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Prolonged Fever in Children: An Inpatient Diagnostic Framework for Infections in Australia

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ABSTRACT

There are many causes of fever in children, ranging from common and self-limiting to serious and life threatening. Careful assessment of children with prolonged fever without an obvious or identified source requires detailed history and examination with consideration of infections unique to the specific geographical region and individual exposure risks. Previous recommendations for diagnostic work-up have provided valuable insights, but none have been tailored to the Australian inpatient setting. Recognising this gap, a diagnostic approach for infections specifically designed for the Australian child admitted to hospital with prolonged fever ($\geq 38.0^{\circ}\text{C}$) exceeding 7 days is provided.

Level of Evidence: National Health and Medical Research Council Level V.

1 | Background

Fever is a common presentation prompting medical attention in children. Typically, the cause of the fever becomes apparent with time and/or resolves without treatment. However, when a fever persists without an identifiable cause, even the experienced paediatrician may find themselves challenged, especially when determining the appropriate infectious diagnostic work-up.

Pyrexia of unknown origin (PUO) was first defined in adult populations in the 1960s by American physicians Petersdorf and Beeson, with the original criteria including: (i) fever exceeding 38.3°C on several occasions, (ii) illness persisting for more than 3 weeks duration and (iii) failure to reach a diagnosis following 1 week of inpatient investigation [1]. Since then, the definition of PUO in the adult and paediatric literature has varied, particularly around the duration of fever required. Most studies on paediatric PUO have primarily focused on descriptive analyses,

delineating baseline characteristics and discharge diagnoses of children presenting with fever without a discernible source lasting between 14 and 21 days [2–7]. Few studies have evaluated fever durations of 5–7 days [8–10] and/or proposed streamlined diagnostic approaches to the infectious work-up.

While it is important to consider both infectious and the numerous non-infectious causes of PUO, which include malignancy, rheumatic and inflammatory causes, this review will focus solely on infections to consider. The approach to the non-infectious causes of PUO is covered elsewhere [11–14]. Studies to date, including a systematic review [15], have consistently demonstrated that infection is the most commonly identified discharge diagnosis [7, 10, 15–17]. In the systematic review, bacterial infections were most common, with brucellosis, urinary tract infections, tuberculosis, and typhoid fever emerging as the most common bacterial organisms [15]. It is important to note that although the systematic review aimed to consider

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and compare the aetiology of infection in developed and developing countries, studies were largely conducted in tropical low-income regions and/or in tuberculosis or typhoid endemic regions [15]. Regardless, viral infections, notably Epstein Barr virus (EBV) and primary Cytomegalovirus (CMV) were shown to be common infectious aetiologies globally [12, 15] while fungal infections were rare and parasitic infections, particularly leishmaniasis, were more prevalent in developing countries [15].

Despite robust guidelines addressing acute fever [18, 19] and fever in returned travellers [20–22], a notable gap exists for guidelines structuring the diagnostic work-up in children with prolonged fever without a focus. Previous recommendations [5, 11–14, 17, 23–27] have offered valuable insights, yet none have been tailored to the Australian inpatient setting. Consequently, this article aims to address the aforementioned gap by providing a diagnostic approach for the Australian child admitted to hospital with prolonged fever of $\geq 38.0^{\circ}\text{C}$ lasting more than 7 days without an identifiable source. It considers relevant geography and exposures and encompasses infections to consider, diagnostic recommendations, and a clinical framework. Opportunistic infections in the immunocompromised host, neonatal infections, hospital-acquired infections and non-infectious causes fall beyond the scope of this review.

2 | Clinical Assessment

A commonly overlooked aspect in assessing children with prolonged fever without a focus is the omission of a comprehensive bedside clinical evaluation. Repeated history-taking, serial examinations and continuous observation are essential components in the assessment of a child with prolonged fever and should not be underestimated.

3 | Patient History

The patient's medical history should include careful consideration of the following key elements:

- Immune status (immunocompetent vs. immunocompromised).
- Aboriginal and/or Torres Strait Islander status and/or ethnic background.
- Country of birth and childhood vaccination history [28].
- History of fever including measurement (subjective vs. objective), onset and pattern where applicable.
- History of clinical features that may have since resolved, such as conjunctivitis or rash (potentially indicative of Kawasaki's Disease) or a preceding sore throat or skin infection (potentially indicative of Acute Rheumatic Fever).
- History of unintentional weight loss, night sweats or unusual bleeding/bruising, which could indicate malignancy.
- History of joint pain or swelling, which could indicate a bone and/or joint infection, Acute Rheumatic Fever or a rheumatological diagnosis.
- Detailed questioning around home life and potential infective exposures including property type (urban vs. rural), drinking

water source, ingestion of soil (intentional or unintentional), consumption of unpasteurised animal milk [29] or imported foods/substances, contact with pets or animals (at home or outside the home) and likelihood of arthropod bites.

- Detailed questioning surrounding domestic and international travel, including the timeframe of travel, destinations visited, activities undertaken and preventative measures taken.
- Documentation of any recent antibiotic or steroid treatments. Consideration should also be given to drug fever.
- Previous significant microbiological findings, including the isolation of multi-resistant organisms.
- Previous similar episodes or symptoms that may suggest an auto-inflammatory or fever syndrome.
- Past history or family history of Acute Rheumatic Fever or rheumatic heart disease.
- Sexually transmitted infections should be considered.

4 | Physical Examination

The physical examination should encompass a thorough head-to-toe examination. Key clinical findings to consider include current or preceding:

- Height and weight to assess growth trends.
- Neurological signs, which may be subtle, such as a change in personality, unexplained lethargy or confusion or more overt signs of meningism.
- Abdominal tenderness, to suggest intraabdominal pyogenic infection, or flank tenderness to suggest pyelonephritis.
- Respiratory findings, noting reduced air entry of occult pneumonia, may be subtle.
- Inability to weight bear, a limp, focal bony tenderness, or joint pain or swelling to suggest bone or joint infection.
- Presence of lymphadenopathy or hepatosplenomegaly.
- Thorough review of the skin for cellulitis, rash or skin lesions, hidden tick or eschar, as well as mucosal or oral changes like conjunctival injection or strawberry tongue.
- Ear, nose and throat examination, including consideration of sinus, mastoid and dental infection.
- Auscultation for a murmur, with particular consideration of endocarditis, especially in children with congenital or acquired cardiac defects.
- Specific assessment and consideration of current and historical signs of Kawasaki Disease and Acute Rheumatic Fever.

5 | Diagnostic Work-Up for Infection in the Child With Prolonged Fever

To supplement the clinical history and examination in the undifferentiated inpatient, a tiered diagnostic approach to the work-up of children with prolonged fever is suggested in Figure 1. In haemodynamically stable children, culturing and observing prior to the commencement of antibiotic therapy are preferred.

Initial testing for an undifferentiated fever includes Tier 1 investigations. Full blood count (FBC) includes differential count and film and serial trend analysis of white cells including neutrophils, lymphocytes and eosinophils and platelet count. Pyuria and bacteraemia can be intermittent so repeated specimen collection, ideally prior to antibiotics, is advised. Faeces investigation for bacterial, viral and parasite enteropathogens is generally reserved for children with diarrhoea. Cerebrospinal fluid analysis is not routinely recommended unless neurological concerns are present or arise, but may need to be reconsidered in the event of persistent fevers without a focus, recognising that clinical findings of central nervous system infections can be subtle, particularly in young children [31]. In the event of ongoing fevers without an identifiable focus despite serial clinical reviews, consider Tier 2 and Tier 3 investigations.

Medical imaging should be used judiciously. Chest radiographs (CXR) can identify hilar lymph nodes in tuberculosis or a mediastinal mass in malignancy. Abdominal ultrasound may be needed for suspected appendicitis or intra-abdominal collection, including hepatic, splenic or renal abscesses, with retroperitoneal and subphrenic abscesses being silent in the early stages [8]. Osteomyelitis may also go initially undiagnosed, especially if involving the spine or pelvis, and magnetic resonance imaging (MRI) or bone scans should be considered, especially in children with an abnormal musculoskeletal examination. If sedation is required, consider performing other investigations concurrently.

Table A1 presents overlooked endemic infectious diseases and relevant exposures in Australia. Additionally, with increasing globalisation, diseases that were traditionally thought of as travel-related are becoming more relevant and should also be considered. It is important to consider potential exposures and onset of illness with respect to expected incubation periods. This informs the appropriateness of diagnostic investigations, their timing and interpretation. Nucleic Acid Amplification investigations, most commonly Polymerase chain reaction (PCR) are most useful early in infection in the seronegative window period and often become nondetectable once a serological response has occurred. Serology is most useful when both acute and convalescent samples are collected, usually at 7–21-day intervals. Serial samples should be tested in parallel to demonstrate significant changes in antibody levels, seroconversion or evidence of past infection.

When interpreting any investigation, it is important to consider the limitations of the test. For example, with syndromic multiplex PCRs, knowledge of the specific targets included should be noted. This varies from laboratory to laboratory, and additional testing may be required. For instance, many faecal multiplex PCRs may not include *Vibrio* species or *Cyclospora*, necessitating additional culture or ova cyst parasite (OCP) examination on two or more occasions because of the intermittent excretion of parasites and reduced test sensitivity. This is also the case for syndromic multiplex respiratory bacterial and viral pathogens. High background rates of serology for some infections exist, and serological IgM cross-reactivity for a number of infectious agents frequently occurs.

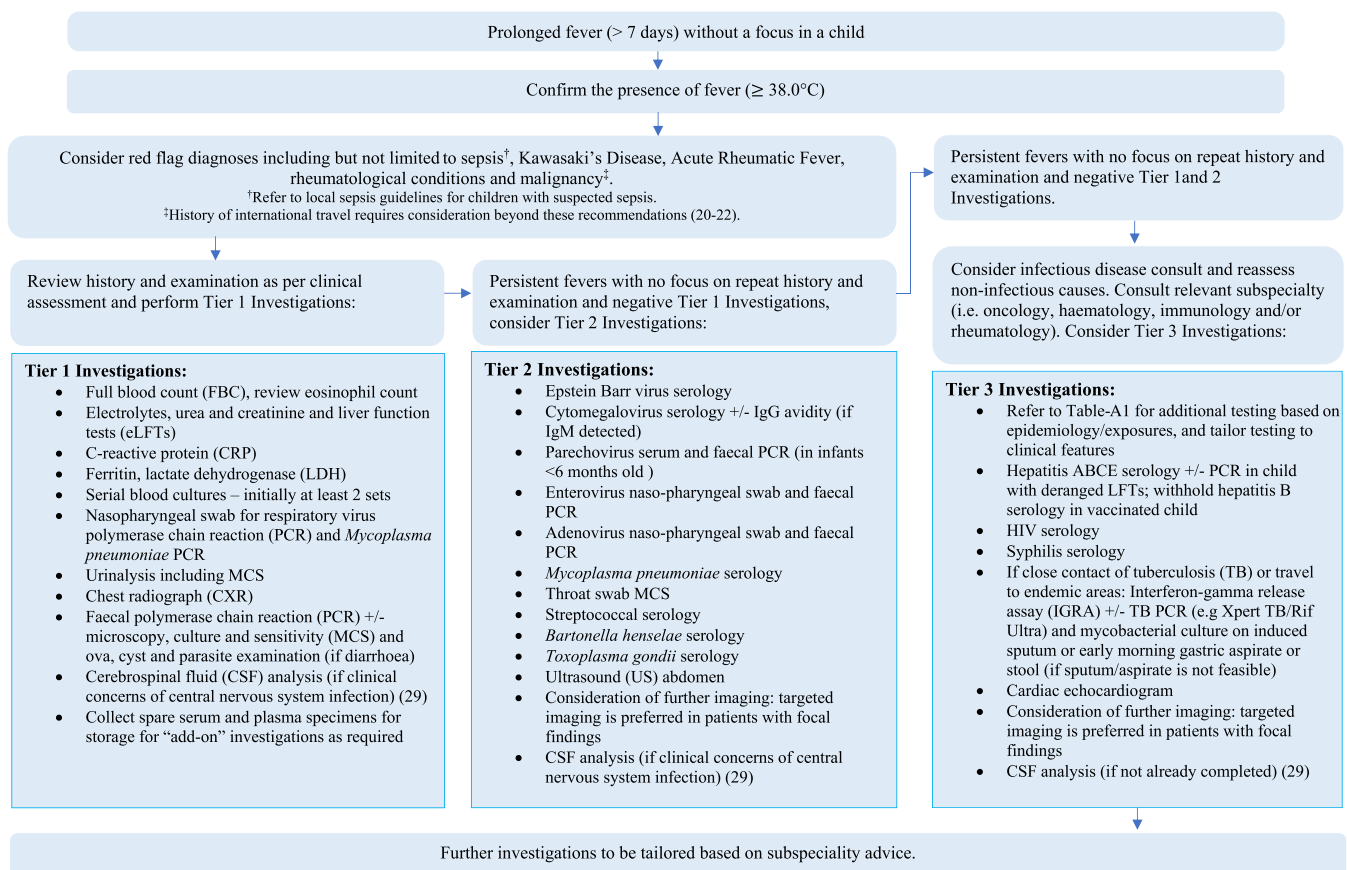


FIGURE 1 | A tiered diagnostic approach for a child admitted to hospital with prolonged fever without focus in Australia.

Notably, laboratories may have stored serum samples available to clarify misleading serological results. Importantly, the possibility of an anergic response (negative tuberculin skin test or gamma release interferon assay) with acute tuberculosis should also be considered.

Conflicts of Interest

The authors declare no conflicts of interest.

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TABLE A1 | Exposures and infections to consider in the diagnostic work-up of a child admitted to hospital with prolonged fever without a focus in Australia.

Endemic region	Exposure	Disease	Pathogen	Incubation period	Clinical features	Investigations
Section 1: domestic, farm or wild animals						
Australia wide	Consumption of contaminated food. Contact with unusual pets including tortoises, turtles and rodents.	Nontyphoidal salmonellosis [32]	<i>Salmonella enterica</i>	6–72h	Usually begins as an acute enterocolitis; on occasions bacteraemia and/or focal infection develop.	Blood culture (days 1–7 of illness). Stool for bacterial polymerase chain reaction (PCR) and microscopy, culture and sensitivity (MCS).
Australia wide	Cat bite or scratch (particularly kittens) which carry infected fleas.	Cat scratch disease [33]	<i>Bartonella henselae</i>	3–30 days	Localised cutaneous and lymph node disease near the site of inoculation is most common. Disseminated disease involving the liver, spleen, eye, musculoskeletal system or central nervous system can also occur in some children.	Swab or aspirate of primary papule or tissues (lymph node, granuloma, liver or bone) for PCR. Culture is possible but is difficult and requires prolonged incubation. Serum for serology ^a .
Australia wide	Direct or indirect contact with kittens. Consumption of undercooked meat.	Toxoplasmosis [34]	<i>Toxoplasma gondii</i>	5–23 days	Fever, lymphadenopathy (typically bilateral cervical adenopathy), lymphocytosis and transaminitis. Rarely, chorioretinitis or disseminated disease in the immunocompetent.	Serum for serology ^a .
Australia wide	Contact with cats and dogs. Ingestion of contaminated dirt.	Toxocariasis (Visceral and Ocular Larva Migrants) [33]	<i>Toxocara canis</i> <i>Toxocara cati</i>	Weeks to years	Visceral larva migrans: eosinophilia, fever and hepatomegaly. Ocular visceral migrans: unilateral visual loss, eye pain, white pupil, or strabismus.	Serum for serology ^a . Ophthalmology review if eye symptoms present.
Australia wide	Contact with rats.	Rat bite fever [33]	<i>Streptobacillus moniliformis</i>	3–10 days	Abrupt onset fever with myalgia, migratory polyarthralgia and/or arthritis and/or purpura (occasionally pustular) rash, usually on the hands or feet. Usually, the bite site has healed when systemic symptoms appear.	Blood, skin pustule swab and/or joint aspirate for MCS.
Eastern Australia	Consumption of snails or slugs or unwashed greens. Ingestion of contaminated dirt.	Eosinophilic meningitis [30]	<i>Angiostrongylus cantonensis</i> [35]	2–35 days	Insidious onset culminating in a eosinophilic meningoencephalitis. Diagnosis requires a high index of suspicion.	Serum for serology ^a . CSF analysis to review eosinophils, PCR and specific IgG antibodies.
QLD NSW [36]	Pig hunting and slaughter; rarely infected parturient pig dogs. Consumption of undercooked feral pig meat.	Brucellosis [32]	<i>Brucella suis</i>	5–60 days	Insidious onset; fever, malaise, night sweats and arthralgias. Physical findings are variable but may include hepatosplenomegaly and/or lymphadenopathy. Relapses of brucella from distant past infection can occur.	Blood culture (notify pathology prior to sending as sample must be handled as a potential biohazard). Serum for PCR ^b and serology ^a .

(Continues)

TABLE A1 | (Continued)

Endemic region	Exposure	Disease	Pathogen	Incubation period	Clinical features	Investigations
Most diagnoses in VIC and NSW [36]	Inhalation of infected material from pet, wild or farmed birds.	Psittacosis (Ornithosis) [37]	<i>Chlamydia psittaci</i>	5–21 days	A range of clinical manifestations from asymptomatic infection, to mild flu-like illness to systemic illness with severe atypical pneumonia.	Respiratory specimen (nasopharyngeal swab, sputum or bronchoalveolar lavage) for PCR. Serum for serology ^a .
QLD NSW [36] Less commonly in VIC	Direct contact with cattle, sheep, goats and macropods. Inhalation of aerosolised contaminated dust and soil.	Q fever [37]	<i>Coxiella burnetii</i>	2–3 weeks	Most cases will be asymptomatic or subclinical. Acute Q fever can present with a variety of symptoms including a flu-like illness, pneumonia or hepatitis. Transaminitis, lymphopenia and thrombocytopenia are common. Chronic Q fever can present as infective endocarditis or osteomyelitis which may be recurrent and multifocal in children.	Serum or plasma for PCR ^b (in days 1–14 of illness) Serum for serology ^a (from day 7 of illness). Serology results may need specialist input for interpretation, particularly in chronic Q fever.
TAS NSW	Ringtail possum scratch or bite. Inhalation of contaminated dust or aerosols.	Tularemia [38, 39]	<i>Francisella tularensis</i> subsp. <i>holarctica</i> (type B)	1–14 days	Can manifest as one or more clinical syndromes depending on the route and strain of infection. Ulceroglandular cases present with a primary local ulcerative lesion and tender, regional lymphadenopathy.	Blood, skin pustule swab and/or aspirate for PCR and culture (notify pathology prior to sending as sample must be handled as a potential biohazard). Serum for serology ^a .
Section 2: mite, flea or tick [40]						
Australia wide	Flea bite	Murine typhus	<i>Rickettsia typhi</i> <i>Rickettsia felis</i>	2–14 days	Infection most commonly (but not always) begins with formation of a papule at the site of the bite which then becomes an eschar (scab). Subsequently, generalised signs and symptoms may develop including fever, headache, myalgia, lymphadenopathy and rash.	Serum for serology ^a . Tissue or skin swab for PCR (e.g., skin biopsy of rash; swab of eschar). Blood for PCR ^b .
North QLD Litchfield, NT Kimberly, WA	Mite (chiggers) bite	Scrub typhus	<i>Orientia tsutsugamushi</i>			
Eastern Australia	Tick bite	Queensland tick typhus (spotted fever)	<i>Rickettsia australis</i>			
Flinders island, TAS	Tick bite	Flinders island spotted fever	<i>Rickettsia honei</i>			
Section 3: mosquitoes						
Australia wide	Transmitted by multiple mosquito species.	Barmah Forest Virus [32] Ross River Fever [32]	<i>Barmah Forest virus</i> <i>Ross River virus</i> (RRV)	3–11 days 7–9 days	Generally a self-limiting, febrile illness characterised by arthralgia/arthritis. Fatigue and malaise are often prominent and can be prolonged.	Serum for serology ^a noting cross reactions and persistence of IgM are not uncommon and not of clinical significance. Blood for PCR ^b (currently not widely available).

(Continues)

TABLE A1 | (Continued)

Endemic region	Exposure	Disease	Pathogen	Incubation period	Clinical features	Investigations
North QLD acknowledging opposing influences of Wolbachia and climate change and globalisation.	Transmitted by mosquito vector <i>Aedes aegypti</i> .	Dengue [37]	<i>Dengue virus</i> Serotypes 1–4	3–14 days	Classical dengue presents with sudden onset fever, headache, retro-orbital pain, myalgia and rash. Dengue haemorrhagic fever and dengue shock syndrome occur more frequently among children and young adults, particularly when prior infection with another serotype has previously occurred.	Serum for dengue PCR (serotype specific) and/or NS1 antigen (generic) (from onset until day 9 of illness). Serum for serology ^a .
NSW VIC SA [36] Less commonly in QLD	Transmitted by <i>Culex</i> mosquito vectors with water birds and pigs as amplifying hosts.	Japanese Encephalitis [32]	<i>Japanese encephalitis virus</i> (JEV)	5–15 days	Can present encephalitic or with non- encephalitic symptoms such as fever, headache, myalgia and rash.	Whole blood for PCR ^b +/- culture (in acute illness). Serum for serology ^a (notify pathology of clinical suspicion as extended flavivirus serology may be necessary). CSF for PCR and serology. Urine for PCR.
NSW VIC WA NT [36]	Transmitted by <i>Culex annulirostris</i> . Vector with water birds as amplifying hosts.	Murray Valley Encephalitis [37]	<i>Murray Valley encephalitis virus</i> (MVEV)	5–28 days		
Section 4: contaminated water						
Top end Australia	Contaminated water or wet soils after heavy rains or floods.	Melioidosis [32]	<i>Burkholderia pseudomallei</i>	1–21 days	Can be localised (pneumonia or skin lesions) or disseminated (sepsis with abscesses disseminated in multiple internal organs or septic arthritis or osteomyelitis, parotitis, central nervous system disease or lymph nodes). Sub-clinical infections are also possible.	Blood, respiratory secretions, urine, CSF and/or wound sample for MCS (note provisional diagnosis on pathology form to allow for specific media if required). Serum for serology (limited utility in endemic areas).
QLD NSW VIC [36]	Contaminated freshwater or soils after heavy rains or floods. Outdoor water activities. Contact with urine of infected animals including rats.	Leptospirosis [32]	<i>Leptospira sp.</i>	5–14 days	Usually self-limiting and often clinically unapparent. Two distinct syndromes: fever, myalgia (calves and lower back), conjunctival suffusion, headache or multisystem illness including fever, jaundice and renal failure.	Serum for PCR ^b (if < 7 days from symptom onset). Blood culture (if < 10 days from symptom onset) (contact pathology prior to collection as specialised media required). Serum for Leptospira IgM and Leptospira microscopic agglutination test (MAT) ^a (in > 7 days from symptom onset).

^aTwo paired blood samples are often required for the diagnosis—one at presentation and another 7–21 days later, even if the patient has since recovered.^bPCR is most useful in the first 1–2 weeks of infection, in the seronegative window.