

**FEVER OF
UNKNOWN
ORIGIN**
**Pinpointing the
Culprit**

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Pediatric Infectious Disease

Definition

Presence of fever for 8 or more days in a child for whom a careful and thorough history and preliminary laboratory data fail to reveal a probable cause of fever

(Pediatric Feigin, et al. Textbook of Infectious Disease.5th edition)

FUO in pediatrics is more likely an unusual presentation of a common disorder than by a common manifestation of a rare disorder

Causes of FUO

- Infectious diseases
- Connective tissue diseases
- Neoplasms
- Undetermined

Diagnoses in Published Series of Children with Fever of Unknown Origin

	Brewis (1965) ⁶	Dechovitz & Moffet (1968) ⁹	McClung (1972) ⁸	Pizzo et al. (1975) ⁷	Feigin & Shearer (1976) ¹⁰	Lohr & Hendley (1977) ¹¹	Jacobs & Schutz (1998) ¹²
STUDY CRITERIA							
Daily temperature > 38.0°C	5-7	2 weeks	3 weeks	2 weeks	2 weeks	5 weeks	2 weeks
Inpatient evaluation	No	No	Yes, 1 week	No	Yes, 1 week	Yes, 1 week	No
Total cases	165	8	99	100	20	54	146
DIAGNOSIS							
Infection	63 (38%)	2 (25%)	29 (28%)	52 (52%)	7 (35%)	18 (33%)	64 (44%)
Respiratory tract ^a	54	0	14	31	1	2	0
Other	9	2	15	21	6	16	64
Collagen disease	9 (5%)	6 (75%)	11 (11%)	20 (20%)	3 (15%)	8 (15%)	9 (6%)
Inflammatory bowel disease	0	0	3 (3%)	0	1 (5%)	3 (6%)	2 (1%)
Malignancy	3 (2%)	0	8 (8%)	6 (6%)	1 (5%)	7 (13%)	4 (3%)
Miscellaneous	18 (11%)	0	16 (16%)	10 (10%)	2 (10%)	8 (15%)	5 (3%)
No diagnosis	9 (5%)	0	11 (11%)	12 (12%)	6 (30%)	10 (19%)	62 (42%)
OUTCOME							
Resolved during investigation	35 (21%)	0	21 (20%)	-	-	-	62 (42%)
Death(s)	1	1	1	9	2	9	0

^aUpper and lower respiratory tract infections.

Infectious Causes of Fever of Unknown Origin (FUO) in 160 Children in FUO Series

Percent of Cases in Compiled Series^a

Case Reports	< 1%	1-5%	6-10%	11-15%	6-20%
Intra-abdominal/ retroperitoneal abscess	Malaria	Bartonellosis	Tonsillopharyngitis/ peritonsillar abscess	Systemic viral syndrome (not specified)	Infectious mononucleosis (EBV and CMV)
Visceral abscess	Rocky Mountain spotted fever	Otitis media/sinusitis	Lower respiratory tract infection	Urinary tract infection	
Hepatitis	Cystic fibrosis	Tuberculosis			
Odontogenic infection	Brucellosis	Bacterial meningitis/ parameningeal abscess			
Nontuberculous mycobacteria	Blastomycosis	Endocarditis			
Q fever	HSV generalized	Streptococcosis			
Syphilis		Enteric infection			
Tickborne typhus		Tularemia			
Leptospirosis		Ehrlichiosis			
Chronic meningococemia					
Histoplasmosis					
<i>Toxocara canis</i> and <i>T. cati</i>					
Inflammatory pseudotumors					

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus.

^aSeries data collated from references 6-12.

Prolonged Fever in a Pediatric Setting(Firmalo et al.Phil J Ped,1983)

- Childrens Medical Center
- January1,1977 to December 31,1981
- 256 cases
- 90% of infectious origin
- Most common were Typhoid,Primary Tuberculosis,Urinary tract infection

Outcome of Prolonged Fever in Filipino Children: A Review of Thirty Four Cases, (Cosca.Phil J of Ped ,1985)

- UERMMC
- 1977-1982
- Infectious (50 %)
- Malignancy (26 %)
- Collagen Disease (6 %)
- Most common were Typhoid, Malaria, and Extrapulmonary tuberculosis

FUO at the UST (Dy,et al.Phil. J of Micro and Inf Diseases,1992)

- UERMMC
- 1977-1982
- Infectious (50 %)
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- Most common were Typhoid, Malaria, and Extrapulmonary tuberculosis

FUO in Pediatric Patients: a 13 Year Review at PCMC (M.Velarde,J De Castro,RB Soriano,Phil J Ped 1995)

- 59 pediatric patients
- Age range 9 months – 18 years
- October 1,1980- October 31,1993

FINAL DIAGNOSIS OF 59 PATIENTS WITH FUO

Disease category	No. of patients	(%)
Infection	32	54
Malignancy	10	17
Oncology	6	
Hematology	4	
Connective Tissue Disease	8	13.5
Histiocytosis X	4	7
Undetermined	5	8.5
Total	59	100

DISEASE CATEGORY

Disease category	Number	(%)
I. INFECTION	39*	
A. Septicemia	11	28
B. Typhoid fever	7	18
C. Extrapulmonary tuberculosis	7	18
C.1 TB meningitis	3	
C.2 Hepatobiliary TB	1	
C.3 TB of the liver	1	
C.4 TB peritonitis	1	
C.5 Tuberculoma of the brain	1	
D. Malaria	2	
E. Liver abscess	2	
F. Brain abscess	2	
G. Chronic mastoiditis	2	
H. Ineffective endocraditis	2	
I. Amoebiasis, intestinal	2	
J. Hepatitis	2	
J.1 Acute viral hepatitis		
J.2 Fulminant hepatitis		
II. MALIGNANCY	10	
A. Lymphoma	5	50
A.1 Hodgkins lymphoma	3	
A.2 Non hodgkins lymphoma	1	
A.3 Lymphosarcoma	1	
B. Leukemia	4	40
B.1 Acute myelogenous	2	
B.2 Acute lymphocytic	1	
B.3 Preleukemic syndrome	1	
III. CONNECTIVE TISSUE DISEASE	8	
A. Juvenile rheumatoid arthritis	6	75
B. Systemic lupus erythematosus	1	25
C. Rheumatic fever	1	25
IV. Histiocytosis	4	100
V. Underdetermined	5	

* 7 patients had 2 diagnose:

CLINICAL SIGNS AND SYMPTOMS OF FUO PATIENTS

Signs	Number	%
Lymphadenopathy	35	59
Hepatomegaly	21	35
Pallor	12	20
Arthralgia	11	18
Highly colored urine	6	10
Icterisia	3	10
Ascites	2	3
Fusiform fingers	2	3
Nuchal rigidity	2	3
Conjunctival injection	1	1.6
Fever	59	100
Vomiting/poor appetite/cough	12	20
Arthritis	9	15
LBM	7	12
Chills/headache/weight loss/abdominal enlargement	6	10
Colds	4	7
RUQ pain/dyspnea/dysuria/irritability	3	5
myalgia/seizures	2	3
Others: epistaxis/constipation/chest pain hematemesis/dizziness/nausea	1	1.6

Diagnostic Approach

Hospitalize

Advantages

Observe

Repeat history and physical
examination

Analyze available data

Follow-up every potential lead

**First and Most Important
Step**

A COMPLETE ,DETAILED HISTORY AND PHYSICAL EXAMINATION

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HISTORY

- Contact with infected or otherwise ill person



Female *Aedes aegypti*
WHO/TDR/Stammers

History

- History of travel (extend back to birth)
- Contact with persons who have visited distant countries

Possibility that rocks,soils,artifacts from geographically distant regions have been brought to the home

History

- Prophylactic immunizations
- Malarial prophylaxis

History

- If precautions were taken against ingestion of contaminated food or water
- Eating of game meat, raw meat or shellfish
- History of pica

History

- Medications , topical agents.non-prescription items
- History of surgical procedure
- Genetic background

History

Fever

Intermittent- pyogenic infection, tuberculosis, lymphoma, JRA

Relapsing fever- malaria, rat-bite fever, Borrelia infection, lymphoma

Recurrent episodes > 1 year duration- suggestive of metabolic defects, CNS abnormalities of temperature control, immunodeficient states

Physical Examination

- Lymphadenopathy and pallor were common in infections
- Splenomegaly were associated more with infections and neoplasms

(Dy, et al. Phil J of Micro and Inf Dis.,1992)

Physical Examination

- C - Careful
- E - Extensive
- R - Repeated





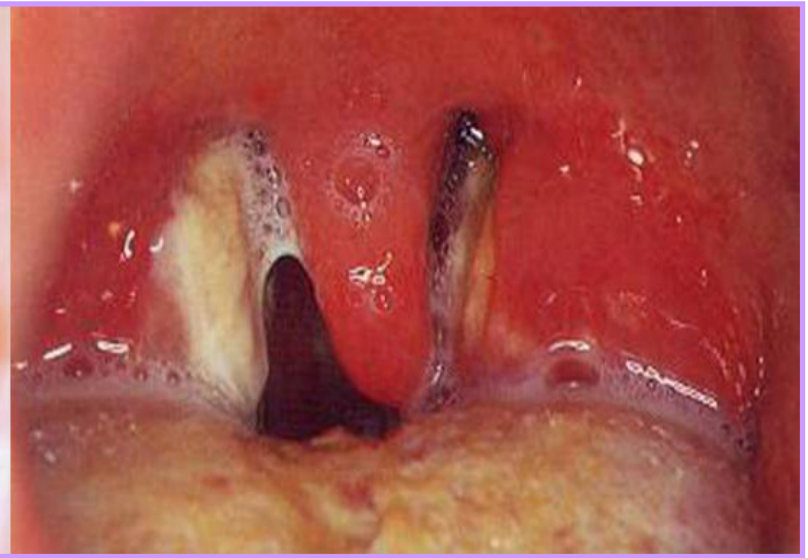






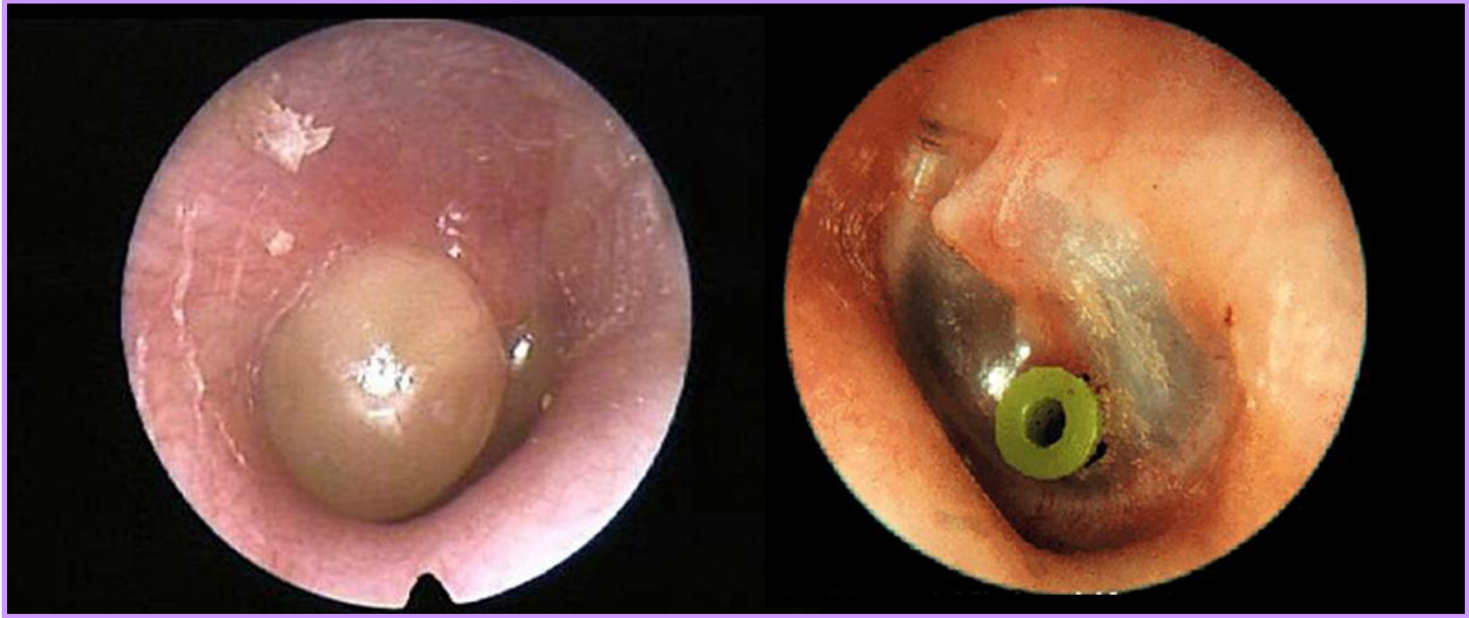


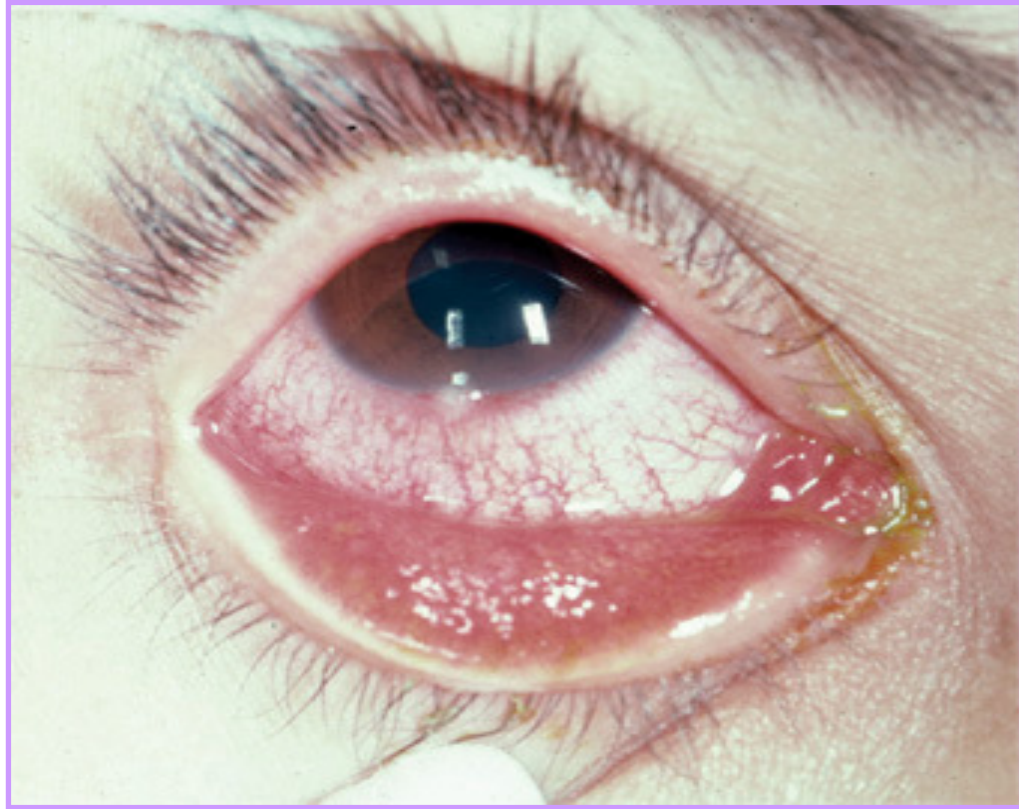


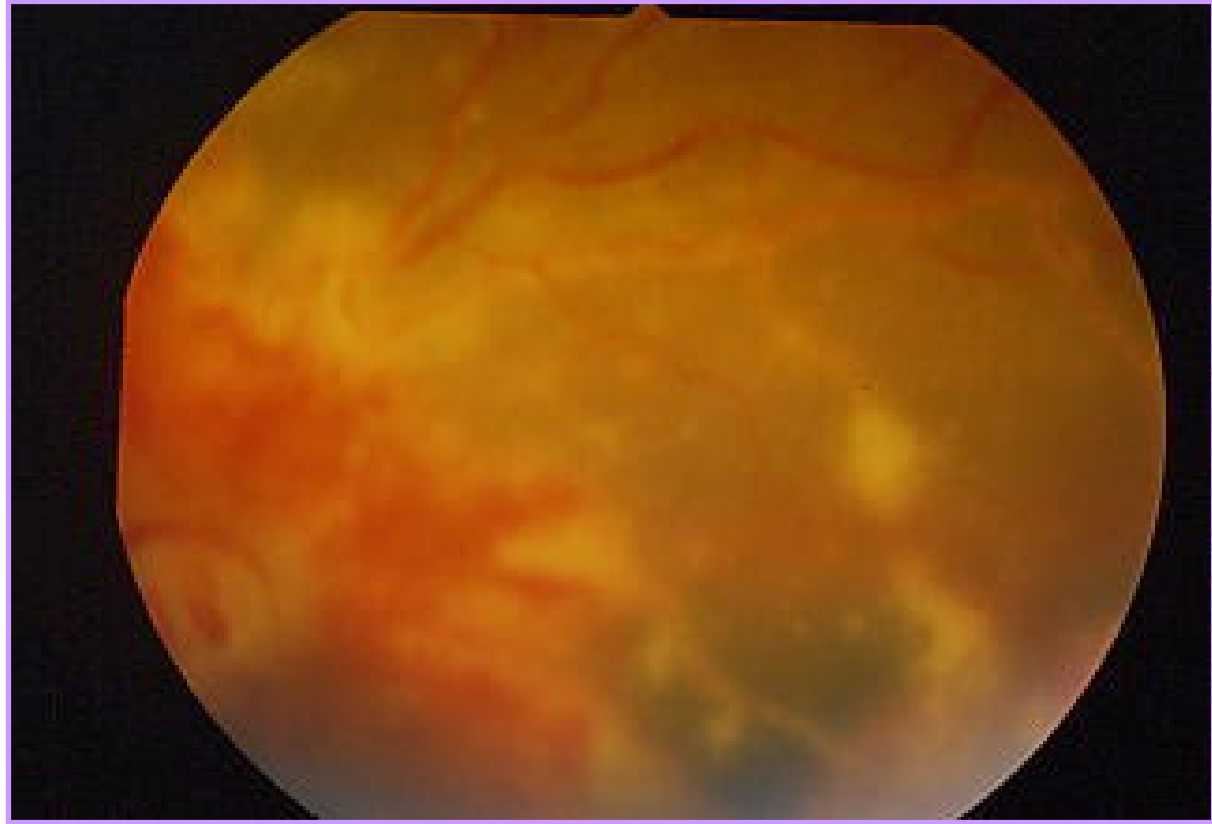
















Septic Joint



Laboratory Evaluation

- Extent dependent on age, duration of fever, history and physical examination
- Directed towards most likely diagnostic possibility
- Tempo adjusted to severity of illness

Laboratory Evaluation

Complete Blood Count

Total and differential WBC

- Leukopenia

Viral

EBV, hepatitis A and B, RSV, rubella

Bacterial

Salmonella, Staphylococcal, Mycobacterial

- Neutropenia
($<1500/\text{mm}^3$) most often associated
with viral infections
- Leukocytosis
Bacteria, virus, fungi, protozoa, spiroch
etes

(Walters.et.al. Pediatric Clinics of NA, June 1996)

Band Count

- Band count as a single parameter is of limited diagnostic value
- ANC is more sensitive than band count in predicting acute bacterial infection
- Morphologic changes in neutrophils especially toxic granulation were helpful in predicting bacterial infection

(Al-Gwaiz. et.al.Med Princ Pract 2007:16:344-347)

Peripheral Blood Cell Morphology

- Provide direct visualization of certain microorganisms
- Detect characteristic footprints left by various infections on morphology of blood cells, yielding diagnostic clues
- (ex Dohle bodies, haemophagocytosis)

Laboratory Evaluation

Peripheral Blood Cell Morphology

- Disclose certain infection predisposing conditions
- Reveal infection-related hematologic and systemic complications

(Potasman.et.al.Postgrad Med J 2008;84;586-589)

Laboratory Evaluation

ESR

- No specific diagnostic value
- General marker of inflammation
- Help determine need for further evaluation
- Monitor progress of disease

Laboratory Evaluation

- ESR and A/G ratio were helpful screening tests in 75 % of patients with serious illness (collagen and malignancy)
- Increased sedimentation rates or reversal of A/G ratio

(Pizzo,et al.,Pediatrics,1975;55 (4);468)

Laboratory Evaluation

Blood cultures

- Aerobic and anaerobic
- Media appropriate (isolation of Francisella, Leptospira, Spirillum)
- Appropriate volumes in children
 - 1 to 2 ml in neonates
 - 2-3 ml in infants
 - 3-5 ml in children
 - 10-20 ml in adolescents

Laboratory Evaluation

- Single sampling may be sufficient
- Multiple samples may be appropriate in certain circumstances (suspected endocarditis, 2-3 samples are desirable to obtain a sensitivity of 96% especially if patient received antibiotics)
- Indwelling intravascular devices - two sets of cultures from different sites are helpful
(Long et. al., Pediatric Infectious Disease. Third edition)

Laboratory Evaluation

Blood cultures were most useful when done serially and correlated clinically especially in conditions as septicemia, enteric fever and endocarditis

(Dy, et al. Phil J of Micro and Inf Dis., 1992)

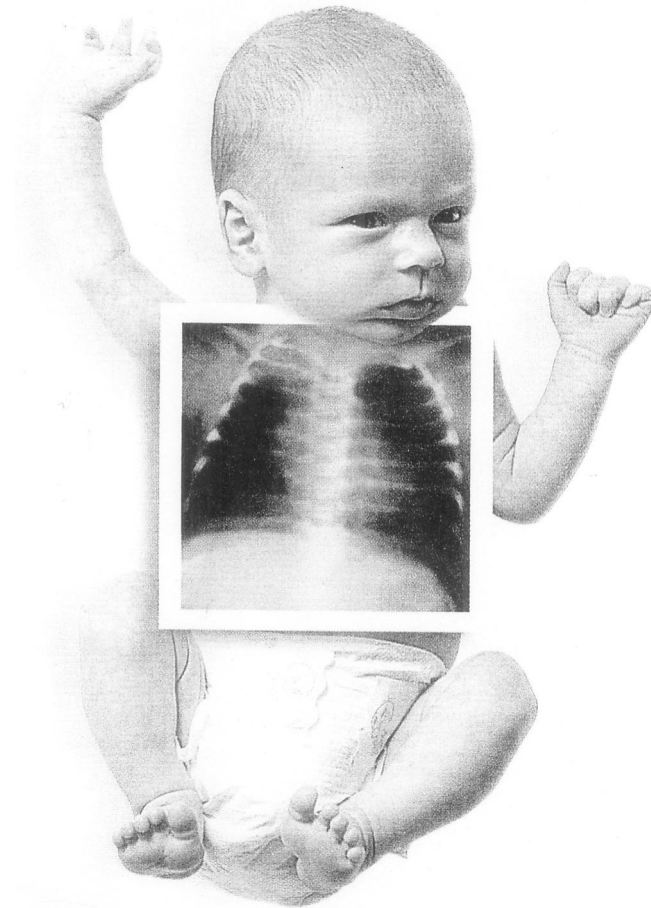
Urine analysis and Urine culture

- Failure to perform and investigate pyuria were the most common laboratory errors

(Mclung, Amer J. Dis Child, 1972, Vol 124)

- Radiographic study of urinary tract
- **only** when indicated

Diagnostic Imaging





Laboratory Evaluation

Intradermal tuberculin skin test

- Negative tuberculin test result still does not rule out tuberculosis



Laboratory Evaluation

Malarial Smear

- Thin and thick smears diagnostic
- Of little diagnostic value, history of exposure and physical examination necessitated therapeutic trial

(Dy, et al. Phil J of Micro and Inf Dis.,1992)

Laboratory Evaluation

Serum tests

- Human immunodeficiency virus
- Salmonellosis
- Brucellosis
- Tularemia
- EBV
- Cytomegalic Inclusion virus
- Other viral infections (Hepatitis antigens)
- Toxoplasmosis
- Fungal infections

Laboratory Evaluation

Bone Marrow

- Recommended as an important tool for detection of occult infection and malignancy
- In immunocompetent children- occasionally useful for diagnosis of selected infectious diseases especially brucellosis and typhoid fever

- 383 pediatric patients who underwent 414 marrow examinations
- Concomitant blood and urine cultures
- 15 (3.6 %) of 414
- Isolates :
 - Salmonella
 - Mycobacterium avium intracellulare
 - Histoplasma capsulatum

Yield of marrow microbial culture in immunocompetent host with prolonged fever was very low(1.9%) but a somewhat better yield was seen in immunocompromised hosts (8.7 %) especially in patients with AIDS

- Helpful in establishing or supporting the diagnosis of opportunistic infection in the febrile immunocompromised host
- Not warranted in a child with prolonged fever with no suggestions of malignancy or immunodeficiency to detect occult infection

(Hayani et.al. J of Ped, June 1990)

Laboratory Evaluation

Biopsy

- If with evidence of organ involvement
- Most definitive approach to investigation of neoplastic cause in FUO
- Helpful in diagnosis of tuberculosis

(Dy, et al. Phil J of Micro and Inf Dis.,1992)

Other tests

- Hepatic enzymes
- Serum chemistries
- Electrolytes
- BUN, creatinine
- ANA > 5 years of age

Laboratory Evaluation

- Echocardiography, electroencephalography, stool culture, examination for ova and parasites generally should be performed in selected cases
- CT, gallium scan, , radioisotope scan
- Ultrasonography
- CSF examination

Guidelines

- Antibiotics or other medications should not be administered empirically as a diagnostic measure
- Empirical trials of broad spectrum antibiotics generally do more to obscure than illuminate and may mask or delay diagnosis of infection such as meningitis, parameningeal infection, endocarditis or osteomyelitis

Guidelines

Exceptions

- Use of non-steroidal agents in children with presumed JRA
- Use of antituberculosis drugs in critically ill children thought to have disseminated TB

(Pediatric Feigin, et al. Textbook of Infectious Disease.5th edition)

Guidelines

- Children with strongly suspected bacteremia and with deteriorating condition
- Children with a chronic illness(HIV) ,severe malnutrition or haemoglobinopathy,which increases risk of serious bacterial infection

(Akpede.et.al. Paediatr Drugs 2001 ,3(4):247-262)