Canadian Paediatric Society

POSITION STATEMENT

Management of well-appearing febrile young infants aged ≤90 days

Principal author(s)

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Abstract

The evaluation and management of young infants presenting with fever remains an area of significant practice variation. While most well-appearing febrile young infants have a viral illness, identifying those at risk for invasive bacterial infections, specifically bacteremia and bacterial meningitis, is critical. This statement considers infants aged ≤90 days who present with a rectal temperature ³38.0°C but appear well otherwise. Applying recent risk stratification criteria to guide management and incorporating diagnostic testing with procalcitonin are advised. Management decisions for infants meeting low-risk criteria should reflect the probability of disease, consider the balance of risks and potential harm, and include parents/caregivers in shared decision-making when options exist. Optimal management may also be influenced by pragmatic considerations, such as access to diagnostic investigations, observation units, tertiary care, and follow-up. Special considerations such as temperature measurement, risk for invasive herpes simplex infection, and post-immunization fever are also discussed.

Keywords: *Fever; Invasive bacterial infection; Risk-stratification; Serious bacterial infection.*

Text box 1. DEFINITIONS[1]-[3]

- **Fever** among infants aged ≤90 days is any rectal temperature ³38.0°C, measured at home or in a clinical setting
- **Serious bacterial infections (SBIs)** include urinary tract infections (UTIs), bacteremia, and bacterial meningitis
- **Invasive bacterial infections (IBIs)** include bacteremia and bacterial meningitis

Background

Approximately 2% of healthy, term newborns are brought to medical attention for fever within their first 3 months of life[1]-[4]. While most of these infants have self-limited viral illness, between 10% and 13% harbour a serious bacterial infection (SBI)[5]. SBIs include urinary tract infections (UTIs), bacteremia, and bacterial meningitis. The prevalence of invasive bacterial infections (IBIs), specifically bacteremia and bacterial meningitis, is greatest in the first month post-birth and decreases with age[6][7]. When evaluating febrile young infants, health care providers (HCPs) must balance the risks of infection against the harms of over-investigation and over-treatment[8][9]. No single management strategy has been universally adopted, which has led to wide variations in care in Canada and elsewhere[5][10][11].

Enhanced clinical care for febrile infants ≤90 days of age has been the focus of several large-scale quality improvement[12] and knowledge translation initiatives[13]. Several risk-stratification criteria exist to identify infants at low risk for SBI[14]-[16]. However, older criteria provide conflicting recommendations, and all use subjective clinical findings and pre-determined laboratory values rather than statistically derived thresholds. They also pre-date widespread use of pneumococcal conjugate and *Haemophilus influenzae* type b vaccines and intrapartum group B streptococcus (GBS) prophylaxis[17][18], and do not incorporate newer diagnostic tests[19]-[21]. Moreover, older strategies were developed to identify SBIs, of which approximately 80% are UTIs[22][23], which in turn distorts prediction for IBIs. Historic strategies lack specificity for IBI, such that thousands of infants routinely undergo invasive cerebrospinal fluid (CSF) testing, prolonged hospitalization, and broad-spectrum antibiotic therapy to prevent rare cases of bacterial meningitis from being missed[5].

Identifying IBIs

A shift toward patient-centred outcomes and value of care in recent decades has placed new emphasis on reducing unnecessary tests and treatments. Newer research has focused on developing statistically derived clinical prediction rules to identify infants with specific risk for an IBI rather than SBI. Several large multicentre studies have derived and validated approaches to identify low-risk infants who can be managed without lumbar puncture (LP), antibiotics, or hospitalization, notably the Pediatric Emergency Care Applied Research Network (PECARN) prediction rule[1], the Step-by-Step method[2], and the Aronson rule[3] (Table 1). These approaches favour newer biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) because, as predictors of IBI, they outperform absolute neutrophil counts (ANC) and white blood cell (WBC) count[19][21][24]. While PCT is the most sensitive and specific biomarker for IBI, test availability and turnaround times vary widely (25,26). PCT is the diagnostic test of choice, when available, and clinicians should use either the PECARN prediction rule or the Step-by-Step method to stratify risk. The Aronson rule does not use PCT, making it reasonable to maintain a lower threshold for LP and hospitalization, even for low-risk infants, when applying this rule[27].

For infants identified as low risk using the Aronson, Step-by-Step, or PECARN strategies, the specific risk for IBI decreases to 0.6% (95% CI 0.2 to 1.2), 0.7% (95% CI 0.3 to 1.5), or 0% (95% CI 0.0 to 0.8), respectively. Because bacteremia is approximately fourfold more common than bacterial meningitis in infants diagnosed with IBI[5][6], the number needed to test (NNT) by LP to exclude one case of bacterial meningitis among low-risk infants ranges between 333 to 2000 (Aronson), 267 to 1333 (Step-by-Step), or 500 to undefinably high (PECARN).

Table 1**. Risk stratification for febrile young infants**

PECARN prediction rule [1]	Low risk if all criteria are met: 1. Urinalysis negative for leukocyte esterase, nitrite, and pyuria (≤5WBC/hpf) 2. ANC ≤4090/µL 3. PCT ≤1.71 ng/mL	Internally validated Sensitivity for IBI: 100% (95% CI 77.2 to 100) Specificity for IBI: 60% (95% CI: 56.6 to 63.3) NPV for IBI: 100% (95% CI 99.2 to 100)
Step-by-Step method [2]	Low risk if all criteria are met: 1. Well-appearing 2. 22 to 90 days old 3. Urinalysis negative for leucocytes 4. PCT <0.5 ng/mL 5. CRP ≤20 mg/L and ANC ≤10,000/µL	Externally validated Sensitivity for IBI: 92.0% (95% CI 84.3 to 96.0) Specificity for IBI: 46.9% (95% CI 44.8 to 49.0) NPV for IBI: 99.3% (95% CI 98.5 to 99.7)
Aronson rule [3] (when PCT is unavailable)	Low risk if ≤1-point: 1. Age <21 days (1 point) 2. Highest temperature measured in the ED • 38.0 °C to 38.4°C (2 points) • ³38.5°C (4 points) 3. ANC ³5185/µL (2 points) 4. Urinalysis positive (leukocyte esterase, nitrite, or >5WBC/hpf (3 points)	Externally validated (27) Sensitivity for IBI: 93.1% (95% CI 85.6 to 97.4) Specificity for IBI: 26.6% (95% CI 25.3 to 28.0) NPV for IBI: 99.4% (95% CI 98.8 to 99.8)

ANC Absolute neutrophil count; CRP C-reactive protein; ED Emergency department; IBI Invasive bacterial infection; NPV Negative predictive value; PCT Procalcitonin; PECARN Pediatric Emergency Care Applied Research Network; WBC/hpf White blood cells per high-powered field

Based on current best evidence and expert opinion, these guidelines are intended to be pragmatic and applicable for clinicians in a broad range of settings (e.g., emergency department [ED], clinic, urban, rural), always recognizing that regional differences exist regarding access to tests, inpatient observation units, follow-up, and tertiary care. The recommendations apply to well-appearing infants £90 days old with a documented history of fever, defined as any rectal temperature ³38.0°C, taken by a caregiver or HCP at home or in a clinical setting[28][29]. Importantly, even well-appearing febrile young infants can deteriorate relatively rapidly, and clinicians should maintain a high index of suspicion for infection in this age group.

Studies of febrile young infants generally exclude infants with commonly accepted risk factors (Table 2). Therefore, given the paucity of evidence regarding these risk factors, individualized care and consideration of conservative management are warranted. Ill-appearing infants should be assessed immediately using a structured assessment tool (e.g., the "Pediatric Assessment Triangle"[30], or similar). The priority for all ill-appearing infants involves supporting the airway, breathing, and circulation. In all such cases, obtain blood and urine cultures and consider deferring LP testing until the infant is hemodynamically stable. Treatment with empiric antibiotics should not be delayed.

Table 2**. Commonly accepted risk factors**

- History of prematurity (gestational age <37 weeks)
- Prior hospitalization or prolonged newborn nursery course
- Chronic medical conditions, chromosomal abnormality, or technology dependence
- Known or suspected immunodeficiency
- Recent antibiotic exposure
- Any focal bacterial infection (e.g., cellulitis, omphalitis, osteoarticular infection)

General principles

- Febrile infants ≤90 days should be managed in a setting where it is possible to perform appropriate evaluation and investigations.
- All infants with fever should receive a complete history and physical examination, including an assessment of vital signs with rectal temperature.
- All infants with fever should have a urinalysis and urine culture/sensitivity. The preferred collection method is by urinary catheter or suprapubic aspiration, rather than a urine bag. Clean catch collection is an acceptable alternative but may be challenging to obtain[31][32].
- Assessing inflammatory markers (i.e., PCT or CRP) improves risk stratification significantly, but should not be relied upon in isolation[19]. Instead, clinicians should consider them alongside other clinical criteria (Table 1).
- An LP should not be delayed in the presence of neurological signs. Herpes simplex virus (HSV) testing and treatment should be started empirically (see HSV section below for details). Consider HSV testing and antiviral treatment for infants being treated for meningitis.
- CSF cell counts are more accurate than protein and glucose values for predicting bacterial meningitis. Infants with CSF pleocytosis, defined as >15 cells/mm^3 for infants £28 days and >9 cells/mm^3 for infants >28 days[33], should be treated empirically for suspected meningitis (Table 3).
- Consider chest radiography (CXR) for infants with significant respiratory symptoms that persist despite nasal suctioning (i.e., increased work of breathing, oxygen saturation £96%[34], particularly when bronchiolitis is not the most likely diagnosis.
- High-risk infants should be treated empirically with antibiotics (Table 3). Narrower spectrum antimicrobials may be administered when results from urine, blood, and CSF cultures are known.
- For hospitalized low-risk infants, those who are clinically well and hydrating are eligible for discontinuation of antibiotics and discharge when all bacterial cultures taken before antimicrobials are negative at 24 h to 36 h (or contain only non-pathogenic contaminants)[35]-[38]. The presence of a laboratory-confirmed respiratory virus other than rhinovirus supports the decision to discharge at 24 h following negative bacterial culture results (see Evidence for viral illnesses section below for details).
- For hospitalized high-risk infants, observation until 36 h of negative bacterial cultures is recommended. Discharge is appropriate providing the infant is well-appearing and drinking sufficiently to maintain clinical hydration.
- For infants discharged directly from an ED or outpatient clinic, clinicians should arrange follow-up with an HCP within 24 h to 48 h and provide parents with anticipatory guidance on signs of clinical concern and when to seek emergency care.
- Clinical decision-making should reflect a combination of physician and parental goals of care, risk tolerance, illness severity, disease probability and, sometimes, pragmatic factors[39]. Clinicians should engage parents in shared decision-making when more than one recommended option exists[40].

AGE-BASED RECOMMENDATIONS

Infants 0 to 28 days old (see also Figure 1 (https://cps.ca/uploads/documents/0-28_days-ENG.pdf)**)**

Febrile infants this age are at highest risk for IBI. An estimated 3.0% (95% CI 2.3 to 3.9) will have bacteremia, and 1.0% (95% CI 0.4 to 2.1) will have bacterial meningitis[6]. All febrile infants this age should undergo diagnostic testing: CBC with differential, inflammatory markers (CRP or PCT), blood culture/sensitivity, urinalysis, and urine culture/sensitivity. The decision to perform an LP for CSF testing may be guided by risk stratification (per Table 1), although any positive blood or urine culture should prompt timely CSF testing. Additional investigations (e.g., viral testing, CXR, ALT) may be considered on a case-by-case basis.

***Infants meeting low-risk criteria for IBI**:*

- An LP is not required but may be influenced by choice of risk-stratification strategy, practical considerations, and shared decision-making.
- Option 1 – Hospitalize for observation without empiric antibiotics, OR
- Option 2 – Perform an LP and hospitalize infants with a normal CSF WBC count, with or without empiric antibiotics.
- Treat infants with CSF pleocytosis empirically for bacterial meningitis (per Table 3).
- Observe hospitalized infants until all bacterial cultures are negative for 36 h, OR for 24 h if a laboratory-confirmed virus other than rhinovirus is present (see Evidence of viral illnesses section below for details).

***Infants at high risk for IBI**:*

- Perform an LP to obtain a CSF cell count, protein, glucose, gram stain and bacterial culture.

- Initiate empiric antibiotics before test results are obtained (per Table 3).
- Hospitalize and monitor these infants closely for at least 36 h pending culture results.

Infants 29 to 60 days old (see also Figure 2 (https://cps.ca/uploads/documents/29-60_days-ENG.pdf)**)**

Febrile infants this age are at lower risk for developing IBI than neonates. An estimated 1.6% (95% CI 0.9 to 2.7) will have bacteremia and 0.4% (95% CI 0.2 to 1.0) will have bacterial meningitis[6]. All febrile infants this age should have diagnostic testing: CBC with differential, inflammatory markers (CRP or PCT), blood culture/sensitivity, urinalysis, and urine culture/sensitivity. Additional investigations (e.g., viral testing, CXR, ALT) may be considered on a case-by-case basis.

Infants meeting low-risk criteria for IBI:

- An LP is not required, but if performed and found to show CSF pleocytosis, hospitalize and treat for suspected meningitis.
- Consider infants with normal inflammatory markers at low risk for IBI, even with a positive urinalysis. A positive urinalysis result by itself is no longer considered to indicate high risk for IBI (see Presumptive UTIs section below for details).
- Treat infants with a positive urinalysis and normal inflammatory markers empirically with either PO or IV antibiotics (per Table 3).
- Option 1 – Discharge home and arrange follow-up with an HCP within 24 h to 48 h, OR
- Option 2 – Hospitalize for observation until all bacterial cultures are negative for 24 h.

Infants at high-risk for IBI:

- Consider infants with abnormal inflammatory markers (per Table 1) at high risk for IBI.
- Perform an LP to obtain CSF cell count, protein, glucose, and bacterial culture/sensitivity.
- Initiate empiric antimicrobials (per Table 3).
- Hospitalize and observe until all bacterial cultures are negative for 36 h.

Infants 61 to 90 days old

Estimates of IBI prevalence in this age group are less precise than for younger infants, but are reported to be <1.5% for bacteremia and <0.25% for bacterial meningitis[5]. Diagnostic testing should include at least a urinalysis and urine culture. However, clinicians may choose to perform investigations and follow risk stratification described for infants aged 29 to 60 days (Figure 2). If so, infants meeting low-risk criteria and those with an isolated UTI do not require hospitalization when clinically well, and follow-up within 24 h to 48 h can be arranged. Treatment of UTIs in this age group is described in the CPS position statement “Urinary tract infection in infants and children: Diagnosis and management” .

Table 3**. Empiric antibiotics and antivirals for infants ≥35 weeks gestational age**

Post-natal age	**Empiric treatment**
0 to 7 days	IV ampicillin 75 mg/kg/dose every 6 h AND IV gentamicin or tobramycin 4 mg/kg/dose every 24 h If meningitis is suspected, add (or replace aminoglycoside with) IV cefotaxime 50 mg/kg/dose every 6 h If HSV risk factors are present, add IV acyclovir 20 mg/kg/dose every 8 h
8 to 28 days	IV ampicillin 75 mg/kg/dose every 6 h AND IV gentamicin or tobramycin 5 mg/kg/dose every 24 h If meningitis is suspected, add (or replace aminoglycoside with) IV cefotaxime 50 mg/kg/dose every 6 h If HSV risk factors are present, add IV acyclovir 20 mg/kg/dose every 8 h
29 to 60 days	IV ceftriaxone 100 mg/kg/dose every 24 h If meningitis is suspected, add IV vancomycin 15 mg/kg/dose every 6 h If HSV risk factors are present, add IV acyclovir 20 mg/kg/dose every 8 h *If UTI is suspected and the infant is low risk, may treat with PO cefixime 8 mg/kg/dose every 24 h
61 to 90 days	IV ceftriaxone 100 mg/kg/dose every 24 h If meningitis is suspected, add IV vancomycin 15 mg/kg/dose every 6 h * If UTI is suspected and the infant is low risk, may treat with PO cefixime 8 mg/kg/dose every 24 h

HSV Herpes simplex virus; IV Intravenous; PO Per os (by mouth); UTI Urinary tract infection

Adapted from reference 13

SPECIAL CONSIDERATIONS

Accuracy and threshold of temperature measurement

Modern risk-stratification criteria all define fever as any rectal temperature of ³38.0°C[1]-[3]. While infants with a subjective or tactile fever may be at higher risk of SBI or IBI[42], a rectal temperature measurement remains the reference standard[28] for this age group. Axillary, oral, or tympanic measurements are inaccurate for core temperature in infants. Despite some association between higher temperatures and IBI risk[43][44], two-thirds of infants with IBI present with a temperature <39.0 º C[44]. Also, many infants who present with history of fever only do not necessarily have a lower risk of IBI than those who are febrile at presentation[45][46]. Therefore, any rectal temperature ³38.0°C should prompt further investigation. Infants with hypothermia (i.e., temperature <36.0°C) are also at elevated risk of infection, and they should be managed the same way as infants with pyrexia[47][48].

Herpes simplex virus (HSV)

HSV infection may be limited to skin, eyes, or mouth (SEM disease), or present as encephalitis (central nervous system [CNS] disease) or disseminated infection. Historically, testing and empiric treatment for HSV have been highly variable[49]. The largest study to date of infants £60 days old undergoing ED evaluation for meningitis found that the median age of HSV infection was 14 days (range 2 to 56 days; IQR 9 to 24 days), and the prevalence was 0.42% (95% CI 0.35 to 0.51) (49), similar to the prevalence of bacterial meningitis. The same cohort was studied to derive an HSV risk score (Table 4). A score <3 points identified infants at low risk (95.6%; 95% CI 84.9 to 99.5) for CNS or disseminated HSV[50]. Note that transaminitis and maternal HSV history were not studied, but when either is present they should raise concern for HSV. Infants deemed at risk, whether based on risk score or other clinical considerations, should have an LP for CSF HSV testing, be treated empirically with IV acyclovir (Table 3), and managed in accordance with the CPS position statement "Prevention and management of neonatal herpes simplex virus infections (https://cps.ca/documents/position/prevention-management-neonatal-herpes-simplex-virus-infections)"[51].

Table 4**. Invasive HSV risk score**

Factor		**Point(s)**
Age	<14 days	3
	14 to 28 days	2
	>28 days	0
Seizure at home		2
Ill appearance*		2
Abnormal triage temperature (³38.0°C or <36.4°C)		1
Vesicular rash		4
Thrombocytopenia (platelets <150,000/µL)		2
CSF pleocytosis (WBC >15/µL if ≤28 days; >9/µL if >28 days)		2
Prematurity (birth <37 weeks gestation)		1

CSF Cerebrospinal fluid; WBC White blood cells

Adapted from reference 50

*"Sick, toxic, shocky", altered or decreased mental status, fussy, inconsolable, meningismus (i.e., positive Kernig or Brudzinski sign or stiff neck), petechial rash, decreased perfusion, decreased pulses

Presumptive UTIs

Historically, UTIs in infants £90 days were believed to pose a risk for bacterial meningitis by means of hematogenous spread. Clinical definitions of UTI are based on urine culture results[52], which are not available at initial evaluation. Therefore, a presumptive diagnosis of UTI at the time of initial evaluation relies upon results of the urinalysis in the presence any positive leukocyte esterase, nitrites, gram stain, or pyuria (defined as ≥10WBC/mm ^{3} by hemocytometer on an uncentrifuged specimen, or ≥5wbc/hpf on a centrifuged specimen)[53]. Urinalysis has high sensitivity and specificity for UTIs in this population[54].

To date, all published risk-stratification rules classify infants with a positive urinalysis as high risk, prompting CSF testing, hospitalization, and empiric antibiotics[55]. However, a large meta-analysis found that in well-appearing infants aged 29 to 60 days, the prevalence of bacterial meningitis was no higher in those with a positive urinalysis (0.25% to 0.44%), compared with infants who tested negative (0.28% to 0.50%)[56]. The PECARN group recently reported that among 697 infants aged 29 to 60 days with a positive urinalysis result, there were no cases of bacterial meningitis compared with 9 of 4153 who had a negative urinalysis (difference -0.2% [95% CI -0.4 to -0.1%])[57]. Thus, for infants 29 to 60 days old, the decision to perform an LP should be guided by inflammatory markers rather than urinalysis alone.

Traumatic lumbar punctures (TLPs)

An LP is 'traumatic' when blood is iatrogenically introduced into the CSF sample, thereby complicating interpretation of the cell count. TLPs occur in 20% to 60% of attempts, depending on provider experience[58][59], and often lead to repeat testing, prolonged hospitalization, and unnecessary antimicrobial use[58].

Several ratio-based correction methods have been proposed to aid interpretation of CSF WBC count for TLPs. One study using a statistically derived corrective ratio that subtracted 1 WBC for every 877 red blood cells in TLP CSF samples outperformed other methods[60]. Rounding up the corrective ratio to 1000:1 performed with similar results[60][61]. These studies support using a correction factor for traumatic CSF samples to reduce unnecessary hospitalization and antibiotic use, particularly for infants aged 29 to 60 days who meet other low-risk criteria[60][61]. CSF correction should not be used for samples that contain >100,000 red blood cells[61].

Evidence of viral illnesses

Clinicians often incorporate knowledge of viral symptoms into clinical decision-making for febrile young infants[62]. Infants with laboratory-confirmed viral infections are at lower risk for SBI than those in whom no virus has been detected[20][63]. However, even with a confirmed viral infection, there remains a non-negligible risk of bacteremia (0.8%; 95% CI 0.3 to 1.4) and bacterial meningitis (0.4%; 95% CI 0.1 to 1.0)[20]. Moreover, infants £90 days with PCR-confirmed rhinovirus infections are more likely to have SBIs than those with other viruses (7.8% versus 3.7%)[64]. Rhinovirus is also a ubiquitous respiratory virus, often with a protracted shedding period, and frequently presents asymptomatically[65]. Thus, even in the presence of respiratory symptoms or a documented viral pathogen, the initial diagnostic evaluation should follow the age-based recommendations above. Clinicians can then use a positive finding for any virus (other than rhinovirus) to guide subsequent management decisions (such as withholding or stopping antibiotics, or hospitalizing or discharging otherwise low-risk infants).

Post-immunization fever

Approximately one-half of infants experience fever following routine vaccinations[66]. Those who have a fever within 24 h of receiving a vaccine are at low risk for SBI (0.6%; 95% CI 0.0 to 1.9). Risk increases, however, when fever persists beyond 24 h (8.9%; 95% CI 1.5 to 16.4)[67]. Inflammatory markers are often elevated post-immunization and are therefore unlikely to help identify infants at risk[67]-[69]. Two studies of recently immunized febrile infants found that all SBI detected were UTIs; not a single case of IBI was found[67][69]. Urine testing is recommended for infants with fever persisting >24 h post-immunization.

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