

**Diagnosis and Management of Febrile Infants
0-3 months
Appendixes**

Appendix A. Search Strategies

Key Questions 1- 5

MEDLINE (1950 to October Week 1 2008)

1. exp fever/
2. (fever\$ or febrile or pyrexia\$.tw.
3. 1 or 2
4. exp bacteremia/
5. exp meningitis, bacterial/
6. exp urinary tract infections/
7. exp herpes simplex/
8. (bacteremia or bacteraemia).tw.
9. (bacteria\$ adj3 meningitis).tw.
10. (urinary adj2 tract\$ adj3 infection\$.tw.
11. (herpes adj2 simplex).tw.
12. ((severe or serious) adj3 bacteria\$ adj4 (infection\$ or illness\$)).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp "sensitivity and specificity"/
15. exp diagnostic errors/
16. predicti\$.tw.
17. sensitivity.tw.
18. specificity.tw.
19. (roc adj curve\$.tw.
20. (false adj2 negative\$.tw.
21. (false adj2 positive\$.tw.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. exp "signs and symptoms"/
24. exp physical examination/
25. exp medical history taking
26. (ill adj2 appear\$.tw.
27. (clinical adj2 examin\$.tw.
28. (medical adj2 histor\$.tw.
29. (rochester adj4 criteri\$.tw.
30. (philadelphia adj4 protocol\$.tw.
31. (milwaukee adj3 protocol\$.tw.
32. exp Clinical Protocols/
33. "Severity of Illness Index"/
34. (scoring adj2 instrument\$.tw.
35. exp risk/
36. risk\$.tw.
37. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 3 and 13 and 22 and 37
39. limit 38 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
40. (infant\$ or newborn\$ or neonate\$.tw.
41. 38 and 40
42. limit 41 to (english language and yr="1973 - 2008")
43. 39 or 42
44. exp clinical laboratory techniques/
45. exp "laboratory techniques and procedures"/
46. exp diagnostic tests, routine/
47. (complete adj2 blood adj3 count\$.tw.
48. urine.tw.
49. Urinalysis/
50. urinalysis.tw.
51. (diagnosis or blood or urine or cerebrospinal fluid).fs,sh.
52. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 37 or 52
54. 3 and 13 and 22 and 53
55. limit 54 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
56. 40 and 54
57. limit 56 to (english language and yr="1973 - 2008")
58. 55 or 57
59. exp time/
60. ((diagnos\$ or therap\$ or treatment\$) adj3 (interval\$ or delay\$)).tw.
61. (immediate adj3 (treatment\$ or therap\$ or diagnos\$)).tw.

62. (diagnosis or drug therapy or therapy).fs,sh.
63. 59 and 62
64. 60 or 61 or 63
65. 3 and 13 and 64
66. limit 65 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
67. 40 and 65
68. limit 67 to (english language and yr="1973 - 2008")
69. 66 or 68
70. Harm Reduction/
71. harm\$.tw.
72. benefi\$.tw.
73. exp prognosis/
74. ((treatment or therap\$) adj2 outcome\$).tw.
75. no-observed-adverse-effect level/
76. adverse effects.fs.
77. adverse.tw.
78. contraindications.fs.
79. Medication Errors/
80. 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
81. exp anti-bacterial agents/
82. exp antiviral agents/
83. Antibiotic Prophylaxis/
84. (antibacteria\$ or antiviral\$ or antiviral\$).tw.
85. 81 or 82 or 83 or 84
86. 3 and 13 and 80 and 85
87. limit 86 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
88. limit 87 to english language
89. 40 and 86
90. limit 89 to (english language and yr="1973 - 2008")
91. 88 or 90
92. Mothers/
93. (mother\$ or maternal).tw.
94. ((medical or clinical) adj2 histor\$).tw.
95. 93 and 94
96. 53 or 95
97. 3 and 13 and 22 and 96
98. limit 97 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
99. limit 98 to english language
100. 40 and 97
101. limit 100 to yr="1973 - 2008"
102. limit 101 to english language
103. 99 or 102
104. Ambulatory Care/
105. Outpatients/
106. ambulatory.tw.
107. outpatient\$.tw.
108. exp primary care/
109. Physicians' Offices/
110. Physicians, Family/
111. (primary adj2 care).tw.
112. (doctor\$ adj2 office\$).tw.
113. (doctor\$ adj2 office\$).tw.
114. exp Community Health Services/
115. Emergencies/
116. exp Emergency Medical Services/
117. emergenc\$.tw.
118. 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117
119. prevalence/
120. prevalen\$.tw.
121. Epidemiology/
122. epidemiology.fs,tw.
123. exp epidemiologic studies/
124. 119 or 120 or 121 or 122
125. 3 and 13 and 118 and 124
126. limit 125 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
127. limit 126 to english language
128. 40 and 125
129. limit 128 to (english language and yr="1973 - 2008")
130. 127 or 129
131. 3 and 13 and 53 and 124
132. limit 131 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
133. limit 132 to english language
134. 40 and 131
135. limit 134 to (english language and yr="1973 - 2008")
136. 133 or 135

137. 43 or 58 or 69 or 91 or 103 or 130
or 136
138. 3 and 13
139. limit 138 to (english language and
yr="1973 - 2008" and "all infant (birth to
23 months)")

140. 40 and 138 (656)
141. limit 140 to (english language and
yr="1973 - 2008") (539)
142. 139 or 141 (1470)
143. from 137 keep 1-757 (757)

EMBASE (1980 to 2008 Week 08)

1. exp fever/
2. (fever\$ or febrile or pyrexia\$.tw.
3. 1 or 2
4. exp bacteremia/
5. exp meningitis, bacterial/
6. exp urinary tract infections/
7. exp herpes simplex/
8. (bacteremia or bacteraemia).tw.
9. (bacteria\$ adj3 meningitis).tw.
10. (urinary adj2 tract\$ adj3
infection\$.tw.
11. (herpes adj2 simplex).tw.
12. ((severe or serious) adj3 bacteria\$
adj4 (infection\$ or illness\$)).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
or 12
14. exp "sensitivity and specificity"/
15. exp diagnostic errors/
16. predicti\$.tw.
17. sensitivity.tw.
18. specificity.tw.
19. (roc adj curve\$.tw.
20. (false adj2 negative\$.tw.
21. (false adj2 positive\$.tw.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20
or 21
23. exp "signs and symptoms"/
24. exp physical examination/
25. exp medical history taking/
26. (ill adj2 appear\$.tw.
27. (clinical adj2 examin\$.tw.
28. (medical adj2 histor\$.tw.
29. (rochester adj4 criteri\$.tw.
30. (philadelphia adj4 protocol\$.tw.
31. (milwaukee adj3 protocol\$.tw.
32. exp Clinical Protocols/

33. "Severity of Illness Index"/
34. (scoring adj2 instrument\$.tw.
35. exp risk/
36. risk\$.tw.
37. 23 or 24 or 25 or 26 or 27 or 28 or 29
or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 3 and 13 and 22 and 37
39. limit 38 to (english language and
yr="1980 - 2008" and infant <to one
year>)
40. (infant\$ or newborn\$ or
neonate\$.tw.
41. 38 and 40
42. limit 41 to (english language and
yr="1980 - 2008")
43. 39 or 42
44. exp "diagnosis, measurement and
analysis"/
45. (complete adj2 blood adj3
count\$.tw.
46. urine.tw.
47. urinalysis.tw.
48. diagnosis.sh.
49. blood.sh.
50. urine.sh.
51. cerebrospinal fluid.sh.
52. 44 or 45 or 46 or 47 or 48 or 49 or 50
or 51
53. 37 or 52
54. 3 and 13 and 22 and 53
55. limit 54 to (english language and
yr="1980 - 2008" and infant <to one
year>)
56. 40 and 54
57. limit 56 to (english language and
yr="1980 - 2008")

58. 55 or 57
59. exp time/
60. ((diagnos\$ or therap\$ or treatment\$) adj3 (interval\$ or delay\$)).tw.
61. (immediate adj3 (treatment\$ or therap\$ or diagnos\$)).tw.
62. (diagnosis or drug therapy or therapy).sh,tw.
63. 59 and 62
64. 60 or 61 or 63
65. 3 and 13 and 64
66. limit 65 to (english language and yr="1980 - 2008" and infant <to one year>)
67. 40 and 65
68. limit 67 to (english language and yr="1980 - 2008")
69. 66 or 68
70. harm reduction/
71. harm\$.tw.
72. prognosis/
73. ((treatment or therap\$) adj2 outcome\$).tw.
74. exp Adverse Drug Reaction/
75. Side Effect/
76. adverse.tw.
77. contraindicat\$.tw.
78. exp Medication Error/
79. benefi\$.tw.
80. 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
81. Antiinfective Agent/
82. (antibacteria\$ or antiviral or antiviral or antibiotic\$).tw.
83. 81 or 82
84. 3 and 13 and 80 and 83
85. limit 84 to (english language and yr="1980 - 2008" and infant <to one year>)
86. 40 and 84
87. limit 86 to (english language and yr="1980 - 2008")
88. 85 or 87
89. mother/
90. (mother\$ or maternal).tw.
91. ((medical or clinical) adj2 histor\$).tw.
92. 89 or 90
93. 91 and 92
94. 53 or 93
95. 3 and 13 and 22 and 94
96. limit 95 to (english language and yr="1980 - 2008" and infant <to one year>)
97. 40 and 95
98. limit 97 to (english language and yr="1980 - 2008")
99. 96 or 98
100. exp ambulatory care/
101. outpatient/
102. ambulatory.tw.
103. outpatient\$.tw.
104. outpatient care/ or primary medical care/ or private practice/
105. general practitioner/
106. (primary adj2 care).tw.
107. (doctor\$ adj2 office\$).tw.
108. Community Care/
109. Emergency/
110. emergency health service/
111. emergenc\$.tw.
112. 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111
113. prevalen\$.tw.
114. exp epidemiology/
115. epidemiology.tw.
116. 113 or 114 or 115
117. 3 and 13 and 112 and 116
118. limit 117 to (english language and yr="1980 - 2008" and infant <to one year>)
119. 40 and 117
120. limit 119 to (english language and yr="1980 - 2008")
121. 118 or 120
122. 43 or 58 or 69 or 88 or 99 or 121
123. 3 and 13
124. limit 123 to (english language and yr="1980 - 2008" and infant <to one year>)

125. 40 and 123
126. limit 125 to (english language and
yr="1980 - 2008")

127. 124 or 126
128. from 122 keep 1-268

EBM Reviews – Cochrane Central Register of Controlled Trials (1st Quarter 2008)

1. exp fever/
2. (fever\$ or febrile or pyrexia\$.tw.
3. 1 or 2
4. exp bacteremia/
5. exp meningitis, bacterial/
6. exp urinary tract infections/
7. exp herpes simplex/
8. (bacteremia or bacteraemia).tw.
9. (bacteria\$ adj3 meningitis).tw
10. (urinary adj2 tract\$ adj3
infection\$.tw.
11. (herpes adj2 simplex).tw.
12. ((severe or serious) adj3 bacteria\$
adj4 (infection\$ or illness\$)).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
or 12
14. exp "sensitivity and specificity"/
15. exp diagnostic errors/
16. predicti\$.tw.
17. sensitivity.tw.
18. specificity.tw.
19. (roc adj curve\$.tw.
20. (false adj2 negative\$.tw.
21. (false adj2 positive\$.tw.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20
or 21
23. exp "signs and symptoms"/
24. exp physical examination/
25. exp medical history taking/
26. (ill adj2 appear\$.tw.
27. (clinical adj2 examin\$.tw.
28. (medical adj2 histor\$.tw.
29. (rochester adj4 criteri\$.tw.
30. (philadelphia adj4 protocol\$.tw.
31. (milwaukee adj3 protocol\$.tw.
32. exp Clinical Protocols/
33. "Severity of Illness Index"/
34. (scoring adj2 instrument\$.tw.
35. exp risk/
36. risk\$.tw.
37. 23 or 24 or 25 or 26 or 27 or 28 or 29
or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 3 and 13 and 22 and 37
39. limit 38 to (yr="1973 - 2008" and
"all infant (birth to 23 months)")
40. (infant\$ or newborn\$ or
neonate\$.tw.
41. 38 and 40
42. limit 41 to (english language and
yr="1973 - 2008")
43. 39 or 42
44. exp clinical laboratory techniques/
45. exp "laboratory techniques and
procedures"/
46. exp diagnostic tests, routine/
47. (complete adj2 blood adj3
count\$.tw.
48. urine.tw.
49. Urinalysis/
50. urinalysis.tw.
51. (diagnosis or blood or urine or
cerebrospinal fluid).fs,sh.
52. 44 or 45 or 46 or 47 or 48 or 49 or 50
or 51
53. 37 or 52
54. 3 and 13 and 22 and 53
55. limit 54 to (yr="1973 - 2008" and
"all infant (birth to 23 months)")
56. 40 and 54
57. limit 56 to (english language and
yr="1973 - 2008")
58. 55 or 57
59. exp time/
60. ((diagnos\$ or therap\$ or treatment\$)
adj3 (interval\$ or delay\$)).tw.

61. (immediate adj3 (treatment\$ or therap\$ or diagnos\$)).tw.
62. (diagnosis or drug therapy or therapy).fs,sh.
63. 59 and 62
64. 60 or 61 or 63
65. 3 and 13 and 64
66. limit 65 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
- 67.40 and 65
68. limit 67 to (english language and yr="1973 - 2008")
69. 66 or 68
70. Harm Reduction/
71. harm\$.tw.
72. benefi\$.tw.
73. exp prognosis/
74. ((treatment or therap\$) adj2 outcome\$).tw.
75. no-observed-adverse-effect level/
76. adverse effects.fs.
77. adverse.tw.
78. contraindications.fs.
79. Medication Errors/
80. 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
81. exp anti-bacterial agents/
82. exp antiviral agents/
83. Antibiotic Prophylaxis/
84. (antibacteria\$ or antiviral\$ or antiviral\$).tw.
85. 81 or 82 or 83 or 84
86. 3 and 13 and 80 and 85
87. limit 86 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
88. limit 87 to english language
89. 40 and 86
90. limit 89 to (english language and yr="1973 - 2008")
91. 88 or 90
92. Mothers/
93. (mother\$ or maternal).tw.
94. ((medical or clinical) adj2 histor\$).tw.
95. 93 and 94
96. 53 or 95
97. 3 and 13 and 22 and 96
98. limit 97 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
99. limit 98 to english language
100. 40 and 97
101. limit 100 to yr="1973 - 2008"
102. limit 101 to english language
103. 99 or 102
104. Ambulatory Care/
105. Outpatients/
106. ambulatory.tw.
107. outpatient\$.tw.
108. exp primary care/
109. Physicians' Offices/
110. Physicians, Family/
111. (primary adj2 care).tw.
112. (doctor\$ adj2 office\$).tw.
113. (doctor\$ adj2 office\$).tw.
114. exp Community Health Services/
115. Emergencies/
116. exp Emergency Medical Services/
117. emergenc\$.tw.
118. 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117
119. prevalence/
120. prevalen\$.tw.
121. Epidemiology/
122. epidemiology.fs,tw.
123. exp epidemiologic studies/
124. 119 or 120 or 121 or 122
125. 3 and 13 and 118 and 124
126. limit 125 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
127. limit 126 to english language
128. 40 and 125
129. limit 128 to (english language and yr="1973 - 2008")
130. 127 or 129
131. 3 and 13 and 53 and 124
132. limit 131 to (yr="1973 - 2008" and "all infant (birth to 23 months)")
133. limit 132 to english language
134. 40 and 131
135. limit 134 to (english language and yr="1973 - 2008")

136. 133 or 135
137. 43 or 58 or 69 or 91 or 103 or 130
or 136
138. 3 and 13
139. limit 138 to (english language and
yr="1973 - 2008" and "all infant (birth to
23 months)")

140. 40 and 138
141. limit 140 to (english language and
yr="1973 - 2008")
142. 139 or 141

Pubmed

#55 OR #56 Limits: Entrez Date from 1973 to 2008

#55 OR #56

#46 AND #53 Limits: Humans, All Infant: birth-23 months

#46 AND #53

(Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR Controlled Clinical
Trial[ptyp]) OR (random*[tiab] OR RCT[tiab] OR RCTs[tiab] OR sham*[tiab] OR
placebo*[tiab]) OR (single blind*[tiab] OR single dumm*[tiab] OR single mask*[tiab])
OR

#49 OR #51

#48 AND #50

infant [mesh] OR infant [tiab] OR infants [tiab] OR newborn* [tiab] OR neonate* [tiab]

#48 Limits: Humans, All Infant: birth-23 months

#46 AND #47

((meta-analysis[ptyp] OR Meta-Analysis[MeSH]) OR (meta analy*[tiab] OR
metaanaly*[tiab] OR met analy*[tiab] OR metanaly*[tiab] OR integrative research[tiab]
OR integrative review*[tiab] OR integrative overview*[tiab] OR reintegration*[tiab] OR
reoverview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab]) OR
(quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative
synthes*[tiab] OR systematic literature review*[tiab] OR systematic review*[tiab] OR
systematic overview*[tiab] OR methodologic literature review*[tiab] OR methodologic
review*[tiab] OR methodologic overview*[tiab]) OR ("technology assessment,
biomedical"[MeSH Terms]) OR (health technology assessment*[tiab] OR biomedical
technology assessment*[tiab] OR HTA[tiab] OR HTAs[tiab]) OR (systematic[sb]))

#21 AND #45

#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44

Urinalysis [mesh] OR Spinal Puncture [mesh] OR urinalysis [tiab] OR spinal puncture* [tiab] OR lumbar puncture [tiab]

Diagnostic Errors [mesh] OR diagnostic error* [tiab] OR diagnostic mistake* [tiab] OR mistaken diagnos* [tiab] OR "error in diagnosis" [tiab] OR "error in diagnoses" [tiab] OR "errors in diagnosis" [tiab] OR "errors in diagnoses" [tiab] OR incorrect diagnosis [tiab] OR incorrect diagnoses [tiab]

diagnostic test [tiab] OR diagnostic tests [tiab] OR diagnostic procedure* [tiab] OR diagnostic evaluation* [tiab] OR diagnostic investigation* [tiab] OR diagnostic work* [tiab] OR diagnostic workup* [tiab] OR diagnostic work-up* [tiab] OR diagnostic result* [tiab]

laboratory test [tiab] OR laboratory tests [tiab] OR lab test [tiab] OR lab tests [tiab] OR laboratory work* [tiab] OR lab work* [tiab] OR laboratory workup* [tiab] OR laboratory work-up* [tiab] OR lab workup* [tiab] OR lab work-up* [tiab] OR laboratory investigation* [tiab] OR laboratory evaluation* [tiab] OR laboratory result* [tiab] OR lab result* [tiab] OR Culture method* [tiab] OR culturing method* [tiab] OR sepsis workup [tiab] OR sepsis work-up* [tiab]

Practice Guideline Field: Publication Type

Practice Guidelines as Topic [mesh] OR Algorithms [mesh] OR Decision Trees [tiab] OR cpg [tiab] OR cpgs [tiab] OR practice guideline* [tiab] OR practice protocol* [tiab] OR clinical guideline* [tiab] OR clinical protocol* [tiab] OR algorithm* [tiab] OR decision tree* [tiab] OR decision-making [tiab] OR clinical decision* [tiab]

(Test [tiab] OR tests [tiab] OR testing [tiab] OR culture* [tiab] OR specimen* [tiab] OR workup* [tiab] OR work-up* [tiab]) AND (cerebrospinal fluid* [tiab] OR CSF [tiab] OR spinal fluid* [tiab] OR blood [tiab] OR WBC [tiab] OR CBC [tiab] OR c-reactive protein* [tiab] OR CRP [tiab] OR procalcitonin [tiab] OR PCP [tiab] OR interleukin-6 [tiab] OR IL-6 [tiab] OR urine [tiab] OR stool [tiab])

"Sensitivity and Specificity" [mesh] OR sensitivity [tiab] OR specificity [tiab] OR "predictive value of tests" [tiab] OR false negative* [tiab] OR false positive* [tiab] OR ROC curve* [tiab] OR Receiver Operating Characteristic* [tiab] OR ROC analys* [tiab]

Risk [mesh] OR risk [tiab] OR risks [tiab] OR predicti* [tiab]

Diagnosis, Differential [mesh] OR differential diagnosis [tiab] OR differential diagnoses [tiab] OR delayed diagnosis [tiab] OR delayed diagnoses [tiab]

Laboratory Techniques and Procedures [mesh]

Severity of Illness Index [mesh] OR "Severity of Illness Index" [tiab] OR "severity of illness indexes" [tiab] OR "severity of illness indices" [tiab]

Philadelphia Criteri* [tiab] OR Rochester criteri* [tiab] OR Yale Observation Scale [tiab] OR Young Infant Observation Scale [tiab]

medical history [tiab] OR clinical history [tiab] OR physical examination* [tiab] OR physical exam [tiab] OR physical exams [tiab] OR clinical exam [tiab] OR clinical exams [tiab] OR clinical examination* [tiab] OR medical exam [tiab] OR medical exams [tiab] OR medical examination* [tiab] OR clinical evaluation* [tiab] OR medical evaluation* [tiab] OR physical evaluation* [tiab] OR clinical symptom* [tiab] OR medical symptom* [tiab] OR physical symptom* [tiab]

Physical Examination [mesh]

Medical History Taking [mesh]

"Herpes Simplex/diagnosis" [mesh]

"Osteomyelitis/diagnosis" [mesh]

"Bacterial Infections/diagnosis" [mesh]

"Meningitis, Bacterial/diagnosis" [mesh]

"sepsis/diagnosis"[mesh]

("fever/diagnosis"[MeSH Terms] OR "fever/etiology"[MeSH Terms])

Diagnosis [mesh]

#3 AND #20

#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

Herpesvirus hominis [tiab] AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

(HSV* [tiab] OR herpes simplex [tiab]) AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

IHI [tiab]

Herpes Simplex [mesh] AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

osteomyelitis [mesh] OR osteomyelitis [tiab]

Listeria Infection* [tiab] AND (serious [tiab] OR severe [tiab] OR invasive [tiab])

Gram negative [tiab] AND bacteria* [tiab] AND infection* [tiab]

Gram-Negative Bacterial Infections [mesh]

Gram positive [tiab] AND bacteria* [tiab] AND infection* [tiab]

Gram-Positive Bacterial Infections [mesh]

meningitis [tiab] AND (bacteria* [tiab] OR listeria* [tiab] OR escherichia [tiab] OR Haemophilus [tiab] OR Hemophilus [tiab] OR meningococc* [tiab] OR pneumococc* [tiab] OR tuberculo* [tiab])

Meningitis, Bacterial [mesh]

sepsis [tiab] OR septicemia [tiab] OR septicaemia [tiab]

urinary tract infections [mesh] OR UTI [tiab] OR UTIs [tiab] OR urinary tract infection* [tiab] OR urinary infection* [tiab] OR urinary tract inflammation* [tiab]

serious bacterial infection* [tiab] OR severe bacterial infection* [tiab] OR invasive bacterial infection* [tiab] OR rare bacterial infection* [tiab] OR SBI [tiab] OR SBIs [tiab] OR serious infection* [tiab] OR severe infection* [tiab] OR invasive infection* [tiab] OR rare infection* [tiab]

Sepsis [mesh]

#1 OR #2

Fever [tiab] OR fevers [tiab] OR feverish [tiab] OR febril* [tiab] OR febricity [tiab] OR pyrexia* [tiab]

Fever [MeSH]

Key Question 6

CINAHL

1. exp FEVER/
2. (Fever or fevers or feverish or febril\$ or febricity or pyrexia\$.ti,ab.
3. exp SEPSIS/
4. (sepsis or septicemia or septicaemia).ti,ab.
5. (serious bacterial infection\$ or severe bacterial infection\$ or invasive bacterial

infection\$ or rare bacterial infection\$ or SBI or SBIs or serious infection\$ or

severe infection\$ or invasive infection\$ or rare infection\$).ti,ab.

6. (serious illness* or serious condition* or serious medical illness* or serious medical condition*).ti,ab.

7. exp Urinary Tract Infections/

8. (UTI or UTIs or urinary tract infection\$ or urinary infection\$ or urinary tract inflammation\$).ti,ab.

9. exp Meningitis, Bacterial/

10. ((meningitis or meningitides or meningeal) adj3 (bacteria\$ or listeria\$ or escherichia or Haemophilus or Hemophilus or meningococc\$ or pneumococc\$ or tuberculo\$)).ti,ab.

11. exp Gram-Positive Bacterial Infections/

12. (Gram positive adj2 bacteria\$ infection\$).ti,ab.

13. exp Gram-Negative Bacterial Infections/

14. (Gram negative adj2 bacteria\$ infection\$).ti,ab.

15. (listeria infection\$ adj3 (serious or severe or invasive)).ti,ab.

16. exp OSTEOMYELITIS/

17. osteomyelitis.ti,ab.

18. exp Herpes Simplex/

19. (Herpes Simplex or HSV or Herpesvirus hominis).ti,ab.

20. (serious or severe or invasive).ti,ab.

21. 18 or 19

22. 20 and 21

23. IHI.ti,ab.

24. exp pneumonia/

25. (pneumonia or pneumonitis or pulmonary inflammation* or lung inflammation or bronchopneumonia or pleuropneumonia).ti,ab.

26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 22 or 23 or 24 or 25

27. limit 26 to (newborn infant <birth to 1 month> or infant <1 to 23 months>)

28. (infant or infants or newborn\$ or neonate\$).ti,ab.

29. 26 and 28

30. 28 or 29

31. exp CAREGIVERS/

32. exp PARENTS/

33. (Caregiver\$ or care giver\$ or caretaker\$ or care-taker\$ or parent\$ or stepparent\$ or step-parent\$ or father\$ or mother\$ or stepmother\$ or stepfather\$ or step-mother\$ or step-father\$).ti,ab.

34. 31 or 32 or 33

35. exp Office Visits/ or exp "Continuity of Patient Care"/

36. ((visit or visits or appointment\$ or clinic or clinics or outpatient) and (repeat\$ or return\$ or recommend\$)).ti,ab.

37. (reassessment* or recall* or follow-up or followup or watchful waiting or expectant management).ti,ab.

38. (continuity adj3 care).ti,ab.

39. or/35-38

40. exp Patient Compliance/

41. (comply or complies or compliant or compliance or noncomply or noncompliant or noncompliance or non-compliant or non-compliance or adherent or adherence or nonadherence or non-adherence).ti,ab.

42. (caregiver\$ acceptance or caregiver\$ attitude\$ or caregiver\$ responsibilit\$ or caregiver\$ behavi\$ or caretaker\$ acceptance or caretaker\$ attitude\$ or caretaker\$ responsibilit\$ or caretaker\$ behavi\$ or care-giver\$ acceptance or care-giver\$ attitude\$ or care-giver\$ responsibilit\$ or care-giver\$ behavi\$ or care-taker\$ acceptance or care-taker\$ attitude\$ or care-taker\$ responsibilit\$ or care-taker\$ behavi\$).ti,ab.

43. (parent\$ acceptance\$ or parent\$ attitude\$ or parent\$ responsibilit\$ or parent\$ behavi\$ or patient\$ acceptance

or patient\$ attitude\$ or patient\$
responsibilit\$ or patient\$ behavi\$).ti,ab.
44. exp Attitude to Health/

Embase

1. exp FEVER/
2. (Fever or fevers or feverish or febril\$
or febricity or pyrexia\$).ti,ab.
3. exp SEPSIS/
4. (sepsis or septicemia or
septicaemia).ti,ab.
5. (serious bacterial infection\$ or severe
bacterial infection\$ or invasive bacterial
infection\$ or rare bacterial infection\$ or
SBI or SBIs or serious infection\$ or
severe infection\$ or invasive infection\$
or rare infection\$).ti,ab.
6. (serious illness* or serious condition*
or serious medical illness* or serious
medical condition*).ti,ab.
7. exp Urinary Tract Infections/
8. (UTI or UTIs or urinary tract
infection\$ or urinary infection\$ or
urinary tract inflammation\$).ti,ab.
9. exp Meningitis, Bacterial/
10. ((meningitis or meningitides or
meningeal) adj3 (bacteria\$ or listeria\$ or
escherichia or Haemophilus or
Hemophilus or meningococc\$ or
pneumococc\$ or tuberculo\$)).ti,ab.
11. exp Gram-Positive Bacterial
Infections/
12. (Gram positive adj2 bacteria\$
infection\$).ti,ab.
13. (Gram negative adj2 bacteria\$
infection\$).ti,ab.
14. (listeria infection\$ adj3 (serious or
severe or invasive)).ti,ab.
15. exp OSTEOMYELITIS/
16. osteomyelitis.ti,ab.
17. exp Herpes Simplex/
18. (Herpes Simplex or HSV or
Herpesvirus hominis).ti,ab.
19. (serious or severe or invasive).ti,ab.

45. ((Health adj3 attitude\$) or health
belief\$).ti,ab.

46. 40 or 41 or 42 or 43 or 44 or 45

47. 30 and 34 and 39 and 46

20. 17 or 18

21. 19 and 20

22. IHI.ti,ab.

23. exp PNEUMONIA/

24. (pneumonia or pneumonitis or
pulmonary inflammation* or lung
inflammation or bronchopneumonia or
pleuropneumonia).ti,ab.

25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or
9 or 10 or 11 or 12 or 13 or 14 or 15 or
16 or 21 or 22 or 23 or 24

26. limit 25 to to infant <to one year>

27. (infant or infants or newborn\$ or
neonate\$).ti,ab.

28. 25 and 27

29. 26 or 28

30. exp CAREGIVER/

31. exp PARENT/

32. (Caregiver\$ or care giver\$ or
caretaker\$ or care-taker\$ or parent\$ or
stepparent\$ or step-parent\$ or father\$ or
mother\$ or stepmother\$ or stepfather\$ or
step-mother\$ or step-father\$).ti,ab.

33. 30 or 31 or 32

34. exp Ambulatory Care/

35. exp Patient Care/

36. ((visit or visits or appointment\$ or
clinic or clinics or outpatient) and
(repeat\$ or return\$ or
recommend\$)).ti,ab.

37. (reassessment* or recall* or follow-
up or followup or watchful waiting or
expectant management).ti,ab.

38. (continuity adj3 care).ti,ab.

39. 34 or 35 or 36 or 37 or 38

40. exp Patient Compliance/

41. (comply or complies or compliant or
compliance or noncomply or
noncompliant or noncompliance or non-

compliant or non-compliance or adherent or adherence or nonadherence or non-adherence).ti,ab.
42. (caregiver\$ acceptance or caregiver\$ attitude\$ or caregiver\$ responsibility\$ or caregiver\$ behavior\$ or caretaker\$ acceptance or caretaker\$ attitude\$ or caretaker\$ responsibility\$ or caretaker\$ behavior\$ or care-giver\$ acceptance or care-giver\$ attitude\$ or care-giver\$ responsibility\$ or care-giver\$ behavior\$ or care-taker\$ acceptance or care-taker\$

attitude\$ or care-taker\$ responsibility\$ or care-taker\$ behavior\$).ti,ab.
43. (parent\$ acceptance\$ or parent\$ attitude\$ or parent\$ responsibility\$ or parent\$ behavior\$ or patient\$ acceptance or patient\$ attitude\$ or patient\$ responsibility\$ or patient\$ behavior\$).ti,ab.
44. exp Attitude to Health/
45. exp Patient Attitude/
46. ((Health adj3 attitude\$) or health belief\$).ti,ab.
47. 40 or 41 or 42 or 43 or 44 or 45 or 46
48. 29 and 33 and 39 and 47

PsycINFO

1. exp HYPERTHERMIA/
2. (hyperthermi\$ or fever or fevers or feverish or febril\$ or febricity or pyrexia\$).ti,ab.
3. (sepsis or septicemia or septicaemia).ti,ab.
4. (serious bacterial infection\$ or severe bacterial infection\$ or invasive bacterial infection\$ or rare bacterial infection\$ or SBI or SBIs or serious infection\$ or severe infection\$ or invasive infection\$ or rare infection\$).ti,ab.
5. (serious illness* or serious condition* or serious medical illness* or serious medical condition*).ti,ab.
6. exp urinary function disorders/
7. (UTI or UTIs or urinary tract infection\$ or urinary infection\$ or urinary tract inflammation\$).ti,ab.
8. exp Bacterial Meningitis/
9. ((meningitis or meningitides or meningeal) adj3 (bacteria\$ or listeria\$ or escherichia or Haemophilus or Hemophilus or meningococci\$ or pneumococci\$ or tuberculo\$)).ti,ab.
10. (Gram positive adj2 bacteria\$ infection\$).ti,ab.
11. (Gram negative adj2 bacteria\$ infection\$).ti,ab.

12. (listeria infection\$ adj3 (serious or severe or invasive)).ti,ab.
13. osteomyelitis.ti,ab.
14. exp Herpes Simplex/
15. (Herpes Simplex or HSV or Herpesvirus hominis).ti,ab.
16. (serious or severe or invasive).ti,ab.
17. 14 or 15
18. 16 and 17
19. IHI.ti,ab.
20. exp PNEUMONIA/
21. (pneumonia or pneumonitis or pulmonary inflammation* or lung inflammation or bronchopneumonia or pleuropneumonia).ti,ab.
22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 18 or 19 or 20 or 21
23. limit 22 to
24. (infant or infants or newborn\$ or neonate\$).ti,ab.
25. 22 and 24
26. 23 or 25
27. exp CAREGIVERS/
28. exp PARENTS/
29. (Caregiver\$ or care giver\$ or caretaker\$ or care-taker\$ or parent\$ or stepparent\$ or step-parent\$ or father\$ or mother\$ or stepmother\$ or stepfather\$ or step-mother\$ or step-father\$).ti,ab.

30. 27 or 28 or 29
31. exp "Continuum of Care"/
32. ((visit or visits or appointment\$ or clinic or clinics or outpatient) and (repeat\$ or return\$ or recommend\$)).ti,ab.
33. (reassessment* or recall* or follow-up or followup or watchful waiting or expectant management).ti,ab.
34. (continuity adj3 care).ti,ab.
35. 31 or 32 or 33 or 34
36. exp compliance/
37. (comply or complies or compliant or compliance or noncomply or noncompliant or noncompliance or non-compliant or non-compliance or adherent or adherence or nonadherence or non-adherence).ti,ab.
38. (caregiver\$ acceptance or caregiver\$ attitude\$ or caregiver\$ responsibilit\$ or caregiver\$ behavi\$ or caretaker\$ acceptance or caretaker\$ attitude\$ or caretaker\$ responsibilit\$ or caretaker\$ behavi\$ or care-giver\$ acceptance or care-giver\$ attitude\$ or care-giver\$ responsibilit\$ or care-giver\$ behavi\$ or care-taker\$ acceptance or care-taker\$ attitude\$ or care-taker\$ responsibilit\$ or care-taker\$ behavi\$).ti,ab.
39. (parent\$ acceptance\$ or parent\$ attitude\$ or parent\$ responsibilit\$ or parent\$ behavi\$ or patient\$ acceptance or patient\$ attitude\$ or patient\$ responsibilit\$ or patient\$ behavi\$).ti,ab.
40. ((Health adj3 attitude\$) or health belief\$).ti,ab.
41. 36 or 37 or 38 or 39 or 40
42. 26 and 30 and 35 and 41

Appendix B. Data Extraction Forms

Key Questions 1- 5

Level 1: Broad Screening Form

1. Is the citation an English-language report?
 - Yes - include
 - No - exclude
 - Cannot tell - include

2. Is the **primary objective** of the citation to diagnose and/or manage healthy infants (0-90 days in age) presenting with fever and/or serious bacterial infections (including bacterial meningitis, bacteremia, urinary tract infection) or herpes?
 - Yes - include
 - No - exclude
 - Unclear - include

3. Additional Criteria (Check the most appropriate):
 - Is a primary study - include
 - Is a systematic review, narrative review, clinical practice guideline or cost-effectiveness analysis - exclude
 - Cannot tell - include

4. Citation may be important for the introduction and/or discussion section: (optional)
 - Yes

5. Participants included in this study were from at least one of the following locations: North America, Australia/New Zealand, Western Europe, Northern Europe (Norway, Sweden, Finland, Denmark), Japan, Taiwan, or Israel
 - Yes - include
 - No - exclude
 - Unclear - include

Note: We are assuming that Western Europe encompasses the United Kingdom, Ireland, France, Belgium, Germany, Netherlands, Switzerland, Luxembourg, Spain, Italy, Greece and Portugal.

Level 2: Full Text Screening Form

1. Is this an English-language report?
 - Yes - include

- No - exclude
2. Is the **primary objective** of the report to diagnose and/or manage healthy infants (0-90 days in age) presenting with fever and/or serious bacterial infections (including bacterial meningitis, bacteremia, urinary tract infection) or herpes??
 - Yes - neutral
 - No - neutral
 - Cannot Tell -neutral
 - Still cannot tell after conflict discussion - exclude
 3. Is the **primary objective** of the report to diagnose and/or manage healthy infants with streptococcus pneumonia, listeria monocytogenes, group b streptococcus, enterococcus sp., and enterobacteriaceae (including E. Coli and klebsiella sp.)?
 - Yes - neutral
 - No - neutral
 - Cannot Tell - neutral
 - Still cannot tell after conflict discussion - exclude
 4. Does this study refer to patients presenting to hospital or to a physician setting (office or community health setting)?
 - Yes - include
 - No - exclude
 - Not clear from the report - exclude
 - Still cannot tell after conflict discussion – exclude

Note: In-patients excluded

5. Participants included in this study were from at least one of the following locations: North America, Australia/New Zealand, Western Europe, Northern Europe (Norway, Sweden, Finland, Denmark), Japan, Taiwan, Singapore, Hong Kong, or Israel
 - Yes - include
 - No - exclude
 - Not clear from the report - exclude
 - Still cannot tell after conflict discussion – exclude
6. Is this study a relevant Systematic Review (SR)?
 - Yes - exclude
 - No – include

Note: All Systematic Reviews will be excluded (however, can be identified from this question)

7. If you answered "No" to both questions 2 & 3, please check this box:
 - [click here](#)

Level 3: Screening by Study Design Form

1. Please choose the study design that corresponds with this study:

- Randomized controlled trial - include
- Controlled clinical trial - include
- Cohort - include
- Case-control - include
- Nested case control - include
- Cross sectional (includes surveys, ecological studies) - include
- Case series - include
- Quasi-experimental studies - include
- Chart review - include
- Systematic review - exclude
- Other or none of the above - exclude
- Unclear - include

2. Does this study report diagnostic test results and outcomes? (specificity, sensitivity, prevalence, npv, ppv, etc.)

- Yes - include
- No - include

Level 4 – Screening by Key Question Form

1. Is this report related to the following category of questions? Please check all that apply.

Note: Please refer to updated review questions for more information regarding each of the listed items.

Q1a: Test characteristics (sensitivity, specificity, predictive values) in studies using individual or a combination of clinical features or formal scoring systems to identify infants with SBI. – include

Q1b: Test characteristics (sensitivity, specificity, predictive values) in studies using individual or a combination of clinical features or formal scoring systems to identify infants with IHI. - include

Q2a: Study on identifying infants at low risk for SBI or IHI according to clinical features, laboratory tests (alone or in combination), and/or formal scoring systems. - include

Q2b: Data on risks resulting from delay in management (dx and tx) in low risk infants. - include

Q3a: Study on identifying infants at high risk for SBI or IHI according to clinical features, laboratory tests and/or formal scoring systems. - include

Q3b: Data on benefits and harms of immediate versus delayed antibiotic (antibacterial and antiviral) treatment in infants at high risk for SBI or IHI. - include

Q4: Data on co-infection (prediction against SBI or IHI based in case of presence of a identified viral infection). - include

Q5: Data on variation on prevalence rate of SBI and IHI in different settings (primary care vs. emergency practice). - include

Q6: Data on influence of parental or clinical setting on compliance (studies will be crossed checked against compliance silo only). – include

None of the above - exclude

2. Comment Box

Key Question 6

Level 1: Broad Screening Form

1. Is the citation an English-language record?

- Yes- include
- No-exclude
- Cannot tell-include

2. Is this a primary study¹ addressing the influence of non-clinical factors² in diagnosis, and management of infants 0-6 months who present with fever or other serious conditions³?

- Yes - include
- No - exclude
- Cannot tell – include

Note:

¹- primary studies do not include systematic reviews, narrative reviews, guidelines, commentaries, and letters

²- non-clinical factors include setting or parental factors that affect the likelihood of compliance with follow up visits and physicians' recommendations

³- serious conditions (pneumonia, urinary tract infection, bacteremia, meningitis, herpes simplex infection, hyperbilirubinemia, failure to thrive, and anemia)

3. Was the study conducted in at least one of the following locations: North America, Australia/New Zealand, Western Europe, Northern Europe (Norway, Sweden, Finland, Denmark), Japan, Taiwan, Hong Kong, Singapore or Israel?

- Yes - include
- No - exclude
- Cannot tell - include

Note: For articles of interest for the introduction or discussion, please use the flag article feature on the upper right hand corner of screen.

Level 2: Full Text Screening Form

1. Is this an English record?

- Yes - include
- No - exclude

2. Is this a primary study in infants 0-6 months old presenting with fever or other potentially serious conditions?

- Yes - include
- No - exclude

3. Is this a primary study addressing possible influence of parental factors¹, and or clinical setting² on likelihood of compliance with return appointments³?

- Yes - include
- No – exclude

¹ - education, insurance status, living situation, history of previous visits with the provider, time/distance required to travel to an appointment, etc.

² - community practice vs emergency department and/or hospital outpatient clinic

³ - Excluding routine child health supervision visits and/or immunizations

4. If “No” was answered to questions 2, or 3, is the study important for introduction or discussion section?

- Yes - neutral
- No - neutral

Appendix C. Evidence Tables

Table 1. Studies with combined clinical and laboratory criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bachur (2001) ¹	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Emergency Department</p> <p>Study period: 1993-1999</p>	<p>N: 5,279/5,279</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion:</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Clinical appearance, age < 13 d + UA (LE⁺ or nitrite⁺); WBC > 20,000/mm³ WBC < 4,100/mm³; T > 39.6°C</p>	<p>Positive culture of urine, blood or CSF</p> <p>(UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen)</p> <p>Diagnosis: SBI: 373 (7.0) UTI: 316 Meningitis: 17 Bacteremia: 40 Bacteremia/meningitis: 8 Bacteremia/UTI: 11</p>	<p>SBI: Sensitivity: 82.0 (78.0, 86.0) Specificity: 76.0 (75.0, 77.0) PPV: 21.0 (19.0, 23.0) NPV: 98.3 (97.8, 98.7)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Broner (1990) ²	<p>Design: Quasi experimental</p> <p>Region: North America</p> <p>Setting: General ED</p> <p>Study period: NR</p>	<p>N: NR/52</p> <p>Age group(s): 4 – 56 d</p> <p>Inclusion / exclusion: Infants with rectal temperature $\geq 38.1^{\circ}\text{C}$</p> <p>Exclusion: NR</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Toxic appearance (i.e., increased irritability, decreased eye contact, unwillingness to feed, and the state of alertness) +</p> <p>1) WBC: $\geq 5,000$ ABC/μL</p> <p>or</p> <p>2) CRP+</p> <p>or</p> <p>3) WBC: $\geq 5,000$ ABC/μL + $\geq 15,000$ WBC/μL</p>	<p>NR</p> <p>Diagnosis:</p> <p>SBI (1): 5 (9.6) (sepsis)</p> <p>SBI (2): 5 (9.6) (sepsis)</p> <p>SBI (3): 5 (9.6) (sepsis)</p>	<p>SBI (1): Sensitivity: 100.0 (46.3, 100.0) Specificity: 49.0 (34.3, 63.7) PPV: 17.2 (6.5, 36.5) NPV: 100.0 (82.2, 100.0)</p> <p>SBI (2): Sensitivity: 100.0 (46.3, 100.0) Specificity: 48.0 (32.4, 61.7) PPV: 16.6 (6.3, 35.4) NPV: 100.0 (81.5, 100.0)</p> <p>SBI (3): Sensitivity: 100.0 (46.3, 100.0) Specificity: 49.0 (34.3, 63.7) PPV: 17.2 (6.5, 36.5) NPV: 100.0 (81.5, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Casper (1983) ³	<p>Design: Quasi-experimental</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1974-1979</p>	<p>N: 305/305</p> <p>Age group(s):</p> <ol style="list-style-type: none"> 1) 0 – 30 d 2) 30 – 60 d <p>Inclusion / exclusion: Infants presenting to community based hospital with rectal temperature $\geq 38^{\circ}\text{C}$ seen in outpatient or well documented fever at home</p> <p>Male (%): 54</p> <p>Ethnicity (%):</p> <ul style="list-style-type: none"> • White/non-Hispanic: 3 • Hispanic: 51 • African/American: 45 • Asian/ South Pacific: 1.3 <p>-----</p> <p>Information on mother: NR</p>	<p>Ill appearance + WBC $\geq 15,000/\text{mm}^3$</p>	<p>Blood, urine, CSF- also stool and nasopharynx when indicated</p> <p>Diagnosis: SBI (Bacteremia only) - (1) 0 – 30 d: 7 (6.5)</p> <p>SBI (Bacteremia only) - (2) 30 – 60 d: 4 (2.0)</p>	<p>SBI (1)- 0 – 30 d: Sensitivity: 28.5 (5.1, 69.7) Specificity: NR PPV: NR NPV: NR</p> <p>SBI (2)- 30 – 60 d: Sensitivity: 75.0 (21.9, 98.6) Specificity: 95.8 (91.7, 98.0) PPV: 27.3 (7.3, 60.6) NPV: 99.4 (96.6, 99.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Condra (2010) ⁴	<p>Design: Prospective Quality indicator</p> <p>Region: US</p> <p>Setting: Padiatric ED</p> <p>Study period: NR (16 months in length)</p>	<p>N: 240/62</p> <p>Age group(s): 29 – 60 d; median 44 d (SD 9.0)</p> <p>Inclusion / exclusion: Met Low Risk criteria (derived from Philadelphia criteria) with full sepsis evaluation/ ill appearing infants. Lack of fu, evidence of focal infection, hx antibiotic tx.</p> <p>Male (%): 55</p> <p>Ethnicity (%): 39 (63%) White, 18 (29) African American, 5 (8) Hipsanic</p> <p>Other: Group B <i>Streptococcus</i> positive or unknown: 8(12.9%); their mothers were treated with Peri-partum antibiotics.</p> <p>----- Information on mother: NR</p>	<p>WBC: ≤15,000/mm³ UA WBC: ≤ 10/hpf CSF Gram stain negative CSF WBC < 8/mm³, or ≤1:500 WBC-RBC (red blood cells) ratio band neutrophil ratio: ≤0.2</p>	<p>NR</p> <p>Diagnosis: SBI: 2 (3.2) all UTI</p> <p>Management: 58 (93.5%) were admitted and 4 (6.5) were discharged</p>	<p>SBI: Sensitivity: NR Specificity: NR PPV: NR NPV: NR (data only for LR infants- test results could not be calculated)</p> <p>Complications: 17 (29.3%) developed a complication during the admission Schedule phone fu were successful on days 2 (77.4%), 7 (85.4%), and 14 (83.9%) after discharge (data on admitted infants) most parents preferred discharge to admission</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Avner (1982) ⁵	<p>Design: Case series</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1979-1981</p>	<p>N: 134/134</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: Prospective sample of infants presenting to pediatric care with rectal temperature $\geq 38^{\circ}\text{C}$ documented at ED or home</p> <p>Male (%): NR</p> <p>Ethnicity (%):</p> <p>-----</p> <p>Information on mother: NR</p>	<p>1) Clinical impression of sepsis (strong or ambivalent) (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern) + WBC $\geq 15,000/\text{mm}^3$ or ESR ≥ 30 mm/h</p> <p>2) Clinical impression of sepsis (negative) (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern) + WBC $\geq 15,000/\text{mm}^3$ + ESR ≥ 30 mm/h</p>	<p>NR</p> <p>Diagnosis:</p> <p>SBI (bacteremia only)- (1): 5 (3.7)</p> <p>SBI (bacteremia only)- (2): 5 (3.7)</p>	<p>SBI (1): Sensitivity: 100.0 (46.3, 100.0) Specificity: 17.0 (11.2, 24.9) PPV: 4.5 (1.6, 10.6) NPV: 100.0 (81.5, 100.0)</p> <p>SBI (2): Sensitivity: 100.0 (46.3, 100.0) Specificity: 17.0 (11.2, 24.9) PPV: 4.5 (1.6, 10.6) NPV: 100.0 (81.5, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Crain (1988) ⁶	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: Unclear</p>	<p>N: 46/35</p> <p>Age group(s): 0 – 15 d</p> <p>Inclusion / exclusion: Prospective sample of infants with rectal temperature $\geq 38.1^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Either: Impression of sepsis + either WBC > 15,000 /mm³ or ESR > 30 mm/h or both</p> <p>or Negative impression of sepsis + both WBC > 15,000/mm³ and ESR > 30 mm/h</p>	<p>NR</p> <p>Diagnosis: SBI: 3 (8.5) Sepsis/meningitis</p>	<p>SBI: Sensitivity: 100.0 (31.0, 100.0) Specificity: 75.0 (56.2, 87.9) PPV: 27.3 (7.3, 60.7) NPV: 100.0 (82.8, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Crain (1990) ⁷	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: 1982-1987</p>	<p>N: 442/442</p> <p>Age group(s): 8 – 57d</p> <p>Inclusion / exclusion: Prospective sample of Febrile infants with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Either: Impression of sepsis + WBC > 15,000 /mm³ or ESR > 30 mm/h, or both; or Negative impression of sepsis + both WBC > 15,000 /mm³ and ESR > 30 mm/h</p>	<p>NR</p> <p>UTI if ≥ 10000 pure growth in bag-collected, or catheter obtained specimen; ≥ 100 pure growth in supra-pubic specimen</p> <p>Diagnosis: SBI (only UTI): 33 (7.4)</p>	<p>SBI: Sensitivity: 46.0 (31.1, 66.1) Specificity: 98.0 (95.7, 98.9) PPV: 64.0 (42.6, 81.3) NPV: 95.9 (93.4, 97.5)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Dagan (1985) ⁸	<p>Design: Quasi-experimental</p> <p>Region: North America</p> <p>Setting: Pediatric ED</p> <p>Study period: 1982-1984</p>	<p>N: 233/233</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: All previously healthy infants with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): 58</p> <p>Ethnicity (%): White/non-Hispanic: 60.9 Hispanic: 12 African/American: 25.3 Asian/ South Pacific: 1.7</p> <p>----- Information on mother: NR</p>	<p>Findings consistent with soft tissue, ear or skeletal infection + WBC $\geq 15,000/\text{mm}^3$</p>	<p>Bacteremia, meningitis, cellulites, osteomyelitis, gastroenteritis, UTI</p> <p>CSF: ≥ 20 cells/ mm^3 in infants younger than 30 days, and > 10 cells/ mm^3 in infants > 30 days</p> <p>UTI: >100000 colonies/ml of a single organism in urine</p> <p>Diagnosis: SBI: 23 (9.8) Bacteremia: 9 Others: NR</p>	<p>SBI: Sensitivity: 95.6 (76.0, 99.7) Specificity: 68.0 (61.2, 74.2) PPV: 24.7 (16.4, 35.2) NPV: 99.3 (95.6, 99.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Dagan (1988) ⁹	<p>Design: Cohort</p> <p>Region: Israel</p> <p>Setting: Padiatric ED</p> <p>Study period: 1985-1986</p>	<p>N: 237/236</p> <p>Age group(s): < 60 d</p> <p>Inclusion / exclusion: Prospective sample of previously healthy (born at term, with no history of perinatal complications, underlying diseases, or antibiotics tx) with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): 57</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>No findings consistent with soft tissue or skeletal infection + UA: < 25 WBC/hpf, WBC: 5,000-15,000/mm³, and 1,500 band forms/mm³</p>	<p>Bacterial meningitis, cellulites, osteomyelitis, septic arthritis, gastroenteritis, UTI, culture positive purulent OM</p> <p>UTI if > 100000 colonies/mL of a single organism</p> <p>Diagnosis: SBI: 23 (9.8) Bacteremia: 9 Others: NR</p>	<p>SBI: Sensitivity: 95.6 (76.0, 99.7) Specificity: 68.0 (61.2, 74.2) PPV: 24.7 (16.4, 35.2) NPV: 99.3 (95.6, 99.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Gomez (2010) ¹⁰	<p>Design: Retrospective Cross sectional</p> <p>Region: Spain</p> <p>Setting: pediatric ED</p> <p>Study period: 2003 – 2008</p>	<p>N: 1125/1018</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Infants 0 – 90 d days, fever $\geq 38.0^{\circ}\text{C}$ at home or on arrival in the Pediatric Emergency Department (blood and urine culture was obtained for all infants)</p> <p>Male (%): 57</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Criteria for discharge without antibiotic tx: well appearing, age > 15 d, negative, normal lab test results (up to 24 hrs of observation in ED).</p> <p>Criteria for hospital admission: age < 15 d, abnormal lab tests (CRP, CBC, urine dipstick)</p>	<p>SBI: isolation of a bacterial pathogen from CSF, blood, or urine.</p> <p>Positive blood culture: growth of a true bacterial pathogen was grown (<i>Streptococcus pneumoniae</i>, <i>Neisseria meningitidis</i>, <i>Enterococcus</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, <i>Staphylococcus aureus</i>, group A and B <i>Streptococcus</i>, <i>Listeria monocytogenes</i>, or <i>Salmonella</i> species).</p> <p>Diagnosis: SBI: 198 (19.4) Bacteremia: 9 UTI: 172 Bacterial meningitis: 4 Sepsis: 2, OM or Cellulitis: 3</p> <p>Most frequently pathogens were <i>Escherichia coli</i> (9), <i>Streptococcus pneumoniae</i>.</p>	<p>SBI: Sensitivity: 87.0 (67.9, 95.5) Specificity: NR PPV: NR NPV: 99.4 (98.2, 99.8)</p> <p>Bacteremia: Sensitivity: 26.1 (11.3, 47.2) Specificity: 95.8 (95.4, 96.3) PPV: 12.5 (5.4, 22.6) NPV: 98.2 (97.9, 98.7)</p> <p>Other: increased probability of having bacteremia with respect to general appearance (not well-appearing vs. well appearing; OR=8.01, 95% CI: 2.76, 23.05) and highest temperature detected ($\geq 39.5^{\circ}\text{C}$ vs. 38.0°C to 39.4°C; OR=3.37, 95% CI: 1.16, 9.36).</p> <p>CRP, WBC, and absolute neutrophil count were not good bacteremia predictors.</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Herr (2001) ¹¹	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Emergency Department</p> <p>Study period: 1999-2002</p>	<p>N: 434/344</p> <p>Age group(s): < 59 d (subgroups: 0- 14; 15-28; 29-45; and 46-59)</p> <p>Inclusion / exclusion: infants presented to the ED for evaluation with temperature $\geq 38^{\circ}\text{C}$-excluded infants with focus of infection and those with incomplete data</p> <p>Male (%): 51</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Full term, no underlying illness, no previous hospitalization, no perinatal antibiotics (if < 14 days old), no sibling with group GBS disease; well appearance without focal infection + WBC: 5,000-15,000/mm³, ABC $\leq 1,500/\text{mm}^3$, enhanced UA (WBC $\leq 9 \text{ mm}^3$ and negative Gram stain), CSF WBC $\leq 5/\text{mm}^3$ and negative Gram stain</p>	<p>Lobar infiltration on CXR, growth of a bacterial pathogen from CSF, blood, stool or soft tissue</p> <p>(UTI =growth of ≥ 50000 cfu/mL of a single pathogenic organism for urine obtained by catheter)</p> <p>Diagnosis: SBI: 41 (12.0) UTI: 25 Pneumonia: 8 Bacteremia: 3 Meningitis: 2 Gastroenteritis: 1 Chlamydia: 1</p>	<p>SBI: Sensitivity: 68.3 (51.7, 81.4) Specificity: 37.6 (32.2, 43.3) PPV: 12.9 (8.8, 18.2) NPV: 89.7 (82.8, 94.2)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Marom (2007) ¹²	<p>Design: Cross Sectional</p> <p>Region: Israel</p> <p>Setting: Peadiatric ED</p> <p>Study period: 1998-2003</p>	<p>N: 449/386</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Consecutive infants presented to peadiatric EDs, with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): 53%</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Unremarkable medical history, good appearance, no focal/physical signs of infection + ESR < 30 mm/h</p> <p>WBC: 5,000-15,000/mm³, normal</p> <p>UA (dipstick: LE, nitrites)</p>	<p>NR</p> <p>(UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL of a single urinary pathogen)</p> <p>Diagnosis: SBI: 108 (28.0) UTI: 54 Acute otitis media: 13 Gastroenteritis: 2 Meningitis: 2 Others: NR</p>	<p>SBI: Sensitivity: 99.1 (94.2, 99.9) Specificity: 59.3 (53.3, 65.1) PPV: 48.6 (41.8, 55.4) NPV: 99.4 (99.3, 99.5)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Pantell (2004) ¹³	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: 219 family practices</p> <p>Study period: 1995 – 1998</p>	<p>N: 3,066/1,746</p> <p>Age group(s): 0 – 90d</p> <p>Inclusion / exclusion: Healthy infants with rectal temperature $\geq 38^{\circ}$ C measured at home or office, hospitalized</p> <p>Male (%): 53.2%</p> <p>Ethnicity (%): White/non-Hispanic: 70 Hispanic: 15 African/American: 8 Asian/ South Pacific: 2 Other: 5</p> <p>----- Information on mother: NR</p>	<p>1) Clinical appearance + WBC < 5,000/ mm³ or WBC > 15,000/mm³</p> <p>2) Clinical appearance + WBC < 5,000/ mm³ or WBC > 15,000/mm³; WBC \geq 5/hpf</p>	<p>Bacteremia with pathogenic organisms and bacterial meningitis</p> <p>Bacteremia/bacterial meningitis: (1): 63 (3.6)</p> <p>Bacteremia/bacterial meningitis: (2): 63 (3.6)</p>	<p>SBI - (Bacteremia/bacterial meningitis) (1): Sensitivity: 83.9 (NC) Specificity: 54.0 (NC) PPV: NR NPV: NR</p> <p>SBI - (Bacteremia/bacterial meningitis) (2): Sensitivity: 87.1 (NC) Specificity: 50.7 (NC) PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Schawrtz (2008) ¹⁴	<p>Design: Cross sectional</p> <p>Region: Israel</p> <p>Setting: ED</p> <p>Study period: 1997 – 2006</p>	<p>N: 644/449</p> <p>Age group(s): 0 – 28 d</p> <p>Inclusion / exclusion: neonates with rectal temperature $\geq 38^{\circ}$ C measured at home or office, hospitalized/ preterm, prior hospitalization or receipt of antibiotics, known chronic dx and a source of infection apparent on physical exam other than acute OM</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Criteria for LR: not ill appearing, WBC 5,000 – 15,000/ mm³, absence of LE in none centrifuged urine on dipstick test, and < 23 WBC/hpf on microscopic exam</p>	<p>SBI: positive bacterial growth of pathogens in blood, urine, CSF or stool culture, or a CXR revealing a lobar infiltrate or a bone or soft tissue infection not present on admission or ER after hospitalization</p> <p><u>Diagnosis:</u> SBI: 87 (19.4%)- 79% male Bacteremia + meningitis + UTI: 2 Bacteremia + UTI: 2 Bacteremia: 1 UTI: 70 Pneumonia: 2 Omphalitis: 1</p>	<p>SBI - Sensitivity: 83.9 (75.6, 90.0) Specificity: 58.6 (56.6, 60.0) PPV: 32.7 (29.5, 35.1) NPV: 93.8 (90.6, 96.1)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Wasserman (1990) ¹⁵	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Army Medical Centre</p> <p>Study period: 1983-1985</p>	<p>N: NR/443</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Consecutive sample of FI with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Clinical judgment for 'low risk' (non-bacterial illness, did not appear ill, benign physical examination + unremarkable initial laboratory screen</p>	<p>Bacteremia, bacterial meningitis, soft tissue infection, UTI and bacterial enteritis</p> <p>Diagnosis: SBI: 53 (12.0) Bacteremia: 8 Meningitis: NR Soft tissue infection: NR UTI: NR Enteritis: NR</p>	<p>SBI: Sensitivity: 90.5 (78.6, 96.5) Specificity: 55.4 (50.3, 60.3) PPV: 21.6 (16.5, 27.7) NPV: 97.7 (94.5, 99.1)</p>

Table 2. Clinical Criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
<p>Bilavsky (2008)¹⁶</p>	<p>Design: Case Control</p> <p>Region: Israel</p> <p>Setting: Peadiatric ED</p> <p>Study period: 2005 – 2006</p>	<p>N: 149 cases/40 cases + 40 controls</p> <p>Age group(s): 0 – 90 d mean 80 d</p> <p>Inclusion / exclusion: Cases= previously healthy infants hospitalized with grunting respirations with fever $\geq 38^{\circ}\text{C}$; Controls= matched with cases for age, days of hospitalization and fever only without grunting)/ NR</p> <p>Note: study also included older infants (age >91 d)</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Grunting respiration in cases vs. no grunting</p>	<p>NR</p> <p>SBI: 3 (7.5%) cases and 2 (5.0%) controls, p=1</p>	<p>SBI:</p> <p>Sensitivity: NR</p> <p>Specificity: NR</p> <p>PPV: NR</p> <p>NPV: NR</p> <p>The association between grunting and SBI was not significant with 3 infants with SBI in the case group vs. 2 infants with SBI in the control group (7.5% vs. 5.0%; OR=1.54 (95% CI: 0.19, 14.1).</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1991) ¹⁷	<p>Design: Case series</p> <p>Region: Taiwan</p> <p>Setting: Pediatric ED</p> <p>Study period: 1986-1990</p>	<p>N: 683/683</p> <p>Age group(s): 30 – 60 d</p> <p>Inclusion / exclusion: infants with temperature <41°C, and sepsis workup-excluded infants with preadmission antipyretic medication within 4 hours, or antibiotics within 72 hours</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	T ≥ 40.0°C	<p>Bacterial meningitis, bacteremia, UTI, salmonella gastroenteritis, septic arthritis, osteomyelitis</p> <p>UTI if ≥ 100000 cfu/hpf</p> <p>Diagnosis: SBI: 34 (5.0) Meningitis: 6 Bacteremia: 8 UTI: 16 Enteritis: 4</p>	<p>SBI: Sensitivity: 21.0 (9.3, 38.4) Specificity: 97.0 (95.2, 98.0) PPV: 26.0 (11.8, 46.6) NPV: 95.8 (94.0, 97.2)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1994) ¹⁸	<p>Design: Case series</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: 1989-1993</p>	<p>N: 367/356</p> <p>Age group(s): 60 – 90 d</p> <p>Inclusion / exclusion: All infants with rectal temperature $\geq 38^{\circ}\text{C}$ excluded infants who were culture negative for bacterial pathogens and received antibiotic treatment within 72 hours; antipyretic medication within 4 hours of presentation</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Ill appearance	<p>Bacterial meningitis, bacteremia, UTI, and salmonella enteritis</p> <p>UTI if ≥ 10000 cfu/mL of a single organism by bladder catheterization</p> <p>Diagnosis: SBI: 33 (9.3) UTI: 17 Meningitis: 5 Bacteremia: 8 Salmonella: 3</p>	<p>SBI: Sensitivity: 33.3 (18.5, 51.9)</p> <p>Bacteremia: Sensitivity: 37.5 (10.2, 74.1)</p> <p>Meningitis: Sensitivity: 100.0 (46.3,100.0)</p> <p>UTI: Sensitivity: 17.6 (4.6, 44.2)</p> <p>Salmonella: Sensitivity: 0</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Broner (1990) ²	<p>Design: Quasi-experimental</p> <p>Region: North America</p> <p>Setting: General ED</p> <p>Study period: Unclear</p>	<p>N: NR/52</p> <p>Age group(s): 4 – 56 d</p> <p>Inclusion / exclusion: Infants with rectal temperature $\geq 38.1^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Toxic appearance (i.e., increased irritability, decreased eye contact, unwillingness to feed, and the state of alertness)</p>	<p>NR</p> <p>Diagnosis: SBI: 5 (9.6) (sepsis)</p>	<p>SBI: Sensitivity: 80.0 (29.8, 98.9) Specificity: 80.0 (66.2, 90.3) PPV: 30.7 (10.3, 61.1) NPV: 97.4 (84.5, 99.8)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Casper (1983) ³	<p>Design: Quasi-experimental</p> <p>Region: North America</p> <p>Setting: Primary care (community based hospital)</p> <p>Study period: July 1974 – December 1979</p>	<p>N: 305/305</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Infants with rectal temperature $\geq 38^{\circ}\text{C}$ seen in outpatient or well documented fever at home</p> <p>Male (%): 54</p> <p>Ethnicity (%): White/non-Hispanic: 3 Hispanic: 51 African/American: 45 Asian/ South Pacific: 1.3 ----- Information on mother: NR</p>	<p>Ill appearance (inconsolable when held or fed or unresponsive to their environment)</p>	<p>NR</p> <p>Diagnosis: Bacteremia (0-90 d)- (1): 11 (3.6) Bacteremia (0-90 d)- (2): 11 (3.6) UTI: 7 (2.3)</p>	<p>Bacteremia (1): Sensitivity: 91.0 (57.1, 99.5) Specificity: 56.6 (49.3, 63.5) PPV: 10.4 (5.4, 18.7) NPV: 99.1 (94.4, 99.9)</p> <p>Bacteremia (2): Sensitivity: 85.7 (42.0, 99.2) Specificity: 73.2 (63.4, 81.3) PPV: 18.2 (76.1, 36.0) NPV: 98.6 (91.8, 99.9)</p> <p>UTI: Sensitivity: 42.8 (11.8, 79.8) Specificity: NR PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Chen (2008) ¹⁹	<p>Design: Case Series</p> <p>Region: Taiwan</p> <p>Setting: Peadiatric Hospital</p> <p>Study period: October 2005- July 2006</p>	<p>N: NR / 44</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Febrile infants with a clinical suspicion of SBI.</p> <p>Male (%): 68</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Presence of at least one of the following: tachypnea, dyspnea, tachycardia, bradycardia, decrease of activity, lethargy, and decrease of appetite</p>	<p>SBI defined as pathogen in blood, CSF, or urine. Pneumonia was diagnosed as the presence of related clinical symptoms such as tachypnea productive cough with consolidation or fluid in lobar fissure/pleura visible on chest X-ray. UTI diagnosed as pyuria in routine urine exam and two sets or urine culture with a single pathogen growth more than 10⁴ CFU/mL from a bladder catheterization or more than 10⁵ CFU/ML collected from a sterile collection bag after sterile preparation.</p> <p>Diagnosis:</p> <p>Total SBI: 23/NR (all infants at high risk)</p>	<p>SBI:</p> <p>Sensitivity: NR</p> <p>Specificity: NR</p> <p>PPV: 52.3 (95% CI: 36.8, 67.3)</p> <p>NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Crain (1982) ²⁰	<p>Design: Case series</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1979-1981</p>	<p>N: 134/134</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: infants with rectal temperature $\geq 38^{\circ}\text{C}$ documented at ED or home</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Clinical impression of sepsis (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern)</p>	<p>NR</p> <p>Diagnosis: SBI (bacteremia): 5 (3.7)</p>	<p>SBI: Sensitivity: 100.0 (46.3,100.0) Specificity: 58.1 (49.1, 66.6) PPV: 8.5 (3.1, 19.4) NPV: 100.0 (93.9, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
King (1987) ^{b21}	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1983-1985</p>	<p>N: NR/97</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: Outpatient infants with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): 50</p> <p>Ethnicity (%): White/non-Hispanic: 21 African/American: 75 Not known: 4</p> <p>----- Information on mother: NR</p>	<p>Septic appearance (yes, no, unsure) based on physical examination, complete history, initial laboratory results</p>	<p>Positive culture of blood, CSF, and urine</p> <p>Diagnosis: SBI (Bacteremia or meningitis): 4 (5.4)</p>	<p>SBI: Sensitivity: 100.0 (39.6,100.0) Specificity: 66.0 (54.9, 74.9) PPV: 11.1 (3.6, 27.0) NPV: 100.0 (92.6, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Mintegi (2009) ²²	<p>Design: Prospective Cohort</p> <p>Region: Spain</p> <p>Setting: ED</p> <p>Study period: 5 consecutive influenza seasons during 2003 – 2008</p>	<p>N: 520/381</p> <p>Age group(s): 0 – 90 d Mean age: 48.8 d (n=88 were neonates)</p> <p>Inclusion / exclusion: Fever without a source $\geq 38^{\circ}\text{C}$, with blood culture and rapid influenza test (RIT)/ infants taking antibiotics prior to ED visit were excluded Note: 26 (6.6%) had underlying dx at presentation to ED</p> <p>Male (%): 53</p> <p>Ethnicity (%): NR (likely to be 100% Hispanic)</p> <p>----- Information on mother: NR</p>	Positive vs. negative influenza test	<p>NR</p> <p>Diagnosis: SBI: Infants with positive RIT: 3/113 (2.65) Infants with negative RIT: 47/268 (17.5)</p> <p>Bacteremia: 8 (4 <i>Streptococcus agalactiae</i>; 2 <i>Neisseria meningitidis</i>, 1 <i>streptococcus pneumonia</i>; 1 <i>staphylococcus aureus</i>)</p> <p>UTI: 34 (only 301/381 had urine culture) UTI in positive RIT: 3/72 (4.17%); UTI in negative RIT: 31/229 (13.5%)</p> <p>Meningitis: 5 (only 110/381 had CSF culture) all with negative RIT (2 <i>S. agalactiae</i>, 2 <i>Listeria monocytogenes</i>, 1 <i>N. meningitidis</i>)</p>	<p>SBI: Sensitivity: 94.0 [83.1, 98.4] Specificity: 33.2 [31.6, 33.9] PPV: 17.5 [15.5, 18.4] NPV: 97.3 [92.5, 99.3]</p> <p>Prevalence of SBI in viral positive infants vs. viral negative: 2.65 [0.0, 5.6] vs. 17.5 [13.0, 22.0] Prevalence ratio: 0.15 [0.04, 0.48] OR: 0.13 [0.03, 0.44]</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Pantell (2004) ¹³	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: 219 family practices</p> <p>Study period: 1995-1998</p>	<p>N: 3,066/1,746</p> <p>Age group(s): 0 – 90d</p> <p>Inclusion / exclusion: Healthy infants with rectal temperature $\geq 38^{\circ}$ C measured at home or office</p> <p>Male (%): 53.2</p> <p>Ethnicity (%): White/non-Hispanic: 70 Hispanic: 15 African/American: 8 Asian/ South Pacific: 2 Other: 5</p> <p>----- Information on mother: NR</p>	<p>1) High risk: age < 30 d and ill-appearing Low risk: age > 30 d and well-appearing</p> <p>2) Moderately or very ill vs. well or minimally ill; age < 25 d; T $\geq 38.6^{\circ}$C</p> <p>3) Clinical appearance</p>	<p>Bacteremia with pathogenic organisms and bacterial meningitis</p> <p>Diagnosis: SBI (Bacteremia/bacterial meningitis)- (1): 63 (3.6)</p> <p>SBI (Bacteremia/bacterial meningitis)- (2): 63 (3.6)</p> <p>SBI (Bacteremia/bacterial meningitis)- (3): 63 (3.6)</p>	<p>SBI (Bacteremia/bacterial meningitis)- (1): Sensitivity: 95.2 (NC) Specificity: 35.49 (NC) PPV: NR NPV: NR</p> <p>SBI (Bacteremia/bacterial meningitis)- (2): Sensitivity: 93.6 (NC) Specificity: 27.3 (NC) PPV: NR NPV: NR</p> <p>SBI (Bacteremia/bacterial meningitis)- (3): Sensitivity: 58.1 (NC) Specificity: 68.1 (NC) PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Rosenberg (1985) ²³	<p>Design: Case series</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: 1981-1982</p>	<p>N: 122/122</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: Infants with auxiliary temperature $\geq 37.8^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Clinical impression of sepsis (irritable, toxic, lethargic)</p>	<p>NR</p> <p>UTI if > 100,000 cfu/ml</p> <p>Diagnosis: SBI (bacteremia): 5 (4.0)</p>	<p>SBI: Sensitivity: 80.0 (29.9, 98.9) Specificity: 37.5 (28.7, 47.2) PPV: 5.4 (1.7, 13.9) NPV: 97.6 (86.2, 99.8)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Wolff (2009) ²⁴	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Pediatric ED</p> <p>Study period: Unclear</p>	<p>N: 2,247/1978</p> <p>Age group(s): 45 – 90 d; median age 64 d in recently immunized infants (RI) and 65 d in infants not recently immunized (NRI)</p> <p>Inclusion / exclusion: infants with a temperature $\geq 38^{\circ}\text{C}$ at home, GP office or ED (based on the 2-month immunization record)/ pre-term infants (< 32 week gestational age), chronic illness, surgery within 7 days, concurrent antibiotic use or focal bacterial infection by examination other than OM.</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Ill appearing (excluded): ill appearing on exam, cyanotic, apneic, mottled, poorly perfused, unresponsive or moribund</p> <p>All other infants were classified as well appearing</p>	<p>Definite SBI: bacterial pathogen isolated in blood or in urine; bacterial pathogen isolated in the CSF; pneumonia; or bacterial pathogen isolated in stool culture (study also reports criteria for possible SBI)</p> <p>Diagnosis: SBI: 130 (6.6) UTI: 105 Bacteremia: 11 Bacteremia/UTI: 4 Meningitis: 3 Pneumonia: 7</p> <p>Prevalence of SBI in NRI (72 hrs prior to ED visit): 7.0% (95% CI: 5.9, 8.3) In RI: 2.8%, (95% CI: 0.6, 5.1) Prevalence of SBI in RI (24 hrs prior to ED visit): 0.6%,(95% CI: 0, 0.9)</p>	<p>SBI: Sensitivity: 95.4 [90.0, 98.1] Specificity: 11.3 [10.9, 11.5] PPV: 7.1[6.7, 7.3] NPV: 97.2 [93.8, 98.8]</p> <p>RI infants were at lower risk of having SBI compared with NRI infants (RR=0.41, 95% CI: 0.19, 0.90). Infants immunized 24 hr were at a lower risk of having SBI than NRI infants (RR=0.09, 95% CI: 0.01, 0.64).</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Stanley (2005) ²⁵	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Pediatric ED</p> <p>Study period: Unclear</p>	<p>N: 5,279/5,279</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: infants with a rectal temperature $\geq 38^{\circ}\text{C}$, with complete test and culture records.</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Temperature $> 40.0^{\circ}\text{C}$	<p>Positive culture of urine, blood or CSF</p> <p>UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen</p> <p>Diagnosis: SBI: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11</p>	<p>SBI: Sensitivity: 7.3† (5.2, 10.1) Specificity: 98.8 (98.4, 99.1) PPV: 38.0 (28.3, 48.8) NPV: 91.4 (90.6, 92.1)</p>

Table 3. Other studies - Prevalence of SBI/IHI in Febrile Infants

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
<p>Andreola (2007)²⁶</p>	<p>Design: Cohort Region: Western Europe Setting: Peadiatric ED Study period: 2004-2005</p>	<p>N: 107 (26.2% of total sample age 0 – 36 months) Age group(s): 0 – 90 d Inclusion / exclusion: All children younger than 3 years admitted to the ED with fever of certain source-excluded infants with antibiotic use within 48 hours before admission; vaccination during the previous 2 days, known immunodeficiencies; any chronic pathology; fever lasting longer than 5 days Male (%): NR Ethnicity (%): NR ----- Information on mother: NR</p>	<p>Yale Observation Scale age 7-90 d, and fever >38°C</p>	<p>SBI by growth of a single pathogen in blood, urine or CSF culture included bacteraemia; UTI, bacterial meningitis; lobar pneumonia, sepsis (UTI: single urinary tract pathogen at $\geq 10^5$ cfu/mL in 2 consecutive urine sample and presence of a renal hypocaptation at DMSA scan performed within the fist week after admission) Diagnosis: SBI: 6 (11.5)</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bilavsky (2009) ²⁷	<p>Design:</p> <p>Region: Israel</p> <p>Setting: Peadiatric Ward</p> <p>Study period: 2005 – 2008</p>	<p>N: 892</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: all febrile infants age ≤ 3 months (including those hospitalized)/ excluded were those with chronic disease, or congenital or acquired immune deficiency, preterm birth (< 32 wks of gestation), and receipt of antibiotics within 48 hrs</p> <p>Male (%): 57.5</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Only WBC and CRPs were measured upon admission-</p> <p>WBC cut offs: $> 15,000$, $> 20,000$, $> 15,000$ or $< 5,000/\mu\text{L}$</p> <p>CRP cut offs: > 8, > 4, or > 2 mg/dL</p>	<p>SBI: growth of pathogen in culture of blood, urine or CSF. Cultures with more than one isolate wre considered to be contaminated.</p> <p>Diagnosis: SBI: 102/892 (11.3)</p>	<p>SBI: Sensitivity: NR Specificity: NR PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1987) ²⁸	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Paediatric ED</p> <p>Study period: 1984 (July – Nov)</p>	<p>N: 159 (subgroup of larger study, n=265 age 0-12 months)</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: Febrile infants less than 12 months of age admitted with the diagnosis of rule out sepsis, with no source of infection identified</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Urine analysis by bag, catheter or suprapubic aspiration	<p>UTI cultures positive if: Suprapubic aspiration specimen: pure colony count of ≥ 1000 cfu/mL Bladder catheterization: ≥ 1000-10000 cfu/mL</p> <p>Diagnosis: SBI (UTI only): 12/159 (7.5)</p> <p>Note: complete urine culture result by method of collection reported for the larger sample</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1991) ¹⁷	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Paediatric ED</p> <p>Study period: 1989 – 1990</p>	<p>N: 161</p> <p>Age group(s): 30 – 60 d</p> <p>Inclusion / exclusion: All infants with rectal temperature $\geq 38^{\circ}\text{C}$ documented at the time of triage in ED</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	NR	<p>SBI included bacterial meningitis, bacteraemia, UTI and bacterial enteritis</p> <p>Diagnosis: SBI: 18 (11.2)</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
DeAngelis (1983) ²⁹	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Peadiatric hospital (outpatient)</p> <p>Study period: 1978- 1981</p>	<p>N: 290</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: Infants with rectal temperature $\geq 38^{\circ}\text{C}$ evaluated at outpatient care</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	NR	<p>Immobile tympani membrane positive bacterial culture or infiltrate on chest roentgenogram</p> <p>Diagnosis: SBI: 39 (13.4)</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Ferguson (2008) ³⁰	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: ED</p> <p>Study period: 2004 – 2005</p>	<p>N: 190</p> <p>Age group(s): 30 – 60 d: n=90 60 – 90 d: n=100</p> <p>Inclusion / exclusion: infants with temperature \geq 38°C who presented to the ED</p> <p>Male (%): 56%</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	NR (clinical variables, microbiologic results including rapid viral testing and cultures was extracted from charts)	<p>NR</p> <p>Diagnosis:</p> <p>SBI (total): 30 – 60 d: 9 (10.0) 60 – 90 d: 10 (10.0)</p> <p>Bacteremia: 30 – 60 d: 1 (1.1) 60 – 90 d: 1 (1.0)</p> <p>UTI 30 – 60 d: 6 (6.7) 60 – 90 d: 5 (5.0)</p> <p>Meningitis 30 – 60 d: 0 60 – 90 d: 0</p> <p>Pneumonia 30 – 60 d: 2(2.2) 60 – 90 d: 4 (4.0)</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Filippine (2001)³¹	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1995-1997</p>	<p>N: 242/113</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: All febrile infants with virology laboratory results-excluded infants if no presenting fever was documented, there was an obvious source of infection on presentation, had congenital anomaly, hardware predisposing them to infection, or were immunocompromised</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Positive virology results to identify infants with HSV</p> <p>HSV:</p> <p>a) HSV encephalitis as HSV positive brain biopsy or autopsy specimen</p> <p>b) probable case of HSV encephalitis as consistent neurologic picture and virologic evidence of HSV (by culture of PCR).</p> <p>c) definite case of disseminated HSV as evidence of HSV infection and evidence of other affected organs.</p> <p>d) SEM disease as laboratory confirmed HSV infection confined to the skin, eye and/or mouth only</p>	<p>Diagnosis:</p> <p>SBI: 27/113 (23.9%)</p> <p>UTI: 20</p> <p>UTI + bacteremia: 5</p> <p>Bacterial meningitis: 2</p> <p>HSV encephalitis: 2 (one infant died)</p> <p>Note: 14 probable case of HSV encephalitis 12/14 with obvious SEM disease on physical examination</p> <p>32 infants also were HSV positive but were diagnosed with transplacental maternal antibody</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Grover (1999) ³²	<p>Design: Diagnostic accuracy study</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1992 – 1993</p>	<p>N: 48 (subgroup in a larger study)</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: All infants less than 2 moths of age seen in pediatric ED including a subgroup with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Ill appearance	<p>Blood, urine and CSF culture positives. Stool cultures for bacterial and viral for infants with diarrhea, chest radiograph for infants with respiratory symptoms</p> <p>Diagnosis: SBI: 12 (25.0)</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Hsiao (2006) ³³	<p>Design: Diagnostic accuracy study</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: 2003 – 2004</p>	<p>N: NR (subgroup of a large study with n=429 age 57-180 d)</p> <p>Age group(s): 57 – 89 d</p> <p>Inclusion / exclusion: infants with rectal temperature $\geq 37.9^{\circ}\text{C}$ who consecutively presented to the ED. Excluded if parent did not sign consent</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Yale Observational Scale	<p>NR</p> <p>(UTI: < 10000 colonies of a single organism /mL)</p> <p>Diagnosis: SBI: NR (8.8)</p> <p>Note: results reported for all infants 57-180 d</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Kuppermann (1999) ³⁴	<p>Design: cross sectional</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: 1994 – 1995 & 1995 – 1996</p>	<p>N: 30 (subgroup of larger study n=432 age 0-2 years)</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Consecutive sample of febrile infants (0-2 years)</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Yale Observation Scale & laboratory (WBC, manual differential count)	<p>Blood, urine and CSF cultures in addition to viral tests</p> <p>Diagnosis: SBI: 7 (23.3)</p>	<p>SBI: Sensitivity: NA Specificity: NA PPV: NA NPV: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Mintegi (2010) ³⁵	<p>Design: Cohort</p> <p>Region: Western Europe</p> <p>Setting: Peadiatric ED</p> <p>Study period: 2003 – 2007</p>	<p>N: 685</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Consecutive previously healthy well appearing infants younger than 3 mo with fever without known source</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Routine blood and urine work was performed</p> <p>WBC: >15,000/mm³, or < 5,000 mm³</p>	<p>Meningitis: positive CSF culture or positive CSF Gram tincture or CSF pleocytosis with negative CSF culture + positive blood culture</p> <p>LP was recommended for febrile infants under 15 d upon visit, with consideration for LP for infants 15 – 28 d</p> <p>Diagnosis:</p> <p>SBI: 97 (14.2%)</p> <p>SBI in infants 20.1%, in infants < 29 d, 12.6% in infants 29 – 60 d (p=0.04)-</p>	<p>SBI:</p> <p>Sensitivity: NA</p> <p>Specificity: NA</p> <p>PPV: NA</p> <p>NPV: NA</p> <p>418 infants without LP were discharged without antibiotics. 38 of these had unscheduled return visits to ED due to persistent fever. 7/418 (1.6%) were admitted to ward, 4 of them were diagnosed with aseptic meningitis. No complications occurred.</p> <p>Study conclusion: the decision to perform the LP in healthy, well appearing febrile infants could be individualized with no subsequent adverse outcomes</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI/Herpes	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Rudinsky (2009) ³⁶	<p>Design: Case series</p> <p>Region: Western Europe</p> <p>Setting: Peadiatric ED</p> <p>Study period: 2002 – 2003</p>	<p>N: infants 0 – 24 months were included n of infants under 90 d NR</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Consecutive previously healthy well appearing infants younger than 3 mo with fever without known source, fever $\geq 38.0^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	WBC: criteria NR	<p>UTI, bacteremia, pneumonia, anor meningitis with positive culture of blood, urine, CSF or chest radiographs.</p> <p>Diagnosis:</p> <p>SBI: 9 infants identified with SBI (total n of infants 0 – 3 mo NR)</p>	<p>SBI:</p> <p>Sensitivity: NA</p> <p>Specificity: NA</p> <p>PPV: NA</p> <p>NPV: NA</p>

Table 4. Studies with laboratory criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bachur (2001) ¹	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: ED</p> <p>Study period: 1993-1999</p>	<p>N: NR/5279</p> <p>Age group(s): 0–90 d</p> <p>Inclusion / exclusion: Retrospective sample of infants with a rectal temperature $\geq 38^{\circ}\text{C}$, with complete test and culture records.</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>UA (LE⁺ or nitrite⁺)</p>	<p>Positive culture of urine, blood or CSF</p> <p>(UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen)</p> <p>Test Results:</p> <p>SBI 373 (7.0) UTI: 316 (6.0%) Meningitis: 17 Bacteremia: 40 Bacteremia/meningitis: 8 Bacteremia/UTI: 11</p>	<p>SBI: Sensitivity: 71.0 (66.0, 76.0) Specificity: NR PPV: NR NPV: NR</p> <p>UTI: Sensitivity: 81.0 (76.0, 85.0) Specificity: NR PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bilavsky (2010) ³⁷	<p>Design: Case Control</p> <p>Region: Israel</p> <p>Setting: 2 EDs</p> <p>Study periods: 2005 – 2009</p>	<p>N: NR/1,257</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: hospitalized febrile infants/ presence of chronic disease, or congenital or acquired immune deficiency, preterm birth (< 35 weeks of gestation) and receipt of antibiotics within 48 hr of presentation to ED</p> <p>Male (%): 59</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>absolute neutrophil count (ANC with thresholds: > 4.65, > 10, > 12.5 K/μL), WBC (various thresholds: > 15, >20, > 20 or < 4.1, > 15 or <5 K/μL), and ratio % of ANC/WBC</p>	<p>Growth of a known pathogen in culture of blood, urine or CSF (UTI, meningitis, bacteremia or bacterial enteritis)</p> <p>Test Results: Total SBI: 134 (10.7%) UTI: 104 Bacteremia + UTI: 9 Isolated bacteremia: 4 Bacteremia + enteritis: 3 Pneumonia: 13 Enteritis: 1 Bacterial meningitis: 0</p> <p>isolated bacteremia was caused by <i>S. pneumonia</i>, <i>S. pyogenes</i> and <i>S. group B</i></p>	<p>SBI: Sensitivity: 38.8 [31.0, 47.3] Specificity: 84.6 [82.4, 86.6] PPV: NR NPV: NR</p> <p>Isolated Bacteremia: Sensitivity:17.2 [11.7, 24.4] Specificity: 93.2 [91.6, 94.6] PPV: NR NPV: NR</p> <p>AUC for ANC =0.77 (95% CI: 0.67, 0.78) and for WBC = 0.69 (95% CI: 0.61, 0.73). For infants \leq 28 d, the AUC for % WBC= 0.73 (95% CI: 0.67–0.78), for % ANC = 0.70 (95% CI: 0.65–0.76), for WBC= 0.67 (95% CI: 0.61–0.73).</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bachur (2001) ³⁸	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: NR</p>	<p>N: 37450/4539 (from original sample of 8815 who were 0-2 years old)</p> <p>Age group(s): 0–90 d</p> <p>Inclusion / exclusion: Retrospective sample of infants with temperature $\geq 38^{\circ}\text{C}$ seen at ED with paired UA and urine culture</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>----- Information on mother: NR</p>	<p>UA: dipstick (LE,⁺ nitrite,⁺ or both) and microscopy (pyuria: ≥ 5 WBC/hpf)</p>	<p>UTI only</p> <p>(UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen)</p> <p>Test Results:</p> <p>73 (8.4) (UTI)</p> <p>172 (7.5) (UTI)</p>	<p>UTI:</p> <p>Sensitivity: 82.0 (71.0, 90.0)</p> <p>Specificity: 92.0 (90.0, 94.0)</p> <p>PPV: 48.4 (39.4, 57.5)</p> <p>NPV: 98.2 (96.9, 99.0)</p> <p>UTI:</p> <p>Sensitivity: 82.0 (75.0, 87.0)</p> <p>Specificity: 94.0 (93.0, 95.0)</p> <p>PPV: 52.6 (46.4, 58.7)</p> <p>NPV: 98.4 (97.8, 98.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Berkowitz (1985) ³⁹	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: ED</p> <p>Study period: 1978-1979</p>	<p>N: 434/239</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: Retrospective sample of FI with temperature $\geq 38^{\circ}\text{C}$ evaluated in acute care walk in clinics (1978-1979)</p> <p>Male (%): 58</p> <p>Ethnicity (%):NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>1) $\geq 15000/\text{mm}^3$ WBC</p> <p>2) $\geq 10000/\text{mm}^3$ PMN</p> <p>3) $\geq 500/\text{mm}^3$ ABC</p> <p>4) $\geq 15000/\text{mm}^3$ WBC + $\geq 500/\text{mm}^3$ ABC</p> <p>5) $\geq 15000/\text{mm}^3$ WBC + $\geq 10000/\text{mm}^3$ PMN</p>	<p>NR (culture results of blood, CSF, and viral; culture- positive infants are referred to as category I)</p> <p>(NR)</p> <p>Test Results:</p> <p>SBI (Sepsis/meningitis 1-5): 10 (4.2)</p>	<p>SBI (1): Sensitivity: 50.0 (NC) Specificity: 77.0 (NC) PPV: NR NPV: NR</p> <p>SBI (2): Sensitivity: 38.0 (NC) Specificity: 93.0 (NC) PPV: NR NPV: NR</p> <p>SBI (3): Sensitivity: 88.0 (NC) Specificity: 61.0 (NC) PPV: NR NPV: NR</p> <p>SBI (4): Sensitivity: 63.0 (NC) Specificity: 84.0 (NC) PPV: NR NPV: NR</p> <p>SBI (5): Sensitivity: 38.0 (NC) Specificity: 94.0 (NC) PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonadio (1987) ⁴⁰	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1986-1987</p>	<p>N: 109/55</p> <p>Age group(s): 0–28 d</p> <p>Inclusion / exclusion: Retrospective sample of Febrile infants with rectal temperature $\geq 38^{\circ}\text{C}$ evaluated for sepsis in paediatric ED. Excluded: Infants currently receiving antibiotic medication at home, or antipyretic within 4 hours of admission</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>----- Information on mother: NR</p>	<p>1) $15000/\text{mm}^3$ WBC</p> <p>2) CBC Differential Ratio < 1 (Low risk)</p> <p>3) $\text{ABC}/\text{mm}^3 > 1500$</p>	<p>NR</p> <p>(UTI if > 100000 cfu/ml)</p> <p>Test Results:</p> <p>SBI (1-3): 8 (14.5) UTI: 3 Gastroenteritis: 2 Meningitis: 2 Bacteremia: 1</p>	<p>SBI: Sensitivity: 0.0 (NA) Specificity: NR PPV: NR NPV: NR</p> <p>SBI: Sensitivity: 87.5 (46.6, 99.3) Specificity: NR PPV: NR NPV: NR</p> <p>SBI: Sensitivity: 50.0 (17.4, 82.5) Specificity: NR PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
Bonadio (1992) ⁴¹	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: NR</p>	<p>N: NR/1009</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: Retrospective sample of consecutive cases of infants with rectal temperature $\geq 38.0^{\circ}\text{C}$ at the time of triage</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>----- Information on mother: NR</p>	<p>1) ABC/mm³ (250, 500, 1000, 2000, 3000)</p> <p>2) Total WBC/mm³ (3000, 10000, 12000, 18000, 20000)</p> <p>3) ABC/mm³ > 250</p> <p>4) ABC/mm³ > 500</p> <p>5) ABC/mm³ > 1000</p> <p>6) ABC/mm³ > 2000</p> <p>7) ABC/mm³ > 3000</p> <p>8) WBC/mm³ > 8000</p> <p>9) WBC/mm³ > 10000</p> <p>10) WBC/mm³ > 12000</p> <p>11) WBC/mm³ > 15000</p> <p>12) WBC/mm³ > 20000</p> <p>C-46</p>	<p>Bacterial meningitis, bacteremia, TI, salmonella enteritis, osteomyelitis and septic arthritis</p> <p>(UTI if > 100000 cfu/mL of a single organism)</p> <p>Test Results:</p> <p>SBI (1-12): 81(8.0) Meningitis: 21 UTI: 29 Bacteremia: 23 Enteritis: 8</p>	<p>SBI: Sensitivity: 93.0 (82.4, 96.1) Specificity: 44.0 (40.8, 47.3) PPV: 13.0 (9.9, 15.4) NPV: 99.0 (96.4, 99.3)</p> <p>Bacteremia: Sensitivity: 80.0 (76.5, 92.7) Specificity: 61.0 (55.5, 63.0) PPV: 16.0 (12.3, 19.2) NPV: 98.0 (96.4, 99.0)</p> <p>Meningitis: Sensitivity: 74.0 (62.9, 82.9) Specificity: 80.0 (76.9, 82.1) PPV: 24.0 (19.0, 30.0) NPV: 97.0 (95.7, 98.2)</p> <p>SBI: Sensitivity: 42.0 (31.2, 53.4) Specificity: 93.0 (91.2, 94.6) PPV: 35.0 (25.5, 45.0) NPV: 96.0 (93.1, 96.1)</p> <p>SBI:</p>	<p>SBI: Sensitivity: 74.0 (62.9, 82.9) Specificity: 28.0 (25.4, 31.4) PPV: 8.0 (6.4, 10.6) NPV: 93.0 (88.7, 95.2)</p> <p>SBI: Sensitivity: 69.0 (57.7, 78.6) Specificity: 52.0 (48.2, 54.7) PPV: 11.0 (8.5, 14.2) NPV: 95.0 (92.6, 96.7)</p> <p>SBI: Sensitivity: 51.0 (39.6, 61.8) Specificity: 72.0 (68.9, 74.8) PPV: 14.0 (10.0, 18.1) NPV: 94.0 (92.3, 95.9)</p> <p>SBI: Sensitivity: 31.0 (21.3, 42.2)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonsu (2003) ⁴²	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: NR</p>	<p>N: 6027/3961</p> <p>Age group(s): 0–89 d</p> <p>Inclusion / exclusion: Consecutive infants presented to paediatric ED with peripheral blood sent concurrently for bacterial culture and total peripheral WBC, with rectal temperature $\geq 38^{\circ}\text{C}$ at triage- excluded infants with leukemia</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>----- Information on mother: NR</p>	<p>1) $\geq 5000/\text{mm}^3$ WBC</p> <p>2) $\geq 10000/\text{mm}^3$</p> <p>3) $\geq 15000/\text{mm}^3$</p> <p>4) $\geq 20000/\text{mm}^3$</p> <p>5) $< 5000/\text{mm}^3$ or $\geq 15000/\text{mm}^3$</p> <p>6) $< 5000/\text{mm}^3$ or $\geq 20000/\text{mm}^3$</p>	<p>Bacteremia coded to be present if standard cultures isolated a pathogen known to cause bacteremia unequivocally in this age group.</p> <p>(NR)</p> <p>Test Results:</p> <p>38 (1.0) (bacteremia)</p> <p>Same Results for all Lab tests</p>	<p>Bacteremia (1): Sensitivity: 79.0 (63.0, 90.0) Specificity: 5.0 (4.0, 6.0) PPV: 0.8 (0.6, 1.2) NPV: 96.2 (92.3, 98.2)</p> <p>Bacteremia (2): Sensitivity: 61.0 (43.0, 76.0) Specificity: 42.0 (40.0, 44.0) PPV: 1.0 (0.6, 1.5) NPV: 99.0 (98.4, 99.4)</p> <p>Bacteremia (3): Sensitivity: 45.0 (29.0, 62.0) Specificity: 78.0 (76.0, 79.0) PPV: 2.0 (1.2, 3.2) NPV: 99.3 (98.9, 99.5)</p> <p>Bacteremia (4): Sensitivity: 24.0 (11.0, 40.0) Specificity: 93.0 (92.0, 94.0) PPV: 3.4 (1.6, 6.6) NPV: 99.1 (98.8, 99.4)</p> <p>Bacteremia (5): Sensitivity: 66.0 (49.0, 80.0) Specificity: 72.0 (71.0, 74.0) PPV: 2.3 (1.5, 3.5) NPV: 99.5 (99.1, 99.7)</p> <p>Bacteremia (6): Sensitivity: 45.0 (29.0, 62.0) Specificity: 88.0 (87.0, 89.0) PPV: 3.6 (2.2, 5.8) NPV: 99.3 (99.0, 99.6)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bonsu (2007)⁴³	Design: Cross-Sectional Region: North America Setting: Padiatric ED Study period: 1993-1999	N: NR/3765 Age group(s): 0–89 d Inclusion / exclusion: Consecutive Febrile infants, temperature in triage ≥ 38°C, presented to paediatric ED Male (%): NR Ethnicity (%):NR <hr style="width: 20%; margin-left: 0;"/> Information on mother: NR	UA (LE,⁺ nitrite,⁺ or protein)	UTI and SBI (no definition for SBI is provided) (UTI if supra-pubic ≥ 1000; 12.6 [6.8, 21.9]catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen) Test Results: UTI with sepsis: 307 (8.1)	SBI: Sensitivity: 84.0 (79.3, 87.8) Specificity: 63.6 (62.0, 65.2) PPV: 17.0 (15.1, 19.0) NPV: 97.8 (97.1, 98.3)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Bresan (2010) ⁴⁴	<p>Design: Cohort</p> <p>Region: Europe (Italy)</p> <p>Setting: Padiatric ED</p> <p>Study period: 2003 – 2007</p>	<p>N: 131/99</p> <p>Age group(s): 0–28 d; mean age 19.6 d</p> <p>Inclusion / exclusion: Fever(rectal $\geq 38^{\circ}\text{C}$, or axillary 37.5°C) without source for less than 12 hrs, good clinical appearance/ underlying diseases, Previously on antibiotics, preterm (<37 weeks gestation)</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>absolute neutrophil count (ANC: > 10,000/ mm³), or WBC (threshold: <5,000/ mm³ or > 15,000/ mm³), or CRP > 20 mg/L</p> <p>measured for infants with fever duration < 12 hours and also for infants with normal lab test after 12 hrs of fever duration</p>	<p>UTI, bacteremia, meningitis, pneumonia, cellulitis, osteomyelitis, septic arthritis identified as growth of pathogens in culture of blood, urine or CSF</p> <p>Test Results: Total SBI (< 12 hrs of fever duration): 25 (25.3) (total SBI identified by repeated blood test: 5/25)</p> <p>management: Immediate antibiotic therapy for 37 neonates (7 – 28 days) who were hospitalized upon admission. Twenty (54.0%) of these neonates were diagnosed with SBI. No treatment outcomes were reported.</p>	<p>SBI for low risk infants determined for fever < 12 hrs vs. > 12 hrs: WBC (threshold: <5,000/ mm³ or > 15,000/ mm³) Sensitivity: 28.0[14.3, 47.6] vs. 80.0 [37.6, 96.4] Specificity: 87.7[78.2, 93.4] vs. 90.6 [79.7, 95.9] PPV: 43.75[23.1, 66.8] vs. 44.4 [18.9, 73.3] NPV: 78.1[68.0, 85.6] vs. 98.0 [89.3, 99.6]</p> <p>SBI for low risk infants determined for fever < 12 hrs vs. > 12 hrs: CRP > 20 mg/L Sensitivity: 48.0 [30.3, 66.5] vs. 100.0 [56.6, 100.0] Specificity: 93.2 [85.1, 97.1] vs. 96.2 [87.2, 99.0] PPV: 70.6 [46.9, 86.7] vs. 71.4 [35.9, 91.8] NPV: 84.2[74.7, 90.5] vs. 100.0 [93.0, 100.0]</p> <p>AUC: ANC= 0.78 (95% CI: 0.69, 0.86) WBC =0.59 (95% CI 0.49, 0.69) CRP = 0.77 (95% CI: 0.67, 0.85)</p> <p>* Repeated blood examination (n=58). 5/58 had SBI. AUC for repeated tests resulted in improved values for CRP (0.99, 95% CI: 0.92, 1.0), ANC (0.85, 95% CI: 0.73, 0.93) and WBC (0.79, 95% CI: 0.66, 0.88).</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Broner (1990)²	Design: Quasi-Experiments Region: North America Setting: ED Study period: NR	N: NR/52 Age group(s): 0–60 d Inclusion / exclusion: Prospective sample of Febrile infants with rectal temperature $\geq 38.1^{\circ}\text{C}$ presented to general ED Male (%): NR Ethnicity (%):NR ----- Information on mother: NR	1) $\geq 15,000$ WBC/μL 2) $\geq 5,000$ ABC/μL 3) ESR ≥ 30 mm/h 4) CRP ⁺	NR (NR) Test Results: SBI (Sepsis 1-4): 5 (9.6)	SBI (1): Sensitivity: 20.0 (1.0, 70.0) Specificity: 80.0 (66.2, 90.3) PPV: 10.0 (0.5, 45.8) NPV: 90.4 (76.4, 96.9) SBI (2): Sensitivity: 80.0 (29.8, 98.9) Specificity: 57.0 (42.2, 71.4) PPV: 16.6 (5.4, 38.1) NPV: 96.4 (79.7, 99.8) SBI (3): Sensitivity: 25.0 (1.0, 70.1) Specificity: 87.0 (73.5, 94.7) PPV: 14.3 (0.7, 58.0) NPV: 91.1 (77.8, 97.1) SBI (4): Sensitivity: 64.0 (17.0, 92.7) Specificity: 67.0 (52.7, 80.4) PPV: 16.6 (4.4, 42.2) NPV: 94.1 (78.9, 98.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Brown (2005)⁴⁵	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1999-2002</p>	<p>N: 206/69</p> <p>Age group(s): 0–28 d</p> <p>Inclusion / exclusion: Retrospective sample of FI presenting to tertiary paediatric ED (1999-2002) with triage temperature $\geq 38^{\circ}\text{C}$, and complete sepsis workup record – excluding infants in whom the triage temperature record was not available or $\leq 38^{\circ}\text{C}$</p> <p>Male (%): 55</p> <p>Ethnicity (%):NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>1) $\geq 5000/\text{mm}^3$ WBC</p> <p>2) $\geq 10000/\text{mm}^3$ WBC</p> <p>3) $\geq 12000/\text{mm}^3$ WBC</p> <p>4) $\geq 15000/\text{mm}^3$ WBC</p> <p>5) $\geq 17000/\text{mm}^3$ WBC</p> <p>6) 5000;10000; 12000; 15000; 17000; 20000; 22000; 25000/mm^3 WBC</p>	<p>Positive culture of blood, urine, CSF, or stool or a clinical diagnosis of cellulitis, fasciitis, omphalitis, osteomyelitis or mastitis- excluded pneumonia</p> <p>Viral: positive viral culture, PCR or immunofluorescence study</p> <p>(NR)</p> <p>Test Results:</p> <p>SBI (1-6): 8 (12.0)</p>	<p>SBI (1): Sensitivity: 100.0 (NC) Specificity: 2.0 (NC) PPV: 12.0 (NC) NPV: 100.0 (NC)</p> <p>SBI (2): Sensitivity: 100.0 (60.0, 100.0) Specificity: 31.0 (19.9, 44.7) PPV: 17.0 (8.0, 30.7) NPV: 100.0 (78.1, 100.0)</p> <p>SBI (3): Sensitivity: 75.0 (35.5, 95.5) Specificity: 53.0 (41.6, 68.0) PPV: 18.0 (7.8, 37.0) NPV: 94.0 (78.9, 98.9)</p> <p>SBI (4): Sensitivity: 50.0 (17.4, 82.5) Specificity: 74.0 (64.4, 87.0) PPV: 21.0 (7.8, 50.2) NPV: 91.0 (79.5, 97.3)</p> <p>SBI (5): Sensitivity: 38.0 (9.0, 76.0) Specificity: 89.0 (78.1, 95.7) PPV: 33.0 (9.0, 69.0) NPV: 91.0 (80.0, 96.7)</p> <p>SBI (6): NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Casper (1983) ³	<p>Design: Quasi-Experimental</p> <p>Region: North America</p> <p>Setting: Primary Care</p> <p>Study period: 1974-1979</p>	<p>N: 305/198</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: Infants presenting to community based hospital with rectal temperature $\geq 38^{\circ}\text{C}$ seen in outpatient or well documented fever at home</p> <p>Male (%): 54</p> <p>Ethnicity (%):</p> <ul style="list-style-type: none"> • White/non-Hispanic: 3 • Hispanic: 45 • African/American: 51 • Asian/ South Pacific: 1.3 • Other: 0 <p>-----</p> <p>Information on mother: NR</p>	<p>$\geq 15,000/\text{mm}^3$ WBC</p>	<p>NR (blood, urine, CSF- also stool and nasopharynx when indicated)</p> <p>(NR)</p> <p>Test Results:</p> <p>SBI (bacteremia):</p> <p>Age 0 – 30 d: 7 (6.5)</p> <p>Age 30 – 60 d: 4 (2.0)</p>	<p>Bacteremia (age: 0 – 30 d)</p> <p>Sensitivity: 28.6 (5.1, 69.7)</p> <p>Specificity: NR</p> <p>PPV: NR</p> <p>NPV: NR</p> <p>Bacteremia (age 30 – 60 d):</p> <p>Sensitivity: 75.0 (21.9, 98.7)</p> <p>Specificity: NR</p> <p>PPV: NR</p> <p>NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Caviness (2008) ⁴⁶	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Padiatric Emergency Department</p> <p>Study period: 2001-2005</p>	<p>N: NR/960</p> <p>Age group(s): 0–90 d</p> <p>Inclusion / exclusion: Every infant aged <28 days evaluated in the ED</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>CSF pleocytosis:</p> <p>≥ 20 WBC/mm³ & > 1 WBC per 500 red blood cells/mm³</p>	<p>HSV infection: a positive HSV test result (HSV DNA detection by PCR, HSV antigen detection by direct fluorescence assay, and viral culture, on any tissue or body fluid obtained before or after death, confirmed with medical record</p> <p>SBI: positive bacterial culture from CSF, blood, or urine; meningitis if CSF bacterial culture was positive, bloodstream infection (bacteremia or septicemia) if blood culture was positive, UTI: ≥10,000 CFU/mL urinary pathogen confirmed with medical record</p> <p>Diagnosis: Total HSV: 3 Total SBI: 119 (12.4) UTI: 78 Bacteremia: 29 Meningitis: 12</p>	<p>HSV: Sensitivity: 66.6% (95% CI: 12.5, 98.2) Specificity: 74.6% (95% CI: 71.4, 77.6) PPV: 1.0% (95% CI: 0.2, 3.9) NPV: 99.8% (95% CI: 98.9, 99.9),</p> <p>SBI: Sensitivity: 31.1 [23.1, 40.3] Specificity: 75.5 (95% CI: 72.0, 78.6) PPV: 18.1 (95% CI: 13.2, 24.2) NPV: 86.2 (95% CI: 83.1, 88.8)</p> <p>Bacteremia: Sensitivity: 34.5 (95% CI: 18.6, 54.3) Specificity: 74.8 (95% CI: 71.6, 77.8) PPV: 4.9 (95% CI: 2.5, 9.1) NPV: 96.8 (95% CI: 95.0, 98.0)</p> <p>Meningitis: Sensitivity: 91.6 (95% CI: 59.7, 99.5) Specificity: 75.5 (95% CI: 72.3, 78.4) PPV: 5.4 (95% CI: 2.8, 9.6) NPV: 99.8 (95% CI: 98.9, 99.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Crain (1982) ²⁰	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Primary Care</p> <p>Study period: 1979-1981</p>	<p>N: 134/99</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: Prospective sample of Febrile infants presenting to paediatric care with rectal temperature $\geq 38^{\circ}\text{C}$ documented at ED or home</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>-----</p> <p>Information on mother: NR</p>	ESR ≥ 30 mm/h	<p>NR</p> <p>(NR)</p> <p>Test Results:</p> <p>SBI (bacteremia): 5 (5.0)</p>	<p>Bacteremia:</p> <p>Sensitivity: 80.0 (29.8, 98.9)</p> <p>Specificity: 93.6 (86.0, 97.3)</p> <p>PPV: 40.0 (13.7, 72.6)</p> <p>NPV: 99.0 (93.0, 99.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
Dayan (2002) ⁴⁷	<p>Design: Cross-Sectional</p> <p>Region: North America</p> <p>Setting: Paediatric ED</p> <p>Study period: 1998-2000</p>	<p>N: 246/232</p> <p>Age group(s): 1–60 d</p> <p>Inclusion / exclusion: Consecutive sample of infants with temperature $\geq 38^{\circ}\text{C}$ presenting at paediatric ED (1998-2000)-excluded were infants without completed Gram stain</p> <p>Male (%): 49</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<ol style="list-style-type: none"> 1) Gram stain, any organisms 2) Microscopy of spun urine (≥ 5 WBC/hpf) 3) Microscopy of urine (≥ 10 WBC/hpf) 4) Any nitrite alone 5) Any LE alone 6) Nitrite + LE 7) UA (LE⁺ or nitrite⁺) 	<p>UTI only</p> <p>(UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 cfu/ mL (cfu/mL) of a single urinary pathogen)</p> <p>Test Results:</p> <p>SBI (UTI only): 27 (14.0%)</p> <p>Same Results for all Lab tests</p>	<p>UTI (1): Sensitivity: 80.0 (62.5,97.5) Specificity: 99.4 (93.8, 100.0) PPV: 95.6[†] (76.0, 99.8) NPV: 96.8 (92.9, 98.9)</p> <p>UTI (2): Sensitivity: 65.0 (44.1, 85.9) Specificity: 92.4 (88.6, 96.4) PPV: 56.6 (37.6, 74.0) NPV: 93.8 (88.7, 96.8)</p> <p>UTI (3): Sensitivity: 45.0 (23.2, 66.8) Specificity: 97.6 (95.4, 99.9) PPV: 75.0 (47.4, 91.6) NPV: 91.5 (86.1, 95.0)</p> <p>UTI (4): Sensitivity: 35.0 (14.1, 55.9) Specificity: 97.7 (95.4, 99.9) PPV: 69.2 (38.8, 89.6) NPV: 90.0 (84.4, 93.8)</p>	<p>UTI (5): Sensitivity: 80.0 (62.5, 97.5) Specificity: 94.2 (90.7, 97.7) PPV: 67.7 (48.5, 82.6) NPV: 96.3 (91.7, 98.5)</p> <p>UTI (6): Sensitivity: 30.0 (10.0, 50.0) Specificity: 100.0 (98.3, 100.0) PPV: 100.0 (60.0, 100.0) NPV: 89.7 (84.2, 93.5)</p> <p>UTI (7): Sensitivity: 85.0 (69.4, 100.0) Specificity: 91.9 (87.8, 96.0) PPV: 62.1 (44.8, 77.0) NPV: 97.4 (93.1, 99.1)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Hoberman (1993) ⁴⁸	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: NR</p>	<p>N: NR/306</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: All febrile infants presented in pediatric ED (1990-1991) with rectal temperature $\geq 38.3^{\circ}\text{C}$ or auxiliary $\geq 37.4^{\circ}\text{C}$ recorded in the ED, or recorded within 24 hours- excluded were infants with antibacterial treatment or bladder catheterization</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Bacteriuria (Any number of bacteria by hpf)</p>	<p>UTI only</p> <p>(UTI if result of standard quantitative and dipslide culture were considered positive if ≥ 10000 CFLU of a single type of organism/mm.)</p> <p>Test Results:</p> <p>14 (UTI)</p>	<p>UTI:</p> <p>Sensitivity: NR</p> <p>Specificity: NR</p> <p>PPV: NR</p> <p>NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
King (1987) ^{a21}	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Primary Care</p> <p>Study period: NR</p>	<p>N: 439 / 245</p> <p>Age group(s): 0–60 d</p> <p>Inclusion/ exclusion: Retrospective sample of Febrile infants with rectal temperature $\geq 38^{\circ}\text{C}$ who presented to University hospital (1978-1982) Prospective sample of outpatients with rectal temperature $\geq 38^{\circ}\text{C}$ (1983-1985)</p> <p>Male (%): 50</p> <p>Ethnicity (%):</p> <ul style="list-style-type: none"> • White/non-Hispanic: 21 • Hispanic: 0 • African/American: 75 • Asian/ South Pacific: 0 • Other: 4 <p>-----</p> <p>Information on mother: NR</p>	<p>1) $\leq 5,000 \text{ WBC}/\text{mm}^3$</p> <p>2) % Immature neutrophils $\geq 20\%$</p> <p>3) ESR $\geq 30 \text{ mm/h}$</p>	<p>NR (blood, CSF, and urine culture results reported)</p> <p>(NR)</p> <p>Test Results:</p> <p>SBI (Bacteremia or meningitis 1):16 (4.6)</p> <p>SBI (Bacteremia or meningitis 2):16 (5.0)</p> <p>SBI (Bacteremia or meningitis 3):4 (5.4)</p>	<p>SBI (1): Sensitivity: 44.0 (20.7, 69.4) Specificity: 96.0 (93.1, 97.7) PPV: 35.0 (16.3, 59.0) NPV: 97.0 (94.5, 98.6)</p> <p>SBI (2): Sensitivity: 69.0 (41.5, 87.9) Specificity: 75.0 (69.7, 79.7) PPV: 12.6 (6.8, 21.9) NPV: 97.0 (94.8, 99.2)</p> <p>SBI (3): Sensitivity: 25.0 (1.3, 78.0) Specificity: 75.7 (63.7, 84.8) PPV: 5.5 (0.2, 29.3) NPV: 94.6 (84.2, 98.6)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Lin (2000) ⁴⁹	<p>Design: Cross-sectional</p> <p>Region: Taiwan</p> <p>Setting: Padiatric ED</p> <p>Study period: 1997-1998</p>	<p>N: 223/162</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: Infants presenting to ED, with rectal temperature $\geq 38^{\circ}\text{C}$. Excluded were infants with past antibiotic treatment, infants in whom urine aspiration was not successful, urine specimens of $< \text{mL}$, and infants with more than one aspiration</p> <p>Male (%): 58</p> <p>Ethnicity (%):NR</p> <p>----- Information on mother: NR</p>	<p>1) UA microscopy (spun urine; ≥ 5 WBC/hpf)</p> <p>2) UA microscopy (hemocytometer; ≥ 10 WBC/μL)</p> <p>3) CRP > 20 mg/L</p> <p>4) ESR > 30 mm/h</p> <p>5) $> 15,000$ WBC/ μL</p>	<p>UTI only</p> <p>(growth of a single pathogen at a concentration of ≥ 100 cfu/mL (cultures with mixed organisms or nonpathogenic Gram-positive cocci were considered contaminated))</p> <p>Test Results:</p> <p>22 (13.5) (UTI)</p> <p>Same Results for all Lab tests</p>	<p>UTI: Sensitivity: 59.0 (36.7, 78.5) Specificity: 93.0 (86.9, 96.3) PPV: 56.5 (34.8, 76.1) NPV: 93.5 (87.7, 96.8)</p> <p>UTI: Sensitivity: 82.0 (59.0, 94.0) Specificity: 94.0 (88.6, 97.3) PPV: 69.2 (48.1, 84.9) NPV: 97.0 (92.2, 99.0)</p> <p>UTI: Sensitivity: 59.0 (36.6, 78.5) Specificity: 90.0 (83.5, 94.2) PPV: 48.1 (29.1, 67.6) NPV: 93.3 (87.3, 96.7)</p> <p>UTI: Sensitivity: 73.0 (49.5, 88.4) Specificity: 78.0 (69.9, 84.2) PPV: 34.0 (21.3, 49.4) NPV: 94.7 (88.5, 97.8)</p> <p>UTI: Sensitivity: 36.0 (18.0, 59.1) Specificity: 80.0 (72.2, 86.0) PPV: 22.2 (10.7, 39.6) NPV: 88.9 (81.7, 93.5)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Maniaci (2010) ^{50,51}	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study duration/ period: 18 months during 2005 – 2007</p>	<p>N: 435/234</p> <p>Age group(s): 0–90 d median age 51 d</p> <p>Inclusion / exclusion: Infants presenting to paediatric ED (with documented temperature \geq 38°C</p> <p>Exclusion: Previous identified immunodeficiency, focal infection, on antibiotics, surgery in past 7 d, immunizations in the past 48 hrs, or antibiotic tx within 48 hrs</p> <p>Male (%): 53</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Procalcitonin levels (PCT) at 0.13 ng/mL</p>	<p>Definite SBI: bacteremia, UTI (from catheterization with \geq 50 000 CFUs/ mL of a single pathogen or 10 000 to 49 000 CFUs/ mL with positive UA results; (3) bacterial meningitis, as a positive CSF culture result with a pathogen or bacteremia with CSF pleocytosis (>10 WBCs per μL); bacterial pneumonia, as a positive pleural fluid culture result with a pathogen or a chest radiograph interpreted ;a bacterial pathogen in stool culture. Possible SBIs were aslos defined result.</p> <p>Diagnosis: Total: 30 (12.8) Bacteremia: 4 Bacteremia + UTI: 2 UTI: 24</p>	<p><u>PCT at 0.13 ng/mL</u> SBI: Sensitivity: 96.7 [81.0, 99.8] Specificity: 30.3 [24.0, 37.5] PPV: NR NPV: 98.3 [89.7, 99.9]</p> <p><u>PCT at 0.12 ng/mL</u> Sensitivity: 95.2 Specificity: 25.5 PPV: NR NPV: 96.1 All cases of bacteremia were correctly identified with <u>0.12 cut off value</u></p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Meehan (2008) ⁵²	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Paediatric ED</p> <p>Study duration/period: 4 years</p>	<p>N: 2003/2820</p> <p>Age group(s): 0–90 d</p> <p>Inclusion / exclusion: Infants presenting to paediatric ED (with rectal temperature $\geq 38^{\circ}\text{C}$)</p> <p>Exclusion: Previous antibiotics, immunodeficiency, intracranial surgery</p> <p>Male (%): 55</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Laboratory: CSF pleocytosis in neonates: WBC ≥ 25 cells/ μL; in infants aged 29 – 90 d: WBC ≥ 10 cells/ μL)</p>	<p>NR</p> <p>Diagnosis: Total SBI: 192/ 2003 (9.6%) UTI: 160 Bacteraemia: 25 Meningitis: 7</p>	<p>SBI: Sensitivity: 12.5 (95% CI: 8.3, 18.2) Specificity: 91.6 (95% CI: 90.2, 92.8) PPV: 13.6 (95% CI: 9.1, 19.8) NPV: 90.8 (95% CI: 89.3, 92.0)</p> <p>Bacteraemia: Sensitivity: 28.0 (95% CI: 12.8, 49.6) Specificity: 91.4 (95% CI: 90.1, 92.6) PPV: 3.9 (95% CI: 1.7, 8.3) NPV: 99.0 (95% CI: 98.4, 99.4)</p> <p>Meningitis: Sensitivity: 71.4 (95% CI: 30.2, 94.8) Specificity: 91.4 (95% CI: 90.1, 92.6) PPV: 2.8 (95% CI: 1.0, 6.8) NPV: 99.9 (95% CI: 99.5, 99.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Olaciregui (2008) ⁵³	<p>Design: Cross Sectional</p> <p>Region: Europe (Spain)</p> <p>Setting: Padiatric ED</p> <p>Study duration/ period: 2004 – 2006</p>	<p>N: 347</p> <p>Age group(s): 4–90 d Mean age: 47 d</p> <p>Inclusion / exclusion: Febrile infants (rectal T. \geq 38°C) with detailed history and physical exam did not reveal a focus of infection with blood test results / exclusion: lack of blood test, fever of more than 7 d duration, antibiotic therapy in the 48 hrs prior to dx and the presence of any type of immunodeficiency</p> <p>Male (%): 52</p> <p>Ethnicity (%): NR (likely to be Hispanic)</p> <p>----- Information on mother: NR</p>	<p>1) PCT at 0.13 ng/mL</p> <p>2) Leucocyte count (5,000 – 15,000), CRP (<30), PCT (<0.5), good general state and –ve urine dipstick</p> <p>3) CRP \geq 30 mg/L</p> <p>4) CRP \geq 20 mg/L (to detect bacteremia)</p>	<p>bacteremia; meningitis; sepsis such as hemodynamic instability, tissue perfusion; UTI; pneumonia by chest x ray; gastroenteritis; cellulitis (blood culture available for 95% of infants)</p> <p>Diagnosis: Total: 82 (23.6) UTI: 69 (4 with bacteremia) Bacteremia: 5 Cellulitis: 2 (1 with bacteremia) Sepsis: 4 (2 with bacteremia) Gastroenteritis: 1 with bacteremia</p> <p>Common organism for bacteremia: <i>S. agalactiae</i>, <i>S. pneumonia</i>, and Gram negative bacilli.</p>	<p>SBI: PCT at 0.13 ng/mL Sensitivity: 63.0 [52.0, 74.0] Specificity: 87.0 [83.0, 91.0] PPV: 59.0 [48.0, 70.0] NPV: 89.0 [85.0, 93.0]</p> <p>Bacteremia: Sensitivity: 86 .0 [58.0, 100.0] Specificity: 93.0 [90.0, 96.0] PPV: 35.0 [19.0, 51.0] NPV: 99.0 [98.0, 100.0]</p> <p>SBI: WBC 5,000 – 15,000, CRP <30, PCT <0.5, good general state, –ve urine dipstick Sensitivity: 96.0 [88.0, 99.0] Specificity: 35.0 [29.0, 42.0] PPV: 32.0 [25.0, 38.0] NPV: 96.0 [92.0, 100]</p> <p>Bacteremia: Sensitivity: 100 [74.0, 100.00] Specificity: 29 [24.0, 35.0] PPV: 6 [3.0, 9.0] NPV: 100 [96.0, 100.0]</p> <p>AUC for PCT (for definite and possible SBI) for < 28 d = 0.73 vs. > 28 d = 0.85 AUC for PCT = 0.77 (95% CI: 0.72, 0.81) and for CRP = 0.79 (95% CI: 0.75, 0.84). In 15 infants with more invasive infection (sepsis, bacteremia, bacterial meningitis), the diagnostic value of PCT (AUC 0.84, 95% CI: 0.79, 0.88) was higher than CRP (AUC 0.68, 95% CI: 0.63, 0.73).</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Reardon (2008) ⁵⁴	<p>Design: Cross Sectional</p> <p>Region: North America</p> <p>Setting: Paediatric ED</p> <p>Study duration/ period: 2002 - 2003</p>	<p>N: 51 (in total age 0 – 90 and older: n= 985)</p> <p>Age group(s): 0–90 d (mean age of total sample 12.6 months)</p> <p>Inclusion / exclusion: Infants presenting to paediatric ED (with rectal temperature $\geq 38^{\circ}\text{C}$ /</p> <p>Note: the study also included older infants and the results are reported for the total sample</p> <p>Male (%): 55</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>UA was considered positive if there was presence of pyuria (≥ 5 WBC/hpf), leukocyte esterase on the urine dipstick, or nitrites on the dipstick</p>	<p>UTI by urine culture at least 10,000 colony forming units</p> <p>Diagnosis: UTI: NR (total UTI is reported for the total sample of infants)</p>	<p>UTI: Sensitivity: 40.0 [7.0, 83.0] Specificity: 85.0 [71.0, 93.0] PPV: NR NPV: NR</p> <p>Study notes: There was no significant difference in the sensitivity or specificity with respect to sex or age of the infants.</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)
Rosenberg (1985) ²³	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Paediatric ED</p> <p>Study period: 1981-1982</p>	<p>N: 1655/122</p> <p>Age group(s): 0–60 d</p> <p>Inclusion / exclusion: Infants presenting to paediatric ED (1981-1982) with auxiliary temperature $\geq 37.8^{\circ}\text{C}$</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>$< 5,000/\text{mm}^3$ or $\geq 15,000/\text{mm}^3$ WBC</p>	<p>NR</p> <p>(UTI if > 100000 cfu/ml)</p> <p>Test Results:</p> <p>SBI (bacteremia): 5 (4.1)</p>	<p>Bacteremia: Sensitivity: 60.0 (17.0, 92.7) Specificity: NR PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results - % (95% CI)	
Schroeder (2005) ⁵⁵	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: Community Office</p> <p>Study period: 1995-1998</p>	<p>N: 3066/1482</p> <p>Age group(s): 0–90 d</p> <p>Inclusion/ exclusion:</p> <p>Male (%): NR</p> <p>Ethnicity (%):NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>1) UA (LE⁺) combined both methods: bag/CATH</p> <p>2) UA (LE⁺) by bag</p> <p>3) UA (LE⁺) by CATH</p> <p>4) UA (Nitrites⁺) both methods: bag/CATH</p> <p>5) UA (Nitrites⁺) by bag</p> <p>6) UA (Nitrites⁺) by CATH</p> <p>7) Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20; WBC/hpf) both methods: bag/CATH</p> <p>8) Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20 WBC/hpf) by bag</p> <p>9) Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20WBC/hpf) by CATH</p>	<p>Test Results:</p> <p>UTI (1-6):152 (10.2) UTI/bacteremia: 16</p> <p>UTI (7):152/1056 (14.4) UTI/bacteremia: 16</p> <p>UTI (8):152/273 (55.6) UTI/bacteremia: 16</p> <p>UTI (9):152/716 (21.3) UTI/bacteremia: 16</p>	<p>UTI (1): Sensitivity: 84.0 (NC) Specificity: 91.0 (NC) PPV: NR NPV: NR</p> <p>UTI (2): Sensitivity: 76.0 (NC) Specificity: 84.0 (NC) PPV: NR NPV: NR</p> <p>UTI (3): Sensitivity: 86.0 (NC) Specificity: 94.0 (NC) PPV: NR NPV: NR</p>	<p>UTI (4) Sensitivity: 39.0 (NC) Specificity: 99.0 (NC)</p> <p>UTI (5): Sensitivity: 25.0 (NC) Specificity: 98.0 (NC) PPV: NR NPV: NR</p> <p>UTI (7-9): Sensitivity: NR Specificity: NR PPV: NR NPV: NR</p>

Table 5. Formal screening criteria

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1990) ⁵⁶	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: 1987-1988</p>	<p>Enrolled: 126</p> <p>Age group(s): 29 – 56 d</p> <p>Inclusion / exclusion: Febrile Infants with rectal temperature \geq 38.2°;</p> <p>Male (%): 53</p> <p>Ethnicity (%): Black: 84 (67%) White: 42 (33%)</p> <p>----- Information on mother: NR</p>	<p>Yale Observation Scale (YOS) score > 10</p>	<p>Isolation of bacterial pathogens from culture of urine, blood, stool, CSF, joint fluid, pneumonia. The study also considered aseptic meningitis (not included in the analysis of this review)</p> <p>Diagnosis Total SBI: 12 (9.5%) UTI: 5 Bacterial sepsis: 4 Other: 3</p>	<p>SBI: Sensitivity: 33.3% (95% CI: 11.3, 64.5) Specificity: 72.8 (95% CI: 63.5, 80.5) PPV: 11.4 (95% CI: 3.7, 27.6) NPV: 91.2% (95% CI: 82.9, 95.8)</p> <p>Bacteraemia: Sensitivity: 75.0 (95% CI: 21.9, 98.6) Specificity: 73.7 (95% CI: 64.8, 81.1) PPV: 8.5 (95% CI: 2.2, 24.1) NPV: 98.9 (95%CI: 93.1, 99.9)</p> <p>Meningitis: Sensitivity: NR Specificity: NR PPV: NR NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1993) ⁵⁷	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1987-1992</p>	<p>N: 747/747</p> <p>Age group(s): 29 – 56 d</p> <p>Inclusion / exclusion: Immunocompetent infants presenting with rectal temperature $\geq 38.2^{\circ}\text{C}$</p> <p>Male (%): 56.2</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	Philadelphia protocol	<p>Bacterial growth in cultures from blood, CSF, urine or stool (obvious cellulites or abscess were considered SBI)</p> <p>(UTI if > 1000 colony-forming units of a single organism)</p> <p>Test Results:</p> <p>SBI: 65 (8.7)</p> <p>UTI: 24</p> <p>Bacteremia: 19</p> <p>Meningitis: 9</p> <p>Cellulitis: 6</p> <p>Gastroenteritis: 13</p> <p>Adenitis: 1</p>	<p>SBI:</p> <p>Sensitivity: 100.0 (93.0, 100.0)</p> <p>Specificity: 42.0 (38.3, 45.9)</p> <p>PPV: 14.1 (11.1, 17.7)</p> <p>NPV: 100.0 (98.3, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1999) ⁵⁸	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1994-1996</p>	<p>N: 254/254</p> <p>Age group(s): 3 – 28 d</p> <p>Inclusion / exclusion: neonates with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): 57.1</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	Philadelphia protocol	<p>Bacterial growth in cultures from blood, CSF, urine or stool- including pneumonia, cellulites, osteomyelitis, abscess</p> <p>(negative if blood and spinal fluid were free of bacterial pathogens at 72 hours (considered contaminated if patients symptoms resolved without treatment); UTI, if $> 10^3$ or more colony forming units/mm of known urinary pathogens)</p> <p>Test Results:</p> <p>SBI: 32 (12.5)</p> <p>UTI: 17</p> <p>Bacteremia: 8</p> <p>Meningitis: 4</p> <p>Cellulitis: 1</p> <p>Gastroenteritis: 2</p> <p>Peritonitis: 1</p> <p>Osteomyelitis: 1</p>	<p>SBI:</p> <p>Sensitivity: 84.4 (67.0, 95.0)</p> <p>Specificity: 46.8 (40.0, 53.0)</p> <p>PPV: 18.6 (12.0, 25.0)</p> <p>NPV: 95.4 (90.0, 99.0)</p> <p>Bacteremia:</p> <p>Sensitivity: NR</p> <p>Specificity: NR</p> <p>PPV: NR</p> <p>NPV: NR</p> <p>Meningitis:</p> <p>Sensitivity: NR</p> <p>Specificity: NR</p> <p>PPV: NR</p> <p>NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baker (1999) ⁵⁹	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1994 - 1996</p>	<p>N: 422/422</p> <p>Age group(s): 29 – 60 d</p> <p>Inclusion / exclusion: Immunocompetent Febrile infants with rectal temperature $\geq 38^{\circ}\text{C}$</p> <p>Male (%): 56</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Philadelphia protocol*</p> <p>LR infants: n= (%)</p> <p>Not LR infants (or HR): n= (%)</p>	<p>Test Results:</p> <p>SBI: 43 (10.2)</p> <p>UTI: 17</p> <p>Bacteremia: 9</p> <p>Meningitis: 5</p> <p>Gastroenteritis: 5</p> <p>Cellulitis: 5</p> <p>Chlamydia pneumonia: 2</p> <p>Enterocolitis: 1</p> <p>Osteomyelitis: 1</p> <p>Septic arthritis: 1</p>	<p>SBI:</p> <p>Sensitivity: 100.0 (89.7, 100.0)</p> <p>Specificity: 26.6 (22.3, 31.4)</p> <p>PPV: 14.0 (10.0, 17.7)</p> <p>NPV: 100.0 (96.0, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Baskin (1992)⁶⁰	Design: Cohort Region: North America Setting: ED Study period: 1987-1990	N: 503/501 Age group(s): 28 - 89 d Inclusion / exclusion: Well appearing infants with rectal temperature $\geq 38^\circ$; no allergies to β-lactam, no vaccination within 48 hrs of presentation to unit - no ear, soft tissue, joint or bone infection on physical examination; not source of infection; and normal laboratory screening - no immunization with diphtheria, and tetanus toxoids and pertussis vaccine within 48 hours Male (%): NR Ethnicity (%): NR ----- Information on mother: NR	Rochester Criteria	Bacterial growth in cultures from blood, CSF, urine or stool (UTI = culture with > 1,000 colonies/ml for supra-pubic samples, and $\geq 10,000$ colonies/ml in bladder catheterizations; test done for 479, 95.2%) Results: SBI: 27 (5.4) Occult bacteremia: 8 UTI + bacteremia: 1 UTI: 8 Gastroenteritis: 10 (%)	SBI: Sensitivity: 52.0 (31.7, 71.6) Specificity: NR PPV: NR NPV: NR

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Bonadio (1993)⁶¹	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: pediatric ED</p> <p>Study period: 1991-1992</p>	<p>N: 242/233</p> <p>Age group(s): 0 – 29 d</p> <p>Inclusion / exclusion: febrile infants with rectal temperature $\geq 38.0^{\circ}\text{C}$. Excluded were infants who were culture-negative for bacterial pathogen and had received antibiotic therapy within 72 hours</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>YIOS score ≥ 7 (affect, respiratory status/effort, peripheral perfusion)</p>	<p>Bacterial meningitis, bacteraemia, UTI</p> <p>(UT if ≥ 10000 cfu/ml of a single bacterial specie; CSF positive if pleocytosis present (total blood cell count > 10 mm³))</p> <p>Test Results:</p> <p>SBI: 29 (12.4%) Meningitis: 10 Bacteremia: 12 UTI: 7</p>	<p>SBI: Sensitivity: 76.0 (NC) Specificity: 75.0 (NC) PPV: NR NPV: 96.0 (NC)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Bonadio (1993)⁶²	Design: Cohort Region: North America Setting: Padiatric ED Study period: 1991-1992	N: 534/534 Age group(s): 29 – 60 d Inclusion/ exclusion: Previously healthy Febrile infants with fever ≥ 100°F reported by caretaker or ≥ 38° at triage Male (%): NR Ethnicity (%): NR <hr/> Information on mother: NR	1) Milwaukee protocol 2) Rochester criteria (n=532)	NR SBI by Milwaukee Total: 24 (4.5) UTI: 11 Meningitis: 4 Bacteremia: 6 Bacterial enteritis: 2 Klebsiella pneumoniae: 1 SBI by Rochester Total: 22 (4.1) UTI: 11 Meningitis: 4 Bacteremia: 6 Klebsiella pneumoniae: 1	SBI by Milwaukee Sensitivity: 96.0 (88.0, 100.0) Specificity: 28.0 (23.0, 36.0) PPV: 5.9 (3.6, 8.2) NPV: 99.3 (98.0, 100.0) SBI by Rochester Sensitivity: 59.0 (36.6, 78.5) Specificity: 26.3 (22.5, 30.3) PPV: 3.3 (1.9, 5.8) NPV: 93.7 (88.0, 96.9)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Brik (1997) ⁶³	<p>Design: Chart Review</p> <p>Region: Israel</p> <p>Setting: Padiatric ED</p> <p>Study period: 1988-1994</p>	<p>N: 492/492</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Charts of all hospitalized Febrile infants with rectal temperature $\geq 38^{\circ}\text{C}$. Excluded were patient with congenital malformation, metabolic inherited diseases or immunological deficiency</p> <p>Male (%): 60</p> <p>Ethnicity (%): NR ----- Information on mother: NR</p>	Philadelphia protocol	<p>Growth of a known bacterial pathogen in cultures of blood, spinal fluid, urine or stool (including cellulites or abscess)</p> <p>Bacterial meningitis, if a) Infants <4 weeks; leukocyte >30 cell/mm³, >60% polymorphonuclear cells, a protein concentration >170 mg/dl, a CSF/blood glucose ratio <0.5-0.6 and the presence of microorganisms on Gram stained smears of CSF; b) Infants 4-12 weeks: leukocyte >10 cells/mm³ in younger infants and 5 cells/mm³ in older infants with >1 polymorphonuclear cell/mm³ in addition to protein concentration >100 mg/dl, glucose concentration 60% lower in CSF than in blood, and finding of bacteria on Gram stained smears</p> <p>Test Results: SBI: 60 (12.3) UTI: 40 Meningitis: 2 Bacteremia: 10 Gastroenteritis: 4 Cellulitis: 2 Adonitis: 1</p>	<p>SBI: Sensitivity: 86.6 (74.8, 93.6) Specificity: 66.6 (62.0, 71.0) PPV: 26.5 (20.6, 33.4) NPV: 97.3 (94.5, 98.7)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Byington (2004) ⁶⁴	<p>Design: Case Series</p> <p>Region: North America</p> <p>Setting: primary pediatric medical center</p> <p>Study period: 1996-2002</p>	<p>N: 894/888 (infants without viral infections)</p> <p>Age group(s): 1 – 90 d</p> <p>Inclusion / exclusion: Infants evaluated for sepsis with temperature $\geq 38^{\circ}\text{C}$. Excluded infants if received oral polio vaccine, a live EV vaccine, or antibiotics (in last 48 hours)</p> <p>Male (%): 55</p> <p>Ethnicity (%):</p> <ul style="list-style-type: none"> • White/non-Hispanic: 63 • Hispanic: 24 • African/American: 1 • Asian/ South Pacific: <1 • Other: 4 <p>-----</p> <p>Information on mother: NR</p>	Rochester criteria	<p>Positive bacterial culture: bacteremia, bacterial meningitis, UTI, soft tissue or bone infection, bacterial pneumonia, or bacterial enteritis</p> <p>Test Results:</p> <p>SBI: 109 (12.3)</p> <p>Types of SBI: bacteremia, UTI, meningitis, pneumonia</p> <p>IHI: 2/101 (2%) tested for HSV were positive for virus identified by skin lesion or mucous membrane</p>	<p>SBI:</p> <p>Sensitivity: 91.7 (84.5, 95.9)</p> <p>Specificity: 36.0 (32.6, 39.4)</p> <p>PPV: 16.6 (13.8, 20.0)</p> <p>NPV: 96.9 (94.0, 98.5)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Chiu (1997) ⁶⁵	<p>Design: Cross sectional</p> <p>Region: Taiwan</p> <p>Setting: Pediatric hospital</p> <p>Study period: 1994-1995</p>	<p>N: 250/250</p> <p>Age group(s): 4 – 28 d</p> <p>Inclusion / exclusion: Well appearing healthy, (born at term, without any prenatal complications and no underlying disease) with rectal temperature > 38°C</p> <p>Male (%): 53.3</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	Rochester criteria	<p>Isolation of a bacterial pathogen from cultures of blood, urine, CSF, joint fluid, stool, pus or other body fluids</p> <p>(UTI if > 100000 colonies/ml of a single pathogen- Enteritis if other foci of infection were excluded and the patient had a diarrhea)</p> <p>Test Results:</p> <p>SBI: 41 (16.4)</p> <p>UTI: 16</p> <p>Bacteremia/Meningitis: 7</p> <p>Bacteremia/Enteritis: 3</p> <p>Enteritis: 2</p> <p>Bacteremia/Osteomyelitis: 1</p> <p>Others: NR</p>	<p>SBI:</p> <p>Sensitivity: 97.6 (92.9, 100.0)</p> <p>Specificity: 62.2 (55.6, 68.8)</p> <p>PPV: 33.6 (25.1, 42.1)</p> <p>NPV: 99.2 (97.7, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Ferrera (1997) ⁶⁶	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: ED of tertiary referral center</p> <p>Study period: 1990-1994</p>	<p>N: 188/134</p> <p>Age group(s): 0 – 28 d</p> <p>Inclusion/ exclusion: Chart of infants with temperature (including rectal) $\geq 38^{\circ}\text{C}$ regardless of chief complaint- Excluded: 1) Incomplete blood, urine, and CSF culture data; 2) Infants with a source for fever on physical examination (septic arthritis, osteomyelitis, cellulites)</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Rochester criteria	<p>Bacterial meningitis, bacteremia, septic arthritis, osteomyelitis, UTI, bacterial enteritis, salmonellosis, or pneumonia</p> <p>(UTI if > 1000 colony forming units/mL of 2 organisms or less in a specimen obtained by catheterization or by supra-pubic aspirate)</p> <p>Test Results:</p> <p>SBI: 22 (16.4) UTI: 13 UTI/meningitis: 1 Bacteremia: 4 Bacteremia/UTI: 1 Bacteremia/meningitis: 1 Listeria meningitis: 1 Pneumonia: 1</p>	<p>SBI: Sensitivity: 86.4 (64.0, 96.4) Specificity: 46.4 (36.3, 56.7) PPV: 26.8 (17.2, 38.8) NPV: 93.8 (81.8, 98.4)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Garra (2005) ⁶⁷	<p>Design: Cohort</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: NR</p>	<p>N: 302/259</p> <p>Age group(s): 0 – 56 d</p> <p>Inclusion / exclusion: Consecutive term infants with rectal temperature $\geq 38.1^{\circ}\text{C}$ (100.6°F). Excluded infants with likely bacterial source of fever (cellulites, abscess, mastitis, or omphalitis, otitis media, or septic arthritis)</p> <p>Male (%): 60.2</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>1) Philadelphia protocol</p> <p>2) Rochester criteria</p>	<p>Bacteremia, UTI, bacterial meningitis, pneumonia or bacterial culture positive enteritis</p> <p>(UTI according to Rochester or Philadelphia protocol)</p> <p>SBI by Philadelphia protocol:</p> <p>Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis: 1</p> <p>SBI by Rochester criteria:</p> <p>Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis: 1</p>	<p>SBI by Philadelphia protocol: Sensitivity: 98.5 (92.0, 100.0) Specificity: 41.9 (38.0, 46.0) PPV: 13.9 (11.0, 17.0) NPV: 99.7 (98.0, 100.0)</p> <p>SBI by Rochester criteria: Sensitivity: 92.4 (84.0, 97.0) Specificity: 49.9 (47.0, 53.0) PPV: 12.3 (10.0, 16.0) NPV: 98.9 (97.0, 100.0)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Jaskiewicz (1994) ⁶⁸	<p>Design: Diagnostic Accuracy Study</p> <p>Region: North America</p> <p>Setting: ED</p> <p>Study period: NR</p>	<p>N: 1057/931</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: Infants with rectal temperature $\geq 38^\circ$, well-appearing - previously healthy - no evidence of skin, soft tissue, bone, joint, or ear infection - laboratory values and sufficient data to determine level of risk with Rochester Criteria</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Rochester criteria</p> <p>LR infants: n= (%)</p> <p>Not LR infants (or HR): n= (%)</p>	<p>Bacteremia, meningitis, osteomyelitis, suppurative arthritis, soft tissue infections (cellulites, abscess, mastitis, omphalitis), UTI, gastroenteritis, pneumonia</p> <p>Test Results:</p> <p>SBI: 66 (7.0)</p> <p>UTI: 34</p> <p>Skin/soft tissue infection: 18</p> <p>Bacteremia: 16</p> <p>Gastroenteritis: 4</p> <p>Pneumonia: 1</p>	<p>SBI:</p> <p>Sensitivity: 92.4[†] (82.5, 97.2)</p> <p>Specificity: 50.0 (46.5, 53.3)</p> <p>PPV: 12.3 (9.6, 15.6)</p> <p>NPV: 98.9 (97.2, 99.6)</p> <p>Bacteremia:</p> <p>Sensitivity: 87.5 (60.4, 97.8)</p> <p>Specificity: 47.5 (44.2, 50.8)</p> <p>PPV: 2.8 (1.6, 4.8)</p> <p>NPV: 99.5 (98.2, 99.9)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Kadish (2000) ⁶⁹	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: NR</p>	<p>N: 394/372</p> <p>Age group(s): 1 – 28 d</p> <p>Inclusion / exclusion: Previously healthy Febrile infants with documented rectal temp. $\geq 38^{\circ}\text{C}$. Excluded 1) no sepsis evaluation at time of admission (CBC, UA, CSF, cell count, blood, urine, and CSF cultures); 2) inpatients; 3) with congenital heart disease</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>1) Boston protocol</p> <p>2) Philadelphia protocol</p>	<p>Bacterial growth in cultures from blood, CSF, urine or stool – including pneumonia, septic arthritis, cellulites, osteomyelitis, abscess (UTI, if > 50000 colonies/mL of a single organism was isolated)</p> <p>SBI by Boston protocol: Total: 45 (12.1)</p> <p>UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1</p> <p>SBI by Boston protocol: Total: 45 (12.1) UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1</p>	<p>SBI by Boston protocol: Sensitivity: 82.0 (67.4, 91.5) Specificity: 68.0 (62.8, 73.1) PPV: 26.0 (19.4, 34.4) NPV: 97.0 (93.0, 98.4)</p> <p>SBI by Philadelphia protocol: Sensitivity: 87.0 (72.5, 94.4) Specificity: 55.0 (49.5, 60.5) PPV: 21.0 (15.5, 27.6) NPV: 97.0 (92.8, 98.7)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Kaplan (2000) ⁷⁰	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1993-1997</p>	<p>N: 3166/2190</p> <p>Age group(s): 28 – 90 d</p> <p>Inclusion / exclusion: Retrospective sample of infants with rectal temperature $\geq 38^{\circ}\text{C}$; excluded Infants without 3 culture results at screening)</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Boston criteria	<p>Positive cultures of blood, CSF or urine</p> <p>(UTI if ≥ 10000 cfu/mL of a single urinary pathogen by supra-pubic aspiration, or bladder catheterization)</p> <p>Test Results: SBI: 191 (8.7)</p>	<p>SBI: Sensitivity: 88.5 (82.8, 92.5) Specificity: 56.2 (54.0, 58.4) PPV: 16.2 (14.0, 18.6) NPV: 98.1 (97.0, 98.7)</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Stanley (2005) ²⁵	<p>Design: Chart Review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1993-2000</p>	<p>N: 5279/5279</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Retrospective sample of infants with a rectal temperature $\geq 38^{\circ}\text{C}$, with complete test and culture records</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Rochester or Philadelphia criteria	<p>Positive culture of urine, blood or CSF</p> <p>(UTI if supra-pubic ≥ 1000; catheterized ≥ 10000 colony forming units/mL (cfu/mL) of a single urinary pathogen)</p> <p>Test Results:</p> <p>SBI: 480 (9.1)</p> <p>UTI: 305</p> <p>Meningitis: 10</p> <p>Bacteremia: 39</p> <p>Bacteremia/meningitis: 8</p> <p>Bacteremia/UTI: 11</p> <p>Pneumonia: 70</p> <p>Cellulitis: 26</p> <p>Bacterial enteritis: 11</p>	<p>SBI:</p> <p>Sensitivity: 99.8 (98.6, 99.9)</p> <p>Specificity: NR</p> <p>PPV: NR</p> <p>NPV: NR</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Criteria to identify infants at risk for SBI - outcome	Diagnosis detail Definition Criteria Patient diagnosis	Results- % (95% CI)
Zorc (2005) ⁷¹	<p>Design: Cross sectional</p> <p>Region: North America</p> <p>Setting: Peadiatric ED</p> <p>Study period: 1999-2001</p>	<p>N: 1513/995</p> <p>Age group(s): 1 – 60 d</p> <p>Inclusion / exclusion: Infants with rectal temperature $\geq 38^{\circ}\text{C}$. Excluded if taken antibiotics within 48 hours; no consent received</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	Yale Observation Scale (YOS) > 10	<p>Test Results: SBI (UTI only): 91 (9.0%)</p>	<p>SBI (UTI only): Sensitivity: 4.4 (1.4, 11.5) Specificity: 92.6 (90.6, 94.1) PPV: 5.6 (1.8, 14.5) NPV: 90.5 (88.5, 92.3)</p>

Table 6. Studies in Febrile infant with delayed (question 2a) or immediate (question 3a) treatment

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
<p>Baker (1999)⁵⁹</p>	<p>Eligible for screening: NR Screened: NR Enrolled: 422 Number of site(s): 1 Design: Chart Review Region: North American/ U.S Setting: Paediatric ED Study duration (period): 1994-1996</p>	<p>General: 422 immunocompetent Febrile infants with rectal temperature \geq 38°; age 29-60 days Age: mean NR Male (%): 56 Ethnicity (%): NR Fever: mean NR Medication: NR ----- Information on mother: NR</p>	<p>Clinical criteria: according to protocol Laboratory criteria (normal): as in Rochester criteria As in Philadelphia Formal scoring systems: Philadelphia Protocol ----- LR infants: n= 101 (24%) HR infants: n= 321 (76%) Sensitivity: 100 % Specificity: NR PPV: NR NPV: 100% (95%CI: 96-100 %) Diagnosis: SBI: 43 (10%) UTI: 17 (4%) Meningitis: 5 (1.2%) Bacteraemia: 9 (2.1%)- 3 with other bacterial infections Other: 15 (3.5%)</p>	<p>Initial management of LR n: Hospitalized: 7/101 (6.9%) protocol deviation Discharged: 94/101 (93.1%) [all who where available for repeat physical exam at 24 and 48 hrs] Treatment: No antibiotics: 94/101 (93.1%) LR Infants diagnose with SBI (FN): NA Management of FN(s): NA Initial management of HR: n: 321 Hospitalized: 311 Discharged: 10 Immediately treated: 300 Delayed treatment: 21 Treatment: Empirical antibiotics: 300 (93.5%) No antibiotics: 21 (6.5%) protocol deviation-3 of which had SBI (TP)- all were subsequently treated with antibiotics</p>	<p>Outcomes Overall mortality: 0 Harms of delayed treatment: .NA Infants not treated with antibiotics: 3 infants with SBI who were mismanaged in HR group received antibiotics and recovered well. Outcomes in infants treated with antibiotics: NR</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Baker (1993) ⁵⁷	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 747</p> <p>Number of site(s): 1</p> <p>Design: Cohort</p> <p>Region: North American/ U.S</p> <p>Setting: Pediatric ED</p> <p>Study duration (period): 60 months (1987-1992)</p>	<p>General: 747 consecutive immunocompetent infants with rectal temperature $\geq 38.2^{\circ}$; age 29-56 days</p> <p>Age: mean NR Male (%): 56.2 Ethnicity (%): NR</p> <p>Fever: mean NR Medication: NR</p> <p>----- Information on mother: NR</p>	<p>Clinical criteria: focus of infection</p> <p>Laboratory criteria (HR): WBC: $\geq 15000/\text{mm}^3$ UA: >10 wbc/hpf; or positive on bright film microscopy CSF: $\geq 8/\text{mm}^3$ Chest X-Ray: infiltrate Other: positive Gram stain</p> <p>Formal scoring systems: Infant Observation score (not LR > 10) in addition to clinical and laboratory</p> <p>----- LR infants: n= 139 (18.6%) Not LR infants : n=148 (19.8%) HR infants: n= 460 (61.6%)</p> <p>Sensitivity: 98% (95%CI: 92-100%) Specificity: 42% (95%CI: 38-46%) PPV: 14% (95%CI: 11-17%) NPV: 99.7% (95%CI: 98-100%)</p> <p>Diagnosis: SBI: 65 (8.7%)</p> <p>Note: observation score identified 43/65 infants with SBI (66.2%)</p>	<p>Initial management of LR n: 139 Hospitalized: 8 (5.8%) after original discharge within 24-48 hours Discharged: 131 (94.2%)</p> <p>Treatment: No treatment: 285 (99.3%) Antibiotic treatment: 2 (0.7%)</p> <p>Infants diagnosed with SBI (FN): 2 (0.7%), one with Bacteremia, and one with viral meningitis Management of FN(s) infants: Antibiotic tx after 24 hrs of hospitalization</p> <p>Initial management of HR Hospitalized: 460 (100%) for 72 hrs Discharged: 0 Immediately treated: 460 (100%)</p> <p>Treatment: Antibiotic treatment (unspecified) in all</p>	<p>Outcomes: Overall mortality: 0 / NR</p> <p>Harms of delayed treatment n=2 recovered without complications</p> <p>Infants not treated with antibiotics: NR Infiltration of IV line 0 vs. 5 (3.4%) Contaminated culture urine/blood/CSF: 11 (7.9%) / 4 (2.9%) / 1 (0.7%) vs. 13 (8.8%) / 4 (2.7%) / 2 (1.4%) Suspected drug rash: 0</p> <p>Outcomes in infants treated with antibiotics (n=460): Infiltration of IV line 87 (18.9%) Contaminated culture urine/blood/CSF: 31 (6.7%) / 12 (2.6%) / 5 (1.1%) Suspected drug rash: 2 (0.4%)</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Baskin (1992)⁶⁰	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 503</p> <p>Number of site(s): 1</p> <p>Design: Cohort</p> <p>Region: North America/ U.S.</p> <p>Setting: pediatric ED</p> <p>Study duration: 39 months (1987-1990)</p>	<p>General: 503 well appearing infants with rectal temperature $\geq 38^{\circ}$; no allergies to β-lactam, no vaccination within 48 hrs of presentation to unit); age ≥ 28 days and < 90 days</p> <p>Age: 28- 60 d: 336(67%) 61-89 d: 167 (33%) Male (%): NR Ethnicity (%): NR</p> <p>Other: Acute Illness Observation Score, mean (SD): with SBI 8 (3.2) vs. without SBI 7.3 (2.2), not significant</p> <p>Fever, mean (SD): With SBI: 39° (0.6°) Without SBI: 38.7° (0.6°) Medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria: comprehensive history and physical exam</p> <p>Laboratory criteria: (inclusion) WBC: NR UA: < 10 leukocytes /hpf or negative dipstick test for leukocyte esterase activity CSF: 10×10^6 cells/L CRP: NR Stool: NR Chest X-Ray: no infiltrate</p> <p>Formal scoring systems: Rochester criteria for SBI patients ----- LR infants: 503 (100%) Not LR infants (or HR): 0 (all excluded upon screening)</p> <p>Sensitivity: overall: 0.52, in 13/25 evaluable infants; 0.56, 5/9 with Bacteremia Specificity: NR PPV: NR NPV: NR</p> <p>Diagnosis: SBI: 27 (5.4%) UTI: 8 (1.6%) Meningitis: NR Bacteremia: 8 (1.6%) UTI+ Bacteremia: 1 (0.2%) Gastroenteritis: 10 (2%)</p>	<p>Management of LR n: 503 Initially hospitalized: 0 Discharged: 503 (100%) Hospitalized on second visit: n=23 after 2-24 hours (n=7 of 23 who were hospitalized after had positive urine or CSF cultures; n=2 had persistent fever; n= 2 with isolation of B.pertussis from respiratory tract secretions, no treatment information is provided)</p> <p>Treatment: Antibiotics: 100% IM ceftriaxone upon entry and a 2nd dose for 494 (98%) parenteral tx in one patient with Bacteremia diagnosed with osteomyelitis 7 days after initial admission [Note: 48 f/u calls in 475 (94%) 7-day call for 482 (96%)] No treatment: 0 LR Infants diagnose with SBI (FN): NA Management of infants with SBI (FN): NA</p> <p>Initial management of not LR: NA</p>	<p>Outcomes</p> <p>Overall mortality: 0</p> <p>Harms of delayed treatment:</p> <p>Patient with UTI: 2/6 tested infants had grade 4 reflux by voiding cystourethrogram</p> <p>Patients with bacterial gastroenteritis without Bacteremia: 1/10 was hospitalized due to increasing bloody diarrhea</p> <p>No complication resulted from administration of ceftriaxone on 7 day follow up</p> <p>Outcomes in infants treated with antibiotics No information</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Bonadio (1993) ⁶²	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 534</p> <p>Number of site(s): 1</p> <p>Design: Cohort</p> <p>Region: North American/ U.S</p> <p>Setting: Paediatric ED</p> <p>Study duration: 1 year (1991-1992)</p>	<p>General: 534 previously healthy Febrile infants with fever $\geq 100^{\circ}\text{F}$ reported by caretaker or rectal temperature $\geq 38^{\circ}$ at triage; age 4-8 weeks</p> <p>Age: mean NR Male (%): NR Ethnicity (%): NR</p> <p>Fever: mean NR Medication: NR</p> <p>----- - Information on mother: NR</p>	<p>Clinical criteria: complete physical (clinical appearance, focus of infection)</p> <p>Laboratory criteria (normal): According to Milwaukee protocol (does not include stool leukocyte counts)</p> <p>Formal scoring systems: Milwaukee Protocol</p> <p>----- LR infants: 143 (26.8%) Not LR infants (or HR): 391 (73.2%)</p> <p>Sensitivity: 96% (95%CI: 88-100%) Specificity: 28% (95%CI: 23-36%) PPV: 5.9% (95%CI: 3.6-8.2%) NPV: 99.3% (95%CI: 98-100%)</p> <p>Diagnosis: SBI: 24 (4.5%) UTI: 11 (2.1) – 9 had abnormal UA</p> <p>Note: Rochester criteria was applied to 22 cases of SBI (2 cases of salmonella enteritis were omitted). 13/22 were correctly identified- sensitivity= 59% (9 were missed, 2 with meningitis, 4 with Bacteremia, 3 with UTI)</p>	<p>Initial management of LR n: 143 Hospitalized: 8 (5.6%) within 72 hrs after initial discharge- one with SBI Discharged: initially 100% Treatment: IM Ceftriaxone 50 mg/kg No treatment: 0</p> <p>Infants diagnosed with SBI (FN): n=1(0.7%) with <i>Moaxella catarrhalis</i> Bacteremia</p> <p>Management FN(s): reevaluation within 24 hrs of discharge; hospitalized for 72 hrs, treated with parenteral antibiotic</p> <p>Initial management of HR Hospitalized: 391 (100%) Discharged: 0 Immediately treated: 391 (100%) Treatment: Antibiotics: 391 (100%) parenteral ampicillin 50 mg/kg/day or cefotaxime 50 mg/kg/day, 48-72 hrs</p>	<p>Outcomes</p> <p>Overall mortality: NR</p> <p>Harms of delayed treatment no complications occurred (infant was afebrile and negative repeat blood culture after 24 hrs)</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics: NR</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Brik (1997) ⁶³	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 492</p> <p>Number of site(s): 1</p> <p>Design: Chart Review</p> <p>Region: Israel</p> <p>Setting: Peadiatric ED</p> <p>Study duration: 5 years (1988-1994)</p>	<p>General: all hospitalized Febrile infants with rectal $\geq 38^{\circ}\text{C}$; age younger than 3 months; infants with congenital malformations, metabolic inherited diseases, immunological deficiency excluded</p> <p>Age: 47 (22) days; range 3-90</p> <p>< 4 weeks 108 (22%)</p> <p>Male (%): 60</p> <p>Ethnicity (%): NR</p> <p>Fever: 38.6°C (0.5); range $38-40.3^{\circ}\text{C}$</p> <p>Medication: NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Clinical criteria: Yale Observation Scale (YOS) ≥ 16 considered HR</p> <p>Laboratory criteria (HR):</p> <p>WBC: 5000-15000/mm³ UA: < 10 WBC/ hpf</p> <p>CSF: <8 WBC/mm³ & -ve Gram stain; HR if ≥ 5000 red blood cells/ mm³ in absence of intracranial bleeding. [lumbar puncture in 38% of infants upon admission; 67% of HR vs. 24% of LR; 67% of infants 0-2 mo vs. 29% of older infants] Chest X-Ray: evidence of infiltrate (all infants)</p> <p>Formal scoring systems: YOS [LR= YOS ≥ 10, no recognized bacterial infection, normal lab results]</p> <p>-----</p> <p>LR infants: n= 296 (60%) HR infants: n= 196 (40%)- n=10 had no CSF [abnormal CSF & assignment of HR: p < 0.006)</p> <p>Sensitivity: 85%; YOS: 20%; laboratory + clinical: 87% Specificity: 65%; YOS: 92.8%</p> <p>PPV: YOS: 28% NPV: YOS: 89%; laboratory + clinical: 92%</p> <p>Diagnosis:</p> <p>SBI: 60 (12%) UTI: 40 (8%)</p> <p>Meningitis: 2 (0.4%) Bacteremia: 10 (2%)</p> <p>Gastroenteritis: 4 (0.8%) Cellulitis: 2 (0.4%) Other: 2 (0.4%)</p>	<p>Initial management of LR n: 296</p> <p>Hospitalized: 100%</p> <p>Treatment:</p> <p>No antibiotic therapy: 216 infants with no CSF (73%)</p> <p>Systemic antibiotic: 50 (17%), 48-72 hours pending culture</p> <p>Full course antibiotic: 30 (10%) in patients with no CSF and positive bacterial focus</p> <p>Infants diagnose with SBI (FN): 8 (3%); n=1 bacteremia; n=7 UTI</p> <p>Management of FN(s) infants: NR</p> <p>Initial management of not LR (HR): NR</p> <p>Initial management of infants with no CSF data: n: 306</p> <p>Hospitalized: 100%</p> <p>Treatment:</p> <p>No antibiotic: 73%</p> <p>Antibiotic therapy: 17%; 48-72 hours pending culture</p> <p>Full course antibiotic: 10% (infants with SBI)</p> <p>[Note: 176/186 CSF yielded satisfactory samples; 16 (9%) showed abnormal findings, 2 with SBI ; 7/186 were traumatic and 3/186 failed to yield CSF]</p>	<p>Outcomes</p> <p>Overall mortality: NR</p> <p>Harms of delayed treatment NR</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics: NR</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
<p>Chiu CH. Lin TY (1997)⁶⁵</p>	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 250</p> <p>Completed: NR</p> <p>Number of site(s): 1</p> <p>Design: Cross Sectional</p> <p>Region: Taiwan</p> <p>Setting: Pediatric ED</p> <p>Study duration: 12 months (1994-1995)</p>	<p>General: 250, 0-28 days</p> <p>Well appearing healthy, born at term, without any prenatal complications and no underlying disease, and rectal temperature > 38°</p> <p>Age: median = 16; range 4-28 days</p> <p>Ethnicity: NR</p> <p>Male (%): 53.3</p> <p>Ethnicity (%): NR</p> <p>Mean temperature: NR</p> <p>Previous medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria: well appearing; no physical evidence of soft tissue, skeletal, ear, eye or umbilical infection</p> <p>Laboratory criteria (normal): all infants</p> <p>WBC: 5000-15000/mm³</p> <p>UA: (supra-pubic)<10 wbc/hpf (urine samples inadequate in 49 infants, 19.6% collected by bag)</p> <p>CRP: < 20 mg/l</p> <p>CSF: if suspected to have meningitis</p> <p>Pus: eyes, ears, mouth</p> <p>Stool: no pus (if presented with diarrhea)</p> <p>Chest radiograph: done for most infants</p> <p>Formal scoring systems: Not used</p> <p>-----</p> <p>LR infants: 131 (52.4%)</p> <p>Not LR infants: 119 (47.6%)</p> <p>Sensitivity: 97.6% (95%CI: 92.9-100%)</p> <p>Specificity: 62.2% (95%CI: 55.6-68.8%)</p> <p>PPV: 33.6% (95% CI: 25.1-42.1%)</p> <p>NPV: 99.2% (95%CI: 97.7-100%)</p> <p>Diagnosis:</p> <p>SBI: 41 (16.4%)</p> <p>Bacteremia &/or meningitis 11 (4.4%)</p> <p>Meningitis: 5 (2%)</p> <p>UTI: 12 (4.8%)</p> <p>Other: 13 (5.2%)</p> <p style="text-align: right;">C-87</p>	<p>Management of LR</p> <p>n: 131 (52.4%)</p> <p>Hospitalized: 100%</p> <p>Discharged: 0</p> <p>No antibiotics: initially 100% [73 (55.7%) on 2nd or 3rd hospital day]</p> <p>Antibiotic treatment: initially 0%</p> <p>Reclassified LR: 58 (44.3%) due to persisting fever, poor general activity, abnormal wbc (>15000) on repeat test</p> <p>Infants diagnose with SBI (FN): 1/131 (0.8%) with UTI (E-coli); patient was given 7 day antibiotic in 2nd hospital day due to persistent fever (>48 hours)</p> <p>Initial management of not LR (HR): n: 177 (119 HR + 58 reclassified)</p> <p>Hospitalized: all 100%</p> <p>Discharged: 0</p> <p>Immediately treated: all initially identified as HR</p> <p>Treatment: parenteral antibiotics (no other information provided)</p>	<p>Outcomes</p> <p>Overall mortality: 0</p> <p>False negative infant/s: mild dilation of left renal pelvis on renal sonogram; normal retrograde voiding cystourethrogram</p> <p>LR infants not treated with antibiotics: fever resolved with no relapses during 3-4 remaining hospital days or at return visits.</p> <p>Reclassified LR: no treatment result reported</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Dagan (1988) ⁸	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 237</p> <p>Number of site(s): 1</p> <p>Design: Cohort</p> <p>Region: Israel</p> <p>Setting: Peadiatric ED</p> <p>Study duration: 17.5 months (1985-1986)</p>	<p>General: born at term, with no history of perinatal complications, underlying diseases, or antibiotics tx with rectal temperature $\geq 38^{\circ}\text{C}$; age younger than 2 months</p> <p>Age: median 34 (range 3-60) days</p> <p>Age groups: < 15 days: 29 (12%) 15-30 days: 64 (27%) 31-45 days: 86 (36%) 45 days: 59 (25%)</p> <p>Male (%): 57 Ethnicity (%): NR</p> <p>Fever: range 38-39.6°C Medication: NR</p> <p>Information on mother: NR Infants from families of low socioeconomic status</p>	<p>Clinical criteria (LR): no finding consistent with soft tissue, or skeletal infection, no purulent OM</p> <p>Laboratory criteria (normal): WBC: 5000-15000/mm³; band forms < 1500/ mm³ UA: > 10 leukocyte/hpf CSF: NR (obtained only if categorized as HR) Stool: < 25 WBC/hpf if diarrhea presented</p> <p>Formal scoring systems: not used ----- LR infants: n= 148 (63%) Not LR infants (or HR): n= 88 (37%) (TP=21; FP=67, TN=148, FN=0)</p> <p>Diagnosis: SBI: 22 (9.3%)- 21 from HR group; additional n=1 initially too ill to be evaluated UTI: (%) Meningitis: (%) Bacteraemia: (%)</p>	<p>Initial management of LR n: 148 (63.0%) Inpatient observation < 24 hours: 75 (51%) Hospitalized: 17 (11%) including 3 infants initially observed as inpatients Discharged: 134 initially discharged, 3 were recalled and admitted- final discharge rate = 131 (88.5%) Treatment: No antibiotics (no treatment): 137 (92.6%) 11 (7.4%) treated with antibiotics</p> <p>Infants diagnose with SBI (FN): 0 Management of FN(s) infants: NA</p> <p>Initial management of not LR n: 88 Hospitalized: NR (at least 8 were not hospitalized- these infants were not treated either) Discharged: NR Treatment: No treatment: 15 (15%) Antibiotics: NR</p> <p>Note: If infants were too ill to be evaluated, they were treated immediately after cultures</p>	<p>Outcomes</p> <p>Overall mortality: Not reported</p> <p>Harms of delayed treatment NA</p> <p>Infants not treated with antibiotics: No details provided.</p> <p>Outcomes in infants treated with antibiotics: No details provided.</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Dore-Bergeron (2010) ⁷²	<p>Eligible for screening: NR</p> <p>Screened: 129 suspected URI</p> <p>Enrolled: 118</p> <p>Number of site(s): 1</p> <p>Design: Cohort</p> <p>Region: Canada</p> <p>Setting: Paediatric ED</p> <p>Study duration: 2005 – 2007</p>	<p>General: all children age 30 – 90 d with a presumed diagnosis of UTI</p> <p>Data reported for children in day treatment centre (DTC) and hospital admissions (HA)</p> <p>Age: median (range) DTC 66 (33-85) d</p> <p>Age groups: 30 – 60 d days: DTC 25 (43%); HA 31 (69%) >= 62 d: DTC 33 (56.9), HA 14 (31.1)</p> <p>Male (%): DTC 63.8, HA 73.3</p> <p>Ethnicity (%): NR</p> <p>Fever: mean DTC 38.3°C, HA 38.7°C</p> <p>Medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria for outpatient management: non-toxic appearing, normal renal function, with no other exclusion criteria</p> <p>Criteria for exclusion from DTC (hospitalization): age < 30 d, toxic appearance or dehydration, abnormal renal function, dubious parental compliance, hx of UTI surgery, abnormal CSF findings, or other serious medical conditions.</p> <p>Laboratory criteria (normal): NR</p> <p>Formal scoring systems: not used</p> <p>-----</p> <p>LR infants: n= 67 (57%) Not LR infants (or HR): n= 51 (43%)</p> <p>Diagnosis: UTI: 58-67 (86%)</p>	<p>Initial management of LR N (n=67): outpatient single IV injection of gentamicin and ampicillin (2.5-5 mg/kg per dose gentamicin and ampicillin, each single dose) and 2-3 doses of oral amoxicillin</p> <p>At 24 hrs post admission at DTC: IV gentamicin (5 mg/kg/day for 2.7 days) until the infant was a-febrile or urine culture results were available. Oral antibiotics for 10 days were administered if culture positive</p> <p>Infants diagnose with SBI: 58</p> <p>Initial management of hospitalized infants: n = 51 no data reported</p> <p>Hospitalized: 100%</p> <p>Treatment: NR</p> <p>No treatment: NA</p> <p>Antibiotics: NR</p> <p>Note: 2 infants with mildly elevated protein levels in CSF (0.44 g/L and 0.48 g/L) and WBC (11 cell/μL, & 5 cell/μL) were treated at the DTC instead of being hospitalized; 14 infants were hospitalized but the reason was not indicated in their chart.</p>	<p>Outcomes</p> <p>Overall mortality: 0</p> <p>7/58 (12.0%) UTI treated in the DTC were hospitalized (i.e., treatment failures) due to severe concomitant gastroesophageal reflux (n=1), hydronephrosis (n=1), concomitant bacteremia (n=5). These 7 infants had no serious events during their hospitalization.</p> <p>Infants not treated with antibiotics: No details provided.</p> <p>Outcomes in infants treated with antibiotics: No details provided.</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Herr (2001) ¹¹	<p>Eligible for screening: NR</p> <p>Screened: 434</p> <p>Enrolled: 404</p> <p>Number of site(s): 1</p> <p>Design: Chart Review</p> <p>Region: North America/U.S.</p> <p>Setting: Paediatric ED</p> <p>Study duration (period): 8 months (1999-2000)</p>	<p>General: 404 infants with temperature $\geq 38^{\circ}\text{C}$; age < 2 months</p> <p>Age: mean 34 days (range 2-60 days)</p> <p>a) 0-14 d 49 (12.1%) b) 15-28 d 104 (25.7%) c) 29-45 d (34.2%) d) 46-60 d 113 (28%)</p> <p>Male (%): 51 Ethnicity (%): NR</p> <p>Fever: mean NR Medication: NR</p> <p>Information on mother: NR</p> <p>Note: (1) n=30 with incomplete data were not included in the final analysis; 2/30 (6.7%) had SBI</p> <p>(2) all information for results also reported by age groups</p>	<p>Clinical criteria: well appearing, no focal infection (except OM), hx of illness or antibiotics, prematurity</p> <p>Laboratory criteria (normal): WBC: 5000-15000/mm³ Absolute band count: ≤ 15000 mm³ Enhanced UA: WBC ≤ 9/ mm³ CSF: ≤ 5 mm³ & -ve Gram stain Stool: WBC < 5/hpf if diarrhetic Chest X-Ray: no lobar infiltrates if with respiratory signs</p> <p>Formal scoring systems: Pittsburg Criteria</p> <p>-----</p> <p>LR infants: 187 (46.3%) [Clinical exam 60/404 (14.9%) laboratory 127/404 (31.43%)] Not LR infants (or HR): laboratory criteria 217/404 (53.7%) [a= 31 (63.3%), b= 79 (76%), c= 91 (66%), d= 76 (67.3%)] Sensitivity: 100% (95%CI: 89.7-100%); enhanced UA: 96% (95% CI: 98-100%) Specificity: NR PPV: NR NPV: 100% (95%CI: 96.7-100%) enhanced UA: 99.7% (95% CI: 98.5-100%)</p> <p>Diagnosis: SBI: 28 (12.9%) [a=3 (9.7%), b= 9 (11.4%), c= 19 (20.9%), d= 10 (13.2%)] UTI: 25 (6.3%)- 4/25 also bacteremia, male vs. female p<0.01 Meningitis: 2 (0.5%) Bacteremia: 3 (0.7%) Respiratory: 10 (2.5%)</p>	<p>Initial management of LR n: 184 Hospitalized: 100% Discharged: 0 Treatment: Without IV antibiotics: 83 (65.3%) including 18 (41.9%) of infants under 28 days</p> <p>With IV antibiotics: 44 (34.7%)- reason for treatment was not documented in most cases</p> <p>Infants diagnose with SBI (FN): 0 with SBI based on clinical + laboratory criteria</p> <p>Management of FN(s) infants: NA (no cases of SBI observed)</p> <p>Initial management of not LR Hospitalized: 100% Discharged: 0 Immediately treated: 100% Treatment: Antibiotics: 100%</p>	<p>Outcomes</p> <p>Overall mortality: 0</p> <p>Harms of delayed treatment NA (no cases of SBI observed)</p> <p>Infants not treated with antibiotics: No harms reported.</p> <p>Outcomes in infants treated with antibiotics: No harms reported</p> <p>Additional data on n (%) / n with SBI (%) for individual lab tests: WBC: 39 (17.8%) / 0 Band count: 19 (8.7%) / 2 (10.5%) CSF: 56 (25.6%) / 1 (1.8%) E-UA: 22 (10%) / 6 (27%) CRC: 2 (0.9%) / 2 (100%) Combined: 81 (37%) / 19 (23%)</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Jaskiewicz (1994)⁶⁸	<p>Eligible for screening: NR</p> <p>Screened: 1057</p> <p>Enrolled: evaluated 1005 and included 931 (3 studies)</p> <p>Number of site(s): Multiple sites</p> <p>Design: Diagnostic Accuracy Study</p> <p>Region: North American/ U.S</p> <p>Setting: Paediatric ED</p> <p>Study duration: (1) 1987-1992 (2) 1984-1988 (3) 1985-1988</p>	<p>General: 1005 infants with rectal temperature $\geq 38^\circ$, well-appearing - previously healthy - no evidence of skin, soft tissue, bone, joint, or ear infection - laboratory values and sufficient data to determine level of risk with Rochester Criteria, age ≤ 60 days (931 FI in study 1 &2, 74 in study 3)</p> <p>Age: mean NR 0-30 d: 436 (43.3%) 30-60 d: 569 (56.7%)</p> <p>Male (%): NR Ethnicity (%): NR</p> <p>Fever: NR Medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria: as in Rochester</p> <p>Laboratory criteria (normal): As in Rochester</p> <p>Formal scoring systems: Rochester Criteria (for all patients or only for n=74 from study 3?)</p> <p>-----</p> <p>LR infants: n= 511 (50.8%) Not LR infants (or HR): n= 494 (49.15%)</p> <p>Sensitivity: NR Specificity: NR PPV: NR NPV: SBI: 98.9% (95% CI: 97.2-99.6%) Bacteraemia: 99.5% (95% CI: 98.2-99.9%)</p> <p>Diagnosis: SBI: 66/931 (7.1%) UTI: 31 (47%) Meningitis: 1 (1.5%) Bacteraemia: 11 (1.5%) Skin or soft tissue: 18 (27.3%) Pneumonia: 1 (1.5%) Gastroenteritis: 4 (6.1%)</p>	<p>Initial management of LR n: 511 Hospitalized: (3) n=74 (41 parenteral antimicrobial, 33 observation); Discharged: (1) n=86 (IM ceftriaxone)</p> <p>Treatment: Antibiotic: 308 (60.3%) No antibiotics: 203 (39.7%)</p> <p>LR Infants diagnose with SBI (FN): 5/511 (1%) – 3 UTI, 1 with isolated <i>Yersinia enterocolitica</i>, and 1 with <i>Neisseria meningitidis</i></p> <p>Management FN(s): 1/5 was outpatient & treated as with IM ceftriaxone prior to diagnosis and was treated with this agent as inpatient upon dx (7d) – all 5 received antibiotic tx</p> <p>Initial management of not LR N: 494 Hospitalized: NR Discharged: NR Treatment: NR</p>	<p>Outcomes</p> <p>Overall mortality: NR</p> <p>Harms of delayed treatment all 5 patients did well</p> <p>Infants not treated with antibiotics: no results reported</p> <p>Outcomes in infants treated with antibiotics: no results reported</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Jordan (2009) ⁷³	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 328</p> <p>Number of site(s): 1</p> <p>Design: Cohort (prospective)</p> <p>Region: Spain</p> <p>Setting: Paediatric ED</p> <p>Study duration: 2003-2004</p>	<p>General: 328 febrile neonates (age < 29 days) with rectal temperature $\geq 38^{\circ}$ without an apparent source</p> <p>Age: range (3-28 days)</p> <p>Male (%): 56.4</p> <p>Ethnicity (%): NR</p> <p>Fever: mean NR</p> <p>Medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria (HR): Not used</p> <p>Laboratory criteria (HR): Not used</p> <p>Formal scoring systems: Not used</p> <p>-----</p> <p>LR infants: NA</p> <p>HR infants: NA</p> <p>Sensitivity: NA</p> <p>Specificity: NA</p> <p>PPV: NA</p> <p>NPV: NA</p> <p>Diagnosis (bacterial):</p> <p>SBI (total): 62/328 (18.9%)</p> <p>UTI: 49/62 (79.0%)</p> <p>UTI/bacteremia: 8/62 (13.0%)</p> <p>Sepsis: 3/62 (5.0%)</p> <p>Meningitis/bacteremia: 2/62 (3.0%)</p> <p>Diagnosis (viral):</p> <p>Enterovirus: 10/328 (3.0%)</p>	<p>Initial management of infants:</p> <p>Hospitalized: 6 (2 neonates with meningitis, 1 neonate with sepsis, and 3 neonates with enterovirus)</p> <p>Discharged: NR</p> <p>Treatment: NR</p> <p>Infants diagnosed with SBI (FN): NA</p> <p>Management of FN infants: NA</p> <p>Initial management of HR: NA</p>	<p>Outcomes</p> <p>Overall mortality:</p> <p>- 2 of the 6 infants with enterovirus died.</p> <p>None of the two infants who died had SBI.</p> <p>- 1 neonate with fulminant <i>S. agalactiae</i> sepsis died</p> <p>Harms of delayed treatment: NR</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics: Of 13 neonates with hematogenous bacterial spread, 11 (84.6%) had a good evolution and 2 (15.3%) had a moderate disability</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Watt (2010) ⁷⁴	<p>Eligible for screening: NR</p> <p>Screened: 1501</p> <p>Enrolled: 668</p> <p>Number of site(s): 1</p> <p>Design: Cohort (retrospective)</p> <p>Region: US</p> <p>Setting: Paediatric ED</p> <p>Study duration: 1997-2006</p>	<p>General: 668 febrile neonates (age < 90 days) with rectal temperature $\geq 38^\circ$ without an apparent source</p> <p>Age: 0 – 90 d</p> <p>Male (%): 57.0%</p> <p>Ethnicity (%): NR</p> <p>Fever: mean NR</p> <p>Medication: NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Clinical criteria (HR): NR</p> <p>Laboratory criteria (HR): NR</p> <p>Formal scoring systems: Not used</p> <p>-----</p> <p>LR infants: NA</p> <p>HR infants: NA</p> <p>Sensitivity: NA</p> <p>Specificity: NA</p> <p>PPV: NA</p> <p>NPV: NA</p> <p>Diagnosis:</p> <p>SBI (total): 72/668 (10.8%)</p> <p>UTI: 52/72 (72.2%)</p> <p>Bacteremia: 11/72 (15.3%)</p> <p>Meningitis: 2/72 (3.0%)</p> <p>UTI/bacteremia: 6/72 (8.3%)</p> <p>Meningitis/bacteremia: 1/72 (1.4%)</p>	<p>Initial management of infants: almost all neonates received a complete blood, urine, and CSF sample/culture workup</p> <p>Hospitalized:</p> <p>Discharged:</p> <p>Treatment: The immediate antibiotic treatment was given to 562 infants (out of 668 infants) over 10 years</p> <p>Infants diagnosed with SBI (FN): NA</p> <p>Management of FN infants: NA</p> <p>Initial management of HR: NR</p>	<p>Outcomes</p> <p>Overall mortality: NR</p> <p>Harms of delayed treatment: NR</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics:</p> <p>Ampicillin resistance for all infants with SBI was 41.7% over the 10-year period; the corresponding resistance rate for the infants with UTI was 46.6%</p> <p>6 infants who had ampicillin resistant bacteremia had switched their antibiotics, 4 of which stayed 2 extra days in the hospital and the other two had venous catheters for at least 2 extra days</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Kaplan (2000) ⁷⁰	<p>Eligible for screening:</p> <p>Screened: 3166</p> <p>Enrolled: 2190</p> <p>Number of site(s): 1</p> <p>Design: Chart Review</p> <p>Region: North America/U.S.</p> <p>Setting: Paediatric ED</p> <p>Study duration: 5 years (1993-1997)</p>	<p>General: 2190 infants with rectal temperature $\geq 38^{\circ}$; age 28-90 (infants without 3 culture results were excluded at screening, therefore study did not use a consecutive sample)</p> <p>Age: mean NR</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>Fever: mean NR</p> <p>Medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria (HR): focal bacterial infection, or pre-existing illness, ill appearing (judged by physician), or require hospital admission</p> <p>Laboratory criteria (HR):</p> <p>Peripheral leukocyte: $\geq 20000/\text{mm}^3$</p> <p>UA: ≥ 10 leukocytes/hpf</p> <p>CSF: leukocyte ≥ 10 WBC/ mm^3; also red blood cell count $\geq 10\ 000/\text{mm}^3$</p> <p>Also at HR were patient with missing laboratory values</p> <p>Formal scoring systems: Not used</p> <p>-----</p> <p>LR infants: n= 1146 (52%)</p> <p>HR infants: n= 1044 (48%)</p> <p>Detection rate: 8.7% (95%CI: 7.7-10.0%); TP: 169/191 (88%)</p> <p>Diagnosis:</p> <p>SBI: 191 (8.7%; 95% CI: 7.7-10.0%)</p> <p>UTI: 165 (7.6%; 95% CI: 6.5-8.8%)</p> <p>Positive blood culture: 28 (1.3%; 95% CI: 0.9-1.8%)</p> <p>Meningitis: 8 (0.4%; 95% CI: 0.2-0.7%)</p>	<p>Initial management of infants n: 2190</p> <p>Hospitalized: 39% (42% of 28-60 day old vs. 34% of 61-90 day infants)</p> <p>Discharged: 61% (all infants with positive culture were admitted subsequently and treated with antibiotic therapy)</p> <p>Treatment:</p> <p>All patients diagnosed with SBI were treated with antibiotics</p> <p>Infants diagnosed with SBI (FN): 22 (12%)</p> <p>Management of FN(s) infants: All patients diagnosed with SBI were treated with antibiotics.</p> <p>Initial management of HR: NR</p>	<p>Outcomes</p> <p>Overall mortality: NR</p> <p>Harms of delayed treatment</p> <p>SBI detected after 24 hours in 3 LR. They were treated with antibiotics and all did well</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics: No complications reported (all SBI infants who received antibiotics did well).</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Marom (2007) ¹²	<p>Eligible for screening: NR</p> <p>Screened: 449</p> <p>Enrolled: 386 (infants without complete lab results were excluded)</p> <p>Number of site(s): 2</p> <p>Design: Cross sectional</p> <p>Region: Israel</p> <p>Setting: Paediatric ED</p> <p>Study duration: 5 years (1998-2003)</p>	<p>General: 404 consecutive Febrile infants with rectal temperature $\geq 38^{\circ}$; neonates (age unspecified)</p> <p>Age: mean NR Male (%): 53 Ethnicity (%): NR</p> <p>Fever: NR Medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria: unremarkable medical history, good appearance, no focal physical signs of infection</p> <p>Laboratory criteria (normal): WBC: 5000-15000/mm³ UA: normal by dipstick method ESR: < 30 mm at the end of the first hour</p> <p>Formal scoring systems: Not used</p> <p>----- LR infants: n= 166 (43%) Not LR infants (or HR): n= 220 (57%)</p> <p>Sensitivity: NR Specificity: NR PPV: NR NPV: 99.4% (95%CI: 99.35-99.45%)</p> <p>Diagnosis: SBI: 108 (28%) UTI: (14%) Meningitis: (0.5%) Bacteraemia: (%) Other: AOM (9.3%); pneumonia (2.3%); cellulitis (1.3%); gastroenteritis (0.5%)</p>	<p>Initial management of LR n: 166 Hospitalized: 100% Discharged: if in good health and no SBI or possible SBI after 48-72 hours Immediately treated: 100% Treatment: Antibiotics: Ampicillin 100 mg/kg/day + gentamicin 5 mg/kg/day; or ampicillin 200 mg/kg/day+ cefotaxime 150 mg/kg/day for at least 48-72 hours - treatment discontinued if infants tested negative for SBI</p> <p>Infants diagnose with SBI (FN): 1/166 (0.6%) with UTI (36 hour post admission) [UA normal in 12/54 (12.9%) with UTI] Management of FN(s) infants: NR</p> <p>Initial management of not LR Hospitalized: 100% Discharged: 0 Immediately treated: 100% Treatment: Same as infants in LR group</p>	<p>Outcomes</p> <p>Overall mortality: 0</p> <p>Harms of delayed treatment Infant with UTI received treatment and experienced uneventful hospitalization</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics: NR</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
<p>McCarthy 1990⁷⁵</p>	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 86</p> <p>Number of site(s): 2</p> <p>Design: Case Series</p> <p>Region: North America/ U.S.</p> <p>Setting: General Emergency Department</p> <p>Study duration: 29 months</p>	<p>General: 86 Febrile infants with mean rectal temperature = 38.8°C; age < 2 months</p> <p>Age: mean 36 days</p> <p>Age groups:</p> <p>a) ≤ weeks: 63 (14.2%)</p> <p>b) 3-4 weeks: 95 (21.4%)</p> <p>c) 5-8 weeks: 198 (44.7%)</p> <p>d) 9-12 weeks: 87 (19.6%)</p> <p>Gender: 41% male</p> <p>Ethnicity (%):</p> <ul style="list-style-type: none"> • White/non-Hispanic: 63 (73%) • Hispanic: 5 (6%) • Black: 15 (17%) • Asian: 2 (2%) • Other/missing: 1 (1%) <p>Fever: mean 38.8 on Day 1 of the study</p> <p>Medication:</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Clinical criteria: previously healthy infants without physical finding of otitis media, skin or musculoskeletal infection</p> <p>Laboratory criteria (normal):</p> <p>WBC: 5000-15000/mm³</p> <p>ABC: ≤ 1,500/ mm³</p> <p>UA: (≤ 10 WBC/hpf</p> <p>Stool: stool ≤ 5 WBC/hpf (only in infants with diarrhea)</p> <p>Formal scoring systems: Not used</p> <p>-----</p> <p>LR infants: n= 86 (NR)</p> <p>Not LR infants (or HR): not included in the study</p> <p>Sensitivity: NA</p> <p>Specificity: NA</p> <p>PPV: 98.8 (95% CI: 92.7, 99.9)</p> <p>NPV: NA</p> <p>Diagnosis:</p> <p>SBI: 1 (NA)</p> <p>Meningitis: 1</p>	<p>Initial management of LR n: 86</p> <p>Hospitalized: 0</p> <p>Discharged: 100%; followed up after 24 hours</p> <p>Immediately treated: 100%</p> <p>Treatment: Ceftriaxone 50 mg/kg</p> <p>Infants diagnose with SBI (FN): 1/86 (NA) with Neisseria Meningitis</p> <p>Initial management of not LR:</p> <p>Hospitalized: NA</p> <p>Discharged: NA</p> <p>Immediately treated: NA</p> <p>Treatment: NA</p>	<p>Outcomes</p> <p>Overall mortality: 0</p> <p>Harms of delayed treatment: 12/86 with transient complications related to intramuscular infusion of ceftriaxone; 6 infant were hospitalized, one due to SBI and 5 other due to medical or social reasons</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics: NA</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
<p>Pantell (2004)¹³ and Companion study: Newman (2002)⁷⁶</p>	<p>Eligible for screening: NR</p> <p>Screened: 3131</p> <p>Enrolled: 3066</p> <p>Number of site(s): 573 physicians</p> <p>Design: Cohort</p> <p>Region: North America/U.S.</p> <p>Setting: Family practices belonging to the Pediatric Research in Office Settings Network</p> <p>Study duration: 3 years (1995-1998)</p>	<p>General: 3066 Febrile infants with rectal temperature $\geq 38^{\circ}$ C measured at home or office; age 0-3 months</p> <p>[1-30 days: 775 (25%) 31-60 days 1120 (40%) > 60 days 1436 (47%)]</p> <p>Age: 7.0 (3.4) weeks Male (%): 53.2 Ethnicity (%):</p> <ul style="list-style-type: none"> • White/non-Hispanic: 2150 (70%) • Hispanic: 453 (15%) • Black: 246 (8%) • Asian: 67 (2%) • Other/missing: 150 (5%) <p>Fever: 38.7° C (0.5°) Medication: -----</p> <p>Mother: Socioeconomic status: Insured (Medicaid): 1074 (35%)</p>	<p>Clinical criteria: see text Laboratory criteria (normal): see text; 726 (23.7%) without complete lab data Formal scoring systems: NR</p> <p>Study used the following models only for Bacteremia / bacterial meningitis:</p> <p>1) Clinical appearance; (2) Clinical + WBC; (3) Clinical + WBC & UA; (4) Guideline models; (5) Tree structured analysis model; (6) PROS practitioners' actual experience</p> <p>Sensitivity: Model (1): 58.1%; Model (2): 83.9%; Model (3): 87.1%; Model (4): 95.2%; Model (5): 93.6%; Model (6): 97.1%;</p> <p>Specificity: Model (1): 68.1%; Model (2): 54.0%; Model (3): 50.7%; Model (4): 35.2%; Model (5): 27.3%; Model (6): 35.5%;</p> <p>Diagnosis: SBI: 62 or 63 with bacterial meningitis & bacteremia; UTI: 167(5.4%) Meningitis: 14 (5 also with other infection) (0.5%); Bacteremia: 54 (%); URT infection: 785 (25.6%); Gastroenteritis: 222 (7.2%)¹²</p> <p>Low risk for UTI: 807/ 3066 (26.3%) It was estimated that 7.6% (61/807) would have had a positive culture, yet only 0.3% (2/807) of these infants were diagnosed with UTI.⁵⁹</p>	<p>Initial management n: 3066 Hospitalized: 1975 (64%)- 60.1% younger infants vs. 27.3% older infants, $p<0.001$) Discharged: 0 Treatment: Antibiotic treatments: 61/63 with Bacteremia or bacterial meningitis [68.2% of younger infants vs. 53.7% of older infants ($p<0.001$)]</p> <p>Initial management of LR n: NR Details not provided</p> <p>Infants diagnosed with SBI (FN): Model (4): 3; Model (6): 2</p> <p>Management of FN(s) infants: Model (6): infant one was treated upon dx. Infant two initially was sent home without antibiotics; became more ill next day and was diagnosed with meningitis</p> <p>Initial management of not LR (or HR): Model (5): Hospitalized: 36% of meningitis & bacteremia Treatment: parenteral antibiotics 98%; ceftriaxone 36%; ampicillin + cephalosporin 34%; ampicillin + gentamycin 22%; other combinations 8%</p>	<p>Outcomes</p> <p>Overall mortality: 0</p> <p>Harms of delayed treatment Model (6): 1st infant with GBS did well following treatment. 2nd infant with meningitis was followed for one year and achieved normal developmental milestones¹²</p> <p>Two children with UTI experienced delayed diagnosis and treatment, and recovered uneventfully.⁵⁹</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics: NR</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Wasserman (1990) ¹⁵	<p>Eligible for screening: NR</p> <p>Screened: NR</p> <p>Enrolled: 443</p> <p>Number of site(s): 1</p> <p>Design: Chart Review</p> <p>Region: North America/ U.S.</p> <p>Setting: military medical center</p> <p>Study duration: 28 months</p>	<p>General: 443 Febrile infant with rectal temperature $\geq 38^{\circ}\text{C}$; age younger than 3 months</p> <p>Age: mean NR</p> <p>Age groups:</p> <p>a) \leq weeks: 63 (14.2%)</p> <p>b) 3-4 weeks: 95 (21.4%)</p> <p>c) 5-8 weeks: 198 (44.7%)</p> <p>d) 9-12 weeks: 87 (19.6%)</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>Fever: mean NR</p> <p>Medication: -----</p> <p>Information on mother: NR</p>	<p>Clinical criteria (LR): well appearing, no benign physical examination</p> <p>Laboratory criteria (normal): Criteria: WBC, UA (by catheter or suprapubic aspiration) in all patients; CSF in most patients</p> <p>Formal scoring systems: -----</p> <p>LR infants (infants treated without antibiotics): n= 221 (49.9%) [a=20 (32%), b= 50 (53%), c= 113 (57%), d=38 (44%)]</p> <p>Not LR infants (Outcomes in infants treated with antibiotics): n= 222 (51.1%) [a=43 (69%), b= 45 (47%), c= 85 (43%), d=49 (56%)]</p> <p>Sensitivity: NR; Specificity: NR; PPV:NR; NPV:NR</p> <p>Diagnosis:</p> <p>SBI: 53 (12%) [a=16 (25%), b=12 (13%), c=13 (6.6%), d=12 (14%)]</p> <p>UTI: NR [a= 7.9%, b=1.1%), c= 1.5%, d= 3.4%]</p> <p>Bacteremia & or bacterial meningitis: 8 (1.8%) [a= 3 (4.8%), b= 2 (2.1%), c=1 (0.5%), d= 2 (2.3%)] Other: NR</p>	<p>Initial management of LR n: 221</p> <p>Hospitalized: 100%</p> <p>Discharged: 0</p> <p>Treatment: No antibiotics: 100%</p> <p>Infants diagnose with SBI (FN): n=5 (2.3%); 1 bacteremia, 3 UTI, 1 Salmonella</p> <p>Management of FN(s) infants: infant with bacteremia: 10 days parenteral antibiotics; UTI and Salmonella infants were treated with antibiotics after culture results</p> <p>Initial management of not LR n: 222</p> <p>Hospitalized: 100%</p> <p>Discharged: 0</p> <p>Treatment: Oral antibiotics: 58 (26%) [a= 1 (2%), b= 8 (8%), c=27 (14%), d=22 (25%)] Parenteral antibiotics: 164 (74%) [a= 42 (67%), b= 37 (39%), c= 58 (29%), d= 27 (31%)]</p>	<p>Outcomes</p> <p>Overall mortality: 1 infant with viral upper resp. infection died from SIDS</p> <p>Harms of delayed treatment: all infants did well. Infants not treated with antibiotics: No complications reported.</p> <p>Outcomes in infants treated with antibiotics: No complications reported.</p> <p>N=1 infant with E-coli (UTI) initially treated with ampicillin had +ve blood culture. Gentimicine was added despite clinical improvement. Infant did well.</p> <p>Change in treatment was reported in 28 infants, 5 due to +ve blood or urine results, 10 due to OM, 1 chest infiltrate & 12 for other reasons.</p>

Study ID	Number of Infants Setting	General information at baseline: Infants, Mothers	Criteria and results of Diagnostic tests	Management	Treatment results
Watt (2010) ⁷⁴	<p>Eligible for screening:</p> <p>Screened:</p> <p>Enrolled:</p> <p>Number of site(s):</p> <p>Design:</p> <p>Region:</p> <p>Setting: Paediatric ED</p> <p>Study duration:</p>	<p>General:</p> <p>Age: mean</p> <p>Male (%):</p> <p>Ethnicity (%): NR</p> <p>Fever: mean NR</p> <p>Medication: NR</p> <p>Information on mother: NR</p>	<p>Clinical criteria (HR):</p> <p>Laboratory criteria (HR):</p> <p>Formal scoring systems: Not used</p> <p>-----</p> <p>LR infants:</p> <p>HR infants:</p> <p>Sensitivity:</p> <p>Specificity:</p> <p>PPV:</p> <p>NPV:</p> <p>Diagnosis:</p>	<p>Initial management of infants:</p> <p>Hospitalized:</p> <p>Discharged:</p> <p>Treatment:</p> <p>Infants diagnosed with SBI (FN):</p> <p>Management of FN infants:</p> <p>Initial management of HR: NR</p>	<p>Outcomes</p> <p>Overall mortality: NR</p> <p>Harms of delayed treatment</p> <p>Infants not treated with antibiotics: NR</p> <p>Outcomes in infants treated with antibiotics:</p>

Table 7. Co-infection in febrile infants (studies assessing risk of SBI in infants with or without other infections)

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
<p>Bilavsky (2008)⁷⁷</p>	<p>Design: Quasi-experimental</p> <p>Region: North America</p> <p>Setting: NR</p> <p>Study period: 2006-2007</p>	<p>N: NR/448</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: All febrile infants who were hospitalized – excluded infants with a chronic disease, pre term infants, infants who received antibiotics within 48 hours of presenting to ED and infants without documented fever</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Type(s) of infection studies: Bronchiolitis</p> <p>Method: <u>Bronchiolitis:</u> acute wheezing or chest retractions in association with an URT infection or by cough or rhinorrhea detected on physical examination</p> <p><u>RSV:</u> nasopharyngeal aspirates collected from infants with bronchiolitis for RSV antigen detection by rapid enzyme linked immunoassay (results for RSV reported only for patients with bronchiolitis & could not be used for this review)</p>	<p>N with infection: 136 Infection (+) & SBI: 3 Prevalence (%) [95% CI]: 2.20 [0.60, 6.00]</p> <p>N without infection: 312 Infection (-) & SBI: 30 Prevalence (%) [95% CI]: 9.62 [6.35, 12.89]</p>	<p>Prevalence ratio (%) [95% CI]: (rate ratio) 0.23 [0.05, 0.76]</p> <p>OR [95% CI]: 0.21 [0.05, 0.74]</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Byington (1999) ⁷⁸	<p>Design: Chart review</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1996-1997</p>	<p>N: NR/ 345</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Healthy infants with documented fever $\geq 38^{\circ}\text{C}$ with complete sepsis evaluation-excluded infants who received polio vaccine</p> <p>Male (%): 51%</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Type(s) of infection studies: Nonpolio EV</p> <p>Method: <u>Nonpolio EV:</u> enteroviruses by PCR assay (polio and non polio viruses)</p>	<p>N with infection: 89 Infection (+) & SBI: 6 Prevalence (%) [95% CI]: 6.70 [2.8, 13.3]</p> <p>N without infection: 256 Infection (-) & SBI: 38 Prevalence (%) [95% CI]: 14.84 [10.5, 19.20]</p>	<p>Prevalence ratio (%) [95% CI]: 0.45 [0.17, 1.06]</p> <p>OR*[95% CI]: 0.41 [0.15, 1.07]</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
<p>Byington (2004)⁶⁴</p> <p>Companion Kuppermann (1999)³⁴</p>	<p>Design: Case series</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1996-2002</p>	<p>N: NR/1385</p> <p>Age group(s): 1 – 90 d</p> <p>Inclusion / exclusion: Febrile infants with temperature $\geq 38^{\circ}\text{C}$ evaluated for sepsis (bacterial cultures of blood, urine, and CSF)-excluding infants who had received antibiotics in the 48 hours preceding the evaluation; infants who received polio vaccine, a live enterovirus vaccine</p> <p>Male (%): 55%</p> <p>Ethnicity (%): White/non-Hispanic: 63% Hispanic: 24% Black: 1% Asian/Pacific Islander: <1% Other: 4%</p> <p>----- Information on mother: NR</p>	<p>Type(s) of infection studies: EV, RSV, Influenza A/B, parainfluenza, rotavirus</p> <p>Method: <u>EV</u>: PCR; ARUP EV-RT, or by culture on specimens from CSF, stool, nasopharyngeal and throat swab</p> <p><u>RSV</u>: enzymed linked immunoabsorbent assay, by PCR, or by direct fluoroscent assay detection performed on nasal wash specimens</p> <p><u>Herpes</u>: culture of skin lesions or mucuous membranes</p> <p>Varicella infection: (in a single infant) dx made by history of exposure and physical exam of vesicular skin rash consistent with varicella</p>	<p>N with infection: 491 Infection (+) & SBI: 21 Prevalence (%) [95% CI]: 4.30 [2.80, 6.20]</p> <p>N without infection: 894 Infection (-) & SBI: 110 Prevalence (%) [95% CI]: 12.30 [10.15, 14.45]</p>	<p>Prevalence ratio (%) [95% CI]: 0.34 [0.21, 0.55]</p> <p>OR*[95% CI]: 0.32 [0.19, 0.52]</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Dagan (1985) ⁸	<p>Design: Quasi-experimental</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1982-1984</p>	<p>N: NR/233</p> <p>Age group(s): 0 – 90 d Age 0 – 30 d 92 (39%) Age 31 – 60 d 107 (46%) Age 61 – 90 d 34 (15%)</p> <p>Inclusion / exclusion: Previously healthy infants suspected of sepsis and hospitalized for sepsis workup</p> <p>Male (%): 58%</p> <p>Ethnicity (%): White/non-Hispanic: 60.9% Hispanic: 12% Black: 25.3% Asian/Pacific Islander: 1.7%</p> <p>----- Information on mother: NR</p>	<p>Type(s) of infection studies: Nonpolio EV RSV, influenza</p> <p>Method: <u>Nonpolio EV</u> <u>RSV, influenza:</u> viral culture on specimens of throat swab, stool or rectal swab, CSF and blood during July to November; nasopharyngeal/ throat swab, stool or rectal swab, and CSF during November through June; nasal wash specimens and nasopharyngeal/ throat swab, stool or rectal swab, and CSF during December through May</p> <p>Concurrent immuno-electrophoresis for rotavirus antigen in stool and viral culture of urine, vesicle, or eye swab specimens performed when indicated.</p>	<p>N with infection: 137 Infection (+) & SBI: 4 Prevalence (%) [95% CI]: 2.92 [0.10, 5.34]</p> <p>N without infection: 96 Infection (-) & SBI: 19 Prevalence (%) [95% CI]: 19.79 [11.82, 27.76]</p>	<p>Prevalence ratio (%) [95% CI]: 0.14 [0.04, 0.44]</p> <p>OR*[95% CI]: 0.12 [0.03, 0.40]</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Kuppermann (1997) ⁷⁹	<p>Design: Quasi-experimental</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1994-1996</p>	<p>N: NR/86</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion/ exclusion: All febrile infants with rectal temperature $\geq 38^{\circ}\text{C}$ ($\geq 39^{\circ}\text{C}$ for infants 3-24 months)- infants with vaccination or antibiotics within 48 hours of presentation to ED; focal bacterial infection other than otitis media, an identifiable viral infection other than bronchiolitis, known chronic illness, or a known immunodeficiency that would affect the risks of bacterial infections, currently taking immunosuppressive medication including corticosteroids, parent refusal to sign consent</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Type(s) of infection studies: Bronchiolitis</p> <p>Method: <u>Bronchiolitis:</u> clinical evaluation of diffuse wheezing and or retractions in association with a history of rhinorrhea or upper respiratory signs on examination,</p>	<p>N with infection: 36 Infection (+) & SBI: 0 Prevalence (%) [95% CI]: NA</p> <p>N without infection: 50 Infection (-) & SBI: 7 blood culture 1; urine culture 6 Prevalence (%) [95% CI]: Blood culture (+) 2.00 [1.88, 5.88] Urine culture (+) 12.0 [3.00, 21.00]</p>	<p>Prevalence ratio (%) [95% CI]: NA</p> <p>OR*[95% CI]: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Levine (2004) ⁸⁰	<p>Design: cross sectional</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1998-2001</p>	<p>N: 1248/1169</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: All febrile infants with rectal temperature $\geq 38^{\circ}\text{C}$ by history or in ED- excluded infants that used antibiotics within 48 hours of ED presentation or parent refusal to sign consent</p> <p>Male (%): 55%</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Type(s) of infection studies: RSV</p> <p>Method: RSV: nasopharyngal aspirates for rapid RSV antigen detection via enzyme immunoassay for indirect florescent antibody</p>	<p>N with infection: 244 Infection (+) & SBI: 17 (14 UTI, 3 bacteremia, 0 meningitis) Prevalence (%) [95% CI]: SBI 7.0% [4.1, 10.9] UTI 5.4% [3.0, 8.8] Bacteremia 1.1% [0.2, 3.2] Meningitis 0 [0, 1.2]</p> <p>N without infection: 925 Infection (-) & SBI: 116 UTI, 22 bacteremia, 8 meningitis) Prevalence (%) [95% CI]: SBI 12.5% [10.5, 14.8] UTI 10.1% [8.3, 12.2] Bacteremia 2.3% [1.4, 3.4] Meningitis 0.9% [0.4, 1.7]</p>	<p>Prevalence ratio (%) [95% CI]: SBI: 0.60 [0.30, 0.90] UTI</p> <p>Adjusted OR [95% CI]: (adjusted for age, temperature, Yale Observation Score and WBC count) SBI 0.58 [0.33, 0.99]</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Luginbuhl (2008) ⁸¹	<p>Design: Prospective cohort</p> <p>Region: North America</p> <p>Setting: Primary Care</p> <p>Study period: Feb 28 1995- April 25, 1998</p>	<p>N: 3131/3066</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: Infants presenting to primary care with documented fever $\geq 38^{\circ}\text{C}$; infants with bronchiolitis</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>-----</p> <p>Information on mother: NR</p>	<p>Type of infection studies: Bronchiolitis</p> <p>Method: <u>Bronchiolitis:</u> NR <u>RSV:</u> NR</p>	<p>N with infection: 0/218 had SBI</p> <p>N without infection: 212/2848 (n with SBI/n with culture)</p> <p>UTI: 167/1537 with culture (11%)</p> <p>Bacteremia: 49/1657 with culture (3%)</p> <p>Meningitis: 14/971 with culture (1%)</p> <p>Bacteremia or bacterial meningitis: 63/1750 with culture (4%)</p>	<p>Upper limit of 1-sided 95% CI for those with culture, p value: Total: 2.4, p < 0.001</p> <p>UTI: 4.2, p = 0.001</p> <p>Bacteremia only: 2.6, p = 0.071</p> <p>Meningitis: 7.5, p = 1.00</p> <p>Bacteremia or bacterial meningitis: 2.5, p = 0.31</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Rittichier (2005) ⁸²	<p>Design: Case series</p> <p>Region: North America</p> <p>Setting: Primary care</p> <p>Study period: 1996-2002</p>	<p>N: 1779/1061</p> <p>Age group(s): 0 – 90 d</p> <p>Inclusion / exclusion: All febrile infants with temperature $\geq 38^{\circ}\text{C}$, and a completed sepsis evaluation with bacterial cultures of blood, urine, and CSF was perform</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Type(s) of infection studies: enterovirus (EV)</p> <p>Method: <u>enterovirus:</u> PCR of blood, CSF or both in 93% of infants</p>	<p>N with infection: 214 (20%) Infection (+) & SBI: Prevalence (%) [95% CI]: 7.00 [3.59, 10.43]</p> <p>N without infection: 847 Infection (-) & SBI: NA Prevalence (%) [95% CI]: NA</p>	<p>Prevalence ratio (%) [95% CI]: NA OR*[95% CI]: NA</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Smitherman (2005) ⁸³	<p>Design: chart review</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: 1997-2001</p>	<p>N: NR/292 age 0 – 28 d: 62 age 29 – 90 d:230</p> <p>Age group(s): 0 – 90 d age 0 – 28 d (21.2%) age 29 – 90 d (78.8%)</p> <p>Inclusion / exclusion: infants 0-36 months (including a sub-sample of 0- 90 d) evaluated during 5 consecutive influenza season presenting with fever; documented influenza by rapid antigen testing and or by viral culture – excluded: antibiotic use within the preceding 48 hours; an immuno-compromised host; increased risk for infection secondary to indwelling or foreign bodies; conditions that would increase risk of bacteraemia, UTIs or pneumonia</p> <p>Male (%): NR</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Type(s) of infection studies: Influenza A</p> <p>Method: <u>Influenza A:</u> <i>positive if</i> documented positive Directigen Flu A rapid antigen testing test or positive VC for influenza A; <i>negative if:</i> viral studies were negative for influenza A</p> <p>Viral studies: by nasopharyngeal washes and aspirates (nasopharyngeal and pharyngeal specimens)</p> <p>Pneumonia: possible probable or definite focal parenchymal density on CXR by attending radiologist</p>	<p>N with infection: <u>Influenza A:</u> age 0 – 90 d: 58 (20.0%) age 0 – 28 d: 13 (21.0%) age 29 – 90 d: 45 (19.6%) Infection (+) & SBI: NR Prevalence (%) [95% CI]: NR</p> <p>N without infection: <u>Influenza A:</u> age 0 – 90 d: 234 (80.0%) age 0 – 28 d: 49 (79.0%) age 29 – 90 d: 185 (80.4%) Infection (-) & SBI: NR Prevalence (%) [95% CI]: NR</p>	<p>Prevalence ratio (%) [95% CI]: NR</p> <p>OR*[95% CI]: including pneumonia (age 29 – 90 d) 0.21 [0.05, 0.93]</p> <p>excluding pneumonia (age 29 – 90 d) 0.19 [0.03, 1.44]</p>

Study ID	Study Characteristics	N (screened/enrolled) General information at baseline	Type of infection Method used to identify infection	Results:	Prevalence ratio (%) [95% CI] Odds Ratio (OR) [95% CI]
Titus (2003) ⁸⁴	<p>Design: Case control</p> <p>Region: North America</p> <p>Setting: Padiatric ED</p> <p>Study period: Unclear</p>	<p>N: NR/358</p> <p>Age group(s): 0 – 60 d</p> <p>Inclusion / exclusion: Infants admitted with documented fever $\geq 100^{\circ}\text{F}$-excluded infants with congenital heart disease or other significant medical history</p> <p>Male (%): 51%</p> <p>Ethnicity (%): NR</p> <p>----- Information on mother: NR</p>	<p>Type(s) of infection studies: RSV</p> <p>Method: <u>RSV:</u> nasopharyngal aspirates for rapid RSV antigen detection via enzyme immunoassay</p>	<p>N with infection: 174 Infection (+) & SBI: 2 Prevalence (%) [95% CI]: 1.15% [0.43, 2.73]</p> <p>N without infection: 174 Infection (-) & SBI: 22 Prevalence (%) [95% CI]: 12.60% [7.70, 17.60]</p>	<p>Prevalence ratio (%) [95% CI]: 0.09 [0.02, 0.38]</p> <p>OR*[95% CI]: 0.08 [0.01, 0.36]</p>

Table 8. KQ6 Included studies reporting on relevant outcomes for infants 0 – 6 months of age

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Baskin, MN (1992) ⁶⁰ US	-Prospective -ED -1987 – 1997	N=503 infants 28 – 89 d (67% 28-60 d, 33% 61-89 d); with fever without a source – 476 were treated as outpatients and were followed Age: mean 55 (SD 17) d No other characteristic reported	IMI of Ceftriaxone (2 doses within 24 hrs) pending culture results	3 phone calls (1 – 12 hrs; 2 – 48 hrs; 3 – 7 d post discharge) and 1 return visit to the ED in 24 hrs post initial visit	Infants with fu at 24 hrs: 494 (98%) who had a 2 nd dose of ceftriaxone Infants with fu at 48 hrs: 482 (96%) There was concern about 2/476 (0.42%) parents of infants without SBI about parental supervision —These infants were hospitalized > 24 hrs of initial entry
Krief (2008) ^{71,80,85} US	Prospective cross sectional/ to determine the risk of SBIs in FI with or without influenza virus infections 5 pediatric ED clinics (original report of this trial include 8 ED hospitals) 3 consecutive influenza seasons 1998-2001	N=844 FI ≤ 60 d, n=844 FI +ve for influenza virus (original report included 1025 infants) Age: mean 35.8 d, 55% male, median YOS score (IQR 6-8)	Yale Observation Scale (YOS) was used as a tool to determine infants' status. Antibiotic therapy and/or hospitalization, were at the discretion of the responsible physician & not determined by study protocol	One telephone fu on patients discharged from the ED within 4 to 7 d	Compliance with phone fu: 103/132 (78.0%) of discharged infants. 7 (1%) (patients without CSF cultures were determined not to have bacterial meningitis by telephone fu) No information about characteristics of compliant or non-compliant parents/infants was reported.
Dore-Bergeron, MJ (2009) ⁷²	Prospective cohort/ to investigate feasibility of	N=118 FI 30 – 90 d with presumed UTI	Inpatient tx (protocol not described) if any:	In outpatient tx, monitoring the fever	67/118 (56.8%) of FI were admitted to DTC. Rate of parental compliance

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
(10351 commentary) Canada	ambulatory tx at day treatment centre (DTC) One tertiary-care pediatric ED Period: 2005	Age: median age for 67 FI admitted to DTC = 66 d (range: 33– 85 d)	abnormal CSF, toxic appearance, underlying medical problems, abnormal creatinine levels, parental refusal to fu in DTC, or outpatients tx Ambulatory tx protocol: single IVI gentamicin (5 or 2.5 mg/kg)+ 1 dose IVI ampicillin, & 2 or 3 doses oral amoxicillin, to be taken until the 1 st visit to DTC in 24 hrs. At DCT IVI gentamicin daily until the child was afebrile. If UTI was confirmed tx with antibiotics were started.	every 4 hrs + return the child after 24 hrs	with DTC visits: 98.3%. Successful tx in the DTC (attendance at all visits, normalization of temperature within 48 hrs, -ve control urine & BC results, & absence of hospitalization): 86.2% of pts with confirmed UTI Compliance with guidelines of antibiotic tx: 80.4%; hospitalization during the course of tx in DTC: 12.1% Adherence of ED physicians to patient referral to the appropriate setting (DTC or hospital ward): lower but not statistically-significant for younger infants, [crude OR, comparing < 60-day-old children with older children: 0.5 (95% CI: 0.2, 1.5)]

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Condra SC (2010) ⁴ US	Prospective observation/ evaluation of cost and complications in inpatient treatment of febrile infants 29-60 d of age Period: NR – total length of study was 16 months	N = 62 infants 29 – 60 d; fever without a source; met a criteria derived from Philadelphia for Low Risk for SBI 55% male median age: 44 d 39 (63%) White; 18 (29%) African American, 5 (8%) Hispanic (range 29 -60 d) White (63%), African American (29%), Hispanic (8%). 8 (12.9%) Group B Streptococcus +ve or unknown (the mothers treated with peripartum antibiotics)	Despite meeting LR criteria, 56/62 (90.3%) infants were admitted and received IVI antibiotics 6/62 (9.7%) were LRI and discharged from the ED after a full sepsis workup.	3 phone follow-ups with parent and primary care provider (PCP) within the 2 wks after discharge + contact with PCP at 14 d post discharge Questionnaire on 1-Infants' health status 2-compliance 3-hospital charges	Compliance with phone calls after initial discharge (reported for FI who were managed as inpatients 56 (90.32%]): d 2: 77.4%; d 7: 85.4%; d 14: 83.9% All 6 subjects (100%) discharged directly from the ED did have medical follow-up within 48 hours with PCP Parents preferred discharge to admission (66%-70%) 5/6 (83.3%) discharged infants required re-evaluation and 2/6 (33.3%) were hospitalization within 24 hrs of discharge-one for a +ve blood culture (later determined to be a contaminant) and one for continued fever & newly documented pneumonia. Complications in outpatients:
RefID=Reference Identification; US = United States; N = number of participants; yrs = years; mo/s= month/s; wks = weeks; d=day/s; hr/s = hour/s; IMI = intramuscular injection; IVI=intravenous injection; SBI= serious bacterial infection; LRI=low risk infants; FI=febrile infant; =treatment; fu=follow up; #, n, N=number; LR= low risk for SBI; HR= high risk for SBI; SBI=serious bacterial infection; LP=lumbar puncture; BC= blood culture; YOS= Yale Observational Scale; IQR=inter-quartile range; NR= not reported; CSF=cerebrospinal fluid; UTI= urinary tract infection; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; CPT-4=Current Procedural Terminology, Forth Revision					

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Appendix D. Excluded Studies

Key Questions 1-5

Non-English publications

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Key Question 6

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Appendix E. Quality Assessment Forms

Jadad Scale

Total Jadad score range = 0 – 5

Design

Randomization. A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

2. Trials describing an APPROPRIATE method of randomization (table of random numbers, computer generated, coin-toss) receive an additional point. However, if the report describes an INAPPROPRIATE method of randomization (by date of birth, hospital number, alternation), a point is deducted.

- Appropriate (score = 1)
- Not described (score = 0)
- Inappropriate (score = -1)

•

Intervention

Double Blind. A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

3. Was the study described as double blind?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

4. Trials that describe an APPROPRIATE method of double-blinding (placebo identical in colour, shape or taste) receive an additional point. However, if the report describes an INAPPROPRIATE method of double-blinding (tablet vs. injection with no dummy) a point is deducted.

- Appropriate (score = 1)
- Not described (score = 0)

- Inappropriate (score = -1)

Withdrawals and Dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

5. Was there a description of withdrawals and dropouts?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

Quality Assessment of Diagnostic Accuracy Studies (QUADAS)

Total QUADAS score range = 0 – 14

1. Was the spectrum of patients representative of the patients who will receive the test in practice?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

2. Were selection criteria clearly described?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

3. Is the reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

6. Did patients receive the same reference standard regardless of the index test result?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

8. Was the execution of the index test described in sufficient detail to permit replication of the test?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

9. Was the execution of the reference standard described in sufficient detail to permit its replication?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

10. Were the index test results interpreted without knowledge of the results of the reference standard?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

11. Were the reference standard results interpreted without knowledge of the results of the index test?

- Yes (score = 1)
- No (score = 0)
- Unclear (score = 0)

12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

- Yes (score = 1)
- No (score = 0)

- Unclear (score = 0)
13. Were uninterpretable/ intermediate test results reported?
- Yes (score = 1)
 - No (score = 0)
 - Unclear (score = 0)
14. Were withdrawals from the study explained?
- Yes (score = 1)
 - No (score = 0)
 - Unclear (score = 0)

Newcastle-Ottawa Quality Assessment Scale for Case Control Studies

1. Is the definition adequate?
- yes, with independent validation
 - yes, e.g. record linkage or based on self report
 - no description
2. Representativeness of the cases
- consecutive or obviously representative series of cases
 - potential for selection biases or not stated
3. Selection of controls
- community controls
 - hospital controls
 - no description
4. Definition of controls
- no history of disease (endpoint)
 - no description of source

Comparability

5. Comparability of cases and controls on the basis of the design or analysis
- study controls for (select the most important factor)
 - study controls for any additional factor (this criteria could be modified to indicate specific control
 - for a second important factor)

Exposure

6. Ascertainment of exposure
 - secure record (e.g. surgical records)
 - structured interview where blind to case/control status
 - interview not blinded to case/control status
 - written self report or medical record only
 - no description
7. Same method of ascertainment for cases and controls
 - Yes
 - No
8. Non-Response rate
 - same rate for both groups
 - non respondents described
 - rate different and no designation

Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

1. Representativeness of the exposed cohort
 - truly representative of the average in the community
 - somewhat representative of the average in the community
 - selected group of users e.g. nurses, volunteers
 - no description of the derivation of the cohort
2. Selection of the non exposed cohort
 - drawn from the same community as the exposed cohort
 - drawn from a different source
 - no description of the derivation of the non exposed cohort
3. Ascertainment of exposure
 - secure record (e.g. surgical records)
 - structured interview
 - written self report
 - no description
4. Demonstration that outcome of interest was not present at start of study
 - Yes
 - No

Comparability

5. Comparability of cohorts on the basis of the design or analysis

- study controls for (select the most important factor)
- study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor)

Outcome

6. Assessment of outcome

- independent blind assessment
- record linkage
- self report
- no description

7. Was follow-up long enough for outcomes to occur

- Yes (select an adequate follow up period for outcome of interest)
- No

8. Adequacy of follow up of cohorts

- complete follow up - all subjects accounted for
- subjects lost to follow up unlikely to introduce bias - small number lost - > ____ %- (select an adequate %) follow up, or description provided of those lost)
- follow up rate < ____% - (select an adequate %) and no description of those lost
- no statement

Downs & Black Tool For Controlled Clinical Trials, Quasi-experimental, and Cross-sectional Studies

Reporting

1. Is the hypothesis/aim/objective of the study clearly described?

- Yes
- No

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? (If the main outcomes are first mentioned in the Result section, the question should be answered no.)

- Yes
- No

3. Are the characteristics of the patients included in the study clearly described? (In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies a case definition and the source for controls should be given.)

- Yes
- No

4. Are the interventions of interest clearly described? (Treatments and placebo (where relevant) that are to be compared should be clearly described)

- Yes
- No

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? (A list of principal confounders is provided)

- Yes
- No

6. Are the main finding of the study clearly described? [Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.] (This question does not cover statistical tests, which are considered below.)

- Yes
- Partially
- No

7. Does the study provide estimates of the random variability in the data for the main outcome? (In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.)

- Yes
- No

8. Have all the important adverse events that may be a consequence of the intervention been reported? (This should be answered yes if the study demonstrated that there was a comprehensive attempt to measure adverse events.) (A list of possible adverse events is provided)

- Yes
- No

9. Have the characteristics of patients lost to followup been described? (This should be answered yes where there were no losses to followup or where losses to followup were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to followup.

- Yes
- No

10. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?

- Yes
- No

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were delivered.

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? (The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients or a random sample. Random sampling is only feasible where all the relevant population exists. Where a study does not report the proportion of the source population from which the patients are delivered the question should be answered as unable to determine.)

- Yes
- No
- Unable to determine

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? (The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.)

- Yes
- No
- Unable to determine

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? (For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.)

- Yes
- No
- Unable to determine

Internal validity - bias

14. Was an attempt made to blind study subjects to the intervention they have received? (For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.)

- Yes
- No
- Unable to determine

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

- Yes

- No
- Unable to determine

16. If any of the results of the study were based on “data dredging”, was this made clear? (Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.)

- Yes
- No
- Unable to determine

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? (Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.)

- Yes
- No
- Unable to determine

18. Were the statistical tests used to assess the main outcomes appropriate? (The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.)

- Yes
- No
- Unable to determine

19. Was compliance with the intervention/s reliable? (Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.)

- Yes
- No
- Unable to determine

20. Were the main outcome measures used accurate (valid and reliable)? (For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.)

- Yes
- No
- Unable to determine

Internal validity – confounding (selection bias)

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? (For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.)

- Yes
- No
- Unable to determine

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? (For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.)

- Yes
- No
- Unable to determine

23. Were study subjects randomised to intervention groups?(Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.)

- Yes
- No
- Unable to determine

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? (All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.)

- Yes
- No
- Unable to determine

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? (This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non- randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.)

- Yes

- No
- Unable to determine

26. Were losses of patients to follow-up taken into account? (If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.)

- Yes
- No
- Unable to determine

Power

27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? (Sample sizes have been calculated to detect a difference of x% and y%)

- A. < n1 (0)
- B. n1-n2 (1)
- C. n3-n4 (2)
- D. n5-n6 (3)
- E. n7-n8 (4)
- F. n8+ (5)

Appendix F. Protocols and Criteria

Rochester Low Risk Criteria

Previously healthy febrile infants less than 60 days of age are considered to be at low risk for serious bacterial infection if the following criteria are met:

- Infant appears well, non-toxic
- Infant has been previously well
 - Born at term (> 37 weeks)
 - No antenatal or perinatal antimicrobial therapy
 - No treatment for unexplained hyperbilirubinemia
 - Not hospitalized longer than the mother at birth
 - No previous hospitalizations
 - No recent antibiotic use
 - No chronic or underlying diseases
- Infant has no evidence of bacterial infection
 - No skin, soft tissue, bone, joint or ear infection
- The following laboratory parameters are met:
 - WBC count 5000-15000 per mm³
 - Absolute band count < 1500
 - Urinalysis WBC count < 10/hpf
 - Stool WBC count < 5/hpf (if infant has diarrhea)

Refid: 1141, Dagan, R., Powell, K. R., Hall, C. B., and Menegus, M. A., Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis, Journal of Pediatrics, 107(6), 1985, p.855 – 860

Boston criteria

- Age >28 days and <90 days
- Temperature >38.0 ~ C, obtained rectally
- No ear, soft tissue, joint, or bone infection identified on physical examination
- No source of infection identified on initial screening laboratory tests:
 - Cerebrospinal fluid leukocyte count <10 x 10⁶ cells/L
 - Urinalysis demonstrating <10 leukocytes/hpf
 - No infiltrate on chest radiograph, if obtained
 - Peripheral leukocyte count <20 x 10⁹ cells/L
- Judged not to require admission to the hospital for any reason other than parenteral administration of antimicrobial agents (vital signs in the normal range for age and

temperature, not ill appearing , not dehydrated, taking fluids, and having cooperative and reliable parents)

- Caregiver available by telephone
- No antimicrobial agents received within the preceding 48 hours
- No immunization with diphtheria and tetanus toxoids and pertussis vaccine within 48 hours

Refid: 2, 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, 120(1), 1992, p.22 – 27

Philadelphia Protocol

Infant considered to be low risk if appeared well, had no evidence of bacterial infection on physical examination and all laboratory values were within normal ranges:

CBC	<15000 WBC/mm ³ BNR <0.2
Urinalysis	<10WBC/hpf No bacteria on Gram stain
Lumbar puncture	<8 WMC/mm ³ No bacteria on Gram stain
CXR	No evidence of discrete infiltrate
Stool Smear	Negative for blood Few or no WBC on smear

If infants were identified as low risk for SBI and available for repeat physical examination 24-48 hours after the initial assessment they were managed without antibiotics as outpatients.

Refid: 7, Baker MD. Bell LM. Avner JR, The efficacy of routine outpatient management without antibiotics of fever in selected infants, Pediatrics, 103(3), 1999, p.627 – 631

Milwaukee Protocol

- Infants 4-8 weeks
- Rectal temp > 38
- Physical examination with normal clinical appearance [well hydrated, tolerating oral feedings, alert and active, with good muscle tone, no respiratory distress (resp rate < 60 breaths/min, no grunting respirations or intercostal retractions) and no sign of focal infection (middle ear, soft tissue, bone/joint)].
- Normal laboratory data profile:
 - CSF WBC count < 10/ml
 - CBC WBC count < 15,000/ml
 - Urinalysis with < 5-10 WBCs/hpf, no bacteria, negative leukocyte esterase and nitrite
 - No infiltrate on CXR if performed
- Reliable caretaker who understands instruction, has a telephone and transportation and agrees to reevaluation visit within 24 hours
- No allergy to beta lactam antibiotics
- Private pediatrician contacted who agrees to outpatient management
- Infants who fulfill all criteria have an uncompromised presentation, receive IM ceftriaxone 50 mg/kg and are re-evaluated within 24 hours in the emergency department or paediatrician's office

Refid: 8, Bonadio WA. Hagen E. Rucka J. Shallow K. Stommel P. Smith D, Efficacy of a protocol to distinguish risk of serious bacterial infection in the outpatient evaluation of febrile young infants, Clin Pediatr (Phila), 32(7), 1993, p.401 - 404

The Yale Observation Scale

Observation Variable	Normal (1)	Moderate Impairment (3)	Severe Impairment (5)
Quality of cry	Strong, normal tone or content, not crying	Whimpering, sobbing	Weak, moaning, high pitched
Reaction to Parents	Cries briefly, stops or content, not crying	Cries off and on	Continual cry or hardly responds
State Variation	If awake, stays awake If asleep, arouses easily	Eyes close briefly, awakes with prolonged stimulation	Falls to sleep, cannot be aroused
Color	Pink	Pale extremities Acrocyanosis	Pale, cyanotic mottled, ashen
Hydration	Skin, eyes normal Mucous membranes moist	Skin, eyes normal Mouth slightly dry	Skin doughy, tented Mucous membranes dry, Sunken eyes
Response to Social Overtures	Smiles Becomes alert	Brief smile Alerts briefly	No smile, anxious, dull, expressionless Can't be alerted

McCarthy PL, Sharpe MR, Spiessel SZ, et al. Observation scales to identify serious illness in young children. Pediatrics 1982; 70: 802-809

The Young Infant Observation Scale

Affect	Smiles or not irritable (1)	Irritable, consolable (3)	Irritable, not consolable (5)
Respiratory status/effort	No impairment, vigorous (1)	Mild-moderate compromise (tachypnea, retractions, grunting) (3)	Respiratory distress or inadequate effort (apnea, resp failure) (5)
Peripheral perfusion	Pink, warm extremities (1)	Mottled, cool extremities (3)	Pale, shock (5)

Refid: 621, Bonadio, W. A., Hennes, H., Smith, D., Ruffing, R., Melzer-Lange, M., Lye, P., and Isaacman, D., Reliability of observation variables in distinguishing infectious outcome of febrile young infants, Pediatric Infectious Disease Journal, 12(2), 1993, p.111 - 114

Appendix G. Quality Assessment of Included Studies

Quality Assessment Of Diagnostic Accuracy Studies (QUADAS)

Table 1. Quality Assessment On All QUADAS Questions For Each Included Study

Study ID	Q1. Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8. Details of index test described	Q9. Replication	Q10. Index test interpreted without knowledge of RS	Q11. Ref. stand interpreted without knowledge of RS	Q12. Same Clinical Data Available	Q13. Uninterpretable Test Results	Q14. Withdrawals Explained	Total Score
Baskin (1992)¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Yes	Yes	11
Jaskiewicz JA, (1994)²	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	10
Baker MD, (1999)³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
Kadish HA, (2000)⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Yes	12
Baker MD, (1999)⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	13
Baker MD, (1993)⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Yes	Yes	11
Pantell RH, (2004)⁷	Yes	Yes	Yes	Not clear	Yes	Not clear	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	10
Chiu CH, (1997)⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	12
Dayan PS, (2002)⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Yes	Yes	No	Yes	11
Ferrera PC, (1997)¹⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	Yes	12
Bachur RG, (2001)¹¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	12
Andreola B, (2007)¹²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Yes	12
Bonsu BK, (2007)¹³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	11
Marom R, (2007)¹⁴	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes	10

Study ID	Q1. Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8. Details of index test described	Q9. Replication	Q10. Index test interpreted without knowledge of RS	Q11. Ref. stand interpreted without knowledge of RS	Q12. Same Clinical Data Available	Q13. Uninterpretable Test Results	Q14. Withdrawals Explained	Total Score
Garra G, (2005)¹⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	No	12
Stanley R, (2005)¹⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	13
Smitherman HF, (2005)¹⁷	No	Yes	Yes	Yes	Yes	Yes	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	8
Levine DA, (2004)¹⁸	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	11
Titus MO, (2003)¹⁹	No	Yes	Yes	Yes	Yes	Yes	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	No	7
Bonsu BK, (2003)²⁰	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Yes	Not clear	Yes	9
Herr SM, (2001)²¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	13
Bachur R, (2001)²²	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	Not clear	Yes	Not clear	Not clear	8
Kaplan RL, (2000)²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	13
Lin DS, (2000)²⁴	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes	10
Byington CL, (1999)²⁵	Not clear	Yes	Yes	Yes	Yes	Yes	No	No	No	Not clear	Not clear	Yes	Not clear	Yes	7
Brik R, (1997)²⁶	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	12
Chiu CH, (1994)²⁷	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes	9
Hoberman A, (1993)²⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes	11
Bonadio WA, (1993)²⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	13
Bonadio WA, (1992)³⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	10
Bonadio WA, (1991)³¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	Yes	12

Study ID	Q1. Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8. Details of index test described	Q9. Replication	Q10. Index test interpreted without knowledge of RS	Q11. Ref. stand interpreted without knowledge of RS	Q12. Same Clinical Data Available	Q13. Uninterpretable Test Results	Q14. Withdrawals Explained	Total Score
Broner CW, (1990)³²	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Yes	Not clear	Not clear	9
Crain EF, (1990)³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	12
Wasserman GM, (1990)³⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
King JC, Jr., (1987)³⁵	Not clear	Yes	Not clear	Yes	Yes	Yes	No	Yes	No	Not clear	Not clear	Yes	Not clear	Not clear	6
Berkowitz CD, (1985)³⁶	Not clear	Yes	Not clear	Not clear	No	Not clear	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Not clear	3
Dagan R, (1988)³⁷	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	11
Dagan R, (1985)³⁸	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	No	No	Not clear	Not clear	Yes	Not clear	Not clear	6
Bilavsky E, (2008)³⁹	Not clear	Yes	Not clear	Not clear	Yes	Not clear	Not clear	No	No	Not clear	Not clear	Not clear	Not clear	Yes	3
Hsiao AL, (2006)⁴⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	12
Rittichier KR, (2005)⁴¹	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Not clear	Not clear	8
Brown L, (2005)⁴²	Not clear	Not clear	Yes	Not clear	No	Not clear	Not clear	No	No	Not clear	Not clear	Yes	Not clear	Yes	3
Byington CL, (2004)⁴³	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Not clear	Yes	Not clear	No	8
Kuppermann N, (1997)⁴⁴	Yes	Yes	Yes	Not clear	Yes	Not clear	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	7
Bonadio WA, (1994)⁴⁵	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	9
Crain EF, (1988)⁴⁶	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Not clear	9
Bonadio WA, (1987)⁴⁷	Yes	Yes	Not clear	Not clear	Yes	Yes	Not clear	No	Yes	Not clear	Not clear	Yes	Not clear	Yes	7
Rosenberg N, (1985)⁴⁸	Not clear	Yes	Yes	Yes	Yes	No	No	Yes	No	Not clear	Not clear	Yes	Not clear	Not clear	6

Study ID	Q1. Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8. Details of index test described	Q9. Replication	Q10. Index test interpreted without knowledge of RS	Q11. Ref. stand interpreted without knowledge of RS	Q12. Same Clinical Data Available	Q13. Uninterpretable Test Results	Q14. Withdrawals Explained	Total Score
Caspe WB, (1983)⁴⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	Yes	Not clear	Yes	11
Crain EF, (1982)⁵⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	Not clear	11
Wolff M, (2009)⁵¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	No	Yes	10
Gomez B, (2010)⁵²	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	Yes	9
Mintegi S, (2009)⁵³	Not clear	Not clear	Not clear	Not clear	No	Not clear	Not clear	Yes	No	Not clear	Not clear	Yes	No	Yes	3
Jordan I, (2009)⁵⁴	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Not clear	No	Not clear	Not clear	Yes	No	Not clear	6
Rudinsky SL, (2009)⁵⁵	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	No	8
Schwartz S, (2009)⁵⁶	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	No	Not clear	Yes	No	Yes	9
Maniaci V, (2008)⁵⁷	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	No	Yes	11
Bilavsky E, (2008)⁵⁸	Not clear	Not clear	Yes	Not clear	Not clear	Yes	Not clear	No	No	Not clear	Yes	Not clear	No	No	3
Olaciregui E, I, (2009)⁵⁹	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	No	Yes	10
Reardon JM, (2009)⁶⁰	Not clear	No	Yes	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Not clear	8
Bilavsky E, (2009)⁶¹	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Yes	Not clear	Yes	Not clear	No	Not clear	8
Chen C-J, (2009)⁶²	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	No	Yes	Not clear	Not clear	Not clear	No	Not clear	6
Shin SH, (2009)⁶³	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	No	Yes	Not clear	Yes	Not clear	No	Not clear	7
Bressan S, (2010)⁶⁴	No	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear	No	Yes	7
Condra CS, (2010)⁶⁵	No	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	No	No	Yes	7

Study ID	Q1. Spectrum of patients	Q2. Selection criteria	Q3. Ref stand & index test length of time	Q4. Ref stand vs. index test period of time	Q5. Reference standard?	Q6. Same ref. standard?	Q7. Ref. stand independent of index test	Q8. Details of index test described	Q9. Replication	Q10. Index test interpreted without knowledge of RS	Q11. Ref. stand interpreted without knowledge of RS	Q12. Same Clinical Data Available	Q13. Uninterpretable Test Results	Q14. Withdrawals Explained	Total Score
Bilavsky E, (2010)⁶⁶	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Not clear	Not clear	Not clear	Yes	Yes	Yes	9
Watt K, (2010)⁶⁷	Yes	Yes	Yes	Not clear	Yes	Not clear	Yes	Yes	Yes	Not clear	Yes	Yes	No	No	9
McCarthy CA, (1990)⁶⁸	no	Yes	Not clear	Not clear	Not clear	v	Yes	Yes	no	Not clear	Not clear	Yes	no	no	5
Baker MD, (1990)⁶⁹	Yes	no	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	no	8
Caviness AC, (2008)⁷⁰	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	no	8
Meehan WP, (2008)⁷¹	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	No	Yes	9

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