FEVER OF UNCERTAIN SOURCE
in infants 60 days of age or less

Evidence Based Clinical Practice Guideline
Cincinnati children’s Hospital Medical Center
6- 2003
Introduction

• FUS is defined as an acute febrile illness in which the etiology of the fever is not certain after a thorough history and physical examination

• The management of febrile illness in young infants is challenging:
  – The relatively high prevalence of serious bacterial infection (SBI) in this age group
  – The clinical exam alone is unable to reliably predict SBI and culture results are not available immediately
Etiology

• Systemic viral infections are the most common cause of FUS, followed by bacterial infections of the urinary tract, the upper and lower respiratory tracts, and the middle ear [S]

• The most common bacteria isolated are *E coli* (39%), Klebsiella (11%), Group B streptococcus (8%), Enterococcus (6%), *Enterobacter cloacae* (6%) and *Listeria monocytogenes* (6%) [D]
Etiology

• Several important viral pathogens:
  – 50% of infants of FUS from August to October will have documented enteroviral infection [C]
  – Neonatal herpes simplex virus:
    • 30/100,000 live births [D]
    • 7 – 14% of these present with FUS [D]
    • early initiation of therapy improves outcome [D]
Clinical assessment

• Rectal temperatures are preferred:
  – Parental report of fever detected only by touch is likely to be accurate (sensitivity 82-89%, specificity 76-86%) [C]
  – Magnitude of fever can’t predict illness source or severity [C]
• Thorough history and physical examination is important to elicit high risk clinical elements
<table>
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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Fever</td>
<td>Rectal temperature $\geq 38^\circ$ C ($100.4^\circ$ F) (Bonadio 1994 [D])</td>
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<tr>
<td>Fever of uncertain source (FUS)</td>
<td>An acute febrile illness in which the etiology of the fever is not apparent after a thorough history and physical exam</td>
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<td>Serious bacterial infection (SBI)</td>
<td>Meningitis&lt;br&gt; Bone and joint infections&lt;br&gt; Soft tissue infections (cellulitis)&lt;br&gt; Pneumonia&lt;br&gt; Urinary tract infections (UTI)&lt;br&gt; Sepsis / bacteremia&lt;br&gt; Enteritis</td>
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<td>Toxic appearance “Yale Observation Scale”** (see also (Baker 1993 [A], McCarthy 1982 [C]))</td>
<td>Lethargy&lt;br&gt; Poor or absent eye contact&lt;br&gt; Failure of child to recognize parents or failure to interact with persons or objects in the environment&lt;br&gt; Poor perfusion of the extremities&lt;br&gt; Acrocyanosis&lt;br&gt; Mottling&lt;br&gt; Slow capillary refill time of $\geq 2$ seconds in “warm” environment (Gorelick 1993 [C], Schriger 1988 [C])&lt;br&gt; Hyperventilation or marked hypoventilation or cyanosis</td>
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<td>*Study population $\leq 24$ months of age</td>
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<td>Low risk for SBI “Rochester Criteria”</td>
<td>Prior history of being healthy&lt;br&gt; *born at term ($\geq 37$ weeks gestation)&lt;br&gt; *has not been previously hospitalized&lt;br&gt; *has no chronic or underlying illness&lt;br&gt; *was not hospitalized longer than mother&lt;br&gt; *was not treated for unexplained hyperbilirubinemia&lt;br&gt; *has not received and was not receiving antimicrobial agents&lt;br&gt; *no intrapartum history of mother for fever, Group B streptococcus, nor antibiotic treatment&lt;br&gt; No focal bacterial infection on physical exam&lt;br&gt; No evidence of purulent otitis media, skin or soft tissue infection, or bone or joint skeletal infection&lt;br&gt; Negative laboratory screen (see also (Baker 1993 [A], Jaskiewicz 1994 [C], McCarthy 1982 [C]))</td>
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Laboratory Studies

In all infants with FUS:

A. CBC with differential:
   WBC > 15,000/µl or < 5,000/µl;
   WBC band forms > 1,500/µl [C]

B. Blood culture

C. Urinalysis: spun urine > 10 WBC/hpf

D. Urine culture: urine samples should be collected by catheter [D]

E. Lumbar puncture (LP)
Lumbar puncture

- It is recommended that all infants receive a lumbar puncture.
- Exception: In infants 31-60 days **AND** with the presence of all of the following, delaying or omitting a lumbar puncture [C]:
  - Low risk as identified with strict screening criteria utilizing both clinical assessment and diagnostic testing
  - Available reliable follow-up in 12-24 hours
  - Healthcare provider(s) confident that parent will use appropriate observational and follow-up skills;
  - Primary care physician (PCP) and family agree with plan of care;
  - Antibiotic therapy will not be initiated.
Laboratory Studies

The following tests were also considered:

- Stool culture (if child has diarrhea)
- Viral cultures in selected patients and as appropriate to season
- Chest X-ray (if respiratory signs)
Admission Criteria

- All infants 0-30 days of age with FUS be hospitalized [D]
  - 3.2 – 3.5% of fibrile infants 0 – 30 days identified as low risk will have SBI [D]
- Any infant 31-60 days of age with FUS identified as high-risk clinically or by laboratory data be hospitalized [E]
- Low-risk infants 31-60 days may be managed as outpatients or inpatients [A]
  - use of clinical and diagnostic tests criteria for identification of low-risk infants has 98.9 – 100% negative predictive value for SBI [A]
Medications

Antibiotics

- All infants 0-30 days with FUS be treated with intravenous ampicillin plus a 3rd generation cephalosporin or gentamicin.
- Infants 31-60 with FUS vary depending on laboratory and clinical findings:
  - The first line treatment for this group is intravenous 3rd generation cephalosporin alone. [D]
  - Intravenous ampicillin be considered as an addition to the antibiotic regimen for febrile infants 31-60 days in severely ill infants or with findings suggestive of urinary tract infection (UTI) to assure coverage for rare organisms such as *Listeria monocytogenes*, gram-positive cocci or enterococcus [D]
Antibiotics

- Inpatient and outpatient low-risk infants may be managed without antibiotics pending culture results and/or a change in clinical status [A]
- It is recommended that those infants managed as outpatients and treated with antibiotics receive parenteral ceftriaxone [C]

• Duration of initial antibiotic therapies cover a treatment period of 24 to 48 hours with discontinuance or continuation of therapy based on result of cultures or other tests and review of history and clinical response
  Cultures must be checked after a true minimum incubation period of 36 hours
Discharge criteria

- Well-appearing
- Eating well
- Antimicrobial therapies complete or can be continued in the home environment
- Culture results negative after a true minimum incubation period of 36 hours
- Hospitalized infant observed without antibacterial treatment is well-appearing at 24 hours
- Family: confident in ability to care for infant at home