonest joint to be involved in children presenting with polyarthritis, followed by knee joint, and ankle joint.

* In two children predominant presenting clinical feature was seizures.

* ESR was elevated in all children with mean value more than 50.

* Commonest hematological manifestation observed was normochromic, normocytic anemia in 8(80%), followed by thrombocytopenia in 5(50%). Total count was normal in 6(60%). In one child predominant presenting feature was anemia with hemolysis (auto-immune hemolytic anemia)

* Ds-dna was positive in only in 3(30%) cases.

* Death was observed in two children, due to acute renal failure and its complications.

OTHER INFECTIONS CAUSING FUO

* Infective endocarditis : three cases (2/f, 7/f, 9/f).

    * All the three were culture negative, a diagnosis of infective endocarditis was made with Duke criteria.

* Malaria: was positive in two cases(8/12m,2f). Two cases were initially smear negative, and on repeated smear examination found to be positive, both were positive to Plasmodium falciparum.

*. Leptospirosis: two cases (3/m, 8/f) diagnosed with help of rising MAT titer.

OSTEOARTICULAR INFECTIONS

    * Osteomyelitis right femur: two children (9/12m,11/12m) x-ray showed positive muscle sign.

    * Mastoditis : 6/F, CT scan of temporal bone - showed destruction of temporal bone.

* Hepatitis b : three children(2/f,4/m,5/m). The 2/f, presented with FUO without localising signs was found to be positive for IgM Hbc antibodies.

* Cholangitis 1/m presented with FUO. Ultrasonography suggested features of cholangitis. CT scan showed dilated biliary duct suggestive of biliary obstruction and infection.

* Splenic abscess:5/f,had prolonged fever with out any localising signs. Initial screening tests including abdominal ultrasonography, showed hypoechoic area. CT scan showed splenic abscess.

* Liver abscess : 2/f :presented with fever, anemia and hepatomegaly. Ultrasonography showed liver abscess.

* **NONINFECTIOUS INFLAMMATORY DISEASES**

  * Kawasaki disease: 3 / m, presented with fever, maculopapular rash, bluish discoloration of both lower limbs and with cervical lymphadenopathy. Initial screening investigation revealed leucocytosis, anemia, thrombocytosis, with prolonged PT/aPTT. Based on these findings kawasaki disease was suspected and echo was done which revealed, main coronary artery ectasia. Subsequently child developed other manifestations of kawasaki disease, and child also had raynauds syndrome.

  * 4 children (8/F, 6/F, 10/F and 11/M) : Two children presented with fever and myalgia followed by appearance of palpable purpura over the extremities. One child presented with high grade fever, elevated ESR and multiple erythematous plaques and nodules over lower limbs. The other child had fever followed by appearance of urticarial lesions. In all four the diagnosis was made by skin biopsy which revealed vasculitis.

* **MALIGNANCY**

* Hodgkins lymphoma : Four children(8/m,3/m.6/m,4/m). Three year old male child presented with fever, generalised lymphadenopathy and failure to thrive. Lymph node biopsy revealed lymphocyte predominant Hodgkins disease.4/m child presented with anemia and petechiae. Biopsy revealed mixed cellularity type with bone marrow infiltration, and the other two cases were diagnosed as nodular sclerosis by lymphnode biopsy. Non-hodgkins lymphoma was diagnosed in a 5/m by biopsy of the lymph node which revealed lymphoblastic lymphoma.

* Histiocytosis : two children (21/2m, 3/f), 21/2m child presented with fever and seborrheic dermatitis like scalp lesion. Biopsy and immunocytochemistry showed cd1a positivity and diagnosis of Langerhan cell histiocytosis was made.3/f child presented with fever, convulsions, hepatosplenomegaly, anemia, and thrombocytopenia. Bone marrow examination revealed phagocytic macrophages and a diagnosis of Infection - associated hemophagocytic syndrome was made.

* Myelo dysplastic syndrome.1/m child presented with fever bonepain, anemia and thrombocytopenia. Bone marrow aspiration revealed blasts<15% subclassified as refractory anemia with excess blast.

DISCUSSION

The etiological profile, of fever of unknown origin in children between 1 month and 12 years, admitted in Institute of child health, Egmore was studied. The study population included 182 children .

Despite advances in diagnostic tools, FUO remains a challenging clinical problem. The diagnostic spectrum of fever of unknown origin has changed since its original definition over 30 years ago .In contrast, many diseases that previously caused FUO no longer attain this status because of dramatic improvements in diagnostic imaging in the last several decades. The three major categories of causes of FUO--infections, noninfectious inflammatory diseases, and malignancy--remain unchanged from the classic studies of Petersdorf and Beeson. However, the types of diseases that were noted in these categories have changed over the last 50 years. Tuberculosis, although less common now than half a century ago, must always be considered as a cause of FUO. Extrapulmonary tuberculosis are the most likely forms to present as FUO. Abscesses are diminishing in importance, because they are discovered earlier in the workup for fever, before the definition of FUO is met. Rheumatic fever has all but disappeared as a cause of FUO. Several imaging procedures have proved useful in defining the cause of fever early in a workup; in many instances, they allow a diagnosis to be established before the actual definition of FUO is met. Abdominal ultrasound is a low-cost test that can detect abnormalities of the hepatobiliary and genitourinary systems as well as

fluid collections elsewhere in the abdomen. FUO is more likely to be encountered in patients who have culture-negative endocarditis due to inappropriate prior antibiotic use or difficult-to-culture organisms. In most cases, the cause of FUO is a familiar disease with an uncommon presentation, rather than a rare disorder. The causes of FUO differ among various patient groups.

Although the incidence of fever of unknown origin in children may change, most investigators have found that infections [8-23] were the predominant cause, followed by malignancy and connective tissue disorder.

Comparison of present study with FUO case series from various hospitals, which includes atleast four studies from India[17, 19, 22, 24] revealed that apart from rise in malignancy cases, an increase in the noninfectious inflammatory disease category was also noted.

Among 182 cases, infections constitute 68(37.4%),malignancy 44(24.2%), noninfectious inflammatory diseases 40(22%), and undiagnosed in 30(16.5%).

In infancy infections remain as the commonest cause of fever of unknown origin, and no case in this age group remained undiagnosed. Between 1-3years malignancy (especially acute lymphoblastic leukemia) was the commonest cause. Between 3-9 years infections remain the commonest cause of fever of unknown origin. After 9 years, non-infectious inflammatory disease dominates causes of FUO. Pizzo[11] et al., also concluded that in children less

than 6 years were more likely to have an infectious etiology while 80% of collagen inflammatory disease occurred in the group older than 6 years.

Non invasive methods helped in arriving at decisive diagnosis in 102 (67.1%) cases, invasive method helped in diagnosis in 50 cases (32.8%). Kazanjian[16] PH et al., also pointed out that non invasive approach established the diagnosis in many instances.

In the present study history and evolution of the disease made significant contribution in diagnosis of FUO. Chantada[18] et al., also concluded that history and physical examination lead to final diagnosis in 81% of cases.

The incidence of FUO of indeterminate cause ranged from 4.7% to 25% in previous series [8-22], in the present study it was 16.6%. The prognosis of children in present study with undiagnosed fever was relatively good, in agreement with the other case series.

INFECTIONS

Infections remain the most common cause of FUO, constituting about a third of cases in various case series over the last five decades. Although in earlier studies in western literature infections were predominant, now connective tissue[9,10,11,38] disorders are emerging as an important cause of FUO. In present study infections constituted 37.4% of FUO cases, confirming earlier trends that infections were the commonest cause of fever of unknown origin. The increased incidence of infection found in our study, may be attributed to the fact that most of the children were of low socio-economic status, living in crowded areas, and half of them were from slums and hence more prone for infections.

TUBERCULOSIS

Tuberculosis is endemic in this part of our country .The diagnosis was delayed despite a high index of suspicion because of normal chest x-ray, negative skin test, inconclusive imaging and histopathological examination

Studies from, Haq[21] Sa et al., from Dhaka in 1996, Handa[19] r et al 1996 from northern India, Sharma[17] BK et al 1992 from northern India, Kejariwal[24] D et al 2002 from eastern India, showed that among infections ,tuberculosis was the commonest cause of FUO. Study done by Sarala Rajaji et al [22] chennai showed that infections were the common cause of FUO. Among infections enteric fever and tuberculosis lead the category.

In the present study also tuberculosis was the predominant cause under infections. Haq SA et al [21] in their study of 212 children with prolonged fever noted tuberculosis in 52 children (24.55%) as the cause. Pleura was the commonest site, followed by lymphnode and abdomen in their study. In the present study among extrapulmonary tuberculosis, tuberculosis of abdomen was the commonest. Barium meal series helped in diagnosis in all children with intestinal tuberculosis. Findings in barium meal series were pulled up caecum, malabsorption pattern, hypersegmentation or thickened mucosal folds.

Laprotomy with biopsy was needed to confirm tuberculosis in children with ileocecal tuberculosis and adenopathy form.

TYPHOID FEVER

Even though better sanitary facilities are available in our part of country typhoid fever is still a common cause of FUO. In western countries typhoid fever as a cause of FUO is rarity.

Sarala Rajaji[22] et al in their study of 75 children with FUO, found that typhoid fever was the most common cause in 20 (26.6%) patients with FUO. Mouaket AE et al[26] studied 221 children with FUO in Kuwait between 1985-1987, and found out that infections were found in 78%of causes of FUO. Among infections brucellosis constituted 38%, followed by typhoid fever. Gamboa Marrufo[14] JD et al., also concluded that typhoid fever was the commonest cause of FUO in children.

In the present study typhoid fever constitutes 12(6.6%) cases of FUO.

Biswal et al[27] studied 394 cases admitted in between in 1985 and 1992. He noted that cough, respiratory signs and tympanitic note of the abdomen were commonly associated with typhoid fever, He also noted hepatomegaly in 61.9%, encephalopathy in 14.4%,gastrointestinal bleed in 10%, and hepatitis in 6.4% of the patients. Blood culture was positive in 46% of the patients and bone marrow culture was positive in 2% of patients. Jagdish et al [28] in 1994 studied 31 children with typhoid fever and found that hepatomegaly was present in 51.6% and jaundice in 16%.

In the present study blood culture was positive only in 2(16%), the low positivity may be due to antibiotic taken by the patient before admission and most patients were admitted after one week.

URINARY TRACT INFECTIONS

UTI remains one of the common causes of FUO in young infants. Buy H, et al[29]studied 508 infants and children who had fever of uncertain causes or were seriously ill and analysed samples obtained by suprapubic aspiration in infants and children from July 1991 to June 1992. UTI was found in 46(9.16%) children. Among them pyuria was absent in half of the children with bacteriuria. Gamboa Marrufo et al[14] in their study of 180 children with prolonged fever, found out typhoid fever and UTI as common causes of infection.

Matthai J, Ramaswamy M[30]made a prospective in urinalysis 376 children, between 6 months and 5 years of age, with suspected urinary tract infection, 4 parameters of a routine urine examination were correlated with culture reports. In diagnosing urinary infection, the sensitivity and specificity of proteinuria was 79 and 80% respectively, that of bacteriuria 78 and 96% and that of pyuria > 10 wbc/hpf 80 and 82% respectively. 61% among the culture positive groups had all these three parameter present, as against only 0.5% in the culture negative group ($P < 0.001$). All these 3 parameters were absent in 70% in the culture negative group, as against 8% in the culture positive group ($P < 0.001$). Bacteriuria in association with either proteinuria or Pyuria > 10 Wbc/hpf had 98% specificity is diagnosis. In diagnosis of UTI, Pyuria > 10 Wbc/hpf was significantly more specific than the conventional > 5 wbc/hpf. Isolated proteinuria, isolated pyuria, isolated bacteriuria and microscopic haematuria were not features of urinary tract infection in children.

In the present study UTI observed in 12(6.6%) cases of FUO. In the present study UTI was the commonest cause of FUO in infancy. Among 12 culture positive children, proteinuria was present in 6(50%) and pyuria was absent in 4(33%) cases.

BRUCELLOSIS

Handa R et al[31] prospectively studied 121 cases of fever of unknown origin FUO and 50 occupationally exposed individuals. Four patients with FUO had acute brucellosis (3.3%) while 8 (6.6%) had serological evidence of previous brucella infection. Seven of the 50 (14%) asymptomatic, at risk individuals screened were seropositive for brucella. He suggested that persistence of the animal reservoir of infection, low physician awareness, poor availability of diagnostic facilities, and the non existence of regional data bases contribute towards the perpetuation of this zoonosis in India, while it has been eradicated from most developed countries.

Kadri et al[32], over a period of 5 years from 1992 to 1997 subjected total of 3,532 patients of FUO to Wright's tube agglutination test for brucellosis. Of the 3,532 patients tested, 28 (0.8%) were seropositive for brucellosis. Males outnumbered females by a ratio of 3:1.

In the present study Brucellosis was observed in six (3.3%) cases of FUO. There was no well defined literature regarding brucellosis among children and it remains elusive as a cause of FUO in children. The commonest mode of spread in children was through drinking of unpasteurized milk. Brucella melitensis was positive in four cases, and brucella abortus in two cases.

ENDOCARDITIS

Most cases of typical staphylococcal or streptococcal endocarditis are easily diagnosed as a cause acute fever. FUO is more likely to be encountered in patients who have culture-negative endocarditis due to prior antibiotic use or difficult-to-culture organisms. The recently proposed Duke criteria were confirmed to be more sensitive for diagnosis of infective endocarditis. The specificity of the Duke criteria[33] was calculated to be 0.99 (95% confidence interval, 0.97-1) and we should have high degree of suspicion to diagnose infective endocarditis .

In the present study three cases of infective endocarditis masquerading as fever of unknown origin were noted. In two cases of previously well children without a focus, vegetation involving tricuspid valve were found. The suggests that high degree of suspicion should be there to diagnose infective endocarditis. In all the three cases cultures were negative even when three blood samples were taken appropriately, this phenomenon might be due to prior administration of antibiotics . All the three cases were diagnosed with the help of Duke criteria. In one case there was an underlying undiagnosed ventricular septal defect which had predisposed it.

MALARIA

Sarala Rajajee[22] et al in their study of 75 children has found malaria as the cause of fever of unknown origin in eleven children. In the present study all

the children were screened with peripheral smear for malarial parasite before they are included in the study. In the present study though the initial screening test are negative, subsequent peripheral smear examination yielded a positive result. This suggest that repeated peripheral smear examination were needed.

Plasmodium falciparum was the organism responsible for the two cases. These two cases had received chloroquine as out patient. This implies that the two cases might be chloroquine resistant.

MALIGNANCY

In the present study malignancy (24.2%) follows infection (37.4%) as a cause of fever of unknown origin. Cruz Guerrero G[12] et al., and Haq[21] et al., also concluded that after infections, malignancy (especially leukemia) forms an important group. Among malignancy especially acute lymphoblastic leukemia was observed to be the commonest cause of FUO between 1-3 years. Sharma BK et al[17] also observed that lympho reticular malignancies constitutes 21.32% of FUO cases.

Fever, anemia and bone tenderness was present in most of the cases of acute leukemia. Total count is normal in 9(25%) children with leukemia. Among seven children who presented with total count in leucopenic range five children did not show blast cells in peripheral smear. Bone marrow aspiration cytology was the decisive investigation in acute leukemia.

NON INFECTIOUS INFLAMMATORY DISEASES

In the present study after infections and malignancy, NIID (22%) was the commonest of FUO. Steven Vanderschueren[38] et al., also concluded that in his study NIID category has gradually replaced the infectious category as the largest.

Larkin JG[34] et al., studied FUO in a prospective study and concluded that Still's disease, a recently recognised syndrome, is an important and often unrecognised cause of fever of unknown origin. A knowledge of the clinical features of this disease may save patients with undiagnosed fever from prolonged and invasive investigations.

Lafaix C[35] et al., made prospective study in 70 children with FUO, in which infections were the most frequent cause (43 cases). Collagen vascular disorders then followed with 10 cases, the diagnosis of which were made by immunology and histology.

A study published in 1990, was done by Porkodi et al[36]., on the clinical profile of juvenile rheumatoid arthritis. It was an analysis of 100 cases of JRA from south India which revealed a male preponderance(62%),a lower incidence of the systemic onset variety (10%) and an equal incidence of systemic feature when compared with west. Knees and ankles were the joints commonly involved. The incidence of elevated ESR and C reactive protein, with haemoglobin levels below 10g/dl was highest in the systemic onset variety.

Among NIID, Juvenile rheumatoid arthritis was the commonest cause of FUO. Chantada et al.,[18] and Chien ch et al.,[20] also concluded that JRA was the most common collagen - vascular disorder.

In the present study out of 25 cases of juvenile rheumatoid arthritis males out numbered the female in the ratio of 1.27:1 a similar observation has been made by Porkodi et al[36] . In older children non infectious inflammatory diseases was observed to be the commonest cause of FUO. History and evolution forms the main decisive method of diagnosis, as all other investigation were negative in JRA, except for raised inflammatory markers.

Based on American College of Rheumatology 1997 revised diagnostic criteria for systemic lupus erythematosus, ten cases of systemic lupus erthymatosus were diagnosed.

Though skin manifestation was the predominant clinical feature, typical skin manifestation like malar rash was present in only 3(30%) cases. FUO occurring in older children with raised inflammatory markers should arose high degree of suspicion of connective tissue disorder.

CONCLUSION

* A total of 182 children between 1 month-12 years with fever of unknown origin have been studied. Out of these, 106 were male and 76 were female.

* Children in the age group of 3-6 years constitute the majority of the study population 26.9%.

* Infections were the most common cause of FUO constituting 37.4%.

* Among infections tuberculosis was the commonest one causing 12% of FUO. Typhoid (6.6%) and UTI (6.6%) were the next common infections.

* The extrapulmonary tuberculosis was the commonest form tuberculosis observed. Of these extrapulmonary forms, abdominal tuberculosis was most commonly observed.

* Brucellosis was observed as cause of FUO in six cases. The triad of fever, arthralgia / arthritis, and hepatosplenomegaly was observed in all six cases.

* All the three culture negative infective endocarditis cases were diagnosed with the help of duke criteria.

* Malignancy was the second most common cause of FUO occurring in 24.2%. In this group, acute lymphoblastic leukemia (16%) was most commonly observed as a cause FUO, followed by acute myeloid leukemia (3.8%) and Hodgkins lymphoma (2.2%).

* Non infectious inflammatory disorders were the next common cause of FUO, occurring in 22%. Of these Juvenile Rheumatoid arthritis (13.7%) was the commonest, followed by SLE (5.5%) and non - specific vasculitis (2.2%).

* Non invasive methods helped in arriving at decisive diagnosis in 102 (67.1%) cases, invasive method helped in diagnosis in 50 cases (32.8%).

* The diagnostic workup of FUO remains complex; however, considerable evidence exists to guide empiric testing. The diagnostic workup should begin with a thorough history review and physical examination. Routine noninvasive investigations, are recommended in all patients prior to identifying a patient as having FUO.

COMPARISON OF THE DIAGNOSTIC CATEGORIES IN MAJOR SERIES OF FUO

Diagnostic categories	Petersdorf and Beeson[8] n-100	Brewis[25] n-165	Mcclung[10] n-99	Kejariwal D,[24] n-100	Handa R[19] n-122	Barboda [13] n-133	Sarala rajajee[22] n-75	Sharma BK[17] n-150	Present study n-182
Infections	39.6%	38%	28%	53%	43. %	39.4%	78.1%	50%	37.4%
Neoplasms	20.9%	20%	11%	17%	8..3 %	25.0%	9.3%	21.32%	24.2%
NIID	18.7%	5%	14%	11%	15.7 %	19.2%	9.3%	8.67%	22%
Miscellaneous	20.9%	11%	16%	5%	14%	16.3%	2.7%	6.67%	-
Undiagnosed	1.0%	26%	31%	14%	19%	21.8%	-	14%	16.5%

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ANNEXURE

"PROFORMA FOR ETILOGICAL PROFILE OF FEVER OF UNKNOWN ORGIN IN CHILDREN BETWEEN 1 MONTH AND 12 YEARS ADMITTED IN AN URBAN REFERRAL CENTRE CHENNAI".

Name	Age	Sex
Informant	S.No.	
Address	Percapita Income	
IP.No.	DOA	DOD

HISTORY

Fever:	Duration Character:	Chills/Rigor:
Cough:	Expectoration:	Sputum Nature
Haemoptysis	Breathlessness	
Diarrhea/Dysentery	Constipation	Anorexia
Burning Micturition	Oliguria	Haematuria
Pedal Edema	Puffiness of face	Jaundice
Bleeding Tendency	Abdominal pain	Headache
Vomiting	Convulsion	Altered Sensorium
Ear Discharge	Sore Throat	Skin Lesion
Joint Pain	Joint Swelling	PICA
H/O Contact with PT	Exposure to animals	Drugs

GENERAL EXAMINATION

1. Conscious ☐	2. Oriented ☐	3. Tacypnoeic ☐
4. Dyspnoeic ☐	5. Febrile ☐	6. Toxic ☐
7. Pallor ☐	8. Anemic ☐	9. Tongue Coating ☐
10. Cyanosis ☐	11. Jaundice ☐	12. Clubbing ☐
13. Lymphadenopathy ☐	14. Pedal Edema ☐	15. Urticarial Rashes ☐
16. Purpura ☐	17. Hydration ☐	18. Dental Examination ☐
19. BCG SCAR ☐	20. Others	

VITAL SINGS

a. Pulse 1. Rate 2. Rhythm 3. Volume 4. Character 5. Peripheral Pulses

b. Blood Pressure: Normal Hypotension Hypertension

c. Respiration Normal Tachypnoea

ANTHROPOMETRY

a. Height
b. Weight
c. Head Circumference
d. Chest Circumference

SYSTEMIC EXAMINATION

a. Abdomen Contour i. Distended
ii. Scaphoid

Movement Rigidity Tenderness

Liver Spleen Other Masses

Bowel Sounds Rub

b. CVS: S1 S2 S3 Murmurs

c. RS: (a) Breath Sounds: Right Left

Vesicular

Bronchial

(b) Additional Sounds:

a. Rales

b. Rhonchi

c. Rub

d. CNS:

Sensorium Normal Delirious Drowsy Stuporous

Signs of meningeal Irritation

Cerebellar Signs:

Fundus

INVESTIGATIONS:

1.HEMOGRAM : TC DC HB ESR PLATELET COUNT

SMEAR FOR MP QBC PERIPHERAL SMEAR.

2. URINE : ALBUMIN SUGAR DEPOSITS

3. MOTION EXAMINATION

4. BLOOD UREA SUGAR, SERUM CREATININE ,ELECTROLYTES,LFT

5. SERUM URIC ACID

6. BLOOD CULTURE:

	EC	NEC
	1	1
	2	
	3	2

7. URINE CULTURE AND SENSITIVITY

	1.	2.	3.

8.USG

9. LEPTOSPIROSIS: MAT

10. BRUCELLA AGGLUTINATION TITRE

11.BLOOD WIDAL: No of Days after on set of fever

1.

2.

12. ELISA FOR HIV 1 & 2

13. X RAY CHEST

TEST IN RELAVENT CASES

1. SPUTUM OR RGJ: AFB GRAM'S STAIN

2.HBSAG

3.CSF ANALYSIS

4.BMA/BM BIOPSY

5.CT SCAN/MRI

6.ASO/ANA

7.FUNGAL CULTURE

8.X-RAY MASTOID/SINUS

9. OTHERS

OUTCOME :