

PYREXIA UNKNOWN ORIGIN

Facilitators Guide

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Duration **up to 2 hours**

Facilitator **Senior trainee/ANP**

Learner level **Junior trainee/Staff Nurse and Senior trainee/ANP**

Equipment required **None**

OUTLINE

- Basics (10 Minutes)
- Main session (2x 20 Minutes) case discussions covering the key points and evidence
- Advanced session (2x 30 Minutes) case discussions covering grey areas, diagnostic dilemmas; advanced management and escalation
- Quiz questions (10 Minutes)
- Infographic sharing (5 Minutes): 5 take home learning points

PRE-READING FOR LEARNERS

To prepare for this session, learners could read the below case report article
(20 minutes):

Wood M, Abinun M. and Foster H., Pyrexia of unknown origin. Archives of Disease in Childhood, Education and Practice, 89 ep 63-69 (2004)

And/or look at these useful resources from the web:

<https://pedemmorsels.com/fever-of-unknown-origin/> **(5 minutes)**

<https://dontforgetthebubbles.com/recurrent-or-periodic-fevers-in-vestigate-or-reassure/> **(10 minutes)**

<https://dontforgetthebubbles.com/tuberculosis/> **(5 minutes)**

<https://dontforgetthebubbles.com/claire-nourse-tuberculosis-at-dftb17/> **(20 minutes)**

<https://gppaedstips.blogspot.com/search/label/Juvenile%20idiopathic%20arthritis> **(10 minutes)**

<https://www.paediatricfoam.com/?s=kawasaki> **(10 minutes)**

BASICS

The term **pyrexia of unknown origin (PUO)** is used when a patient has more than 8 days with fever (temperature > 38°C) **without a clinical diagnosis** after exhaustive investigations have been carried out (in hospital or in primary care).

Other more specific PUOs are:

- nosocomial PUO
- neutropenic PUO
- HIV-associated PUO

These 3 have specific risk factors and will not be covered in this session.

Fever is a sign of an underlying pathology. In PUO, pyrexia is usually the main symptom while other signs may be very subtle. Many times, the underlying disease is a common pathology that is presenting in an atypical or incomplete way.

Here are 3 main clinical dilemmas for clinicians:

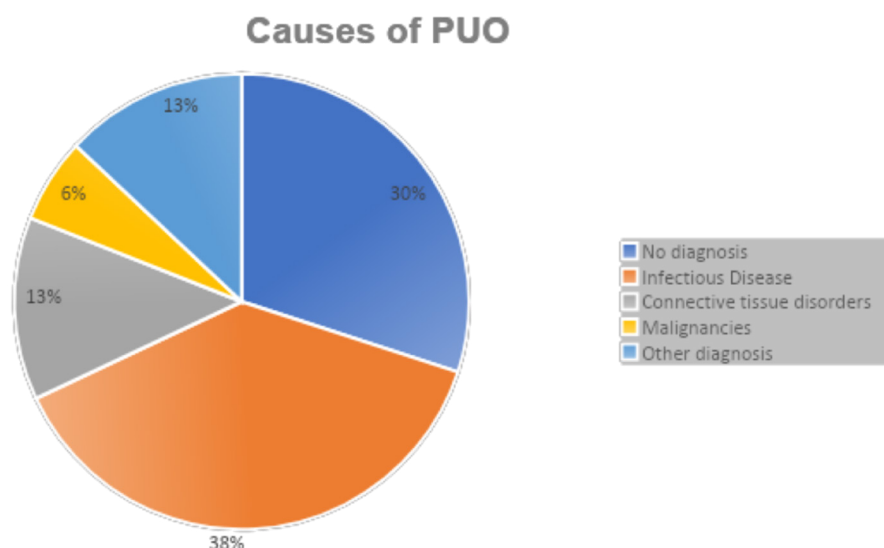
1. How can we discern a benign illness from a life-threatening condition?

In the paediatric population, 30% of PUO will not reach a final diagnosis.

However, in those cases, PUO is often a self-limited and benign episode.

When a definitive diagnosis is reached, the majority of causes are related to infectious diseases (38%), followed by connective tissue disorders/autoimmune pathology (13%) and malignancies (6%) **(Figure 1)**

Figure 1



2. How far should we investigate?

At present, there is not a generic PUO work-up since this wouldn't be efficient. Remember that more than 1/4 of cases are benign and self-limited!

In many cases, PUO is a consequence of a late diagnosis. **Clinical history taking and careful physical examination are crucial to pick up subtle signs and guide the complementary tests and imaging.** New signs and symptoms, which weren't present on initial examination, can appear later on.

In the literature, retrospective studies have shown that when imaging requests are prompted by some examination finding, they are more likely to yield a positive result. Here's a table with possible differential diagnosis based on clinical findings.

Table 1

Diagnosis based on common clinical findings

Rash

-Maculopapular	EBV, Kawasaki Disease, SOJIA, Typhoid fever
-Purpuric	CMV, Endocarditis, Leukaemias, Histiocytosis, Vasculitis
-Erythema Nodosum	TB, Ulcerative colitis, Crohn's disease, Streptococcal infection
-Butterfly rash	SLE, Dermatomyositis

Adenopathies

-Infections	CMV, EBV, TB, Bartonella (Cat-scratch disease)
-Connective tissue disorders	Rheumatoid Arthritis (RA)
-Malignancies	Lymphomas, Leukaemias, Histiocytosis
-Other causes	Sarcoidosis and Primary Immunodeficiencies

Splenomegaly

-Infections	TB, Bartonella, Malaria, Visceral Leishmaniasis, Endocarditis, Brucellosis, Salmonellosis
-Connective tissue disorders	SLE, RA
-Malignancies	Lymphomas, Leukaemias, Histiocytosis, Macrophagic Activation Syndrome
-Other causes	Primary immunodeficiencies

Arthritis

-Infections	TB, Lyme disease, Brucella, Staphylococcal Infection
-Connective tissue disorders	SOJIA, RA, SLE, Rheumatic fever
-Malignancies	Leukaemias
-Other causes	

3. Should we treat empirically or have a wait-and-see approach?

The speed of the complementary tests will depend on the general appearance of the patient. Empirical treatment with antibiotics can blur the microbiology results resulting in a delayed diagnosis. The empirical use of steroids can mask other pathologies and again delay the diagnosis.

For the above reasons, clinicians should reserve empirical treatment with antibiotics or steroids to the sick patient based on clinical assessment.

List of possible causes of PUO: Table 2

Causes of fever of unknown origin

Infectious:

Bacterial infections:

Localised: Pyelonephritis, Sinusitis, Mastoiditis, Pneumonia/pleural effusion, Osteomyelitis, Endocarditis, Intravenous catheter infection

Abscesses (intracranial, dental, intestinal, hepatic, pelvic...)

Systemic infections: Tuberculosis, Brucellosis, Bartonella (cat-scratch disease), Leptospirosis, Q fever (Coxiella), Lyme disease, Salmonellosis (Typhoid fever), Tularaemia.

Viruses: EBV, CMV, Adenovirus, Enterovirus, HIV, Dengue

Fungal: Blastomycosis, Histoplasmosis, Coccidiomycosis

Parasites/protozoos: Malaria, Visceral Leishmaniasis, Toxoplasmosis, Visceral Larva Migrants, Tripanosomiasis

Connective Tissue Disorder

Kawasaki
Systemic Onset of Juvenile Idiopathic Arthritis (SOJIA)
Systemic Lupus Erythematosus
Acute Rheumatic fever

Malignancies

Leukaemia
Lymphomas
Solid tumours (Neuroblastoma)
Hemophagocytic Syndrome
Myelodysplastic syndrome
Histiocytosis

Other

Drug related fevers
Fabricated illness
Inflammatory bowel disease
Central origin fever
Periodic fevers
Metabolic fevers (hyperthyroidism, dehydration)
Primary immunodeficiencies

MAIN SESSION

CASE 1 (30 MINUTES)

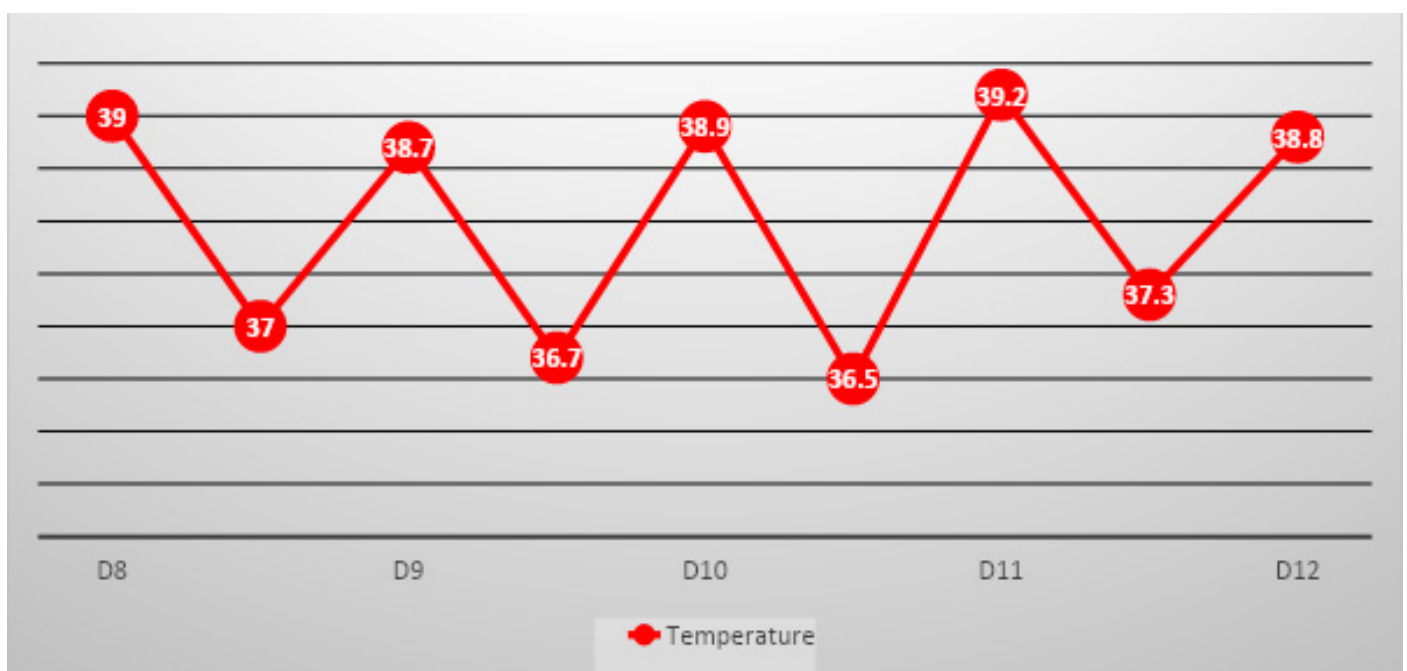
A 14-month-old girl was referred to hospital by GP due to 8 days of fever, non-tender cervical lymphadenopathies (scattered small submandibular, posterior and 1 supraclavicular lymphadenopathies) and mild cough. On examination, the patient has a good general appearance with a mildly red throat and the above described lymphadenopathies. Father is concerned as the child also had a febrile illness the previous week which was labelled as a viral infection.

Blood tests showed raised WCC ($24 \times 10^9/L$) with neutrophilia ($18 \times 10^9/L$). Normal lymphocytes ($6 \times 10^9/L$) with a CRP of 30 mg/L. Chest-X-Ray showed a bilateral bronchial opacification. Patient was admitted and started on Amoxicillin and Azithromycin PO.

Despite 5 days of treatment, the patient is still spiking fevers (see chart below).

Blood culture is negative. Clinically stable, cough has now disappeared. You are classifying this patient as PUO.

1. What questions do you want to ask the parents? Take a detailed history.
2. Why is this patient not getting better despite treatment?
3. What investigations can be prompted by clinical findings?
4. At this point, would you escalate the antibiotic treatment?



1. What questions do you want to ask the parents? Take a detailed history.

In PUO, a detailed clinical history is the most important diagnostic tool that can guide all investigations. **Instead of ordering random tests, ask more questions!**

When taking the history, consider:

- **Characteristics of the fever:** when did it start, duration and intensity. Note that this child had a previous febrile illness which can be part of the same illness.
- **Pattern of fever:** there are several patterns of fever which can help with the diagnosis (**Table 1**). If managed in an outpatient setting, ask the family to do a symptoms diary. From looking at the fever chart, the child has an intermittent fever pattern.

Table 3

Type of fever	Characteristics of fever	Possible causative agent
Intermittent Fever	Sharp febrile peak which goes back to baseline	Bacterial Infections, TB, SOJIA
Remittent Fever	Fever peaks and elevated basal temperature	Viral illness, Endocarditis, lymphomas
Sustained Fever	Persistent fever with minimal variation	Typhoid fever, Brucellosis
Recurrent Fever	Periods of fevers intercalated with afebrile periods	Malaria, Lymphomas, Borellia
Periodic Fever	Febrile periods are intercalated with afebrile periods with a predictable pattern of 6 months	Periodic fever syndromes

- **Age of the child:** PUO in young children is often caused by infections while in older children and teenagers tends to be caused by a connective tissue disorder or a malignancy.

- **Associated symptoms and signs:** headaches, vomiting and diarrhoea, rash, arthralgias, myalgias, bony pain, lymphadenopathies. They can be very subtle therefore a systematic review of all systems is necessary.

- **Systemic symptoms:** fatigue, anorexia, weight loss, sweating.

- **Previous medical history:** a history of many bacterial infections can be related to a primary immunodeficiency. The most common primary immunodeficiencies are:

1. Common variable immunodeficiency
2. Chronic granulomatous disease

Usually the immunodeficiencies are associated with complicated infections, failure to thrive, atopic disease or autoimmune disease.

For more information:

- **Vaccination history:** patient is fully vaccinated as per UK protocol. This includes BCG due to risk factors (Parents are from a country where incidence of TB is > 40/100,000 or more).

- **Regular medications** or any exposure to new medication (think about drug-related fevers).

- **Family History:** Ethnic background, consanguinity. Family is from India and there is no consanguinity.

- **Environmental risk factors:** TB contacts, area where family lives, exposure to animals, vectors (mosquitos, ticks...), food intake (unpasteurised dairy products, uncooked meat and fish), international travels (place, malaria prophylaxis and compliance of prophylaxis).

Patient travelled to India to visit grandparents when she was 9 months old. She was exposed to some mosquito bites. She lived in an urban area for 3 months. Parents were not aware of any TB contacts.

For international travellers, the following website provides relevant information on potential risks and outbreaks occurring on each country:

<https://travelhealthpro.org.uk/>

2. Why is this patient not getting better despite treatment?

When a patient has received a provisional diagnosis plus empirical treatment for at least 48 hours and there is no improvement, clinicians should use a systematic approach to understand the reasons behind the poor response to treatment.

Here's the 4 main questions to be answered:

1. Is there a problem with the medication?

The diagnosis is right but the problem is within the treatment. Issues with the treatment could be related to:

- Drug resistances (MRSA, ESBL bacteria).

This website will provide a map with all antibiotic resistances over the world:

<https://resistancemap.cddep.org/AntibioticResistance.php>, treatments should, when possible, be guided by microbiological culture results.

- Underdosages of the antibiotics which don't reach the effective concentration.

- Very virulent bacteria creating a toxin that requires more antibiotics (eg. Staph. aureus PVL)
- Adherence to treatment (low compliance)
- Malabsorption of medication (for example vomiting, diarrhoea when taking oral medications)
- The selected antibiotics are not reaching the right place of infection (bone, abscess...)

2. Are we targeting the wrong bug?

Antibiotics are mainly covering for bacteria but the actual infection can be caused by other microbes like viruses, atypical bacteria, TB, parasites and fungal infections.

3. Is there a problem with the host?

Consider whether the episode could be only a prolonged febrile syndrome for a common disease due to host problem. The problem can reside in the immunity (immunodeficiencies), structural problems that can predispose to localized infections (for example a patient with previous abdominal surgery who now has an abscess) or whether the patient has a foreign body or a central catheter that can be the source of the infection.

4. The problem is not infectious: fever can be a signs of a tissue connective disorder, malignancies and other illnesses like a central origin related fever, drug related fever or a factitious illness.

3. What investigations can be prompted by clinical findings?

This child has now had at least 12 days of fevers. It could be even longer if we consider that he had a febrile illness labelled as “viral” before this episode. On examination, the main clinical sign are the small cervical lymphadenopathies bilaterally with 1 small supraclavicular lymphadenopathy. This clinical finding can prompt clinician to investigate for:

Table 4

Infectious	Reason for suspicion	Test
Upper respiratory viral illness	Coryzal, submandibular lymphadenopathies	NPA for Virus PCR. Be careful with interpretation of results. A positive result may represent carriage and not necessarily active disease
Systemic viral illness: EBV, CMV	Fatigue, lymphadenopathy, cytopenias, elevated transaminases	EBV and CMV serology Reactive lymphocytes on blood film.
Bacterial localised pneumonia/ pleural effusion	Sick patient with difficulties in breathing	CXR and Chest Ultrasound
Tuberculosis	Lymphadenitis, cough, systemic symptoms (night sweats, weight loss)	Tuberculin skin test IGRA, Gastric aspirate for microscopy and Gen-expert, Fine needle Aspiration for histology and microbiology
Bartonella (Cat-scratch)	Exposure to cats, chronic granulomatous papule	Bartonella serology
Connective Tissue		
Systemic Onset Juvenile Idiopathic Arthritis (SOJIA)	Prolonged fever, arthritis of 1 or more joints, salmon pink rash, adenopathy, hepato-splenomegalies	Elevated ESR, Elevated ferritin, absence of antibodies, rheumatoid factor negative and exclusion of malignancy or infectious process.

Malignancies

Lymphoma

Supraclavicular lymphadenopathies, B symptoms (night sweats, weight loss and fever)

LDH, Uric Acid, Bone marrow aspirate, Chest XR for mediastinal mass. CT/PET

Leukaemia

Fevers, generalised lymphadenopathies, fatigue, easy bruising, bony pain

LDH, Uric acid, pancytopenia, Bone marrow aspirate, flow cytometry.

Other

Histiocytosis

Erythematous skin lesions, oral ulcers, bone pain, lymphadenopathies, cough, shortness of breath, hepatosplenomegaly, malabsorption.

Histological confirmation of Langerhans cells.

4. At this point, would you escalate the antibiotic treatment?

Probably not. Use of antibiotics can delay microbiological diagnosis since the blood cultures' yield is decreased. If the patient has a good general appearance and fevers are well managed with PRN antipyretics, then clinician can consider withholding the antibiotics until a definitive diagnosis is reached.

Reaching the definitive diagnosis:

After 5 days of treatment with amoxicillin and azithromycin and no clinical improvement, basic investigations were repeated and further were added.

BLOOD TESTS

WCC 22 x10⁹/L with neutrophils of 18 x10⁹/L,
Lymphocytes 4 x10⁹/L, CRP 36 mg/L
ESR >60 mm/h
Normal renal and liver function
Blood film normal: No reactive lymphocytes, no lymphoblasts seen
Blood cultures Negative.
CMV Serology: IgM negative, IgG Negative
EBV serology: IgM negative, IgG Negative

MICROBIOLOGY

Mantoux /TST (Tuberculin skin test):
10 mm induration
(Patient received BCG vaccination)
IGRA (Interferon gamma release assay):
Positive
Gastric aspirate for AFB smear:
negative
Gastric aspirate for TB GeneXpert:
negative.

IMAGING

Repeated Chest XR: similar features compared to previous one, peri-bronchial shadowing.

Ultrasound of Lymph-nodes:
Several lymph-nodes with nodal matting and surrounding soft tissue oedema. Prominent vascularity in the hilum.

After 18 days of intermittent fever, cervical lymphadenopathies and some fatigue, the patient underwent a fine-needle aspiration of the supraclavicular lymphadenopathy. The histology showed a caseating granuloma and the microbiology sample showed acid fast bacilli. TB GeneXpert of the sample and culture were positive for non-resistant *Mycobacterium Tuberculosis*. Patient was diagnosed with **tuberculous cervical lymphadenitis (extrapulmonary TB)**.

When to do a biopsy or FNA of a lymph-node?

- Systemic symptoms
- Supraclavicular lymph-node
- Firm and/or fixed lymph-nodes
- CXR changes, abnormal Full blood count or increased ESR
- Adenopathies > 1 cm in a neonate
- Suspicion of TB
- Persistent lymphadenopathies for more than 4 weeks despite antimicrobial treatment
- Sometimes in acute lymphadenitis if a patient is not responding after 48 hours of treatment.

To note, the patient had received the BCG vaccine. However, it has about 50% efficacy which implies that patients with BCG vaccination can still have tuberculosis. BCG is more effective in preventing children from developing disseminated (Miliary) TB or TB meningitis. She was probably exposed to TB and became infected while in India, subsequently developing the disease over the next few months.

Contact tracing of family members is mandatory to identify the source case. Usually, children are not very infectious since the majority of cases tend to be paucibacillary (low bacterial load) unless they have lung cavities or extensive lung involvement.

TB in children often presents in a non-specific way. The typical symptoms are weight loss or failure to gain weight, fever, night sweats and fatigue.

When children present with pulmonary TB, this is usually confined within the intrathoracic nodes. Patients may have persistent cough and asymmetrical and persistent wheeze caused by airway compression due to enlarged tuberculous peri-hilar nodes.

Chest XR can be helpful in the diagnosis of early primary infection by detecting intrathoracic lymph-node enlargement. However, these changes may be subtle as a strong index of suspicion is required. More information on radiological features of paediatric TB can be found on the following link:

[doi: 10.1101/cshperspect.a017855](https://doi.org/10.1101/cshperspect.a017855)

Sputum and gastric aspirate mycobacterial cultures have a low diagnostic yield since most children have paucibacillary TB. Recently, diagnostic sensibility for these samples has increased due to the rollout of new molecular techniques (GeneXpert TB PCR).

TST (Mantoux test) and new immunological assays such as IGRAs detect exposure. TST is performed by injecting 0.1ml of tuberculin purified protein derivative (PPD) intradermally into the inner surface of the forearm.

The skin reaction produced by the PPD should be read between 48 and 72 hours. The reaction is measured in millimetres of induration, not redness.

There are different measures to define a positive result depending on patient background history (for example BCG vaccination) and there are also many causes of false positive and false negative results. For more information

<https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm>.

On the other hand, IGRA is a blood test which measures the body's immune response (interferon-gamma production) to TB antigens. Our patient had a positive Mantoux test (10 mm) but the result might have been affected by previous BCG vaccination. However, this result, combined with a positive IGRA, demonstrated that the child had been previously exposed to TB. Unfortunately, neither of these tests can distinguish between latent infection and active disease.

The patient was treated with Isoniazid (with Pyridoxine), Rifampicin, Ethambutol, and Pyrazinamide for 2 months and Rifampicin and isoniazid for another 4 months. Corticosteroids were not deemed necessary in this case since the lymphadenopathies were not compressing other structures. Empirical treatment of tuberculosis is usually limited to clinical cases where milliary or CNS TB are suspected, as a treatment delay in these cases will often lead to worse outcomes.

CASE 2 (20 MINUTES)

3-year-old boy with a 5-day history of fever and loss of appetite presented to the emergency department with his mother as he had been crying all night and refused to put his T-shirt on. No history of trauma reported. On examination, he looked skinny and he was crying when the right arm was moved. Bloods test showed Hb 9 g/L, WCC $4 \times 10^9/L$ Neutrophils $1.5 \times 10^9/L$ Lymphocytes $2.5 \times 10^9/L$ Platelets $120 \times 10^9/L$. CRP 40 mg/L. Right arm X-Ray was normal. The patient was admitted for observation. On the ward, it was noted that he was spiking fevers every night.

After 3 days of admission, MRI of the right upper limb was performed. MRI showed possible osteomyelitis of the right distal clavicle. He was diagnosed with acute pyogenic osteomyelitis and was started on ceftriaxone 50mg/kg IV OD. Blood cultures (taken before administration of antibiotics) were negative. Fever settled after 5 days of antibiotics. Patient was discharged home on oral antibiotics for 3 weeks.

10 days later, the patient was reviewed in the clinic. Mother was worried since the patient had had fevers again over the last 2 days, felt fatigued and was reluctant to walk.

At this stage, what is the differential diagnosis?

What investigations would you perform?

What treatment would you give? If you were to suspect an autoinflammatory disease, would you give steroids?

What is the role of PET-CT in PUO?

1.What is the differential diagnosis?

Infectious diseases:

Osteomyelitis:

Every time a patient presents with reduced range of movement due to a bony pain, osteomyelitis should be considered. In non-verbal children, it can present with irritability and inability to bear weight. It usually affects the metaphysis of the long bones (femur, tibia...). Therefore, the original diagnosis of clavicle osteomyelitis was quite rare. Now that the patient presented again with fever

and a new similar problem after receiving adequate antibiotic therapy, another diagnosis should be considered.

Septic Arthritis:

It has a similar presentation to osteomyelitis but usually the joint is swollen, red and hot. Ultrasound of the joint can detect joint effusion which can be a sign of septic arthritis. Urgent orthopaedic referral for aspiration +/- surgical washout is necessary.

Connective tissue disorder:

Transient synovitis: Fever and inability to bear weight can be a common presentation for transient synovitis. In this particular case, the initial diagnosis might have been wrong and the first inflammatory/infectious process could have triggered the production of antibodies causing inflammation over the joint.

SOJIA (Systemic Onset of Juvenile Idiopathic Arthritis): Usually the joints affected by the arthritis are hot, tender and erythematous. We can suspect this pathology when there are different joints affected at different times. It is usually associated with systemic symptoms (fever and salmon pink rash, splenomegaly, serositis). Diagnosis is made by elevated ESR, elevated ferritin, absence of antibodies, rheumatoid factor negative and exclusion of malignancy or infectious process.

CRMO (Chronic Recurrent Multifocal Osteomyelitis): this is an idiopathic inflammatory bone disorder with chronic multifocal bone pain. Sometimes systemic symptoms like fever can appear. Clavicle involvement is characteristic of this pathology.

Diagnosis is made by lesion's biopsy: this will show an inflammatory reaction with no microbiological growth.

Malignancies:

Leukaemia: can present with bony pain and fatigue, lethargy and weight loss. Pancytopenia and blast can be seen in the blood film. LDH and uric acid are raised. Definitive diagnosis is reached with the bone marrow aspirate and flow cytometry.

Neuroblastoma: This is a malignancy that usually presents with abdominal mass. Sometimes mass can be found in the thoracic cavity. It appears in children below 5 years. The neuroblasts infiltrate the bone marrow. Therefore, patients can present with bony pain and pancytopenia. Diagnosis is reached by abdominal ultrasound and further imaging to evaluate the stage of the disease. Bone marrow aspirate is necessary along urine Vanillylmandelic Acid (VMA).

Bone tumours (osteosarcoma /Ewing's Sarcoma):

Even though bone tumours are much less common than leukaemia and neuroblastoma, the presence of bony pain and prolonged fevers would prompt the diagnosis. LDH is usually elevated with raised calcium.

X-Ray show bony abnormalities and further imaging with MRI or CT can provide more information. Sometimes biopsy of the lesion is necessary to confirm the diagnosis.

Bone marrow is recommended in Ewing's sarcoma. Metastasis and benign bone tumour should also be considered in the differential diagnosis.

Other:

Histiocytosis: this is a systemic illness which can affect bones. Associated symptoms are erythematous skin lesions, oral ulcers, lymphadenopathies, cough, shortness of breath, hepatosplenomegaly, malabsorption. Diagnosis is reached by seeing Langerhans cells in the biopsy of the lesion.

2. What investigations would you perform?

At this point, the patient has had a fever on and off for more than 3 weeks. A provisional diagnosis of osteomyelitis was made based on imaging findings. However, treatment is failing and the patient is now presenting with new symptoms (unable to bear weight).

Repeated basic investigations:

Full blood count	Hb 8.5 g/L WCC 1.0 x10 ⁹ /L Lymphocytes 9.0 x10 ⁹ /L Platelets 100 x10 ⁹ /L	Blood culture	Negative
Peripheral blood film	Normal	Urine culture	Negative
CRP	15 mg/L	Mantoux test	Negative
ESR	>40 mm/h	HIV serology	Negative
Renal function	Normal range	Sickle cell test	Negative
Liver function	Normal range	Chest XR	Normal
LDH	900 U/L (240-480)	---	---
Uric Acid	12 µmol/L (High)	---	---

If after the above investigations, the clinician does not reach a diagnosis, then:

- Re-take a good clinical history
- Re-assessment of the patient
- Withhold current medications
- Do specific imaging (XR/Ultrasound/MRI of the new affected area)
- Perform immunological studies: rheumatoid factor, ANA and anti-DNA antibodies, Immunoglobulins
- Perform a bone marrow aspirate and trephine for histology, cytology and microbiology.

3. What treatment would you give? If you were to suspect an autoinflammatory disease, would you give steroids?

In this case, the diagnosis of osteomyelitis was discarded. SOJIA vs Leukaemia were the 2 main differential diagnoses. Discussion regarding therapeutic steroid treatment for SOJIA was raised.

Usually in PUO, **steroid treatment should be avoided until malignancy is ruled out**. Steroids are used therapeutically in many oncology protocols. The use of steroids in an unconfirmed case of leukaemia can improve symptoms but it can blur the histological picture required for the diagnosis and confuse the staging process. This would lead to a delayed and potentially incorrect treatment. It is crucial to perform a bone marrow aspirate before steroid treatment is given, especially if there are symptoms and signs compatible with malignancies.

In the above case, the full blood count showed mild pancytopenia which can be related to a bone marrow infiltration. The peripheral blood film was normal. Finally, the patient underwent a bone marrow biopsy and this confirmed the diagnosis of T-cell ALL.

4. What is the role of PET CT in PUO?

PET-CT is an imaging technique that localises anatomical parts with high metabolic activity, detecting hidden infections, malignancies or any inflammatory foci.

PET-CT has proven to be useful in patients with PUO who are generally unwell, sick-looking, since early diagnosis is urgent in those patients. Otherwise, PET-CT can be used in those patients who have had extensive investigations done, have not had clinical improvement and still no diagnosis has been reached.

ADVANCED SESSION

ADVANCED CASE 1 (30 MINUTES)

4-year-old boy presented with 5 days of fever, diarrhoea and vomiting and abdominal pain. No relevant past medical history. Fully vaccinated, BCG not included.

Initial blood test showed WCC $24.5 \times 10^9/L$ with neutrophils of $18 \times 10^9/L$. CRP 139 mg/L. Hb 110 g/L and Platelets of $395 \times 10^9/L$. He was admitted and started on amoxicillin, gentamicin and metronidazole. Blood cultures were negative and urine culture showed a sterile pyuria (WCC 2250 with no growth). Stool sample was negative. Abdominal ultrasound showed free fluid in the right iliac fossa. On examination, his abdomen was soft with some tenderness in lower quadrants. He had a second ultrasound which showed findings suggestive of an appendicular mass. A repeated urine sample had 64 WBC and no growth.

Meanwhile, fevers persisted: on day 7, he was changed to piperacillin-tazobactam and gentamicin. He underwent a laparoscopic appendicectomy on day 8. After operation, he was afebrile for more than 48 hours and antibiotics were stopped. Histological results of the appendix were normal. On day 12 of admission, the patient started again with fever and no focus on examination.

1. Now that the fever has restarted, and considering the previous history, what investigations would you ask?
2. Would you re-start antibiotics?
3. Looking at the pattern of fever below, what can you observe?
4. Would an echocardiogram help in reaching the final diagnosis?

1. Now that the fever has restarted, and considering the previous history, what investigations would you ask?

You should probably start by repeating basic investigations. Results: raised WCC with neutrophilia and thrombocytosis. Hb 101 g/L, WCC $32 \times 10^9/L$ with neutrophils of $24 \times 10^9/L$, Platelets of $961 \times 10^9/L$. He had normal renal and liver function.

Infectious diseases investigations:

Microbiology cultures: Blood cultures were negative, even the prolonged culture

for atypical bacteria. Stool sample was negative for viruses, bacteria and parasites. Urine sample became negative (previous sterile pyuria)

Toxoplasma serology: IgG and IgM negative

CMV serology: **IgM positive** and IgG positive. Second sample sent for CMV IgM negative. CMV PCR was negative. The initial positive IgM CMV was considered to be a false positive. IgM positivity in virology/microbiology assays may be non-specific, in patients with **autoimmune diseases, cross-reactions**.

EBV serology: IgM and IgG negative.

Blood PCR for EBV, CMV and adenovirus negative.

Respiratory sample PCR: negative.

Lumbar puncture: LP was performed on day 14 of admission: WBC < 3/mm³. RBC < 3/mm³. Viral PCR for enterovirus, parechovirus, mumps, VHS1&2 and VVZ negative. Negative culture.

Interferon Gamma Release Assay for TB negative.

Inflammatory conditions Investigations:

Faecal calprotectin: negative. Since the patient had gastrointestinal symptoms and fever, Inflammatory Bowel Disease (IBD) should be considered as a potential differential diagnosis.

ESR: 50 mm/h.

Ferritin 222 ng/mL: important marker for inflammation. Especially high in Hemophagocytic lymphohistiocytosis /Macrophage Activation Syndrome.

Malignancies:

Blood film: no atypical cells. Polychromasia and raised platelet count.

Neutrophilia.

LDH 446 U/L (high)

IMAGING:

Day 12 Chest XR: normal

Day 13 Abdominal Ultrasound: normal kidneys and bladder. Normal liver, spleen, gallbladder and bile ducts. No abnormal masses or bowel wall thickening. Trace of fluid in right iliac fossa postoperatively. No fluid collection.

2. Would you restart antibiotics?

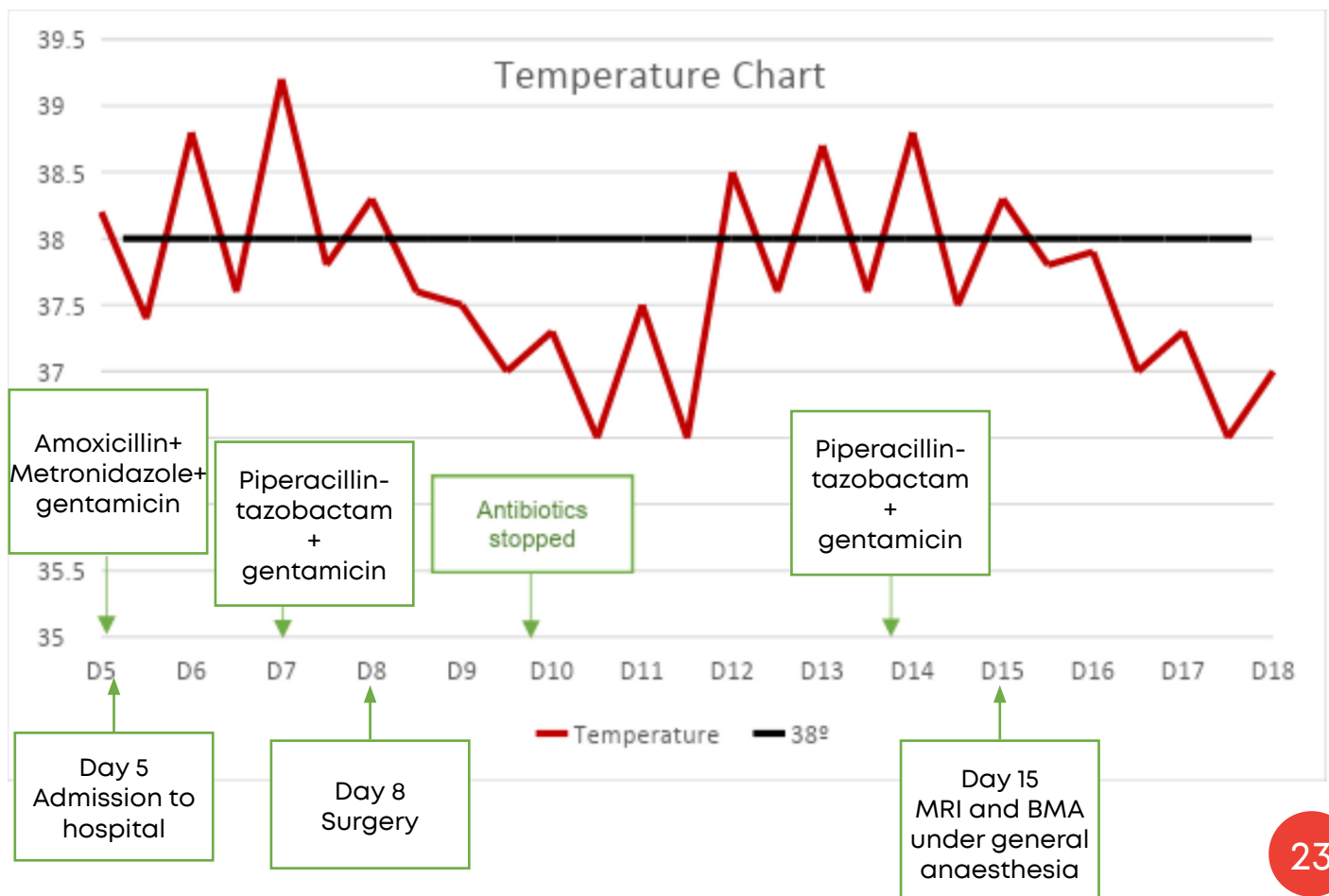
The patient was clinically stable, so it was **decided to wait and hold antibiotic treatment**. The patient continued to have daily fevers up to 39°C. On day 14, he had one bilious vomit and became more lethargic therefore antibiotics were restarted (Piperacillin-Tazobactam and gentamicin). The following day, he underwent a Bone marrow aspirate and MRI under general anaesthesia with results as below:

BMA: Trilineage haematopoiesis. No evidence of abnormal infiltration. No increased haemophagocytic activity. Appearances in keeping with a reactive marrow. Negative for AAFB, both microscopy and culture.

Abdominal MRI: There is moderate distention of the proximal small bowel with an apparent jejunal transition point due to ileus, adhesions or oedema from handling. Some free fluid but no abdominal collections. No retroperitoneal collection. No bone marrow abnormality.

On day 16, he did not spike any temperatures. After 48 hours (on day 18 of admission), he had an evening temperature of 38.5°C.

3. Looking at the pattern of fever below, what can you observe?



The patient had 2 episodes when he was apyrexial:

- the first one between day 9- 11 after antibiotics were escalated (Piperacillin-Ta-zobactam and Gentamicin (D7)) and after surgery under general anaesthesia (D8).
- The second afebrile period was on day 16-18 after being re-started on Piperacillin-Tazobactam and Gentamicin (D15) and after he underwent a procedure under general anaesthesia.

In the first episode, the lack of fever was linked to a good response to antibiotics whereas in the second episode given the fact that a non-infectious condition was highly suspected as a differential diagnosis, the afebrile episode could be linked to the anaesthesia. **link between anaesthetics and immune response as many have an anti-inflammatory effect.**

4. Would an echocardiogram help to reach the definitive diagnosis?

A very important investigation to perform in PUO is an echocardiogram to rule out infective endocarditis. In this case, there were no positive cultures or risk factors to point towards an infective endocarditis but it would be useful to rule out this disease. Echocardiography can also help to diagnose Kawasaki disease. In this particular scenario, it would be an incomplete case of KD.

Reaching the diagnosis:

On day 19, the patient had **an echocardiogram which revealed dilated circumflex artery** and an aneurysm of the left anterior descending artery. This finding confirmed the diagnosis of Incomplete Kawasaki. The ophthalmology review showed no pathological findings.

DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE

Full case of Kawasaki

Fever ($>38^{\circ}\text{C}$) every day for 5 days

+

At least 4 of the following 5 features

1. Non purulent bilateral conjunctivitis
2. Cervical lymphadenopathy
3. Polymorphous rash
4. Lips/oral mucosa involvement
5. Fingers/toes: acute erythema and oedema of palms and soles and then peeling.

Or positive echocardiogram at any time with less than 4 features.

Incomplete case of Kawasaki

Fevers ($>38^{\circ}\text{C}$) every day for 3 days

+

less than 4 features but diagnosis supported by:

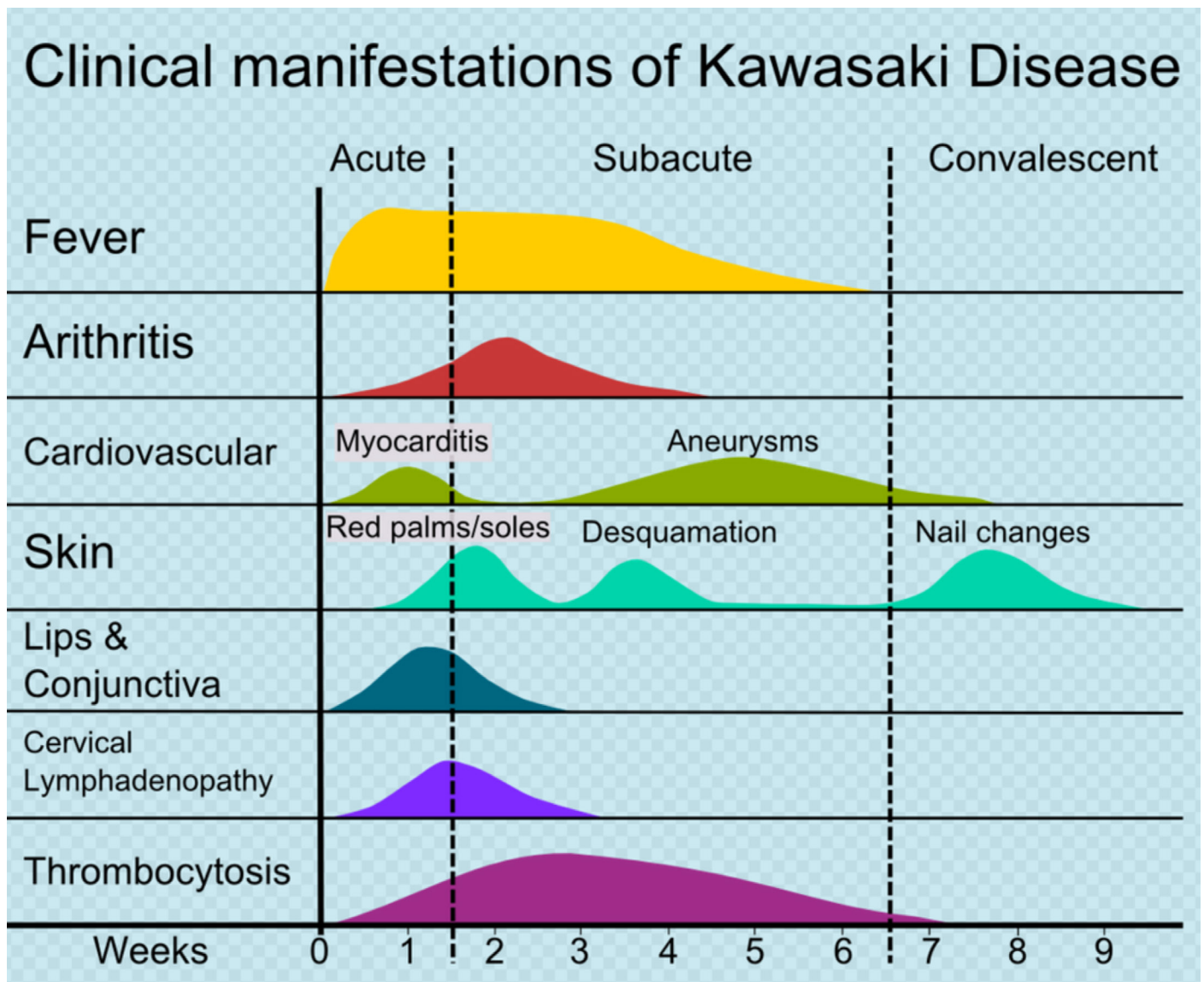
1. Lack of alternative diagnosis (lack to respond to antibiotics, no other pathogen found)
2. High inflammatory markers (high CRP, ESR, Neutrophilia)
3. Present of other clinical features:
 - Irritability without CNS infection
 - BCG scar inflammation
 - Other system involvement: CSF pleiocytosis, uveitis, arthritis, gastroenteritis, myocarditis, dysuria, sterile pyuria.

In our particular case: the patient had prolonged fevers with high inflammatory markers (CRP, ESR, Neutrophilia), irritability without CSF infection, sterile pyuria, low albumin, anaemia, thrombocytosis and lack of alternative diagnosis. Furthermore, he had a characteristic echocardiographic finding of Kawasaki Disease.

Patient was started on IVIG and aspirin. Steroids were included in the treatment since the patient already had evolving coronary and or peripheral aneurysm. For more information on criteria for steroid use in Kawasaki disease, you can read: [Eleftheriou D, et al. Management of Kawasaki disease. Arch Dis Child, 99,1 2013](#) With regards to the antibiotics, gentamicin was stopped while Piperacillin-tazobactam was continued while evaluating response to IVIG. Piperacillin-tazobactam was stopped after 48 hours.

For more information on KD, you can refer to our other module 'Blanching Rashes'

Kawasaki disease is rare but early diagnosis is important to avoid cardiological sequelae. Incomplete Kawasaki can present a clinical challenge to diagnose.



A summary of the timeline of the clinical manifestations of Kawasaki Disease
(Credit courtesy of Wikipedia.org)

ADVANCED CASE 2 (20 MINUTES)

You are in an Ethiopian rural hospital. A 7-year-old boy presents to clinic severely malnourished (marasmic type). Mother is complaining of daily fevers for an unknown period of time.

Patient has cerebral palsy due to an obstructed labour resulting in hypoxic-ischaemic injury. He was in hospital for some time after delivery. He is not vaccinated. He is on phenobarbitone 100mg OD PO for seizures.

You admit the child to the malnutrition ward and start the appropriate treatment with F-75 Milk. Part of the SAM protocol (Severe Acute Malnutrition) includes a course of at least 7 days with Amoxicillin. On examination, the patient has a papular rash over hands and groin compatible with scabies but no other clinical findings. On the ward, he spikes a high temperature (39°C) and he is shivering. Available investigations at your hospital are performed:

Blood tests:

Hb 9.1 g/L

Renal function and CRP not available in this setting.

WCC 12 x10⁹/L with neutrophils 8 x10⁹/L and lymphocytes 4 x10⁹/L

Urine dipstick: leucocytes and nitrates positive
Urine microscopy: many white cells.
No culture available.

Platelets 300 x10⁹/L

Stool: negative for parasites

Blood film: No parasites seen

GGT 61 IU/L

HIV antibodies negative

GOT 72 IU/L

Hepatitis B and C antibodies negative

Bili < 0.5 µmol/L

1. Based on the above clinical picture and results, what is your differential diagnosis and management?

2. Patient was empirically treated but fevers persisted. Given his background of CP and the geographical area, what other infections would you consider?

3. What other non-infectious causes should be considered? How can you reach the diagnoses in this low-resource-setting?

1. Based on the above clinical picture and results, what is your differential diagnosis and management?

This is a very challenging patient. Due to their reduced ability to communicate and cognitive impairment, these children are difficult to assess. Furthermore, this patient is malnourished which increases the risk of infections.

The above results showed a possible UTI which is in keeping with the clinical picture (high fevers, shivering in a patient with high risk of UTI due to his cerebral palsy and poor bladder control). Antibiotics were changed from amoxicillin to amoxicillin-clavulanic to give broader cover for gram negative bacteria (E. Coli, Klebsiella...).

To note, the patient has scabies which is a very common parasitic skin infection that affects mainly the palms and soles and the groin area. If the patient has been scratching over the genital area, it could have triggered a UTI. Furthermore, there are poor hygiene conditions in the area with limited access to water.

The slightly raised GGT and GOT was correlated to the use of phenobarbitone. The hepatitis B and C were negative but the hospital did not have the test for hepatitis A. Nevertheless, the clinical symptoms were not fitting with hepatitis A.

The patient was treated with co-amoxiclav for 7 days. He initially improved and fevers were spacing in time. However, on day 9 he started again with very high fevers and shivering. He was looking unwell during the fever episodes so he was started on ceftriaxone IV. His baseline temperature was always raised, he had abnormal movements and was irritable. Temperature persisted despite treatment.

2. Given his background of CP and the geographical area, what other infections would you consider?

Another urine sample was requested to rule out a **UTI** due to a resistant bacterium, since microbiological cultures were not available in the rural hospital. The urine microscopy was negative for WCC and urine dipstick did not show any abnormalities.

Another important differential diagnosis was **meningitis**. Patient was irritable, had abnormal movements and a fever. The abnormal movements consisted of small twitching of the arms while crying inconsolably. There were considered either shivering or behavioural but there was a lot of discussion if those movements could represent a seizure event. Furthermore, mother was unable to describe the usual seizures that he had at home. The team subsequently realised that there was an error with the regular medications: he was prescribed 100mg of phenobarbitone but mother clarified that at home he was taking 200mg, therefore his daily phenobarbital dose was increased to 200mg OD. To note, the patient did not have any devices (VP shunt) which could increase the risk of infections. In this rural setting, clinicians were not able to perform a lumbar puncture due to lack of laboratory equipment, so the patient was started on ceftriaxone high dose empirically.

Pneumonia can be a common cause of infection in patients with cerebral palsy since they can have drooling, unsafe swallow prompting for aspiration. Usually, pneumonia in these children can be very silent. In addition, poor nutritional status can increase the risk of severe pneumonia. Patient was not desaturating or with respiratory symptoms but a chest XR was done (in a private clinic) and no lung abnormalities were detected. Furthermore, based on local antimicrobial resistances, the antibiotics he received earlier should have been covered for the most common bacteria causing pneumonia. Gastric aspirate for GeneXpert MTB/Rif was negative.

Dental infections with abscesses can also present with fever and no other major symptoms. The patient had poor oral hygiene plus the lack of proper tongue movement, drooling and lack of routine dental care made him more prone to these types of infections. These infections are mainly due to anaerobes which should be covered by amoxicillin-clavulanic or ceftriaxone. On examination, no suspicious dental masses were found.

Viruses can also cause non-specific symptoms. However, they shouldn't last for very long. He did not have any gastrointestinal symptoms or respiratory symptoms. No palpable lymph-nodes. Unfortunately, in the hospital there were no laboratory diagnoses for viruses. Full blood count differential was never lymphocytic.

The most common **parasites** in this rural area are intestinal parasites (Giardia, Entoamebas) and blood parasites (Malaria). Entoamebas can present with a dysentery which can cause fever. However, our patient did not have any diarrhoea.

This area has a moderate risk of malaria, especially during the rainy season. Patients with malaria present with very unspecific symptoms: from fever with general malaise or headache and vomiting to seizures, coma and shock. Therefore, any patient with a fever in a tropical setting should prompt investigations for malaria. **The most important element in the clinical diagnosis of malaria is a high index of suspicion.**

To reach the laboratory diagnosis, parasites should be seen or detected in blood. Blood film microscopy (thin and thick blood films) is the gold standard for malaria diagnosis, identifies the Plasmodium species and also quantifies the parasitaemia. However, in low resource settings, where microscopy is not always available or reliable, rapid diagnostic tests (RDT) are used to diagnose malaria. The RDTs detect Plasmodium antigens confirming the presence of parasites in the blood but don't provide any information regarding the species or the parasitaemia.

Patients with malaria can be classified into severe or non-severe malaria based on clinical and laboratory findings as per the WHO 2015 Malaria Guidelines. This classification is crucial as it will guide treatment. The most important complications of malaria infection in children are cerebral malaria, severe anaemia, respiratory distress due to acidosis and hypoglycaemia.

Severe Malaria

Clinical findings	Laboratory
<ul style="list-style-type: none">- Impaired consciousness/unrrousable coma (Glasgow score <11, Blantyre score <3)- More than 2 convulsions in 24 hours- Prostration- Deep breathings/respiratory distress- Shock- Bleeding- Jaundice with parasitaemia > 2%	<ul style="list-style-type: none">- Severe anaemia with parasitaemia- Acidosis- Hypoglycaemia- Hyperparasitaemia- Haemoglobinuria- Renal impairment

Patients with severe malaria should receive parental antimalarial treatment with Artesunate and supportive management followed by a full course of oral artemisin combination therapy (ACT). Patients with non-severe malaria can be managed with oral antimalarial medication.

On admission, the initial blood film was negative for haemo-parasites. Repeat blood films and a Malaria RDT (rapid diagnostic test which detects Plasmodium falciparum antigens in blood after 20 minutes) were requested. Repeat Blood film revealed presence of Plasmodium falciparum trophozoites with a parasitaemia of 2%.

So the patient was diagnosed with Severe Malaria given the suspicion of CNS involvement and started on IV Artesunate. The patient had a good clinical response with resolution of fever and completed a course of oral Artemisin combination treatment (Artemeter Lumefantrine). However, after one week, the fever reappeared. This time, it was a low-grade fever with maximum peaks at 38.5. Repeat blood tests were normal.

3. What other non-infectious causes should be considered? How can you reach the diagnoses in this low-resource-setting?

Malignancies: In this case, blood film did not reveal any blasts, chest XR was normal and abdominal ultrasound did not reveal any masses. BMA was not available locally and since the patient was otherwise well, this was not considered necessary.

Connective tissue disorders:

SOJIA, AR are very uncommon but still a differential diagnosis of persistent fever. In this setting, no resources were available for auto-antibodies testing, therefore clinical findings are the main way of diagnosing it. Since the patient did not have any rash, arthritis... this diagnosis was not considered.

Acute Rheumatic Fever (ARF): this condition is quite common in low resource countries due to increased risk of streptococcal tonsillitis due to poor hygiene, overcrowding, poor accessibility to health facilities, fake drugs... Acute rheumatic fever is an illness caused by an inflammatory reaction to streptococcal infection. It causes an acute, generalised inflammatory response. This illness targets specific parts of the body including the heart, joints, brain and skin. ARF typically leaves no lasting damage to the brain, joints or skin, but can cause persisting heart damage. Our patient did not meet the Jones' Criteria of ARF.

Miscellanea (other possible causes of fever):

Central origin fever: children affected with cerebral palsy or other neurological disorders relatively often present with chronic intermittent febrile episodes persisting for months. These episodes are not related to any infections but are actually arising from an abnormal thermal regulation resulting from the brain injury.

Hyperthermia from severe dystonia: children with cerebral palsy with dystonia can present with fevers and elevated basal temperature associated with elevated creatinine phosphokinase levels.

Drug related fever: medications can trigger fevers. Common medications used in cerebral palsy are anticholinergic drugs (e.g. hyoscine) which can provoke unwanted fevers as a side effect. In addition, withdrawal of medications can present with fever (baclofen withdrawal syndrome).

Lastly, **factitious fever** is a very challenging diagnosis. Sometimes admissions to hospital and close measurement of fevers plus observation of patient and carer interaction is as important as complementary tests.

After 2 months of intermittent fever, it finally stopped. Basal temperature was always slightly elevated. Patient was diagnosed with central origin fever.

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QUIZ QUESTIONS (10 MINUTES)

Question 1.

The majority of PUOs are caused by:

- A**
Malignancy
- B**
Connective Tissue Disorder
- C**
Infections
- D**
Other diagnosis
- E**
Unknown diagnosis

Infectious Diseases are the main cause of PUO (about 38%), especially in younger children. No diagnosis is reached in 30% of cases but these tend to be benign and self-limited. This is followed by connective tissues disorders (13%) and Other diagnosis (13%). Lastly, malignancies are very uncommon but very important to consider given the severity of the disease.

Question 2.

A patient admitted to your hospital has been spiking fevers every day for 12 days. No other clinical findings are present. What is your next step?

- A**
Repeat basic investigations, re-take clinical history, re-examine the patient, perform a Bone marrow aspirate.
- B**
Repeat basic investigations, re-take clinical history, re-examine the patient and do adequate imaging depending on clinical findings.
- C**
Perform a PET-CT to localise the pathology.
- D**
Perform autoimmune studies.
- E**
Perform a bone marrow aspirate.

In many PUO cases, clinical findings are very subtle and can appear days after the fever. Therefore, re-taking the clinical history and re-examining the patient carefully is key to guide the complementary tests.

Question 3.

A Turkish 5-year-old girl presented with high fevers, profuse night sweating for 21 days. Clinical detailed history revealed that parents are not consanguineous. She doesn't have any relevant past medical history. She is fully vaccinated. The whole family was in Turkey for 2 months over the summer holidays.

They were living in a farm in rural Turkey where they had goats, cows and chickens. They were drinking fresh milk from the cow. Based on the history,

what diagnosis would you consider?

A

Tuberculosis

D

Toxoplasmosis

B

Bartonella (Cat-scratch)

E

Lyme Disease

C

Brucellosis

Brucellosis is a zoonotic infection caused by ingestion of unpasteurized milk from infected animals. It is also known as the Mediterranean fever. It is caused by a bacterium called *Brucella melitensis*. The main symptoms are fever, profuse sweating and joint and muscle pain.

Question 4.

An unaccompanied asylum seeker from Uganda has just arrived in the UK. He refers to being a 12-year-old. He has had fevers for a prolonged time. On examination, he has splenomegaly. Blood tests revealed pancytopenia. Blood film is negative for malaria. HIV and hepatitis B, C negative. He said that in his country many people have these symptoms and they call it

Kala-azar. **What kind of tropical infection is he referring to?**

- | | |
|------------------------------------|-------------------------------------|
| A
Visceral Leishmaniasis | D
Visceral Larva Migrans |
| B
Schistosomiasis. | E
Echinococcus granulosus |
| C
Non falciparum malaria | |

Kala-azar is the local term for Leishmaniasis. This is a parasitic disease spread by the sand-fly. Main symptoms are fever, enlargement of spleen and liver and pancytopenia. Leishmaniasis is the second-largest parasitic killer in the world after malaria. Diagnosis is made by histological finding of amastigotes on spleen aspiration/bone marrow aspiration and RK39 Antigen detection.

INFOGRAPHICS:(2 minutes)

- 1** Fever is the most common body response to infection but it may also be caused by non-infectious illness.
- 2** Infectious Diseases are the main cause of PUO (about 38%), especially in younger children. This is followed by connective tissue disorders (13%) and other miscellaneous diagnosis (13%). Lastly, malignancies are very uncommon (6%) but very important to consider given the severity of the disease. **See Figure 1 and Table 2**
- 3** In nearly 30% of PUO cases, no definitive diagnosis is reached despite extensive investigations. However, the disease tends to be benign and self-limiting.
- 4** Detailed history taking and careful examination are crucial to guide complementary tests and reach diagnosis. The rapidity of the investigations and the use of broad-spectrum antibiotics depend on the general appearance of the patient.
- 5** Before giving steroid treatment to a patient, ensure that malignancies are ruled out.

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Antoon J, Peritz D, Parsons M., Skinner A., Lohr J. Etiology and resource use of fever of unknown origin in Hospitalized children. Hospital Pediatrics, 8 (3): 135-140(2018)

For malaria:

https://apps.who.int/iris/bitstream/handle/10665/79317/9789241548526_eng.pdf;jsessionid=AD1DDC86455A8D51D25CFEEADF7E1C75?sequence=1

Website resources:

<https://pedemmorsels.com/fever-of-unknown-origin/>

<https://dontforgetthebubbles.com/ent-infections-immunodeficiency/>

<https://dontforgetthebubbles.com/recurrent-or-periodic-fevers-investigate-or-reassure/>

<https://dontforgetthebubbles.com/tuberculosis/gate-or-reassure/>

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