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Evaluation and Management of Febrile Infants <= 90 Days

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Introduction

Hi, my name is Karina Paliotti, and I'm a fourth-year medical student at McGill University. This podcast was put together with the help of Dr. Christos Karatzios, Pediatric Infectious Disease specialist at the Montreal Children's Hospital and Assistant Professor in the Faculty of Medicine at McGill University. The script was reviewed and edited by Dr. Brett Burstein, Emergency physician at the Montreal Children's Hospital, Clinician-Scientist at the Research Institute of the McGill University Health Centre, and lead author of the Canadian Pediatric Society (CPS) statement on the topic.

This podcast will provide an overview of the evaluation and management of febrile infants. PedsCases last covered this topic in 2010 - now 14 years later - there have been multiple new changes and developments that we will discuss. Factors, including changing bacteriology, greater awareness about the costs of unnecessary care, new biomarkers and clinical prediction tools, have modified the approach presented in our previous podcast. It is important to mention that significant variability in practice remains due to differing guidelines, variations in local resources and clinician experience. Our discussion is based on the CPS statement published in 2023 [1] and the American Academy of Pediatrics (AAP) guidelines from 2021 [2]. Ultimately, our goal is to provide an overview of the most up-to-date approach to fever in children less than 3 months of age. Please note that this podcast focuses on community-acquired infections and does not cover hospital-acquired infections or fever in hospitalized patients.

After listening to this podcast, the learner should be able to:

1. Define the terms fever and invasive bacterial infections
2. Identify the most common etiologies of fever in young infants
3. List factors associated with higher risk of serious illness
4. Outline the approach to fever in children less than 3 months

Definitions

Fever remains an extremely common presentation in pediatrics, whether in the emergency, inpatient unit or outpatient setting. **Fever** for children less than 3 months old is defined as a core body temperature of 38 °C (100.4 °F) or greater, and is best estimated by a rectal temperature. **Fever without a focus** is attributed when history and physical exam fail to establish a cause. The large majority of presentations are due to self-limited viral illness, however the age-old challenge lies in distinguishing such cases from potentially life-threatening bacterial infections which we don't want to miss. [3]

The term serious bacterial infections (SBIs) has historically been used to refer the collection of three infection types namely, urinary tract infections (UTIs), bacteremia and bacterial meningitis. Nowadays, there is an emphasis on ruling out the most dangerous infections, and the term **invasive bacterial infections** (IBIs) has become the preferred terminology which includes bacteremia and bacterial meningitis, both associated with greater morbidity and mortality.

Epidemiology, bacteriology, and common etiologies of fever

It is estimated that together, UTIs and IBIs occur in 7-13% of children presenting with fever in this age group. **UTIs are by-far most common**, occurring in 5-13% of these cases, however 1-2% will have bacteremia, and more rarely bacterial meningitis, occurring in 0.2-0.5% of cases. [1, 3, 5-7]

An inverse relationship between the prevalence of IBIs and age has been demonstrated, with the greatest prevalence in the **first month**, followed by a continuous stepwise decrease over the next 8 weeks. [1] By the third week of life, over 21 days old, the rate of IBIs has been shown to drop as low as 0.2%. [2, 5-6]

A decrease in the frequency of certain infections has been observed over the years and is thought to be multifactorial, namely due to: (1) routine prenatal screening and perinatal prophylaxis against Group B *Streptococcus* (GBS) infections, (2) more widespread vaccination against *Streptococcus pneumoniae* and *Haemophilus influenza type B* as well as herd immunity, and (3) improvements in food safety and public health education about *Listeria monocytogenes* infections. ***Escherichia coli*** (E. Coli) is now considered to be the most common causative organism of UTIs and IBIs. Others include GBS, *Staphylococcus aureus, Klebsiella species* and *Enterococcus*. [1, 3, 5-6]

Fever in this age group can also be caused by focal infections that typically have focal symptoms or signs such as pneumonia, gastroenteritis, omphalitis, osteomyelitis, septic arthritis, cellulitis, and other skin and soft tissue infections. [3]

Serious viral infections

In addition to bacterial infections, we should always consider serious viral infections in our differential. Herpes simplex virus (HSV) infection is of particular concern in neonates less than 4 weeks old, given the risk of significant morbidity and mortality. [4]

The most common and significant cause of neonatal HSV is intrapartum exposure. Rates are highly variable worldwide, and in Canada, infection occurs in approximately 6 per 100,000 live births. Preventative obstetrical practices including maternal prophylaxis with antiviral therapy at 36 weeks gestation until delivery as well as elective delivery by c-section in mothers with genital lesions, have helped to reduce rates of transmission overall. [4]

An invasive HSV risk score has been developed which identifies predictors of serious illness, including age, prematurity, ill appearance, abnormal temperature, seizures at home, vesicular rash, thrombocytopenia and cerebrospinal fluid (CSF) pleocytosis, which can help to guide further investigations. Management for HSV infection will be discussed in the next sections.

Evaluation of high-risk vs. low-risk for serious illness

There are important risk factors to elicit on history that put an infant at higher risk of invasive infections. These include: [1,2]

- Age < 28 days
- Prematurity (gestational age < 37 weeks)
- Rectal temperature > 38.5^{o}C
- Hypothermia (core temperature < 35°C)
- Presence of focal infection
- Prior antibiotic use, chronic illness or comorbidities, including congenital or chromosomal abnormality, documented or suspected immune compromise, technology dependent
- Maternal risk factors (particularly in neonates < 14 days old), including peripartum fever, GBS positive, prolonged rupture of membranes or history of genital HSV

History & Physical Exam

General aspects of a child's appearance or behavior remains the best indication of serious illness. Children who are **ill-appearing** or **toxic** are at highest risk for IBIs.

When assessing a child's appearance and behaviour – it's important to consider that young infants really only do 3 things: **eat**, **sleep** and **pee/poop**. Abnormalities in any of these on history can suggest that the infant is unwell. This can include:

- Eating – Poor feeding
- Sleeping – Lethargy or irritability
- Pee/Poop – Decreased urine output

Your physical exam can focus on the **vitals** and the pediatric assessment triangle, which includes **appearance**, **work of breathing** and **circulation**. [1, 2]

- Vitals: tachycardia, bradycardia, hypothermia (especially for neonatal HSV infection)
  Appearance: poor tone, focal neurological symptoms, seizure(s), weak or inconsolable cries
- Work of Breathing: decreased respiratory efforts or respiratory distress, including tachypnea, nasal flaring, grunting, retractions, head bobbing or abdominal breathing
- Circulation: poor perfusion, including mottling (lacy pattern of reddish and pale areas on skin), cyanosis (blue-ish colour skin, particularly nail beds, fingers and lips) and pallor (pale skin especially face and palms), or poor peripheral pulses

Investigations

With the changes in bacteriology and advances in technology and testing, new biomarkers have emerged in the past decade that have proven to be good predictors for IBIs if elevated in the blood. [a] These biomarkers, also known as inflammatory markers, include **C-reactive protein** (CRP) and **procalcitonin** (PCT). CRP is produced by the liver and is the more commonly available test. PCT is produced mainly by thyroid C cells and tends to rise earlier in the blood in response to infection, specifically in cases of bacterial infections when compared to CRP. In general, **CRP greater than 20 mg/L** and **PCT levels above 0.5 ng/mL** are considered abnormal and suggest increased risk of serious infection. [1, 6]

The CPS statement highlights different approaches that use specific thresholds of these biomarkers to help with risk stratification, including the **Pediatric Emergency Applied Research Network (PECARN) prediction rule**, the **Step-By-Step method** and **Aronson rule**. PCT is considered the diagnostic test of choice if the test is available, and the PECARN prediction rule is generally favored because of it's high sensitivity. The Aronson rule does not use PCT and therefore it is recommended to maintain a higher level of precaution when applying this rule. You can checkout the CPS statement and/or our podcast note for more details about the individual criteria.

Management of febrile infants

Many different algorithms exist to provide help with decision points such as initial testing, lumbar puncture (LP), hospitalization and empiric use of antibiotics. The CPS guideline separates infants 0-28 days, 29-60 days and 61-90 days, and therefore we will discuss management of these infants separately [1,7-8]. It is important to remember that, **regardless of age**, if an infant is **ill-appearing** or has any of the high-risk **factors**, they should be **admitted and treated empirically**. [2, 6]

Infants less than 28 days of age

The general approach is to proceed with caution given their **higher risk of IBIs**. All infants should undergo: CBC and differential, blood culture, urinalysis and urine culture using sterile technique (catheter or suprapubic aspiration) and inflammatory markers (CRP and PCT). **Risk stratification**, including PECARN prediction rule, Step-By-Step method or Aronson rule, should be used at this point to guide decision to perform lumbar puncture (LP) for CSF culture and analysis. For well-appearing infants who satisfy low-risk criteria, a **lumbar puncture may be deferred**, depending on clinical criteria, practical considerations and family shared-decision making.

For neonates whom HSV exposure is a concern, including presence or history of maternal HSV lesions, maternal fever at or around time of delivery, infant vesicles, seizures or neurologic deficits, HSV PCR must be done in blood and CSF samples. Infant lesions should be swabbed to also undergo PCR. CSF pleocytosis in absence of positive Gram stain or leukopenia may also be a sign of neonatal HSV infection and warrants HSV PCR on all samples. [1, 2, 4]

Respiratory viral panel and chest x-ray may be added if respiratory symptoms are present. Stool culture and microscopy (for the presence of leukocytes) may also be requested if diarrhea is present. [2, 3, 8]

For this age group, appropriate antibiotic choices remain **intravenous** (**IV) Ampicillin** and **IV Gentamicin or Tobramycin,** plus **IV Cefotaxime** if meningitis is suspected to cover Group B Strep, *E. Coli* and *Listeria monocytogenes*. **Empiric IV Acyclovir** should be started in patients undergoing HSV testing pending results.[1, 2, 8]

The infant can be discharged if bacterial cultures remain negative for 24-36 hours, the infant is clinically improving and there is no other reason for hospitalization. If bacterial infection or HSV is identified in cultures or PCR, treatment continues with antibiotics and/or acyclovir targeting the pathogen. [1, 2, 8]

Infants between 29 to 60 days

Selective testing and management is generally accepted given lower risk of serious infection in this subgroup. A good starting point for investigations includes: CBC and differential, blood culture, urine analysis and culture, and inflammatory markers (CRP or PCT). Chest x-ray, respiratory viral panel, stool culture and microscopy may also be ordered depending on the clinical picture.

If **inflammatory markers return elevated**, a **lumbar puncture** for CSF analysis and culture should be performed, **empiric antibiotics** should be started and hospitalization is required. Empiric antibiotics of choice **include IV Ceftriaxone**, with addition of **IV Vancomycin** if meningitis is suspected, and **IV acyclovir** if HSV testing is pending [1, 2, 8]

On the other hand, if inflammatory markers remain within normal limits and urinalysis is negative and patient is otherwise hemodynamically stable and well, they may be either admitted to hospital for observation with no antimicrobial therapy, or followed as outpatient without therapy. It is important to determine whether follow-up is uncertain as it will impact management, and lead to admission to hospital. Close follow-up including re-evaluation in 24 hours for at least 72 hours, or immediately if any change in clinical status, is essential. [1, 2, 8]

If a pathogen or source has been identified by 24-36 hours, antibiotics can be tailored accordingly and continued until adequate course is completed. If cultures remain negative after 24 to 36 hours and HSV PCRs return negative, all antimicrobial therapy may be discontinued and patient discharged if hospitalized. [1, 2, 8]

Infants over 61 to 90 days of age

Most clinicians manage these infants similarly to those between 29-60 days old. **IV Ceftriaxone** remains appropriate for this age group, with addition of **IV Vancomycin** for meningitis or **IV Acyclovir** if HSV suspected. If a source is determined, antimicrobial therapy may be tailored accordingly.

If well-appearing and deemed low-risk per risk-stratification criteria, a urinalysis and urine culture should be done at minimum, given the high incidence of UTIs in this age group. If an isolated UTI is detected, and patient remains well, **oral Cefotaxime** can be provided as outpatient therapy with follow-up in 24-48 hours.

Key take-home messages

1- If an infant less than 3 months presents with fever without a focus, it's important to consider UTIs and IBIs as well as neonatal HSV infection first in your differential and rule them out!

2- **UTIs are most common cause of fever in infants.** *E. Coli* is now considered the most common pathogen with decreases in rates of GBS, Listeria, *H. influenzae* and *Streptococcus pneumoniae* infection over the years. Newer biomarkers, namely CRP and PCT, are favoured predictors of IBIs.

3- Infants less than 28 days remain at **greatest risk** for IBIs and **require observation in hospital**. Ill-appearing and/or high-risk infants according to risk-stratification criteria should undergo lumbar puncture for CSF testing and be started on empiric antibiotic therapy immediately. Lumbar puncture and antibiotic therapy may be deferred for well-appearing and low-risk infants, pending blood and urine culture results. **IV Ampicillin and Gentamicin** remain great choices for adequate microbial coverage. **IV Cefotaxime** should be added if meningitis is suspected, and **IV Acyclovir** if HSV is suspected.

4- Children over 28 days should be **stratified based on clinical appearance, risk factors and inflammatory markers** to decide on need for hospitalization, further investigations and antibiotic therapy. If therapy is indicated, a good choice is **IV Ceftriaxone**, with addition of **IV Vancomycin** for meningitis, and **IV Acyclovir** if HSV is suspected.

5- Close follow-up needs to be certain when a patient is discharged with or without antimicrobial therapy. Re-evaluation in 24 hours for at least 72 hours is important, and counselling for concerning signs and to return immediately if parents or guardians notice a deterioration in their child's condition is imperative.

Conclusion

That concludes the podcast! Thank you for listening!

References

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