**Identification of Pediatric Sepsis for Epidemiologic Surveillance**

**Using Electronic Clinical Data**

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**eTable 1: Quality Improvement Electronic Criteria to Identify Sepsis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Criteria** | **Unit** | | | |
| **PICU** | **ED** | **Oncology** | **Med-Surg Ward** |
| Blood culture order | Required | Not required | Not required | Required |
| New qualifying antimicrobial ordera | New order 1 hr before to 12 hrs after blood culture | New order and administration in the ED via sepsis pathway | New order within 12 hours of new fever | New order 1 hr before to 4 hrs after blood culture |

a”New antimicrobial order” requires that patient not ordered for that antibiotic within prior 24 hours

bQualifying antimicrobials include acyclovir, amikacin, ampicillin, aztreonam, cefepime, cefotaxime, ceftriaxone, ciprofloxacin, clindamycin, gentamicin, imipenem, linezolidmeropenem, metronidazole, oxacillin, piperacillin, and vancomycin

**eTable 2: Adjudication Criteria for Severe Sepsis and Septic Shock**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No infection** | **Suspected or Proven Infection Types** | | | |
| **Suspected or Proven Viral Infection** | **Suspected**  **Bacterial Infection** | **Documented Bacterial/Fungal infection** | **Culture-negative Infection** |
| * All microbiology tests negative * Low clinical suspicion for infection (based on notes) * Includes presumed aspiration w/out definitive evidence of infection (regardless of antibiotic treatment) * Patient did not receive a treatment course of antimicrobials | * Negative bacterial cultures * Radiological studies not diagnostic of bacterial infection (e.g. clear lobar PNA, abscess) * Positive viral testing or strong clinical suspicion for viral infection | * Negative bacterial cultures but suspected source of bacterial infection (typically documented in progress notes): * UTIa * Pneumoniac * CNS/meningitis * Peritonitis * Abscess * Endocarditis * Mediastinitis * Osteomyelitis * Sinusitis * Pharyngitis * Gastroenteritis * Suspected toxic shock syndrome | * Documented bacterial or fungal infection * UTIb * Pneumoniad * Positive pathogenic culture from typically sterile site * Culture-positive toxic shock syndrome | * Cultures negative for BACTERIAL, FUNGAL, or VIRAL infection * High suspicion documented in progress notes for infectious etiology to symptoms * Treatment for at least 5-7 days with broad spectrum antimicrobials (not including prophylactic antimicrobials) |

**aSuspected UTI** (any of the following criteria met):

1. Urinalysis positive for leukocyte esterase or nitrites or ≥10 WBCs
2. Urinalysis positive for bacteria plus temp instability and symptoms

**bDefinite UTI**

1. Urine culture positive with ≥105 CFU of 1-2 organisms with temp instability or symptoms

**cPossible Pneumonia:**

1. At least 1 of the following on chest x-ray: new or progressive and persistent infiltrate, consolidation, cavitation, or pneumatoceles that is not clearly atelectasis per attending radiologist AND
2. At least 3 of the following: fever or hypothermia (>38.4°C or <36.5°C) with no other recognized cause, leukopenia (< 4,000 WBC/mm3) or leukocytosis (≥ 15,000 WBC/mm3), new onset purulent sputum or change in character of sputum or increased respiratory secretions or suctioning requirements, new onset or worsening cough or dyspnea or apnea or tachypnea, rales or bronchial breath sounds, or worsening gas exchange (hypoxemia or increased oxygen requirements)
3. Declarative diagnosis of pneumonia by infectious disease consultant

**dDefinite Pneumonia:**

1. Pneumonia read on CXR AND
2. Positive culture from blood or pleural fluid OR positive mycoplasma PCR

**Organ Dysfunctions Defining Severe Sepsis/Septic Shock (modified from Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2-8):**

1. **Septic Shock** = **Cardiovascular dysfunction**: Provision of 40ml/kg fluid boluses within a 6 hour period for Systolic BP < 5th percentile for age\* (see table) or vasoactive infusion support (epinephrine, norepinephrine, dopamine, etc) for hypotension or poor perfusion (excludes low dose dopamine or milrinone for right heart support in pulmonary hypertension patients)
2. **Severe Sepsis** = Two or more organ system dysfunctions
   1. **Respiratory:** Use of CPAP, BiPAP, or invasive mechanical ventilation (or increased duration of support or increased settings in chronically ventilated patient, not including increased FiO2 without increases in other support) for lung disease
   2. Renal: creatinine ≥ 2 times normal for age OR ≥ 1.5 times baseline (for patients with pre-existing kidney disease) OR new renal replacement therapy (dialysis, CVVH, CRRT, etc)
   3. **Hepatic:** total bilirubin ≥ 4 mg/dL OR alanine aminotransferase (ALT) ≥ 2 times normal for age or ≥ 2 times baseline (for patients with chronic liver dysfunction)
   4. **Hematologic:** Platelets < 80

OR

Plate count decline of at least 50% in platelets from highest value over past 3 days (chronic thrombocytopenia)

OR

INR >2.0

* 1. **Neurologic:** GCS ≤ 11 (only assess GCS in absence of sedation) OR alteration in mental status from baseline NOT due to sedation. Goal is to detect altered mental status due to brain hypoperfusion (agitation/severe irritability, inconsolability, etc.).

|  |  |
| --- | --- |
| **Age** | **Systolic BP < 5th %ile\*** |
|
| **0 to 7 days** | <60 |
| **8 to 30 days** | <65 |
| **31 d to < 2 yrs** | <70 |
| **2 to < 6 yrs** | <75 |
| **6 to < 13 yrs** | <85 |
| **> 13 yrs** | <90 |

NOTE: For new episodes that flag within the QI cohort in which the patient already has an established (i.e., no longer “acute”) sepsis course, the new episode should be adjudicated with regard to the presence of NEW/WORSENING/EVOLVING infection and/or NEW/WORSENING/EVOLVING organ dysfunction at the time of the new episode.

**eTable 3: Patient Characteristics for All Eligible Hospital Encounters**

| Variable | Total Study Period | Derivation Period | Validation Period |
| --- | --- | --- | --- |
| Number of hospital encounters | 832,550 | 93,897 | 64,388 |
| Age, years | 5 (1-11) | 5 (1-11) | 5 (1-11) |
| Age categories) |  |  |  |
| <1 month | 13,809 (2) | 1,581 (2) | 1,218 (2) |
| 1 to < 12 months | 113,465 (14) | 12,382 (13) | 9057 (14) |
| 12 to <24 months | 103,463 (12) | 11,345 (12) | 7983 (13) |
| 2 to <5 years | 182,876 (22) | 19,746 (21) | 13,731 (21) |
| 5 to <12 years | 233,294 (28) | 27,071 (29) | 17,542 (27) |
| 12 to <18 years | 159,827 (19) | 18,800 (20) | 12,754 (20) |
| ≥18 years | 25,816 (3) | 2,972 (3) | 2103 (3) |
| Sex, male | 439,511 (53) | 49,042 (52) | 33,936 (53) |
| Race |  |  |  |
| White | 231,918 (28) | 25,621 (27) | 18,107 (28) |
| Black | 470,076 (57) | 50,694 (54) | 34,014 (53) |
| Asian | 28,586 (3) | 3,715 (4) | 2,516 (4) |
| Multiple races | 16,211 (2) | 2,140 (2) | 1,535 (2) |
| Other | 85,759 (10) | 11,727 (13) | 8216 (13) |
| Number of CCC present |  |  |  |
| None | 717,534 (86) | 80,591 (86) | 55,004 (85) |
| One | 64,595 (8) | 7,016 (8) | 4,772 (7) |
| Two | 24,376 (3) | 3,111 (3) | 2,206 (4) |
| Three or more | 26,045 (3) | 3,179(3) | 2,406 (4) |
| Type of CCC |  |  |  |
| Cardiovascular | 13,662(2) | 1621 (2) | 1210 (2) |
| Respiratory | 11,635 (1) | 1256 (1) | 1066 (2) |
| Neurologic/Neuromuscular | 25,626 (3) | 3096 (3) | 2209 (3) |
| Hematologic/Immunodeficiency | 25,825 (3) | 2950 (3) | 1985 (3) |
| Oncologic | 22,482 (3) | 2612 (3) | 1750 (3) |
| Renal/Urologic | 8579 (1) | 1171 (1) | 839 (1) |
| Gastrointestinal | 30,096 (4) | 3762 (4) | 2778 (4) |
| Metabolic | 14,974 (2) | 1949 (2) | 1475 (2) |
| Other congenital/Genetic | 17,872 (2) | 1887 (2) | 1361 (2) |
| Neonatal | 3,673 (<1) | 390 (<1) | 345 (1) |
| Technology dependent | 32,854 (4) | 4163 (4) | 3053 (5) |
| Solid organ transplantation | 3890 (<1) | 280 (<1) | 214 (<1) |
| Admitted to hospital | 207,368 (25) | 22,462 (24) | 22,309 (24) |
| Admitted through emergency department | 123,149 (59) | 13,613 (61) | 9,487 (61) |
| Admitted through other process | 84,219 (41) | 8,696 (39) | 6,092 (39) |

CCC, chronic comorbid conditions

Data are presented as median (interquartile range) or n (%)

**eTable 4: Multivariable Poisson Regression Model for Incidence of Sepsis Episodes Among All Hospital Encounters, 2011-2018**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **aIRR** | **95% Confidence Interval** | ***P Value*** |
| Year | 1.07 | 1.06, 1.08 | <0.001 |
| Age, years | 1.02 | 1.01, 1.02 | <0.001 |
| Sex |  |  |  |
| Female | Reference |  |  |
| Male | 1.0 | 0.95, 1.06 | 0.94 |
| Race |  |  |  |
| White | Reference |  |  |
| Black | 0.59 | 0.55, 0.63 | <0.001 |
| Asian | 1.08 | 0.95, 1.23 | 0.22 |
| Multiple races | 0.98 | 0.82, 1.15 | 0.77 |
| Other | 1.25 | 1.17, 1.34 | <0.001 |
| CCC, number of categories | 2.16 | 2.14, 2.19 | <0.001 |

aIRR, adjusted incidence rate ratio; CCC, chronic comorbid conditions

Reported incidence rate ratio is adjusted for all other variables listed.

**eTable 5: Multivariable Logistic Regression Model for Mortality Among Sepsis Episodes Identified by the Surveillance Algorithm, 2011-2018**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **aOR** | **95% Confidence Interval** | ***P Value*** |
| Year | 0.97 | 0.93, 1.03 | 0.38 |
| Age, years | 1.0 | 0.98, 1.01 | 0.72 |
| Sex |  |  |  |
| Female | Reference |  |  |
| Male | 0.97 | 0.78, 1.21 | 0.78 |
| Race |  |  |  |
| White | Reference |  |  |
| Black | 0.61 | 0.46, 0.82 | 0.001 |
| Asian | 0.36 | 0.17, 0.76 | 0.007 |
| Multiple races | 0.46 | 0.20, 1.08 | 0.08 |
| Other | 0.87 | 0.66, 1.14 | 0.30 |
| Location at sepsis onset |  |  |  |
| Community-acquired | Reference |  |  |
| Hospital-acquired | 2.95 | 2.32, 3.74 | <0.001 |
| CCC present |  |  |  |
| No | Reference |  |  |
| Yes | 3.18 | 1.94, 5.21 | <0.001 |
| Number of organ dysfunctions |  |  |  |
| One | Reference |  |  |
| Two | 2.78 | 2.05, 3.78 | <0.001 |
| Three | 6.15 | 4.45, 8.49 | <0.001 |
| Four | 12.31 | 8.49, 17.83 | <0.001 |
| Five | 21.38 | 13.21, 34.57 | <0.001 |
| Six | 45.77 | 16.99, 123.3 | <0.001 |

aOR, adjusted odds ratio; CCC, chronic comorbid conditions

Reported aOR is adjusted for all other variables listed.

**eFigure Legends**

**eFigure 1: Patient Flow Diagram**

Total number of hospital episodes in the study period from January 1, 2011 through January 31, 2019, including number of hospital episodes included the in derivation and validation cohorts, number of suspected sepsis episodes flagged by the institutional quality improvement (QI) criteria, and the number of suspected sepsis episodes confirmed with or without sepsis after manual adjudication. All 832,550 hospital episodes were used for the epidemiology analyses while a subset of 93,987 hospital episodes were used for the derivation cohort and a separate subset of 64,388 hospital episodes were used for the validation cohort.

**eFigure 2: Test Characteristics using Derivation and Validation Cohorts**

The 2x2 tables comparing adjudication of suspected sepsis episodes with categorization of sepsis by the surveillance algorithm in the derivation (A) and validation (B) cohorts. Calculation of the test characteristics for the surveillance algorithm relative to the adjudicated reference-standard is shown.

**eFigure 3: Proportion of Sepsis Episodes that Included Hyperlactatemia Over Time**

The proportion of sepsis episodes identified by the surveillance algorithm in which criteria for organ dysfunction included hyperlactatemia (defined as blood lactate ≥2.0 mmol/L) with or without other organ dysfunctions (blue line) or included hyperlactatemia as the only organ dysfunction (orange line). There was no association between calendar year and the proportion of sepsis episodes that included hyperlactatemia as organ dysfunction (odds ratio 1.01, 95% confidence interval 0.99, 1.04; p=0.27). Error bars indicate 95% confidence intervals.