Neonatal fever in the term infant: evaluation and management strategies flashcard...

Abstract The presence of fever in the neonatal period demands urgent evaluation from healthcare providers since signs and symptoms of a serious bacterial infection in this age group can be nonspecific.

Current practice guidelines recommend that febrile neonates should be presumed to have a serious bacterial infection and undergo a sepsis evaluation and hospitalization until the results of diagnostic testing are known. However, less than 50% of outpatient practitioners in a recent study followed these recommendations without apparent adverse outcomes even though the rate of serious bacterial infections in the neonatal period is higher than febrile infants 1-3 months of age. In this article we examine various clinical scenarios that healthcare providers confront when caring for febrile neonates, including whether febrile neonates with respiratory syncytial virus are at increased risk for developing a serious bacterial infection and whether diagnostic testing and empiric antiviral therapy for herpes simplex virus should be part of the standard evaluation of febrile neonates. Although the discovery of inflammatory mediators that are elevated during the early stages of infection has the potential to improve diagnostic capabilities in this age group, there is enough evidence to support international guidelines recommending hospitalization and sepsis evaluations in febrile neonates.
KEY WORDS: neonate, fever, sepsis, guidelines, infection Introduction Fever (temperature ? 38.

0° C) in the neonatal period (? 0 days) can be an important underlying cause of severe infection because of the immaturity of the neonatal immune system. In fact, the annual incidence of severe sepsis in United States in children ? 19 years of age is highest in neonates (3. 60 per 1, 000

population) with over a 10% case fatality rate leading to an estimated 1361 deaths per year [1] compared to 1. 6 million deaths annually in developing countries [2].

Infections during the neonatal period can also lead to adverse neurodevelopmental outcomes such as cerebral palsy [3, 4]. In 2003, revised evidence-based guidelines recommended that because serious bacterial infections (SBIs) can present in otherwise well-appearing infants [5], febrile infants between 1-28 days of age should be presumed to have an SBI and undergo a complete sepsis evaluation, receive empiric antibiotics and be admitted to the hospital for further monitoring [6]. Recent guidelines from the United Kingdom continue to emphasize the potential risk of serious illness in febrile infants aged 0-3 months and recommend they be seen by a health care professional within 2 hours [7]. Recognizing that SBIs have been demonstrated to occur more frequently in neonates than in infants between 1-3 months of age [8], these guidelines similarly recommend that infants < 1 month of age should be observed in the hospital with empiric antibiotic initiated until the results of blood, urine and cerebrospinal fluid (CSF) are known. These recommendations apply to neonates with a parental report of fever, even if they are afebrile at the time of evaluation, since the rate of SBI is not necessarily lower in these patients [9].

Despite published guidelines, there is wide variation in levels of adherence to these recommendations [6, 10-12]. In a study of 3066 infants 3 months of age and younger, of whom 775 infants were 0-1 month of age, the above guidelines were followed only 45. 7% of the time [6]. Hospitalization for rule-out sepsis evaluation in these young infants can be associated with a high

level of parental stress, breastfeeding problems and iatrogenic complications [13, 14]. Additionally, 42% of parents in one study would prefer outpatient therapy to being hospitalized for evaluation of febrile infants [13]. A management strategy that avoids hospitalizing every febrile neonate while not missing an SBI that could lead to an adverse outcome is needed.

This article will examine the outcomes of term febrile neonates in developed countries and whether guidelines that are employed in febrile infants from 1 month to 3 months of age are reliable in infants < 1 month of age. Recent data from the use of inflammatory markers in febrile infants will also be presented to examine whether they offer an improvement over traditional screening laboratories used to develop the guidelines and perhaps allow some febrile neonates to avoid hospitalization. Other controversies surrounding the management and treatment of febrile infants such as ancillary diagnostic testing in febrile neonates with RSV and when to consider empiric acyclovir for herpes simplex virus encephalitis will also be addressed. Early and late-onset neonatal sepsis Since the introduction of intrapartum antibiotic prophylaxis guidelines in 1996 to prevent early-onset Group B Streptococci (GBS) sepsis, the rate of early-onset GBS has declined 50-80% to a rate of 0. 3 cases per 1, 000 live birth without an appreciable change in the rate of late-onset GBS disease [15-17].

Since the initiation of these guidelines there has been an improvement in mortality rates and greater survival of infants beyond 7 days of life suggesting an association with GBS disease prevention efforts [18]. In 2002, after results of a large US multistate, retrospective study demonstrated that routine screening for GBS during pregnancy prevented more cases of early-

onset disease than a risk-based approach [19], the CDC recommended that all pregnant women at 35-37 weeks gestation should undergo rectal and vaginal screening for GBS [17]. Concerns arose that universal screening would lead to increased antibiotic usage and could result in an increased rate of early-onset disease attributable to other organisms, particularly Gram-negative organisms such as Escherichia coli [20], while increasing the likelihood of drug-resistant pathogens [21]. However, several multicenter studies have documented a stable rate of non-GBS pathogens in early onset neonatal sepsis with the widespread usage of intrapartum antibiotic prophylaxis administered to women at risk of delivering a GBS-infected infant [22-26].

The pathogens most responsible for early onset sepsis are GBS in 40% of cases, Escherichia coli in 16. 5%, Streptococcus viridans in 7. 4%, and Staphylococcus aureus in 6. 4% [27]. Another study reported GBS in 40.

7% of cases, E. coli in 17. 2%, Streptococcus viridans in 16. 4% and Enterococcus species in 3.

9% [23]. In developing countries Gram negative organisms such as Klebsiella, E. coli, Pseudomonas and Salmonella are more common, and while GBS is rare, other Gram positive organisms such as coagulase negative staphylococci, Streptococcus pneumoniae, and Streptococcus pyogenes are more common [2]. In industrialized nations late onset sepsis Gram-positive cocci such as coagulase-negative Staphylococcus aureus and Gram-negative rods such as Enterobacter species are common etiologies, particularly in neonatal units [28-30]. Guidelines for the management of febrile infants

Over the past fifteen years there have been several trials that have examined clinical criteria in assessing whether febrile infants <90 days can be reliably classified as being low risk for an SBI [31-34]. These low isk criteria can be found in Table 1 while the overall rate of SBI in low and high risk febrile infants can be found in Table 2.

Five hundred three febrile infants between 28 to 89 days of age who were enrolled under the Boston criteria had a serious bacterial infection rate of 5. 4% (27/503). The results of this study popularized the concept of administering outpatient ceftriaxone to febrile infants after a full sepsis evaluation was performed as an alternative to hospital admission since all of the enrolled patients under the Boston criteria were well on follow-up. Investigators were not able to identify a laboratory value or clinical score that would have reliably discriminated between infants with and without an SBI.

In fact, only 13 of the 25 infants with an SBI who were able to be evaluated according to an earlier version of the Rochester criteria [35] would have been classified as being at high risk for an SBI. The Philadelphia criteria [32] were used to enroll 747 febrile infants 29 to 56 days of age. Two hundred eighty-seven infants met low-risk criteria and were assigned to either inpatient observation or outpatient observation status without antibiotic administration. The overall SBI rate was 8.

7% but only 1 of the 287 low risk infants had an SBI (0. 03%). When a normal band-to-neutrophil ratio (<0. 2) was added to the screening criteria to identify low-risk infants, every infant who had a SBI was identified.

This study enrolled infants with temperatures at least 38. 2? C and required infants to have a WBC count < 15, 000/mm3 while the Boston criteria allowed a WBC count of <20, 000/mm3 to be considered low risk for an SBI. Although there was not a significant difference in WBC count between the group who had an SBI and the group that didn’t have an SBI in the Boston study, at least 3 of the 9 infants who were bacteremic had a WBC count that would have placed them in the high risk group in the Philadelphia study which may partly explain the differences in the rate of SBI between the two studies. Although the Philadelphia and Boston criteria used formal infant observation scores [36], there was no significant difference in observation scores between infants who had a bacterial source of infection and those who didn’t. This demonstrates the subtlety in how an SBI can present in this age group and the need for a full sepsis workup to guide management strategies.

Use of the Rochester criteria [33] identified 437 febrile infants ? 60 days who were considered low-risk for developing an SBI. Five infants (1. 1%) developed an SBI, including 2 with bacteremia. There were 224 infants ? 30 days of age who were classified as low risk and two (0.

9%) developed an SBI. One was an E. coli UTI while the other developed Neisseria meningitidis, both of whom did well. The Pittsburgh criteria [34] utilized an enhanced urinalysis of uncentrifuged urine for hemocytometer cell count and Gram stain since previous work has reported that an enhanced UA had greater sensitivity and positive predictive value than a standard UA [37]. The overall rate of SBI in 404 eligible infants was 10.

1%, however, in the 127 infants ? 60 days that met low-risk criteria (well-appearing, previously healthy, and normal screening labs) there was not a single reported SBI. These criteria demonstrated that a substantial number of 1-3 month old febrile infants who are well-appearing can avoid inpatient admission provided they have a normal sepsis workup and have close outpatient follow-up. Subsequently, practice guidelines were developed that supported this approach [38, 39]. The utility of viral testing in febrile infants during rule-out sepsis evaluations has also been examined [40-43]. The use of enterovirus polymerase chain reaction identified a significant portion of young febrile infants in two studies [40, 41], while human herpes virus 6 was found in 10% of febrile infants ? 0 days of age in another study [43].

The applicability of these tests to assess whether antibiotics can be safely deferred in febrile infants is somewhat limited because of the time needed to get results. However, testing for influenza A and B viruses during influenza season decreased the need for ancillary blood tests, urinalysis, chest roentgenogram, cerebrospinal fluid analysis and antibiotic treatment in a study of 206 infants 0 to 36 months of age. Although there were a total of 14 positive blood cultures in these infants all of them occurred among influenza-negative patients [42]. Neonates with Serious Bacterial Infections Table 3 lists the rate of serious bacterial infections in febrile neonates [44-51]. Comparing the rate of SBI in febrile neonates with rate of SBI in febrile infants 1-3 months of age in Table 2, febrile neonates are at a higher risk for SBI than older febrile infants. This supports some earlier studies which examined febrile neonates as a subgroup of older febrile infants [52-54] and

also demonstrates that febrile infants who fall into the low-risk screening categories can still have SBIs that are missed [55].

The overall rate of SBI in febrile neonates listed in Table 3 is 15. 8% (317/2006). The overall rate of SBI in the one-three month age group in Table 2 is 8. 9% (144 /1618). Neither the Boston criteria in Table 2 or Wu et al [50] in Table 4 were counted in the overall rate of SBI since they only enrolled low-risk infants. Marom et al [51] considered acute otitis media (AOM) as an SBI which is controversial since this has not been shown in other studies to predict a higher risk of SBI in infants < 2 months of age [34, 56].

If the 36 patients who had AOM in Marom et al were not classified as an SBI the rate is 14. 0% (281/2006). Even in the low-risk category the rate of SBI is higher in neonates compared to 1-3 month old infants (3. 1% vs 2. 9%, respectively), although the Pittsburgh and Rochester criteria did have low rates of SBI in neonates who met their strict screening criteria as part of a larger group of older febrile infants. However, the overall rate of neonatal SBI in the Rochester criteria may be higher since investigators added 74 low-risk infants from the Febrile Infant Collaborative Study Group without stating how many overall neonates were screened to arrive at these 74, since either ill-appearance or abnormal labs would have automatically excluded these individuals.

Additionally, the 72 ill-appearing infants in the study did not have a breakdown according to age so if any of these patients were neonates it would have impacted the overall rate of SBI in neonates as well. Another important aspect of these studies is that the majority of febrile infants fell

into the high-risk criteria after a complete history, physical exam and screening labs were performed, which makes it difficult to recommend anything other than a complete sepsis evaluation so that an SBI is not missed. It is important to note that all of the studies enrolled febrile infants through an emergency department where presenting infants may have been sicker than if they were seen in an outpatient setting. For example, a large prospective study enrolled 3, 066 febrile infants ? months of age from 573 outpatient physicians in the United States and Puerto Rico. Seven hundred seventy-five of these infants were between 1-30 days of age. Only 45.

7% of the time did practitioners follow the recommendations of a complete sepsis evaluation, hospitalization and antibiotics although these infants were more significantly more likely than older infants to have a WBC count, blood culture and lumbar puncture, empiric antibiotics initiated and be hospitalized [8]. The overall rate of bacteremia or bacterial meningitis in infants 1-30 days of age was 4. % (32/775) compared to a rate of 1. 9% (23/1220) in infants > 1-2 months of age and (8/1071) 0. 7% in infants 2-3 months of age. The rate of bacteremia and meningitis in well or minimally ill-appearing infants < 25 days of age was 3.

4% (13/384). Although practitioners initially treated 61 of the 63 infants with bacteremia or meningitis, the 2 infants not treated were both well-appearing infants < 30 days of age, one of whom had group B streptococci bacteremia and the other had a WBC count of 15300 cells/mm3 (< 1500 bands/mm3), which would have put the infant in the high-risk criteria. However, this patient was sent home without antibiotics and developed pneumococcal meningitis over the next day. Urinalysis was obtained in 54% of the subjects

with 10% of infants age ? 30 days diagnosed with a UTI with an associated 17% bacteremia rate [57].

The predicted probability of a febrile infant who was not initially tested with a urinalysis should have numbered an additional 61 cases. However, in patients who had follow-up available, there were only 2 additional infants who developed a UTI. There were a total of 76 infants who did not have follow-up available so the rate of UTI may have been higher. Neonates pretreated with antibiotics A delay in performing a lumbar puncture may complicate the diagnosis of bacterial meningitis, particularly in infants who have been pretreated with antibiotics. Delaying an LP can affect the results of CSF testing since sterilization of CSF has been shown to occur within 60 minutes in patients with meningococcal meningitis and less than 5 hours in patients with pneumococcal meningitis.

Although these are not the most common pathogens in neonatal meningitis, sterilization of the CSF in patients with GBS can occur between 24 and 48 hours [58]. CSF parameters such as an abnormal glucose, protein and a low WBC count can not be used to definitively exclude meningitis since as many as 12. 6% of neonates with culture-proven meningitis may have ? 21 WBC/mm3 [59, 60]. The use of cerebrospinal latex agglutination testing for the detection of bacterial antigens is not currently recommended in patients who have received antibiotics prior to lumbar puncture since testing did not identify any additional cases of bacterial meningitis in study of 176 pediatric patients [61].

Blood cultures are positive in less than two-thirds of neonates with meningitis making the decision to defer an LP until a pathogen is isolated from the blood an unreliable clinical strategy [60, 62]. A promising technique that utilizes PCR amplification to detect the 16S rRNA gene of bacteria has been clinically useful in analyzing CSF from patients who have been treated with antibiotics prior to lumbar puncture [63, 64]. However, until there is a reliable technique to exclude bacterial meningitis in infants pretreated with antibiotics, CSF cultures should be obtained prior to their initiation. Dilemma of when to test and empirically treat for herpes simplex virus (HSV) infections Neonatal herpes simplex virus is commonly acquired during birth from an infected maternal genital tract. Unfortunately, in more than 60% of infants with neonatal herpes simplex virus infection there has been no maternal history or physical signs present to suggest an active HSV infection.

Although the seroprevalence of HSV-2 in pregnant women is approximately 20-30%, and the seroprevalence of HSV-1 is even greater in the general population, infection with either in the neonatal period is rare with incidence rates between 5. cases per 100, 000 live births in Canada and 20-50 cases per 100, 000 live births in the United States [65, 66]. Experts in the study of neonatal HSV infection do not suggest that acyclovir be routinely added to antibiotics in neonates who are admitted to rule out sepsis. HSV infections, however, should be considered in the differential diagnosis of acutely ill infants because of its significant morbidity and mortality.

There is an approximately 15% mortality rate of HSV CNS infection with 70% of survivors having some degree of developmental impairment at 12 months of age [67]. Although neonates with HSV CNS involvement can present with

fever alone [68], typically there is an absence of fever but clinical signs such as skin vesicles [67], seizures [67, 69, 70], dysthermia [70], tachypnea [69], and lethargy [67, 70] are commonly present. Despite clinical suspicion of HSV CNS involvement, HSV PCR is only positive in approximately 2% of those patients [68, 71]. Because HSV PCR testing can remain negative in the first few days of illness, testing of additional CSF samples may be necessary if a clinical suspicion of HSV CNS involvement remains high [72, 73]. Although there is typically a CSF pleocytosis with CNS involvement, this might not be present in the early stage of the infection. The occurrence of a bloody lumbar puncture is commonly associated with testing for HSV, however, traumatic lumbar punctures routinely occur in pediatric patients making interpretation difficult and should not be the sole determinant of whether to initiate therapy [67, 74].

Non-infectious causes of fever in the neonateAlthough the primary consideration of evaluating fever in the neonates is to evaluate for evidence of infection, there are multiple non-infectious causes of fever in the neonate (Table 4). Clinicians should ask about infant bundling and environmental conditions in febrile neonates, however, fever should rarely be attributed to bundling [75, 76]. Clinicians should also inquire whether neonates are receiving sufficient nutritional intake, particularly in breast-fed infants born to primiparous mothers. Nearly two percent of neonatal hospitalizations in one pediatric center were due to hypernatremic dehydration in breast-fed infants.

Fever was a presenting symptom in 20% of these patients and 63% underwent a full sepsis evaluation including lumbar puncture and treatment

with antibiotics without any reported cases of bacteremia or meningitis [77]. Hereditary autoinflammatory syndromes are caused by mutations in genes that encode proteins which mediate inflammation and can present with fever in the neonatal period. Characterized by recurrent fever and multisystemic inflammation that lack identifiable pathogens and don’t produce high-titer autoantibodies, unlike autoimmune disorders, they are a group of 8 diseases that all share similar clinical features such as cutaneous and musculoskeletal involvement with varying degrees of ocular and abdominal involvement [78]. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and neonatal-onset multi-system inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular syndrome (CINCA), have been reported in neonates [79]. Two autosomal recessive conditions that can present with fever in the neonatal period include Crisponi and Stuve-Wiedemann syndromes [80, 81].

The former is characterized by abnormal facial features, facial muscle contractions simulating tetany, camptodactyly, and is usually fatal within the first few months of life. The latter is also associated with camptodactyly along with congenital bowing of the long bones of the lower limbs and cardiovascular abnormalities. Because fever can be caused by intracranial hemorrhage, hildren who present with lethargy and seizures and don’t have a readily identifiable diagnosis should undergo neuroimaging. The presence of a subdural hematoma is a cardinal sign of non-accidental injury, particularly if other clinical signs of abuse are not evident [82]. Spinal neurenteric cysts, resulting from an embryonic defect where an intraspinal

cyst is lined by alimentary tract mucosa, have been reported to cause fever in neonates and can lead to acute myelopathy [83].

Other rare reported non-infectious causes of fever in the neonate include hemophagocytic syndrome where upregulation of tissue macrophages result in uncontrolled hemophagocytosis and the release of inflammatory cytokines that can present clinically like sepsis but can be rapidly fatal if not diagnosed promptly [84], and anhidrotic ectodermal dysplasia, where affected neonates have anhidrosis, hyptotrichosis and abnormal dentition [85]. Fever in neonates with respiratory syncytial virusA common dilemma practitioner’s face is whether to initiate a sepsis evaluation in a febrile neonate that has bronchiolitis since viruses may predispose infants to secondary bacterial infections due to a direct effect of viruses at infected tissues sites and alterations in neutrophil function [86]. Although no study has exclusively enrolled febrile neonates with documented RSV infection and examined the rate of SBI, Table 5 summarizes recent studies that have examined the rate of SBI in febrile infants where febrile neonates with RSV bronchiolitis were a subset of enrolled patients. Four of the studies [87-90] were retrospective in design and even though full sepsis evaluations occurred in only approximately 50% of febrile infants [87, 88, 90], two of the studies did not report a single case of bacteremia [87, 89] while the remaining two had bacteremia rates of <1. 0% [85, 88].

In these four studies there was only a single case of meningitis reported in an RSV-positive infant, a 45 day old who presented with apnea, fever and cyanosis while the rates of UTI ranged from 0 to 7. %. The specific documentation of RSV in a young febrile infant may be of help in determining

whether a complete sepsis evaluation is warranted since the rate of SBI may be lower in these infants compared to patients who are RSV-negative [87, 89, 91] In a three year, multicenter, prospective, cross-sectional study which enrolled 1248 infants younger than 60 days of age, the rate of SBI was significantly lower in RSV-positive patients compared to RSV-negative patients (7. 0% vs.

12. 5%). The rate of UTI in RSV-positive patients was significantly lower than in RSV-negative patients (5. 4% vs 10.

1%). The rate of bacteremia in RSV-positive patients was 1. 1% compared to 2. 3% in RSV-negative patients and not a single RSV-positive patient had bacterial meningitis, although these rates did not reach statistical significance between groups [91].

Viral testing as part of a routine sepsis evaluation in patients with bronchiolitis can therefore be used to assist in the evaluation of these febrile infants. In a study of 1385 febrile infants 1 to 90 days of age who underwent some form of viral diagnostic testing and who were classified as either high-risk or low-risk for SBI by Rochester criteria, infants with a documented viral infection were significantly less likely to have an SBI than infants without a documented viral infection (4. 2% vs 12. 3%).

RSV was tested in 643 patients with 159 positive (25%). None of these febrile RSV positive patients had bacteremia while 4 (2. 5%) had a SBI [92]. Despite the low rates of serious bacterial infection in RSV-positive febrile infants, particularly meningitis and bacteremia, caution should be used in extrapolating the data from these findings in young infants to an exclusive

neonatal population since two studies that enrolled RSV-positive febrile neonates ? 28 days of age did report a 6. 1% and 10% rate of UTIs [90, 91], with one study reporting a 3.

7% rate of bacteremia [91]. At the minimum, we recommend obtaining a urine culture in febrile neonates with documented RSV infection. The use of inflammatory mediators in the evaluation of febrile neonates Inflammatory mediators are released as part of the host response to infection and have been studied in febrile infants and children to determine their effectiveness in identifying the likelihood of an SBI. In a study of 408 children aged 7-days to 36-months who presented to an emergency department with fever without a source the ability of procalcitonin (PCT), C-reactive protein (CRP), white blood cell (WBC) count and absolute neutrophil count (ANC) were assessed in predicting an SBI [Table 6]. A total of 94 children (23%) developed an SBI, and although all four variables were higher in patients with SBI, only CRP and PCT were significant predictors of an SBI when body temperature and Infant Observation Scores [35] were introduced in a multiple logistic regression analysis.

Additionally, when CRP < 32 mg/L and PCT <0. 8 ng/mL were combined the sensitivity for ruling out an SBI increased to 92. 6%. PCT was higher in patients with more invasive infections and performed better in patients with fever < 8 hours.

There was also not a difference in performance in infant < 3 months versus children aged 3-36 month [93]. Interleukin (IL)-6 levels > 95 pg/mL, an early mediator in the host’s initial response to bacteremia, were shown in a prior

study that enrolled 0-36 month of age to have a 99. 6% negative predictive value for bacteremia with a prior probability of 2. 5% [94]. Galetto-Lacour et al [95] enrolled 124 children 7 days of age to 36 months of age who presented to the emergency department with fever without a source and had CRP, PCT, IL-6, IL-8 and IL-1Ra drawn to assess their ability to predict an SBI.

A total of 28 (23%) developed an SBI. PCT, CRP and IL-6 were significantly higher in the group of children with an SBI compared to IL-8 and IL-1Ra while PCT and CRP were superior to IL-6 in discriminating between SBI and benign infection. When PCT > 0. 9 ng/mL or CRP > 40 mg/L the sensitivity for detecting an SBI rose to 96% with a specificity of 67% and a negative predictive value of 98% [95]. There was no difference in performance of the tests between children < 1 year of age and > 1 year of age.

In another study by Galetto-Lacour et al [96], 99 children were enrolled with a 29% rate of SBI. The sensitivity for diagnosing an SBI was 93% and the specificity was 74% for PCT > 0. 5 ng/mL. Both the sensitivity and specificity of CRP > 40 mg/L was 74%.

The sensitivity increased to 97% when both were combined. Only 3% of enrollees with PCT <0. 5 ng/mL had an SBI, while 10% of enrollees with CRP < 40 had an SBI. However, there is a concern that inflammatory mediators may not perform as accurately during the immediate newborn period in detecting early onset sepsis since levels may be confounded by maternal factors, perinatal complications and severity of infection [97, 98]. In one study, different cut-off points for CRP, IL-6 and PCT were used within the first 48 hours of life to improve sensitivities, with PCT superior to CRP or IL-6 [98].

MxA protein is expressed in peripheral blood and has been shown to be a marker of viral infection since it is not induced by cytokines typical of bacterial infections.

A level above 234 ng/mL it (remove) was shown to 92. 6% specific for viral infection while performing better than CRP and WBC count. Unfortunately, in the 30 infants < 3 months of age, 5 infants with a ormal MxA level had an SBI [99]. CD64 is expressed on the surface of neutrophils in response to bacterial infection and when a CD64 index of 2.

30 was used in combination with ANC <7500 or > 14500/mm3, a recent study demonstrated a 95% sensitivity for diagnosis sepsis with a negative predictive value for ruling out sepsis of 93% [100]. However, this was utilized in a neonatal intensive care unit with premature infants which may not be reproducible in outpatient term neonates presenting for evaluation of fever. The discovery of inflammatory mediators that are elevated during a febrile illness has the potential to predict which infants are at such low risk of developing an SBI that a full sepsis evaluation can be safely deferred. However, because of varying cut-off levels reported in these studies, conditions other than infection that can affect levels immediately after birth, the length of illness/fever/timing of blood sample, they have not replaced conventional strategies in the evaluation of febrile infants. Pharmacotherapy in febrile neonates evaluated for an SBI While a recent Cochrane review concluded no demonstrated superiority of one antibiotic regimen [101], empiric antibiotic coverage of these pathogens usually includes ampicillin and gentamicin or ampicillin and cefotaxime. Ampicillin is used for the rare

instance that Listeria monocytogenes is the offending pathogen, but also has activity against Group B streptococci and many E.

coli isolates. The addition of a second agent (gentamicin or cefotaxime) provides additional coverage for ampicillin-resistant E. coli. Cefotaxime utilization requires less laboratory monitoring (no serum concentrations needed) and is less nephro- and ototoxic, but may be more likely to pressure bacterial flora towards resistant organisms [102]. A recent retrospective review comparing gentamicin and cefotaxime as secondary agents demonstrated an association between cefotaxime use and increased mortality although causality was not established [103]. A reasonable approach would be to use gentamicin with ampicillin except in the setting of renal dysfunction or inability to monitor serum concentrations.

Historically, intramuscular ceftriaxone was occasionally used in the place of cefotaxime when intravenous access was not available as the agents have similar antimicrobial activity. This choice is limited by the fact that ceftriaxone may cause biliary sludging in neonates and also has the potential to compete with bilirubin for binding sites on albumin, increasing the risk for kernicterus [104]. In addition, the US Food & Drug Administration recently released a report of five neonatal deaths associated with concomitant ceftriaxone and calcium use [105]. Ceftriaxone is a less than ideal antibiotic choice for neonatal sepsis as safer alternatives are available. Antibiotic dosing, pharmacokinetics and pharmacodynamics Beta lactam antibiotics (ampicillin, cefotaxime) have a wide therapeutic index and are generally well-tolerated with few side-effects. Maximizing the dose administered will ensure optimal penetration to the site of infection (table 7) [106].

Beta lactams exhibit time-dependent killing of microorganisms; efficacy is predicted by the amount of time the antibiotic serum concentration is above the minimum inhibitory concentration (MIC) of that antibiotic with regards to the pathogen. Conversely, aminoglycosides (gentamicin) have a narrow therapeutic index and need to be carefully dosed taking renal function, age, fluid status, concomitant medications and disease states into consideration (table 7). Gentamicin displays concentration-dependant killing; efficacy is predicted by the ratio of peak concentration to MIC (i. . higher peak = better microbial kill). Target peak serum concentrations for gentamicin are 4-12 mcg/mL and are guided by infection site.

Higher peak concentrations are warranted for sepsis and meningitis while lower concentrations are acceptable for urinary tract infections or synergy for gram positive infections. Target trough concentrations are <1 mcg/mL but still detectable. Some sources recommend < 2 mcg/mL as a trough goal, but this provides no advantage over a goal of < 1 mcg/mL and may predispose to drug accumulation and renal injury. Conclusion Although not every infant < 1 month of age has an infection they should be considered to have one until proven otherwise.

The results of several prospective clinical studies in febrile infants between the ages of 1-3 months has identified criteria that allow healthcare providers to categorize infants who are at low risk for developing an SBI and therefore do not automatically require hospitalization and empiric antibiotics provided that reliable follow-up can be ensured. Since febrile infants < 1 month of age are at a higher risk of developing a serious bacterial infection than febrile 1-3 month infants, recommendations to perform a full sepsis evaluation and

hospitalize these infants until the results of diagnostic testing are known is an evidenced-based one that attempts to minimize potential adverse outcomes that can arise from missing a potentially serious infection. The discovery of various biochemical markers that are early mediators in response to bacterial infection represent an exciting development for practitioners who care for febrile infants since they may eventually allow more precise categorization of the risk for SBI in young, febrile infants than current strategies. Future prospective studies in the outcomes of febrile infants < 1 month of age utilizing biochemical markers as part of the criteria to assess risk for serious bacterial infections and/or assessing presenting location (office-based practitioners versus emergency department) of these infants may further refine the recommendations for management. Febrile infants who have RSV bronchiolitis appear to have an overall lower risk of SBI than febrile infants without RSV bronchiolitis, however, obtaining a urine culture in febrile neonates with RSV should be strongly considered because the incidence of UTI in this clinical setting is not negligible. Finally, empiric testing and treatment for HSV infection is not indicated for every febrile neonate.

BIBLIOGRAPHY [1]. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003; 167: 695-701. [2].

Vergano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. Arch Dis Child Fetal Neonatal Ed 2005; 90: F220-F224. [3].

Graham EM, Holcroft CJ, Rai KK, Donohue PK, Allen MC. Neonatal cerebral white matter injury in preterm infants is associated with culture positive infections and only rarely with metabolic acidosis. Am J Obstet Gynecol 2004; 191: 1305-1310. [4.] Nelson KB, Dambrosia JM, Grether JK, Phillips TM.

Neonatal cytokines and coagulation factors in children with cerebral palsy. Ann Neurol 1998; 44: 665-675. [5]. Baker MD, Avner JR, Bell LM. Failure of infant bservation scales in detecting serious illness in febrile 4-to 8-week old infants. Pediatrics 1990; 85: 1040-1043.

[6]. ACEP Clinical Policy Committee and the Clinical Policies Committee and Clinical Policies Subcommittee on Pediatric Fever. Clinical policy for children younger than three years presenting to the emergency department with fever. Ann Emerg Med 2003; 42: 530-545.

[7]. Richardson M, Lakhanpaul M, on behalf of the Guideline Development Group and the technical team. Assessment and initial management of feverish illness in children younger than 5 years: summary of NICE guideline. BMJ 2007; 334: 1163-1164. 8]. Pantell RH, Newman TB, Bernzweig J, et al.

Management and outcomes of care of fever in early infancy. JAMA 2004; 291: 1203-1212. [9]. Bonadio WA. Incidence of serious infections in afebrile neonates with a history of fever.

Pediatr Infect Dis J 1987; 6: 911-914. [10]. Zerr DM, Del Beccaro MA, Cummings P. Predictors of physician compliance with a published guideline on Management of febrile infants.

Pediatr Inf Dis J 1999; 18: 232-238. [11]. Belfer RA, Gittelman MA, Muniz AE. Management of febrile infants and children by pediatric emergency medicine and emergency medicine: comparison with practice guidelines.

Ped Emer Care 2001; 17: 83-87. [12]. Al-Zamil FA. The dogma of identifying occult bacterial infections in young febrile children: a survey of primary care physicians. Int J Clin Pract 2000; 54: 486-488. [13].

Paxton RD, Byington CL. An examination of the unintended consequences of the rule-out sepsis evaluation: a parental perspective. Clin Pediatr 2001; 40: 71-77. [14].

DeAngelis C, Joffe A, Wilson M, Willis E. Iatrogenic risks and financial costs of hospitalizing febrile infants. Am J Dis Child 1983; 137: 1146-1149. [15]. Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis.

Lancet Infect Dis 2003; 3: 201-213. [16]. Centers for Disease Control and Prevention. Early-onset and late-onset neonatal group B streptococcal disease: United States, 1996-2004.

MMWR Morb Mortal Wkly Rep 2005; 54: 1205-1208. [17]. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC.

MMWR Recomm Rep 2002; 51: 1-22. [18]. Lukacs SL, Schoendorf KC, MD, Schuchat A. Trends in sepsis-related neonatal mortality in the United States, 1985–1998. Ped Infect Dis J 2004; 29: 599-603.

[19]. Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. N Eng J Med 2002; 347: 233-239. [20].

Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. Am J Obstet Gynecol 1998; 179: 879-883. [21]. Joseph TA, Pyati SP, Jacobs N.

Neonatal early-onset Escherichia coli disease: the effect of intrapartum ampicillin. Arch Pediatr Adolesc Med 1998; 152: 35-40. 22]. Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset Escherichia coli infections in the era of widespread intrapartum antibiotic use.

Pediatrics 2006; 118: 570-576. [23]. Hyde TB, Hilger TM, Reingold A, et al, for the Active Bacterial Core surveillance (ABCs) of the Emerging Infections Program Network. Pediatrics 2002; 110: 690-695. [24]. Baltimore RS, Huie SM, Meek JI, Schuchat A, O'Brien KL.

Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics 2001; 108: 1094-1098. [25]. Daley AJ, Isaacs D, and the Australasian Study Group for Neonatal Infections.

Ten-year study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and Escherichia coli neonatal sepsis in Australasia. Pediatr Infect Dis J 2004; 23: 630-634. [26]. Alarcon A, Pena P, Salas S, Sancha S, Omenaca F.

Neonatal early onset Escherichia coli sepsis: trends in incidence and antimicrobial resistance in the era of intrapartum antimicrobial prophylaxis. Pediatr Infect Dis J 2004. 23: 295-299. [27]. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study.

Pediatrics 2000; 105: 21-26. [28]. Nambiar S, Singh N. Late Onset Neonatal Gram-Negative Bacillary Infection in Australia and New Zealand: 1992–2002. Pediatr Infect Dis J 2006. 25: 25-29.

[29]. Gordon A, Isaacs D. Change in epidemiology of health care-associated infections in a neonatal intensive care unit. Pediatr Infect Dis J 2002; 21: 839-842. [30].

Rubin LG, Sanchez PJ, Siegel JS, et al. Evaluation and treatment of neonates with suspected late-onset sepsis: a survey of neonatologists' practices. Pediatrics 2002; 110: e42. [31]. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone.

J Pediatr 1992; 120: 22-27. [32]. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. N Engl J Med 1993; 329: 1437-1441. [33].

Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection – an appraisal of the Rochester criteria and implications for management. Pediatrics 1994; 94: 390-396. [34].

Herr SM, Wald ER, Pitetti RD, Choi SS. Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. Pediatrics 2001; 108: 866-871. [35]. McCarthy CA, Powell KR, Jaskiewicz JA, et al. Outpatient management of selected infants younger than two months of age evaluated for possible sepsis.

Pediatr Infect Dis J 1990; 9: 385-389. [36]. McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. Pediatrics 1982; 70: 802-809. [37].

Hoberman A, Wald ER, Penchansky L, Reynolds EA, Young S. Enhanced urinalysis as a screening test for a urinary tract infection. Pediatrics 1993; 91: 1196-199. [38]. Baraff LJ, Bass JW, Fleisher, et al. Practice guidelines for the management of infants and children 0 to 36 months of age with fever without source.

Pediatrics 1993; 92: 1-12. [39]. Baraff LJ. Management of fever without source in infants and children. Ann Emerg Med.

2000; 36: 602-614. [40]. Kawashima H, Kobayashi K, Aritaki K, et al. Diagnosis and evaluation of febrile infants under 4 months of age in Japan by using RT-PCR for enterovirus. J Infect 2006; 53: 16-20. [41].

Byington CL, Taggart EW, Carroll KC, Hillyard DR. A polymerase chain reaction-based epidemiological investigation of the incidence of nonpolio enteroviral infections in febrile and afebrile infants 90 days and younger. Pediatrics 1999; 103: e27. [42]. Benito-Fernandez J, Vazquez-Ronco M, Morteruel-Aizkuren E, Mintegui-Raso S, Sanchez-Etxaniz J, Fernandez-

Landaluce A. Impact of rapid viral testing for influenza A and B viruses on management of febrile infants without signs of focal infection.

Pediatr Infect Dis J 2006; 25: 1153-1157. [43]. Byington CL, Zerr DM, Taggart EW, et al. Human herpesvirus 6 infection in febrile infants ninety days of age and younger. Pediatr Infect Dis J 2002; 21: 996-999. [44].

Bonadio WA, Romine K, Gyuro J. Relationship of fever magnitude to rate of serious bacterial infections in neonates. J Pediatr 1990; 116: 733-735. [45]. Chiu C-H, Lin T-Y, Bullard MJ. Application of criteria identifying febrile outpatient neonates at low risk for bacterial infections.

Pediatr Infect Dis J 1994; 13: 946-949. [46]. Ferrera PC, Bartfield JM, Snyder HS. Neonatal fever: utility of the Rochester criteria in determining low risk for serious bacterial infections. Am J Emerg Med 1997; 15: 299-302. [47].

Chiu C-H, Lin T-Y, Bullard MJ. Identification of febrile neonates unlikely to have bacterial infections. Pediatr Infect Dis J 1997; 16: 59-63. [48].

Baker MD, Bell LM. Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. Arch Pediatr Adolesc Med 1999; 153: 508-511. [49].

Kadish HA, Loveridge B, Tobey J, Bolte RG, Cornell HM. Applying outpatient protocols in febrile infants 1-28 days of age: can the threshold be lowered? Clin Pediatr 2000; 39: 81-88. [50]. Wu W-J, Chen H-M, Chung P-W, Yen J-B, Chiu C-H.

Ambulatory care of selected febrile outpatient neonates unlikely to have bacterial infections. Int Pediatr 2004; 19: 52-56. [51]. Marom M, Sakran W, Antonelli J, et al. Quick identification of febrile neonates with low risk for serious bacterial infection: an observational study.

Arch Dis Child Fetal Neonatal Ed 2007; 92: F-15-18. [52]. King JC, Berman ED, Wright PF. Evaluation of fever in infants less than 8 weeks old. South Med J 1987; 80: 948-952.

[53]. Bonadio WA, Webster H, Wolfe H, Gorecki D. Correlating infectious outcome with clinical parameters of 1130 consecutive febrile infants aged zero to eight weeks. Ped Emerg Care 1993; 9: 84-86. [54].

Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. J Pediatr 1985; 107: 855-860. [55].

Anbar RD, Richardson-de Corral V, O'Malley PJ. Difficulties in universal application of criteria identifying infants at low risk for serious bacterial infection. J Pediatr 1986; 109: 483-485. [56]. Turner D, Leibovitz E, Aran A, et al. Acute otitis media in infants younger than two months of age: microbiology, clinical presentation and therapeutic approach.

Pediatr Infect Dis J 2002; 21: 669-674. 57]. Newman TB, Bernzweig JA, Takayama JI, Finch SA, Wasserman RC, Pantell RH. Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study. Arch Pediatr Adolesc Med 2002; 156: 44-54.

[58]. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: Refining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001; 108: 1169-1174. [59].

Dawson KG, Emerson JC, Burns JL. Fifteen years of experience with bacterial meningitis. Pediatr Infect Dis J. 1999; 18: 816-822. [60]. Garges HP, Moody MA, Cotton CM, et al.

Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters. Pediatrics 2006; 117: 1094-1100. [61]. Nigrovic LE, Kupperman N, McAdam AJ, Malley R. Cerebrospinal latex agglutination fails to contribute to the microbiologic diagnosis of pretreated children with meningitis. Pediatr Infect Dis J 2004; 23: 786-788.

[62]. Riordan FAI, Cant AJ. When to do a lumbar puncture. Arch Dis Child 2002; 87: 235-237. [63].

Schuurman T, de Boer RF, Kooistra-Smid AMD, van Zwet AA. Prospective study of use of PCR amplification and sequencing of 16S ribosomal DNA from cerebrospinal fluid for diagnosis of bacterial meningitis in a clinical setting. J Clin Microbiol 2004; 42: 734-740. [64]. Welinder-Olsson C, Dotevall L, Hogevik H, et al. Comparison of broad-range bacterial PCR and culture of cerebrospinal fluid for diagnosis of community-acquired bacterial meningitis. Clin Microbiol Infect 2007; 13: 879-886. [65]. Tita ATN, Grobman WA, Rouse DJ. Antenatal herpes serologic screening: an appraisal of the evidence. Obstet Gynecol 2006; 108: 1247-53. [66]. Kropp RY, Wong T, Cormier L, et

al. Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study. Pediatrics 2006; 117: 1955-1962. [67]. Kimberlin DW, Lin C-Y, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001; 108: 223-229. [68]. Filippine MM, Katz BZ. Neonatal herpes simplex virus infection presenting with fever alone. J Hum Virol 2001; 4: 223-225. [69]. Cohen DM, Lorch SA, King RL, Hodinka RL, Cohn KA, Shah SS. Factors influencing the decision to test young infants for the herpes simplex virus infection. Pediatr Infect Dis J 2007; 1156-1158. 70]. Toth C, Harder S, Yager J. Neonatal herpes encephalitis: a case series and review of clinical presentation. Can J Neurol Sci 2003; 30: 36-40. [71]. Cimolai N, Thomas EE, Tan R, Hill A. Utilization of herpes simplex PCR assays for cerebrospinal fluid in a pediatric health care setting. Can J Microbiol 2001; 47: 392-396. [72]. Kimberlin DW, Lakeman FD, Arvin AM, et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. J Infect Dis 1996; 174: 1162-1167. [73]. DeTiege X, Heron B, LeBon P, Ponsot G, Rozenberg F. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. Clin Infect Dis. 2003; 36: 1335-1339. [74]. Frenkel LM. Challenges in the diagnosis and management of neonatal herpes simplex virus encephalitis. Pediatrics 2005; 115: 795-797. [75]. Cheng TL, Partridge JC. Effect of bundling and high environmental temperature on neonatal body temperature. Pediatrics 1993; 92: 238-240. [76]. Grover G, Berkowitz CD, Lewis RJ, Thompson M, Berry L, Siedel J. The effects of bundling on infant temperature. Pediatrics 1994; 94: 669-673. [77]. Moritz ML, Manole MD, Bogen DL, Ayus JC. Breastfeeding-associated hypernatremia: are we missing the diagnosis? Pediatrics 2005; 116: e343-e347. [78]. Hull

KM, Shoham N, Chae JJ, Aksentijevich I, Kastner DL. The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations. Curr Opin Rheumatol 2003; 15: 61-69. [79]. Padeh S. Periodic fever syndromes. Pediatr Clin N Am 2005; 52: 55-605. [80]. Crisponi G. Autosomal recessive disorder with muscle contractions resembling neonatal tetanus, characteristic face, camptodactyly, hyperthermia and sudden death: a new syndrome. Am J Med Genet 1996; 62: 365-371. [81]. Raas-Rothschild A, Ergaz-Schaltiel Z, Bar-Ziv J, Rein AJJT. Cardiovascular abnormalities associated with the Stuve-Wiedemann Syndrome. Am J Med Genet 2003; 121A: 156-158. [82]. Kurtz J, Anslow P. Infantile herpes simplex encephalitis: diagnostic features and differentiation from non-accidental injury. J Infect 2003; 46: 12-16. [83]. Kadhim H, Guzman PP, Saint Martin C, et al. Spinal neurenteric cyst presenting in infancy with chronic fever and acute myelopathy. Neurology 2000; 54: 2011-2015. [84]. Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome in children: an important diagnostic consideration in fever of unknown origin. Clin Infect Dis 2003; 36: 306-312. [85]. Wasserteil V, Bruce S. Fever and hypotrichosis in a newborn: anhydrotic ectodermal dysplasia. Arch Dermatol 1986; 122: 1325-1326. [86]. Abramson JS, Mills EL. Depression of neutrophil function induced by viruses and its role in secondary microbial infections. Rev Infect Dis 1988; 10: 326-341. [87]. Antonow JA, Hansen K, McKinstry CA, Byington CL. Sepsis evaluations in hospitalized infants with bronchiolitis. Ped Infect Dis J 1998; 17: 231-236. [88]. Liebelt EL, Qi K, Harvey K. Diagnostic testing for serious bacterial infections in infants aged 90 days or younger with bronchiolitis. Arch Pediatr Adolesc Med 1999; 153: 525-530. [89]. Titus MO, Wright SW. Prevalence of serious bacterial infections in febrile infants with respiratory syncytial virus

infection. Pediatrics 2003; 112: 282-284. [90]. Oray-Schrom P, Phoenix C, St. Martin D, Amoateng-Adjepong Y. Sepsis workup in febrile infants 0-90 days of age with respiratory syncytial virus infection. Ped Emer Care 2003; 19: 314-319. [91]. Levine DA, Platt SL, Dayan PS, et al, for the multicenter RSV-SBI study group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Pediatrics 2004; 113: 1728-1734. [92]. Byington CL, Enriquez FR, Hoff C, Tuohy R, Taggart EW, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. Pediatrics 2004; 113: 1662-1666. [93]. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J 2007; 26: 672-677. [94]. Galetto-Lacour A, Gervaix A, Zamora SA, et al. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localizing signs, Eur J Pediatr 2001; 160: 95-100. [95]. Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. Pediatrics 2003; 112: 1054-1060. [96]. Strait RT, Kelly KJ, Kurup VP. Tumor necrosis factor-? , Interleukin-1? , and Interleukin-6 levels in febrile, young children with and without occult bacteremia. Pediatrics 1999; 104: 1321-1326. [97]. Kafetzis D, Tigani S, Costalos C. Immunologic markers in the neonatal period: diagnostic value and accuracy in infection. Expert Rev Mol Diagn 2005; 5: 231-239. [98]. Chiesa C, Pellegrini G, Panero A, et al. C-reactive protein, interleukin-6 and procalcitonin in the immediate postnatal period: influence of illness severity, risk status, antenatal and perinatal

complications, and infection. Clin Chem 2003; 49: 60-68. [99]. Nakabayashi M, Adachi Y, Itazawa T, et al. MxA-based recognition of viral illness in febrile children by a whole blood assay. Pediatr Res 2006; 60: 770-774. [100]. Bhandari V, Wang C, Rinder C, Rinder H. Hematologic profile of sepsis in neonates: neutrophil CD64 as a diagnostic marker. Pediatrics 2008; 121: 129-134. [101]. Mtitimila EI, Cooke RWI. Antibiotic regimens for suspected early neonatal sepsis. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No. : CD004495. DOI. 10. 1002/14651858. CD004495. pub2. [102]. Kalenic S, Francetic I, Polak J, Zele-Starcevic L, Bencic Z. Impact of ampicillin and cefuroxime on bacterial colonization and infection in patients on a neonatal intensive care unit. J Hosp Infect. 993; 23: 35-41. [103]. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics. 2006, 117; 67-74. [104]. Papadopoulou S, Efremidis S, Karyda, et al. Incidence of ceftriaxone-associated gallbladder pseudolithiasis. Acta Pediatrica 1999; 88: 1352-1355. [105]. US Food and Drug Administration Center for Drug Evaluation and Research. Information for Healthcare Professionals Ceftriaxone (marketed at Rocephin). Accessed 19, January 2008. URL: http://www. fda. gov/Cder/drug/InfoSheets/HCP/ceftriaxone. htm [106]. Lee C, Robertson J, Shilkofski N. Drug Doses. In: Robertson R, Shilkofski N Eds, The Harriet Lane Handbook: A Manual for Pediatric House Officers. Philadelphia, Elsevier Mosby. 2005; 700-830. Table 1. Criteria for assessing febrile infants at low risk for SBIa Boston criteria [31]Philadelphia criteria [32]Rochester criteria [33]Pittsburgh criteria [34] 1. Infant appears well 2. No antibiotics within preceding 48 hours 3. No immunizations with

diphtheria and tetanus toxoid and pertussis vaccine within 48 hours 4. No ear, soft tissue, joint, or bone infection on exam 5. Laboratory values: WBC <20000/mm3 <10 WBC per high- power field (if microscopy done) or dipstick negative for leukocyte esterase CSF < 10 cells/mm3 No infiltrate on chest radiograph if obtained1. Infant appears well 2. No evidence of infection on physical exam 3. Laboratory values: WBC <15000/mm3 < 10 WBC on spun urine and few bacteria, or none, by microscopy CSF < 8 cells/mm3 No evidence of infiltrate on CXR1. Infant appears well 2. Infant previously healthy Born at term Didn't receive antibiotics No prior hospitalizationsNo underlying illness Not hospitalized longer than mother 3. No evidence of skin, soft tissue, bone, joint or ear infection 4. Laboratory values: WBC 5000-15000/mm3 Band count ? 1500/mm3 ? 10 WBC on spun urine by microscopy ? 5 WBC on stool smear if diarrhea1. Infant healthy Full term No chronic illness Not hospitalized previously No perinatal antibiotics No antibiotics in past week No siblings with GBS 2. Well-appearing 3. Lab values: WBC 5000-15000/mm3 Band count ? 1500/mm3 WBC ? 9/mm3 enhanced UA & negative Gram stain Stool WBC < 5 if diarrhea CXR normal if respiratory symptomsAbbreviations: SBI, serious bacteria infection; WBC, white blood cell; CSF, cerebrospinal fluid; UA, urinalysis; CXR, chest x-ray aSerious bacterial infection includes bacterial growth in blood, urine, spinal fluid, stool, skin or soft tissue Table 2 Results of common clinical criteria used to assessed the rate of SBI in febrile infants Study (Year) Age # enrolledOverall rate (%) of SBISBI rate (%) in low risk groupSBI rate (%) in high risk groupOverall rate (%) of SBI in neonatesSBI rate (%) in low risk neonates Boston (1992)28-89 days 503Not-applicable27/503 (5.)aNot-applicableNot-applicableNot-applicable Philadelphia (1993)29-56 days 74765/747 (8.

7)1/287 (0. 3)a64/460 (13. 9)bNot-applicableNot- applicable Rochester (1994)? 60 days 1003 82/1003 (8. 2)5/437 (1. 1)a77/566 (13. 6)b32/436 (7. 3)c2/227 (0. 9)c Pittsburgh (2001)? 60 days 40441/404 (10. 1)0/127 (0)a 41/277 (14. 8)b12/110 (10. 9)0/43 (0) Abbreviations: SBI, serious bacteria infection awell-appearing and normal screening labs bnot-well appearing or abnormal screening labs cnumbers include 74 infants who were prospectively identified as already being at low risk for SBI. Table 3. Rate of SBI in febrile neonatesAuthor (Year) Number enrolledCharacteristics of studyNumber (%) and kind of SBI Overall rate (%) of SBI Bonadio (1990) [44]371Previously healthy; LP, CBC, Blood culture Urine culture, Chest radiograph, Stool culture6/371 (1. 6) meningitis 5/371 (1. 3) bacteremia 11/355 (3. 1)UTI 2/92 (2. 2)enteritis24/371 (6. 5) Chiu (1994) [45]254WBC, CRP or ESR, UA, blood & urine culture, stool culture if diarrhea; No sign of infection on exam, WBC 5-15, 000/mm3, CRP <20 mg/l or ESR <30 mm/hr & normal UA considered low risk for bacterial infection13/254 (5. 1) bacteremia or meningitis 16/254 (6. 3) UTI 16/254 (6.) Other infections45/254 (17. 7) 8/134 (6. 0) Low-risk 37/120 (30. 8) High-risk Ferrera (1997) [46]134CSF, Blood, urine cultures in all patients; classified as high-risk or low-risk based on Rochester criteria13/134 UTI 4/134 Bacteremia 4/134 Meningitis 1 other22/119a (18. 5) 19/71(26. 8) High-risk 3/48 (6. 3) Low-risk Chiu (1997) [47]250Blood, Urine cultures in all. Patients who looked well, No sign of infection on exam, WBC 5-15000/mm3 & <1500 bands, CRP < 20 mg/L, and normal UA were considered low risk. 11/250 (4. 4) bacteremia or meningitis 16/250 (6. 4) UTI 14/250 (5. 6)other41/250 (16. 4) 1/131 (0. 8)Low-risk 40/119 (33. 6) High-risk Baker (1999) [48] 254CBC; UA; CXR; blood, urine and CSF cultures; stool culture obtained if diarrhea; Classified as high risk or

low risk based on Philadelphia criteria17/254 (6. 7) UTI 8/254 (3. 1)b bacteremia 4/254 (1. 6) meningitis 2/254 (0. 8) enteritis 5/254 (2. 0) other32/254 (12. 6) 5/109 (4. 6) Low-risk 27/145(18. 6) High-risk Kadish (2000) [49]372CBC; UA; CSF cell count; blood, urine, CSF cultures; Rates of SBI were assessed in low-risk infants according to Philadelphia and Boston Criteria32/372 (8. 6) UTI 12/372 (3. 2) bacteremia 5/372 (1. 3) meningitisc45/372 (12. 1) 8/231 (3.) Boston 6/186 (3. 2) Philadelphia Wu (2004) [50]112 Looked well; no evidence of infection on exam; WBC 5, 000-15, 000/mm3 & <1500 bands; CRP <20mg/L; UA <10 WBC; normal stool exam if diarrhea present were considered low risk 1/112 (0. 9) bacteremia and meningitis 2/112 (1. 8) UTI3/112 (2. 7) Low- risk Marom (2007) [51]386CSF , Blood, Urine cultures; Benign medical history; good appearance; no focal signs of infection; ESR < 30 mm at end of first hour; WBC 5-15, 000/mm3 and a normal UA were considered low risk. 54/386 (14. 0) UTId 2/386 (0. 5) meningitis 52/386 (13. 5) other108/386 (28. 0) 1/166 (0. 6)Low-risk 107/220 (48. 6) High-risk Abbreviations: SBI, serious bacterial infection; LP, lumbar puncture; CBC, complete blood count; CPR, c-reactive protein; ESR, erythrocyte sedimentation rate; UA, urinalysis; CXR, chest x-ray a15 infants were not classified and were not included in the low and high risk % of SBI b four infants with bacteremia had other concominant bacterial diseases c10 infants has more than one serious bacterial disease d4 infants had bacteremia associated with UTI Table 4. Non-infectious causes of fever in the neonate Bundling in a warm environment Hypernatremic dehydration in breast-fed infantsHereditary autoinflammatory syndromes Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) Neonatal-onset multi-system inflammatory disease (NOMID)/ Chronic infantile neurologic

cutaneous articular syndrome (CINCA) Spinal neurenteric cyst Non-accidental injury Stuve-Wiedemann syndrome Crisponi syndrome Hemophagocytic syndrome Anhidrotic ectodermal dysplasia Table 5. Rate of SBI in febrile infants with RSV bronchiolitis Author (Year)# enrolled (age) # neonates enrolled (%)# UTI (%) # bacteremia (%) # meningitis (%) Antonow [87] (1998) 282 (? 60 days) 146 RSV+ 90 febrile 59 (22. 5)2/59a (3. 4) 3/282b overall UTI (1. 1) 1/ 282 (0. 4)c overall 1/282 (0. 4)c overall Liebelt [88] (1999) 216 (? 90 days) 120 RSV+ 91 febrile 28 (13. 0)0/680/1000/53 Titus [89] (2003)174 (? 8 weeks) All RSV+ and febrileunknown2/147 (1. 4)0/1700/111 Oray-Schrom [90] (2003)191 (0-90 days) All RSV+ 101 febrile41/191 (22. 5)2/41 (4. 9)d 6/85 tested (7. 1) overall 1/1200/69 Levine [91] (2004)269/1248 RSV+ All febrile (? 60 days)411/1268 (33. 0) 82 RSV+5/82 (6. 1) 14/261 (5. 4) 3/82 (3. 7) 3/267 (1. 1) 0/82 0/251 Byington [90] (2004)159/1385 RSV+ All febrile (0-90 days)unknown4/159 (2. 5)e0 0Abbreviations: SBI, serious bacterial infection; RSV, respiratory syncytial virus; UTI, urinary tract infection a 1 of the 2 patients did not have RSV testing performed and neither neonate was febrile b Only 140/282 patients underwent sepsis evaluation c Neither bacteremia patient or meningitis patient was a neonate d Only 20/41 infants were tested. The percentage of febrile RSV neonates who had urine cultures obtained was 2/20 (10%). e Results reported as number and percentage of SBI which includes bacteremia, UTI, bacterial meningitis, soft tissue or bone infection, bacterial pneumonia, or bacterial enteritis. Table 6. Optimal statistical cutoff values for markers in detecting an SBI Diagnostic marker Optimal cutoff valueSensitivitySpecificity C-reactive protein32 mg/L 93; 40 mg/L94 40mg/L9584. 0%93; 89%94 79%9575. 5%93; 75%94 79%95 Procalcitonin0.

8 ng/mL93; 0. 9 ng/mL94 0. 5ng/mL9569. 1%93; 93% 94 93%9585. 3%93; 78%94 74%95 White blood cell count > 15, 000/mm351. 6%93; 68%94 52%9575. 5%93; 77%94 74%95 Band count > 1500/mm329%94; 11%9591%94; 93%95 Table 7. Dosages of drugs commonly used for neonatal infectionsa Ampicillin Postnatal Age < 7 days: Postnatal ? 7 days: WeightMax DoseFrequencyWeightMax DoseFrequency gt; 2000 grams50 mg/kg/doseQ8H> 2000 grams50 mg/kg/doseQ6H ? Group B streptococcal meningitis: 200 mg/kg/day divided Q8H? Group B streptococcal meningitis: 300 mg/kg/day divided Q6H Cefotaxime Postnatal Age < 7 days: Postnatal > 7 days: WeightMax DoseFrequencyWeightMax DoseFrequency > 2000 grams50 mg/kg/doseQ8H> 2000 grams50 mg/kg/doseQ6H Gentamicin Postnatal Age < 7 days: Postnatal > 7 days: WeightDoseFrequencyWeightDoseFrequency > 2000 grams4 mg/kg/doseQ24H> 2000 grams4. 0 mg/kg/doseQ12-18H Acyclovir DoseFrequency 20 mg/kg/doseQ8H a assumes normal renal function Chart adapted from Ref 106.