Don't Forget The Bubbles

PYREXIA UNKNOWN ORIGIN

Learners Guide

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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)** Read it

https://dontforgetthebubbles.com/recurrent-or-periodic-fevers-investigate-or-reassure/ **(10 minutes)** Read it

https://dontforgetthebubbles.com/tuberculosis/ **(5 minutes)** Read it

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

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

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

MAIN SESSION

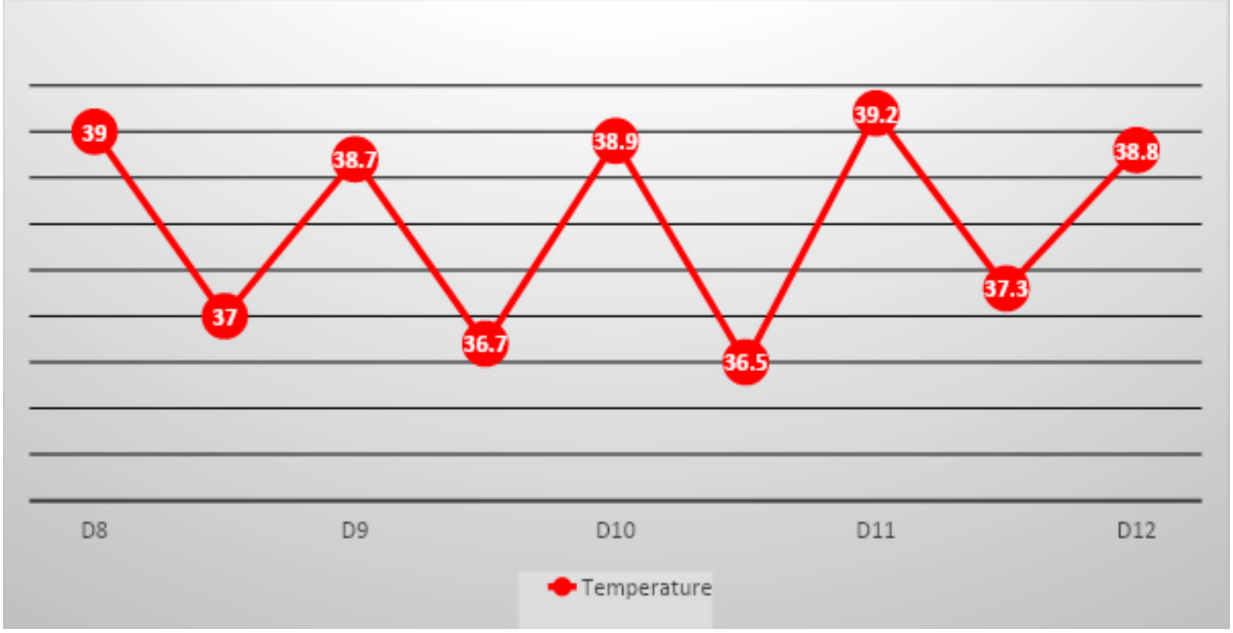
CASE 1 (30 MINUTES)

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 ($24x10^9$/L) with neutrophilia ($18x10^9$/L). Normal lymphocytes ($6 x10^9$/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.

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



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 x109/L Neutrophils 1.5 x109/L Lymphocytes 2.5 x109/L Platelets 120 x109/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?

ADVANCED SESSION

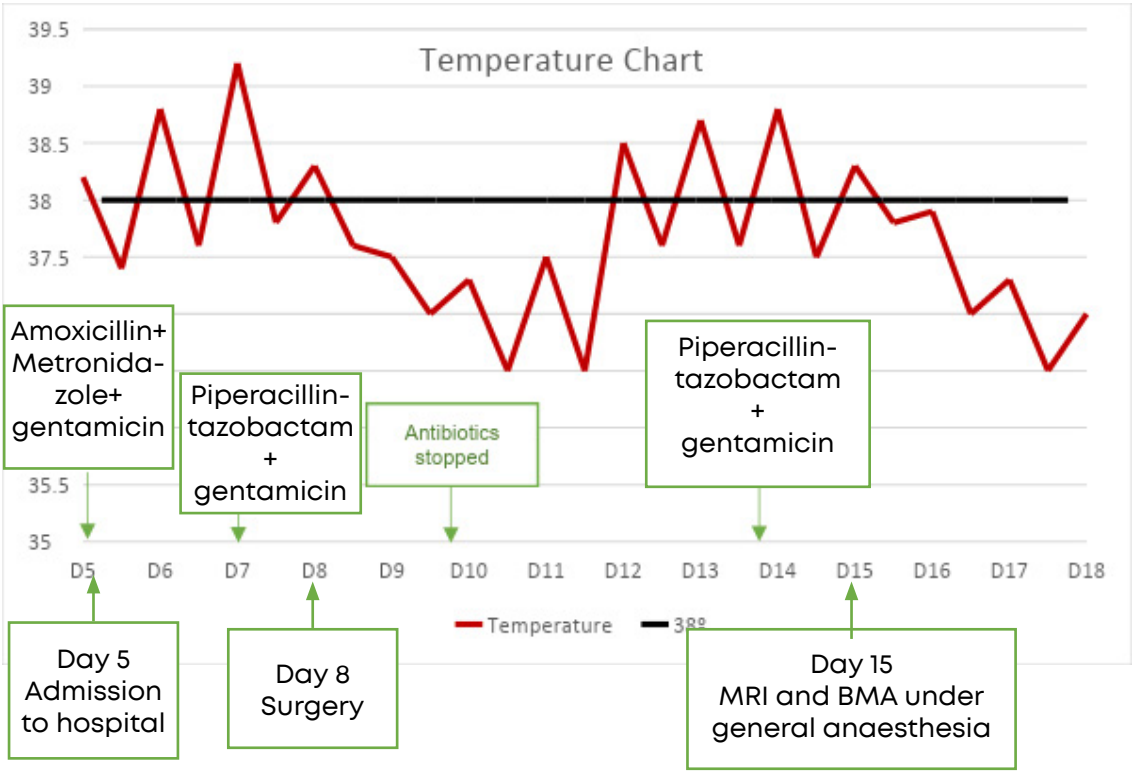
ADVANCED CASE 1 (30 MINUTES)

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 x10^9/L with neutrophils of 18 x10^9/L. CRP 139 mg/L. Hb 110 g/L and Platelets of 395 x10^9/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.

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

Would you re-start antibiotics?

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



Would an echocardiogram help in reaching the final diagnosis?

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	

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

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

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

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

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.

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

B
Bartonella (Cat-scratch)

C
Brucellosis

D
Toxoplasmosis

E
Lyme Disease

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

B
Schistosomiasis.

C
Non falciparum malaria

D
Visceral Larva Migrans

E
Echinoccocus granulosus

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.

REFERENCES

A roadmap for fever of unknown origin in children- Rigante, D; Esposito S., International Journal of Immunopathology and Pharmacology. Vol.26 no 2, 315-326 (2013)

Fever in Children and Fever of Unknown Origin- Rajeshwar Dayal, Dipti Agarwal, Indian Journal of Paediatrics, 83 (1): 38-43 (2016)

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

Barbi E, Marzuillo P, Neri E, Naviglio S, Krauss BS. Fever in Children: Pearls and

Pitfalls. Children (Basel). 2017;4(9):81. Published 2017 Sep 1. doi:10.3390/children4090081

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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