Does this child have fever > 7 days with no obvious source despite in depth investigation?

Stabilise toxic/septic looking child using resuscitation guidelines, call for senior help

YES

Is this child toxic or septic looking?

NO

Baseline investigations

- FBC and blood film
- U+E, LFT, CRP, ESR
- Blood films for malaria x3 if exposure likely
- Serial blood cultures
- EBV, CMV serology
- Serum saved for other possible serology
- Urine analysis and culture
- Stool M,C+S
- Tuberculin/Mantoux test, Quantiferon

YES

Does this child have fever > 7 days with no obvious source despite in depth investigation?

Take focussed history and examination. Key points:
- Characteristics of fever, associated symptoms
- Immunisations
- Immunodeficiency, Exposure to animals, Travel,
- Vital signs
- Skin and rashes, eyes, ENT, lymph nodes
- Musculoskeletal, abdominal masses

Refer to table 2 for guidance on specific clinical signs and their

General management

If patient is stable, and no immediate infection is found, avoid empirical antibiotics until investigations complete.
- Vital signs should be measured 4 hourly: observe the pattern and height of fevers
- Treat fevers symptomatically but avoid excess antipyretics
- Observe for rashes: e.g. JIA has a transient rash in the evenings
- Consider factitious fevers: observe carers closely if concerns

Differential diagnoses and further investigations to consider, depending your assessment and findings
- See table 2 for guidance of clinical conditions and associated investigations

Autoimmune and vasculitic disorders

Features: Systemically unwell, diagnostic rashes, murmurs, joint swellings, clues from travel history, exposure to animals, bites

Refer to table 1 for differentials

Investigations
- Serial blood cultures
- Stool MC+S,enterovirus + enteric viruses
- Viral and bacterial throat/surface swabs

Haem/onc Malignancy

Features: bone pains, weight loss, night sweats

- Leukaemia
- Lymphoma
- Nephroblastoma (Wilm's tumour)
- Neuroblastoma
- Atrial myxoma
- HLH

Investigations
- FBC and film, Ferritin, Triglycerides
- Immunophenotyping
- Bone marrow
- HLH genetics (GOS lab)+/-
- Imaging, ECHO
- Urinary VMA
- Refer Oncology Team

Other causes

- Thyrotoxicosis
- Autonomic dysfunction
- Hypothalamic central fevers
- Drug related
- Periodic fevers
- HyperIgE syndrome
- Factitious fever
- Immunodeficiency

Investigations
- TFTs, Thyroid Peroxidase antibodies
- TSH receptor antibodies, US thyroid
- Endocrine/Neuro R/V
- Immunoglobulin subsets, Tlymphocytes
- HIV testing

Bacterial Multisystem Or localised infection

Virus, parasite, fungus, spirochetes

Features: Systemically unwell, diagnostic rashes, murmurs, joint swellings, clues from travel history, exposure to animals, bites

Refer to table 1 for differentials

Investigations
- Serial blood cultures
- Stool M,C+S,enterovirus + enteric viruses
- Viral and bacterial throat/surface swabs
Pyrexia of unknown origin Guideline

Introduction

In the paediatric population, pyrexia of unknown origin (PUO) is described as fever of ≥38.0°C, which persists for more than 7 days, despite intensive investigation. It is important to distinguish children with ‘fever without source’ from children with ‘pyrexia of unknown origin’. The former present with a fever of unclear source, and usually have underlying infections, which are identified after initial investigations. These children are usually clinically unwell and require urgent evaluation and empirical treatment (particularly young children). In contrast, children with PUO require a more comprehensive and focused evaluation, and may not require immediate empirical therapy. The most common causes of PUO are infections, inflammatory/vasculitic disorders and malignancies or common illnesses presenting atypically.

History and Examination

Details about the height, duration and timing of fever are important. Night-time fevers and sweats may indicate TB or lymphoma. Cyclical fevers every 3-4 days may suggest malaria. Enquire about the method of temperature measurement.

Immunocompromised children are at greater risk of infections such as CMV and toxoplasmosis, and asplenic children are at particular risk of infections from encapsulated organisms. Immunisation and medication history is crucial. Under-immunised children are at higher risk for infections such as Streptococcus pneumoniae and Haemophilus influenzae. Recent immunisations may point towards a vaccine reaction. Enquire about BCG vaccination. Ingestion of anticholinergics or amphetamines can result in drug fever and prolonged antibiotic use can also result in fever.

For children with a history of recent travel, refer to the trust guideline ‘Fever in the returning traveller’. Recent travel, or contact with a person from abroad, may point towards non-endemic infections such as typhoid, malaria, TB or brucellosis. Exposure to animals, animal waste or contaminated water could suggest leptospirosis. A recent visit to a woodland area might expose a child to tick bites, therefore potential Lyme disease.

Examination

The clinical examination should be thorough, giving special attention to the following:
- General appearance and vital signs
- Skin and rashes, petechial rash
- Eyes
- Ears, nose and throat
- Lymph nodes
- Abdominal masses
- Musculoskeletal

Certain physical findings may reveal an obvious source of fever, which will help to focus the course of diagnostic investigations. Any toxic or septic appearing child should always be stabilised following the appropriate resuscitation guidelines.
Diagnostic Investigations

All children with PUO should have:
- FBC and blood film
- U+E, LFT, CRP, ESR
- Blood films for malaria x3 if the diagnosis a possibility
- Serial blood cultures
- EBV, CMV serology
- Serum saved for other possible serology
- Urine analysis and culture
- Tuberculin/Mantoux test, Quantiferon
- CXR

Further investigations should be guided by the history, examination findings and associated risk factors that could point to a specific aetiology.

- Stool studies: culture, ova and parasites in patients with loose stools or recent travel
- Bone marrow: for diagnosis of malignancy, histiocytic disorders and haemophagocytic disease (not for infections)
- HIV serology: for high risk children
- Syphilis
- Serum anti-nuclear antibodies
- Immunoglobulin levels: if there is evidence of recurrent or persistent infections and in those with persistent fever and a negative initial evaluation
- Abdominal imaging (ultrasound): if inflammatory bowel disease is suspected, consider if fever may be due to psoas abscess
- Sinuses or mastoid imaging: if sinusitis is a possible aetiology
- Echocardiography/ECG: if concerns of infective endocarditis
- Ophthalmologic examination: can be helpful to evaluate uveitis or leukemic infiltration

Below is a table summarising key history and examination findings, their associated clinical conditions and diagnostic investigations suggested for these conditions.

<table>
<thead>
<tr>
<th>History/examination finding</th>
<th>Associated condition</th>
<th>Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>TB</td>
<td>Tuberculin, CXR</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>Blood film, imaging, LDH</td>
</tr>
<tr>
<td></td>
<td>Thyrotoxicosis</td>
<td>TFTs, thyroid antibodies</td>
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<tr>
<td></td>
<td>Inflammatory bowel disease</td>
<td>Barium study, OGD</td>
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<tr>
<td>Sweating/night sweats</td>
<td>TB</td>
<td>Quantiferon, CXR</td>
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<tr>
<td></td>
<td>Lymphoma</td>
<td>Node biopsy, bone marrow</td>
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<tr>
<td></td>
<td>Thyrotoxicosis</td>
<td>Thyroid USS</td>
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<tr>
<td>Contact with domestic animals</td>
<td>Cows</td>
<td>Brucellosis, TB, Q fever</td>
</tr>
<tr>
<td></td>
<td>Wild animals</td>
<td>Lyme disease</td>
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<tr>
<td></td>
<td>Rats (canals)</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td></td>
<td>Birds (parrots)</td>
<td>Psittacosis</td>
</tr>
</tbody>
</table>

Pyrexia of unknown origin guidelines. Authors: S Bhoobun, K Doehrolt

Date of review: December 2019
<table>
<thead>
<tr>
<th>Rashes</th>
<th>Typhoid fever</th>
<th>Blood/stool culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose spots</td>
<td></td>
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<tr>
<td>Janeway lesions</td>
<td>Bacterial endocarditis</td>
<td>Serial blood culture, ECHO</td>
</tr>
<tr>
<td>Diffuse rash with desquamation mucous hyperaemia</td>
<td>Toxic shock syndrome</td>
<td>TSS- Toxin</td>
</tr>
<tr>
<td>Erythema/oedema of hands and feet; periungual peeling of digits</td>
<td>Kawasaki disease</td>
<td>ECHO</td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>Lyme disease</td>
<td>Lyme serology</td>
</tr>
<tr>
<td>Petechial rash</td>
<td>Bacterial endocarditis</td>
<td>Blood cultures</td>
</tr>
<tr>
<td></td>
<td>Rocky mountain spotted fever, Leukaemia</td>
<td>Serology, blood film</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Rheumatic fever</td>
<td>ASOT, throat swab</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>Sarcoidosis, TB, cat-scratch</td>
<td>Bartonella serology</td>
</tr>
<tr>
<td>Severe pruritus</td>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Malar (butterfly) rash</td>
<td>SLE</td>
<td>Autoantibodies</td>
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<tr>
<td>Lymphadenopathy</td>
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</tr>
<tr>
<td>Isolated cervical nodes</td>
<td>Kawasaki, Cat-scratch disease</td>
<td>Bartonella serology</td>
</tr>
<tr>
<td>Disseminated lymphadenopathy</td>
<td>EBV, CMV, toxoplasmosis, malignancy, tick-borne illnesses</td>
<td>Serology</td>
</tr>
<tr>
<td>Cardiac</td>
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<td></td>
</tr>
<tr>
<td>Heart Murmur</td>
<td>Bacterial endocarditis (BE)</td>
<td>Blood cultures</td>
</tr>
<tr>
<td>Pericardial friction rub</td>
<td>Pericarditis</td>
<td>ECHO</td>
</tr>
<tr>
<td>Respiratory</td>
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<td></td>
</tr>
<tr>
<td>Crackles</td>
<td>Pneumonia/TB</td>
<td>CXR, Mantoux</td>
</tr>
<tr>
<td>Red/sore throat</td>
<td>EBV/CMV</td>
<td>Serology, PCR</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis</td>
<td>Serology, urine</td>
</tr>
<tr>
<td></td>
<td>Rheumatic fever</td>
<td>ASOT/Throat swab</td>
</tr>
<tr>
<td></td>
<td>Typhoid</td>
<td>Blood, stool culture</td>
</tr>
<tr>
<td>Abdominal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Typhoid</td>
<td>Blood/stool culture</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Hepatitis A-E</td>
<td>Serology</td>
</tr>
<tr>
<td></td>
<td>Leptospirosis</td>
<td>Serology, urine culture</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Hepaticabscess</td>
<td>USS, aspiration</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Typhoid fevers, EBV, CMV, toxoplasmosis, malaria,</td>
<td>Serology, malarial blood film</td>
</tr>
<tr>
<td>Testicular pain</td>
<td>JIA/SLE</td>
<td>ANCA, ANA, rheum factor</td>
</tr>
<tr>
<td></td>
<td>Leukaemia</td>
<td>Blood film</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Brucellosis, EBV</td>
<td>Serology</td>
</tr>
<tr>
<td>Pyuria</td>
<td>UTI</td>
<td>Urine culture</td>
</tr>
<tr>
<td></td>
<td>Renal TB</td>
<td>Early morning urine for TB culture, renal USS</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Encephalitis, brain abscess, malignancy, HLH</td>
<td>CT brain +/- LP</td>
</tr>
</tbody>
</table>

Pyrexia of unknown origin guidelines. Authors: S Bhoobun, K Doeholt

Directorate: Women and Children

Date of review December 2019
**Pyrexia of unknown origin guidelines**

**Authors:** S Bhoobun, K Doerholt  
**Directorate:** Women and Children  
**Date of review:** December 2019

### Symptoms

- Seizures, altered GCS  
- Focal neurological deficit/papilloedema  
- Septic emboli from endocarditis  
- Swollen joints  
- Septic arthritis, JIA, SLE, rheumatic fever, endocarditis, leukaemia, lymphoma, IBD  
- Conjunctivitis  
- Kawasaki disease  
- Uveitis  
- JIA, SLE, sarcoïdosis  
- Chorioretinitis  
- CMV, toxoplasmosis, syphilis

### Causes

#### Infections

- Bacterial, viral, parasitic, rickettsial, and mycobacterial infections can all present with PUO.  
- Unusual and non-endemic infections, such as tuberculosis, malaria, and typhoid (enteric fever), often have a history of recent travel or contact with a person who has travelled recently.

| Bacterial Multisystem | Typhoid  
|-----------------------|---------  
| Tuberculosis  
| Cat-scratch disease  
| Brucellosis  
| Staphylococcal toxic shock syndrome  
| Streptococcal toxic shock syndrome.

| Bacterial Localised | Cardiac and Respiratory  
|-------------------|--------------------------  
| Pneumonia  
| Sinusitis  
| Endocarditis  
| Myocarditis  
| Hepatic and renal  
| Pyelonephritis  
| Liver abscess  
| Cholecystitis  
| Renal abscess  
| Bone and soft-tissue  
| Osteomyelitis  
| Septic arthritis  
| CNS infections  
| Meningitis  
| Cerebral abscess  
| Encephalitis

| Viruses | EBV  
|---------|---------  
| CMV  
| HAV/HBV  
| HIV  
| Enteroviruses

| Parasites and Fungi | Giardiasis  
|-------------------|--------------------------  
| Malaria  
| Histoplasmosis  
| Toxocariasis  
| Toxoplasmosis

| Spirochetes | Spirochetes  
|-------------|--------------------------  
| Leptospirosis (Weil's disease)  
| Lyme disease  
| Syphilis

#### Differential Diagnosis

**Infections**

**Bacterial:**
- Typhoid
- Tuberculosis
- Cat-scratch disease
- Brucellosis
- Staphylococcal toxic shock syndrome
- Streptococcal toxic shock syndrome.

**Hepatic and renal:**
- Pyelonephritis
- Liver abscess
- Cholecystitis
- Renal abscess

**Bone and soft-tissue:**
- Osteomyelitis
- Septic arthritis

**CNS infections:**
- Meningitis
- Cerebral abscess
- Encephalitis

**Viral:**
- EBV
- CMV
- HAV/HBV
- HIV
- Enteroviruses

**Parasitic:**
- Giardiasis
- Malaria
- Histoplasmosis
- Toxocariasis
- Toxoplasmosis

**Spirochetal:**
- Spirochetes
- Leptospirosis (Weil's disease)
- Lyme disease
- Syphilis
Autoimmune and vasculitic disorders
In these cases, fever may be associated with other systemic manifestations such as malaise, arthralgia, rash and multisystem involvement.
- Juvenile Idiopathic Arthritis (JIA)
- SLE
- Sarcoidosis
- Inflammatory bowel disease
- Kawasaki disease
- Rheumatic fever
- Polyarteritis Nodosa

Malignancy
Fever may be the presenting sign in children, or in conjunction with bone pains or haematological symptoms.
- Leukaemia
- Lymphoma
- Nephroblastoma (Wilm’s tumour)
- Neuroblastoma
- Atrial myxoma (very rare)

Other causes
- Thyrotoxicosis
- Autonomic dysfunction
- Hypothalamic central fevers
- Drug reactions and antibiotic fever
- Periodic fever- Familial Mediterranean fever, Hiberian fever, Hyper IgD syndrome
- Factitious fever

Management
If the child has toxic/septic features, they should be managed urgently using appropriate resuscitation guidelines. However many children with PUO will not require immediate empirical treatment, and if they are stable, antibiotics should be withheld until investigations are completed.

- Vital signs should be measured 4 hourly: observe the pattern and height of fevers
- Treat fevers symptomatically but avoid excess antipyretics
- Observe for rashes: e.g. JIA has a transient rash in the evenings
- Consider factitious fever: observe carers closely if concerns

Once the diagnosis is made, appropriate treatment can be commenced. For management of individual diagnoses see relevant guidelines on intranet.

Children less than 3 months old
These children who present with ‘fever without source’ are at greater risk of bacterial infections should be managed using the “Feverish illness in Children” guidelines.

https://www.nice.org.uk/guidance/cg160/chapter/1-recommendations
References

7. Forgie SE, Robinson JL. Paediatric malignancies presenting as a possible infectious disease. BMC Infect Dis 2007;7:44