Ashford and St. Peter's Hospitals
NHS Foundation Trust

Pyrexia of Unknown Origin (PUO)

Clinical Guideline

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Guideline History		
Date	**Comments**	**Approved By**
June 2013	New Guideline	Paediatric Guideline Group
March 2018	Guideline reviewed – Dr. G. Baksh	Paediatric Guideline Group
October 2025	Review. Minimal change. Tertiary support teams updated.	Paediatric Guideline committee

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1.

Pyrexia of Unknown Origin

Introduction

Often confused with “Fever Without a Source”.
Pyrexia of Unknown Origin involves a **prolonged duration of fever.**

Fever without a Source may become Pyrexia of Unknown Origin, if it lasts long enough. The exact incidence of Pyrexia of Unknown Origin is not well defined.
There is no standard definition.
The ability to determine etiologies has improved over time.

If a diagnosis is eventually determined, then it is no longer of “Unknown Origin.”
More likely to be dealing with an **unusual presentation of a common condition** than a common presentation of an unusual condition. [Antoon, 2015]

Definition

Generally, requires duration of fever that is deemed to be excessively long for what was expected. Historically, up to 3 weeks of fever was used. [Petersdorf, 1961]
Now, fever lasting longer than 8 days without a source is often cited.
Ideally, there are documented fevers (≥38.0).

Algorithm Tier 1 for work-up of a child with PUO

Sepsis and NICE traffic light scoring

Algorithm Tier 2 work-up for a child with PUO:

Etiology:(1–4)

1. **Infectious** – ~30% The proportion of infectious causes has decreased in recent years, likely due to improved diagnostic testing. **Bacterial** Pneumonia Urinary tract infection Cellulitis (or line infection) Osteomyelitis, Septic Arthritis ENT Abdominal/pelvic abscess Endocarditis Meningitis **TB** Pulmonary or extra pulmonary **Viral** Gastroenteritis Hepatitis EBV CMV Parvovirus Mycoplasma Herpes HIV Recent vaccination	2. **Rheumatologic / Autoimmune/Inflammatory** – ~20% Juvenile Idiopathic Arthritis Inflammatory Bowel Disease Kawasaki Disease Systemic Lupus Erythematous Serum Sickness Immunodeficiency Syndromes Inflammatory Bowel Disease Periodic Fevers
Parasitic Malaria Toxoplasma Toxocara	
3. **Oncologic** – ~10% **Haematological** Leukaemias; lymphomas; myeloma **Solid organ** Any, especially if disseminated malignancy	4. **Other Causes** – ~5% Familial Dysautonomia Cyclic Neutropenia Thyrotoxicosis Factitious
5. **Drug Fever** – ~5% Often overlooked [*Antoon, 2015*] First step in evaluation is stopping all nonessential medications [*Antoon, 2015*] Many agents, including ibuprofen and acetaminophen, can be a source of drug fever.	6. **Undiagnosed** (often spontaneously resolved) – ~30%
7. **Pseudo-Pyrexia of Unknown Origin** Series of benign, self-limited illnesses over a short period of time [*Tolan, 2010*] This can create the appearance of the child being sick over a protracted course.	

History Taking:(4–6)

History of presenting complaint:

Onset: when was temperature first noted; sudden or gradual onset?
Character: constant or intermittent; Frequency of peaks in temperature? Has the temperature actually been recorded, if so, how high?
Alleviating factors: rest, Paracetamol, Ibuprofen
Timing: night or day, related to exertion?
Associated symptoms/signs (systematic)

- Shivering or rigors
- Sweating (night sweats are particularly important: these are drenching and often require a change of bedclothes)
- Weight loss, Anorexia
- Feeling faint or dizzy; syncope
- Fatigue (has it interfered with daily life?)

System review:

- **CNS**- change in usual behaviour, headache- especially early morning headache, neck stiffness
- **Respiratory**: Cough/Cold, Runny Nose - Infection (Bugs), Cessation of Breathing (Apnoea), Noisy Breathing, Snoring.
- **Cardiovascular**- exercise intolerance, in an infant- unable to finish feeds, sweating, bluish-dusky appearance of peripheries, shortness of breaths
- **GIT-** oral ulcers, sore mouth, pain abdomen, vomiting, bowel habits- constipation/ diarrhoea – how frequent, any blood/mucous, sore bottom
- **GUT**- Urine? Frequency, Amount, Colour, Oduor, Frothy Urine
- **Musculoskeletal**- joint swellings/ pain, infant- reduced movement of a limb, unable to bear weight, limp
- **Haematological** – Pallor, Bruising, Bleeding, Recurrent Infections
- **Endocrine** - Weight. Change, Neck Swelling, recently prefers hot or cold weather (hyperthyroid), excess water intake and increased urine frequency including nighttime (DI)

Travel history:

- In the last year and prophylaxis if used- Tb, typhoid, malaria, hepatitis A or hepatitis E,

History of contact/ Exposure:

- Exposure or contact with possible covid case - PIMS
- Exposure to pets/animals- zoonotic diseases
- Any tick bites (wooded/ grassland area) – Lyme's
- History of eating undercooked meat- toxoplasma.
- Pica – toxocara
- Unpasteurised milk – Tuberculosis bovis, Brucella, listeria
- Raw/undercooked poultry - Campylobacter
- Possible contaminated food/water- E. Coli, salmonella

Drug history:

- NSAIDS,
- immunosuppressives,
- antimicrobials

(including over the counter drugs currently or in the last month) –

Drug fever is a diagnosis of exclusion.(7)

Adolescents: Don't miss

- HEADSS
- Recreational drugs
- Sexual history- STI, pelvic disease in adolescents, Bechet's disease
- H/o recent Tattoos/ piercing – HIV, Hepatitis b/C, IE

Immunisations:

- Up to date or partial

Past history:

- Medical devices – indwelling catheter, central lines (CLABSI)
- Recent blood transfusions,
- H/o surgery including dental procedures in the last few months – post surgical collection/ complication leading to persistent fever

Family history

- Any family members with contagious diseases (tuberculosis or viral illness)

Observations:

Don't underestimate the importance of vitals and growth parameters:

- HR – relative bradycardia, disproportionate tachycardia
- RR- silent tachypnoea
- BP for the height–If high, could point to renal cause / neuroblastoma
- SpO2

- **Fall in growth centiles over time**- PUO possibly from an unrecognised chronic condition and less likely to be acute infections
  Weight loss with prolonged diarrhoea/ pain abdomen- R/o IBD esp. Crohn's

General exam:

Pallor:

- Marked cutaneous pallor could point to lymphoproliferative diseases, autoimmune and inflammatory

Clubbing: Chronic pathology
Oral ulcers: IBD, immunosuppressive conditions
Conjunctival redness: Adenovirus infection, KD (bulbar sparing limbus), and leptospirosis, conjunctival petechiae indicative of infective endocarditis

Skin rashes:

- Malar rash is typical of SLE, dermatomyositis, Parvovirus infection; and
- Petechiae: are present in vasculitis, Infective Endocarditis or leukaemia.
- Erythema Nodosum: Tuberculosis, Ulcerative colitis, Crohn's disease, Streptococcal infection

Lymphadenopathy:

- Esp. supraclavicular with hepatosplenomegaly – malignancy, EBV
- Generalized lymphadenopathy- malignancy like leukaemia, lymphoma should be ruled out. CMV, EBV, Tb

If there's a suspicion of IBD (esp. Crohn's disease) – don't miss perianal exam

Systemic examination

ENT:

- Pharyngeal hyperaemia – EBV, CMV, toxoplasma
- Exudative tonsillitis with splenomegaly – EBV, adenovirus
- Persistent mucopurulent nasal discharge – sinusitis,
- Inflame behind the pinna- mastoiditis
- Asymmetry in the pharynx- bulge in the soft palate and deviation of the uvula to the opposite side- peritonsillar or parapharyngeal abscesses.

Don't miss dental infections leading to PUO

Respiratory

- Reduced air entry in a localized area- occult pneumonia

CVS

- New murmur or change of murmur- Infective endocarditis, Rheumatic fever
- Muffled heart sounds- pericarditis

Abdomen

- Splenomegaly – Infections (Tb, Salmonella, Endocarditis, malaria, Brucellosis), Connective tissue disease (SLE, SoJIA), Malignancy (leukaemia, Lymphoma, HLH/ MAS)

CNS

- Meningeal signs is also useful: children with mild meningism may have subacute or chronic tuberculous or fungal meningitis.
- Locoregional infectious foci such as mastoiditis or vertebral osteomyelitis can also cause meningeal irritation
- Spinal tenderness or limitation of flexion–extension can suggest discitis or spondylodiscitis, as well as neoplasia, such as sarcoma or neuroblastoma.

Musculoskeletal:

- Arthritis/ arthralgia – SoJIA, SLE, Rheumatic fever, Infections (TB, Lyme, Brucella)
- Muscle tenderness- myositis
- Malignancy

Investigations:

Tier 1 Investigations

FBC + film, U&Es, LFTs, TFTs, CRP, ESR Urate, LDH, Ferritin
ASOT, AntiDNaseB,
Blood culture
Throat swab – viral, bacterial, NPA
Urine microscopy & culture
Stool – OCP, viral, bacterial culture
+/- Lumbar puncture
Based on history: Thick and thin films for malaria

First line imaging:
Chest Xray
US abdomen

Tier 2 Investigations

Please avoid ordering every test

Repeat FBC + film, CRP, ESR, ferritin
Serial blood cultures
Viral serology: EBV, CMV, Hepatitis, Parvovirus, Enterovirus, herpes, HIV, toxoplasma, toxocara
Mycoplasma serology
Autoimmune screen: ANA, ANCA, dsDNA, Antiphospholipid antibody, Lupus anticoagulant, C3, C4, Rheumatoid factor (RF), Creatine kinase (CK)
Immunoglobulins and subclasses- IgA, IgG, IgM
TPO antibody

Imaging following MDT discussion
ECHO
CT C/A/P
Whole body MRI

If no progress, seek opinion from:

- Immunology and Infectious Diseases- St George's Hospital
- Renal- Evelina Children's Hospital
- Oncology- Royal Marsden Hospital and Evelina
- Rheumatology- Southampton Children's Hospital

Management:(8,9)

1. Any febrile child who appears seriously unwell should be managed as suspected sepsis, irrespective of the duration or the degree of fever.
2. **Consider admission in any child who:**

    - Appears unwell or temperature >14 days.
    - Fever 7- 14 days – after discussion with the consultant

3. Do NOT rush to start antibiotics in a clinically well child until further discussion. Choice of antibiotics will depend on the likely source of infection.

4. Please record the temperature patten over a period of observation in the ward.

Supporting relevant trust guidelines

1. Blood Culture Guideline for Paediatric Patients

2. Bone and Joint Infection:
   see Osteomyelitis and Septic Arthritis
   see Atraumatic Paediatric Hip Pain and Limping Child ED

3. Febrile Neutropenia and Non-neutropenia in Paediatric Oncology Patients
   CCLG: Managing Febrile Neutropenia in the UK
   RMH: Parent Information: Febrile Neutropenia on Discharge

4. Fever in under 5s

5. Kawasaki Disease

6. Meningitis Guidelines for children older than 3 months

7. Meningococcal Septicaemia in Paediatric ED

8. Myocarditis Guidelines

9. Paediatric Sepsis Six – ED Pathway

10. Paediatric Sepsis Six – ED

2. Supporting Reference

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11. Guideline Governance

a. Scope

This guideline is relevant to all staff caring for all children from 0-18 years old across the emergency department, inpatient ward and outpatient department.

b. Purpose

i. This guidelines aims to facilitate a common approach to the management of children. At times deviation from the guideline may be necessary, this should be documented and is the responsibility of the attending consultant.

ii. This guideline is subject to regular review to ensure ongoing evidence based practice.

c. Duties and Responsibilities

All healthcare professionals responsible for the care of all children 0-18years should be aware of practice according to this guideline.

d. Approval and Ratification

This guideline will be approved and ratified by the Paediatric Guidelines Group.

e. Dissemination and Implementation

i. This guideline will be uploaded to the trust intranet 'Paediatric Guidelines' page and thus available for common use.

ii. This guideline will be shared as part of ongoing education within the Paediatric Department for both medical and nursing staff.

iii. All members of staff are invited to attend and give comments on the guideline as part of the ratification process.

f. Review and Revision Arrangements

a. This policy will be reviewed on a 3 yearly basis by the appropriate persons.

b. If new information comes to light prior to the review date, an earlier review will be prompted.

c. Amendments to the document shall be clearly marked on the document control sheet and the updated version uploaded to the intranet. Minor amendments will be ratified through the Paediatric Guidelines Group. A minor amendment would consist of no major change in process, and includes but is not limited to, amendments to documents within the appendices.

g. Equality Impact Assessment

Background • Who was involved in the Equality Impact Assessment
Author and the supervising consultants.
Methodology • A brief account of how the likely effects of the policy was assessed (to include race and ethnic origin, disability, gender, culture, religion or belief, sexual orientation, age) • The data sources and any other information used • The consultation that was carried out (who, why and how?)
All groups of staff and patients were taken into consideration and there is no bias towards or against any particular group.
Key Findings • Describe the results of the assessment • Identify if there is adverse or a potentially adverse impacts for any equalities groups
There is no evidence of discrimination.
Conclusion • Provide a summary of the overall conclusions
There is no evidence of discrimination.
Recommendations • State recommended changes to the proposed policy as a result of the impact assessment • Where it has not been possible to amend the policy, provide the detail of any actions that have been identified • Describe the plans for reviewing the assessment
This guideline is appropriate for use.

h. Document Checklist

To be completed (electronically) and attached to any document which guides practice when submitted to the appropriate committee for approval or ratification.

Title of the document: Pyrexia of Unknown Origin in Paediatrics
Policy (document) Author: Dr Kirti Gupta
Executive Director: N/A

		Yes/No/ Unsure/NA	Comments
1.	**Title**		
	Is the title clear and unambiguous?	**Y**	
	Is it clear whether the document is a guideline, policy, protocol or standard?	**Y**	
2.	**Scope/Purpose**		
	Is the target population clear and unambiguous?	**Y**	
	Is the purpose of the document clear?	**Y**	
	Are the intended outcomes described?	**Y**	
	Are the statements clear and unambiguous?	**Y**	
3.	**Development Process**		
	Is there evidence of engagement with stakeholders and users?	**Y**	
	Who was engaged in a review of the document (list committees/ individuals)?	**Y**	**Paediatric guideline committee, PID and STRS management support.**
	Has the policy template been followed (i.e. is the format correct)?	**Y**	
4.	**Evidence Base**		
	Is the type of evidence to support the document identified explicitly?	**Y**	
	Are local/organisational supporting documents referenced?	**Y**	
5.	**Approval**		
	Does the document identify which committee/group will approve/ratify it?	**Y**	
	If appropriate, have the joint human resources/staff side committee (or equivalent) approved the document?	**Y**	
6.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	**Y**	
	Does the plan include the necessary training/support to ensure compliance?	**Y**	
7.	**Process for Monitoring Compliance**		
	Are there measurable standards or KPIs to support monitoring compliance of the document?	**Y**	
8.	**Review Date**		
	Is the review date identified and is this acceptable?	**Y**	

		Yes/No/ Unsure/NA	Comments
9.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for coordinating the dissemination, implementation and review of the documentation?	**Y**	
10.	**Equality Impact Assessment (EIA)**		
	Has a suitable EIA been completed?	Y	

Committee Approval (Paediatric Guidelines Group)			
If the committee is happy to approve this document, please complete the section below, date it and return it to the Policy (document) Owner			
Name of Chair	**Alexandra Jones**	**Date**	**17/10/2025**
Ratification by Management Executive (if appropriate)			
If the Management Executive is happy to ratify this document, please complete the date of ratification below and advise the Policy (document) Owner			
Date: n/a			