Febrile infants and children in the Emergency Department: Reducing fever to its simplest form

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Febrile infants and children in the Emergency Department: Reducing fever to its simplest form

Key Points

- **1.** Urinary tract infection (UTI) is the most common occult serious bacterial infection in children under 3 years of age with fever without a focus.
- **2.** In well-appearing children under 3 years of age with fever without a focus, collection of urine is generally the only test that is needed.
 - 3. It may not be necessary to do any tests at all in febrile infants over 3 months of age, particularly if there is clinical evidence of a (viral) source
- or if the fever has been present for fewer than 4 to 5 days.
- 4. When UTI is confirmed in a well-appearing child, collection of blood and cerebrospinal fluid (CSF) for culture is generally not required.

Fever is a common reason for parents to present for assessment of their infants and young children and it accounts for up to 30% of visits to emergency departments (EDs). ^{1,2} Most febrile children under 3 years of age have a viral infection. Those with clinical or laboratory evidence of viral infection are unlikely to have serious bacterial infection (SBI). ^{3,4} Some febrile children will have a minor bacterial infection with an identifiable focus such as otitis media. Of those without localising signs, a small number appear sufficiently unwell that they require investigation for SBI and likely empiric antibiotic treatment until the cause is clear or cultures are negative.

It is the remaining 20%, well-appearing children less than 3 years of age with fever and no focus, who cause the most angst for those working in paediatric EDs. However, most of these children can now be managed without any investigations and with symptomatic treatment only. An exception is febrile neonates, who have an estimated 12% risk of SBI and should usually be admitted and treated with empiric antibiotics until the results of cultures are available. ^{5,6}

The introduction of conjugate vaccines directed against *Haemophilus influenzae* type b (1992 in Australia and 1994 in New Zealand), *Neisseria meningitidis* (serogroup C in 2003 in Australia) and *Streptococcus pneumoniae* (2005 and 2006) has had a huge impact on the epidemiology of fever in children between 3 months and 3 years of age. In the pre-conjugate vaccine era, the prevalence of occult bacteraemia was as high as 11.6% in children with fever without a focus; *S. pneumoniae* accounted for most cases (50%–90%); 3% to 25% were due to *H. influenzae* type b, with the remainder due to Salmonella species and *Neisseria meningitidis*.^{7–9} By the mid-90s, the prevalence had dropped to 3.4% in a study performed at the Royal Children's Hospital in Melbourne. ¹⁰ In the last 10 years, the incidence of occult bacteraemia has continued to drop to approximately 0.25%.

A reduction in rates of occult bacteraemia has also been identified in febrile infants younger than 3 months; this can be attributed to expanded immunisation programs and more consistent adherence to guidelines for the screening and management of group B streptococcus (GBS) colonisation in pregnant women leading to prevention of early-onset GBS disease in newborns. ^{14–16} Greenhow *et al* analysed all cultures of blood, urine and cerebrospinal fluid (CSF) taken from over 200,000 full-term infants 1 week to 3 months of age in paediatric clinics and EDs in the Kaiser Permanente network during a 7-year period. The incidence rate of SBI, including bacteraemia, urinary tract infections (UTI) and meningitis, was 3.75/1000 births. They found that UTIs were identified significantly more often than bacteraemia and meningitis with 92% of occult infections associated with UTIs. ¹⁵ In infants under 3 months of age, *Escherichia coli* is now the most common cause of bacteraemia (3%), *S pneumoniae* (3%), *Klebsiella* species (2%), and *Salmonella* species (2%). ¹⁴

The incidence of SBI has been estimated in other studies to be between 6% and 10% in infants younger than 3 months and between 5% and 7% in children between 3 and 36 months of age. ^{17–19} Urinary tract infection (UTI) is the most common SBI, occurring in up to 8%. ^{11,20} That leaves only a small proportion with bacteraemia and a risk of focal sequelae such as meningitis or osteomyelitis.

In Greenhow's Kaiser Permanente study, 5,396 blood cultures were taken from 224,553 infants aged 1 week to 3 months; ¹⁵ 437 were positive, but 70% of these were deemed to be contaminants, leaving 129 (2%) positive with a pathogen. Taking blood for culture is neither clinically useful nor cost effective as a routine test in well-appearing children with fever.

Many guidelines for the management of infants with fever include the use of various markers to assist in identifying those at low (or high) risk of SBI. White cell count (WCC) is used in most guidelines as a screening tool. However, studies done since the introduction of conjugate pneumococcal vaccine have shown that WCC is neither sensitive nor specific as an indicator of bacteraemia and other SBI in infants. ^{21,22} A WCC threshold of 15×10^9 /L misses half of all SBI while misclassifying a quarter of self-limiting illnesses. ²²

Van den Bruel *et al* performed a systematic review of the diagnostic value of various laboratory tests in identifying SBI in febrile children. ²³ They found that the tests providing most diagnostic value were C-reactive protein (CRP) and procalcitonin (PCT). However, they found few studies and none were of high methodological quality. Moreover, neither CRP nor PCT was found to have sufficient diagnostic value to either confirm or exclude SBI; the results must be interpreted in the light of clinical findings.

The same authors performed a systematic review on the diagnostic value of presenting clinical features and clinical prediction rules in identifying SBI in children. ^{24–26} They identified a number of red flags for SBI, the strongest of which were reduced consciousness, convulsions, cyanosis, rapid breathing, and slow capillary refill. Parental concern and clinician global impression were also identified as

important features. Temperature of more than 40°C has value as a red flag in settings with a low prevalence of SBI.

A combination of clinical and laboratory features would seem to be the most effective means of identifying those children at risk of SBI. There are a number of prediction rules that are in use. The Boston, Philadelphia, and Rochester criteria are all fairly accurate in identifying a low-risk group for SBI in infants under 3 months of age; sensitivity: 84 to 100 %, specificity: 27 to 69 %, negative predictive value: 94 to 100 %, positive predictive value: 3 to 49 %.²⁷ However, each has different inclusion criteria (age, temperature cutoffs and other clinical indicators) and different laboratory criteria for distinguishing high-risk from low-risk infants. Moreover, they do not include information on the risks associated with testing and management strategies, nor factors associated with compliance to follow-up care.

The UK National Institute for Health and Clinical Excellence (NICE) has devised a guideline that provides a traffic light system for the initial assessment and management of febrile children under the age of 5 years. According to the guideline, children with fever without apparent source with one or more amber (examples include pallor, nasal flaring, and dry mucous membranes) or red features (examples include mottled skin, grunting, non-blanching rash and bile stained vomiting) should have investigations performed consisting of full blood count, blood culture, CRP and urine testing for UTI. However, a study designed to determine the accuracy of the system for detecting three common SBIs (UTI, pneumonia, and bacteraemia), found that it failed to identify a substantial proportion of SBI, particularly UTIs. ²⁸

The gap in clinical decision making is currently filled by using overall clinical impression and 'diagnostic safety-netting'; the latter is described as a set of procedures or guidelines that should be followed when a patient is discharged from the ED.²⁹ Pantell *et al* studied over 3,000 infants aged <3 months with fever who were managed by US paediatric clinicians. They found that clinical judgment was at least as sensitive in identifying bacteraemia and bacterial meningitis as investigating according to published guidelines, missing only 2 cases of either, while avoiding unnecessary investigations and treatment in many.³⁰ They suggest that, provided close follow-up is assured, clinical judgment can be employed for well-appearing febrile infants over 25 days of age, rather than investigating all such infants according to guidelines.

Given that the risk of SBI in well-appearing febrile children is low overall and UTI makes up 92% of causes, collection of urine for urinalysis, microscopy and culture may be the only test required in many of these children. The risk of disseminated sepsis with UTI is very low. ^{31,32} Infants with febrile UTI who are not clinically ill in the ED (well appearing, not dehydrated, and no concomitant acute disease) and have no high-risk past medical history can be treated as outpatients after a short period of observation. ³³ Therefore, in well infants, there is generally no need to perform blood tests or other investigations once a UTI has been diagnosed. No follow-up investigations are usually required for children with UTI. Ultrasound is necessary to detect serious complications such as renal or peri-renal abscesses or obstructive

uropathy that may require intervention. Early ultrasound can therefore be restricted to male infants less than 3 months of age or infants not responding to treatment.

Newman *et al* argue that pursuit of a diagnosis of UTI consumes resources and leads to patient discomfort, medical risks, and potential over-diagnosis. ³² They propose that screening for UTI can be withheld or delayed in well-appearing febrile children between 2 months and 2 years of age if signs of other sources are apparent or if the fever has been present for fewer than 4 to 5 days.

In febrile infants in whom UTI has been diagnosed, many guidelines suggest that blood and CSF should be collected for culture because of the risk of concomitant bacteraemia and meningitis. However, this is unnecessary as a routine practice, particularly in infants over one month of age. ^{34,35} The risk of bacteraemia with UTI is around 6%. ^{33,34} Risk factors for bacteraemia included unwell appearance, high risk past medical history (defined as history of genitourinary abnormalities, previous UTIs, bacteraemia, meningitis, previous laboratory evaluation for fever, prematurity or history of a severe systemic disease), and age less than 22 days. Two recent retrospective studies have shown that the risk of concomitant UTI and meningitis in children is low. ^{36,37} Vuillermin et al reviewed the laboratory results from 322 infants, 90 days of age or younger, with an admission or discharge diagnosis of UTI or meningitis. They found sterile pleocytosis in 5 infants with proven UTI, and of these, only one 90-day old male infant with probable bacterial meningitis in association with UTI. Tebruegge et al found no cases of meningitis amongst 499 infants aged 29 days to 12 months or 86 children aged over 12 months with UTI. They found coexistent UTI and meningitis in only 2 cases amongst 163 neonates aged 28 days or less, and both were unwell, presenting with fever, poor feeding, irritability and lethargy. This suggests that a selective, rather than universal, approach to lumbar puncture is appropriate.

Conclusion

SBI in febrile infants and children is uncommon and, when it does occur, UTI is far more likely than bacteraemia or meningitis. Neonates (28 days old and younger) are at higher risk of SBI than older infants. There is no single test or combination of tests and clinical findings that can reliably identify SBI in a febrile child. In wellappearing children under 3 years of age with fever without a source of infection, it is not necessary to do a "full septic work up". In many such children, the only test that is required is collection of urine for urinalysis, microscopy and culture. Even screening for UTI can be delayed for up to 5 days in well-appearing children over 2 months of age with fever without a source. When UTI is confirmed in a wellappearing child, collection of blood and CSF for culture is generally not required. Provided close follow-up is assured, clinical judgment can be employed for wellappearing febrile infants, particularly those over 1 month of age, rather than investigating all such infants according to prescriptive guidelines.

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