Supplementary Appendix

Infection-Specific Definitions of Hospitalization for Serious Infection

We used a pre-specified adjudication process to determine whether each abstracted medical record corresponded to a true infection or not. Previous validation studies and expert clinical knowledge were used to define specific a priori definitions for each infection type. Information abstracted from the medical record was compared to these a priori definitions for each infection type to make the final determination of whether a hospitalization represented a true infection or not.

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I. **Sepsis/Septicemia/Bacteremia/Septic Shock/Generalized Infection**

Either of the following [1 or 2]:

1. **Positive culture of a non-contaminant pathogen**
   i. Positive blood culture [any of the following (1-2)]
      1. Any gram-negative organism, except:
         a. No predominant organism
      2. A gram positive organism, except:
         a. Coagulase-negative *Staphylococcus*
         b. *Bacillus* spp. (other than *Bacillus anthracis*)
         c. *Corynebacterium* spp.
         d. *Propionibacterium* spp.
         e. *Micrococcus*
         f. Diptheroids
         g. Viridians Group Streptococci
         h. Enterococci
         i. *Clostridium perfringens*
         j. *Aerococcus*
         k. *Alcaligenes faecalis*
         l. *Citrobacter*
         m. *Neisseria subflava*
         n. *Stomatococcus*
         o. *Streptococcus bovis*
         p. *Veillonella candidemia*
         q. *Mycobacterium tuberculosis*
         r. *S. salivarius*
         s. “Gram Positive”
         t. “No predominant organism”
         u. *Streptococcus alpha*

2. **At least two of the following, documented at admission +/- 2 days [i-iii]**
   i. **Hypotension**
      1. Systolic BP ≤ 90 mmHg
      2. Reduction of systolic BP of 40mmHg from earliest measurement collected during the admission of interest
   ii. **Two of the following [1-4]**:
      1. Temperature ≥ 38°C or ≤ 36°C
      2. Heart rate ≥ 90 beats/minute
      3. Respiratory rate ≥ 20 breaths/min or PaCO₂ < 32 mmHg
      4. WBC ≥ 10,000 cells/mm³ or ≤ 4,500 cells/mm³ or WBC with > 10 % immature (band) forms
   iii. **Initiation of antibiotic treatment specifically for**
       sepsis/septicemia/bacteremia/septic shock/generalized infection
II. Pneumonia

1. Pneumonia identified through examination (all three of the following [a-c]):
   a. One of the following admission findings indicative of respiratory findings:
      1. New and/or increased cough
      2. Shortness of breath
      3. Pleuritic chest pain
      4. New purulent production
      5. Altered mental status (“agitation” and “lethargy” included)
      6. Crackles
         a. Physical evidence of consolidation such as egophony, whispered pectoriloquy, etc.
   b. One of the following examination findings indicative of systemic infection [1-4]:
      1. Temperature (T ≥ 100.4°F (38°C) or ≤ 96°F) in first 48 hours of admission
      2. Systolic BP < 90mmHg
      3. Shock
         a. Volume nonresponsive hypotension
      4. Blood peripheral WBC (≥ 10.0 x 10⁹/L or ≤ 4.5 x 10⁹/L)
   c. Treatment with antibiotics/antivirals indicated for suspected infection

OR

At least two of the following [1-3]:

1. Two of the following from #1 ([a and b], [a and c], or [b-c])
2. Any of the following findings listed on chest imaging from radiologic report documented at admission +/- 2 days
   a. Pneumonia
   b. Lung abscess
   c. Opacity consistent with pneumonia/lung abscess
   d. Infiltrate consistent with pneumonia/lung abscess
   e. Consolidation consistent with pneumonia/lung abscess
   f. Increased density consistent with pneumonia/lung abscess
   g. Pleural effusion consistent with pneumonia/lung abscess
   h. Interstitial edema consistent with pneumonia/lung abscess
3. Sterile Site Laboratory Findings
   i. Any one of the following [i through v]
      i. Sputum lab findings [any one of the following (1, 2)]:
         1. Sputum culture/PCR/serology/gram stain positive for an agent that is not considered a contaminant [see exclusion list below]:
            a. Aspergillus species, Enterococcus species, viridians group streptococci, and yeast
         2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen
      ii. Blood lab findings [either of the following (1-3)]
         1. Blood culture/PCR/serology positive for an agent that is not considered a contaminant [see exclusion list below]:
            a. Exclusions
               i. Coagulase-negative Staphylococcus
ii. *Bacillus* spp. (other than *Bacillus anthracis*)

iii. *Corynebacterium* spp.

iv. *Propionibacterium* spp.

v. *Micrococcus*

vi. Diptheroids

vii. Viridians Group Streptococci

viii. Enterococci

ix. *Clostridium perfringens*

x. Aerococcus

xi. *Alcaligenes faecalis*

xii. *Citrobacter*

xiii. *Neisseria subflava*

xiv. *Stomatococcus*

xv. *Streptococcus bovis*

xvi. *Veillonella candidemia*

xvii. *Mycobacterium tuberculosis*

xviii. *S. salivarius*

2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen

iii. Pleural fluid lab findings [either of the following (1, 2)]

1. Culture/PCR/serology positive for a bacterial pathogen

2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen

iv. Bronchoscopic specimen or deep endotracheal tube aspiration lab findings [either of the following (1, 2)]

1. Culture/PCR/serology positive for a bacterial pathogen

2. Positive viral study (culture/PCR/antigen screen) for a viral pathogen

v. Urine antigen detection testing [either of the following (1, 2)]

1. *Legionella pneumophila*

2. *Streptococcus pneumoniae*
III. Cellulitis/Soft-Tissue Infection

Both of the following:

1. Any mention of the following with recent onset (<14 days) [any of the following]
   a. Skin erythema
   b. Surgical site infection
   c. Superficial central line infection
   d. Ostomy site infection
   e. Skin infection with associated lymphangitis
2. Antibiotic treatment initiated for suspected infection
IV. Endocarditis

Any one of the following [1-3]:

1. Major Criteria [both of the following]:
   a. Suggestive microbiology [at least one of the following]:
      i. Positive blood culture of an endocarditis organism [any of the following]:
         1. Streptococcus bovis
         2. Viridians streptococci
         3. Staphylococcus aureus
         4. Enterococcus spp.
         5. HACEK organisms
         6. Coagulase negative staphylococci
   b. Evidence of endocardial involvement [at least one of the following]:
      i. New regurgiant murmur (a change in a preexisting murmur does not get scored)
      ii. Echocardiogram suspicious for any of the following:
         1. Intracardiac mass with no alternative explanation
         2. Endocardial abscess
         3. New partial prosthesis dehiscence
         4. Vegetation on valve
2. Minor Criteria [at least 4 of the following]:
   a. Predisposing valvular disease or IV drug use
   b. Temperature ≥ 100.4°F or 38°C
   c. Vascular phenomena
      i. Janeway lesions, conjunctival hemorrhages, arterial emboli, septic pulmonary
         infarcts, mycotic aneurysm, intracranial bleed
   d. Immunologic phenomena
      i. Osler nodes, Roth Spots, elevated Rheumatoid factor, hematuria in non-catheter
         urine, or other evidence of glomerulonephritis
   e. Positive blood cultures
      i. Excluding a single positive culture for coagulase negative staphylococci or a
         single positive culture for an organism that does not fall into the “reasonable
         endocarditis organism” (i.e. coagulase-positive and coagulase-negative S. aureus,
         Enterococcus, viridians group Streptococci, S. bovis, HACEK organisms)
   f. Positive serology for Brucella, Bartonella, Legionella, or Chlamydia
   g. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected
      infection
3. At least one Major Criteria AND 3 minor criteria.
V. **Meningitis/Encephalitis**

Any one of the following [1 or 2]:

1. Both of the following [a-b]
   a. Laboratory Findings [any one of the following (i-ix)]
      i. CSF demonstrates any bacterium
         1. Excluding Diptheroids, Propionibacteria, Bacillus, Coagulase Negative *Staphylococcus*
      ii. CSF demonstrates Diptheroids, Propionibacteria, Bacillus, Coagulase Negative *Staphylococcus* in the setting of past neurosurgical intervention AND physicians elected to treat with antibacterials
      iii. Blood cultures positive for any of the following:
          1. *S. pneumoniae*
          2. *H. influenza*
          3. *Neisseria meningitidis*
          4. Group B Streptococcus
      iv. Stool cultures positive for enterovirus
      v. Throat or sputum cultures positive for *Neisseria meningitidis* in the setting of a rapid onset, overwhelming infection syndrome, including petechiae
      vi. Serology positive for *Mycoplasma, Leptospira, measles, mumps, lymphocytic choriomeningitis virus, arboviruses* (e.g. St. Louis encephalitis virus), or HIV (if historically consistent with acute seroconversion).
      vii. Brain biopsy demonstrates encephalitis
     viii. Positive CSF culture or PCR detection for any of the following
      ix. Acute or convalescent serology demonstrates positive antibody pattern for any of the following:
         1. Encephalitis arbovirus (La Crosse, St. louis, Eastern Equine, Western Equine, Powassan, Japanese, West Nile)
   b. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected meningitis/encephalitis

2. At least two of the following [a-d]
   a. Clinical meningitis/encephalitis [at least two of the following]:
      i. Petechial rash
      ii. Nuchal rigidity (by history or exam)
      iii. Altered sensorium
      iv. Fever
      v. Altered level of consciousness, including “agitation” or “lethargy”
      vi. Behavioral change
      vii. Diminished level of consciousness (not easily roused)
      viii. History of any of the following: headaches, altered mental status, or recent exposure to patient with known bacterial meningitis
      ix. Reduction in fever within 72 hours of starting anti-bacterial
   b. Inflammatory CSF [at least one of the following i-ii]
      i. Pleocytosis: $\geq 15$ WBC/mm$^3$ (after subtracting one WBC for every 1,000 RBC)
      ii. Elevated protein (based on local lab-determined upper limits)
   c. Suggestive Findings [at least one of the following (i-iv)
i. Septic syndrome
ii. Focal neurological deficits documented during examination (such as flaccid paralysis or speech alterations for West Nile Virus)
iii. Abnormal imaging
   1. Computed tomography or magnetic resonance imaging (MRI) demonstrating focal edema or inflammation or hemorrhage
   2. Indicated as “meningitis/encephalitis” or “compatible with meningitis/encephalitis” or “cannot rule out meningitis/encephalitis”
iv. Findings indicating an abnormal electroencephalography (such as focal periodic discharges)
d. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for presumed meningitis/encephalitis
VI. **Pyelonephritis**

At least two of the following [1-4]:

1. Suggestion of infection [at least one of the following]:
   a. Temperature ≥ 100.4°F (38°C)
   b. Peripheral blood WBC ≥ 10,000/mm³
   c. Positive blood culture for any of the following:
      i. Gram Negative Rods
      ii. *Enterococcus spp.*
      iii. *Staphylococcus saprophyticus*
   d. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected infection

2. Strong renal localization [at least one of the following]:
   a. CT, MRI, or Ultrasound Suggestive of Renal Inflammation

3. Minor Criteria [at least two of the following]:
   a. Flank pain
   b. Costovertebral angle tenderness
   c. Complaints of dysuria, frequency, or suprapubic pain
   d. Any pyuria
   e. Urine culture positive for a single organism

4. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected pyelonephritis
VII. **Septic Arthritis/Osteomyelitis**

Any one of the following (1-5):

1. Synovial fluid gram stain or tissue gram stain or special stain demonstrating any organism
2. Joint culture/PCR/serology positive for any organism
3. At least two of the following (a-d):
   a. Positive blood culture/PCR/serology
   b. Joint with acute (< 7 days) worsening of inflammatory features *(at least two of the following)*:
      i. Pain on history
      ii. ROM
      iii. Warmth
      iv. Effusion
      v. Swelling
      vi. Limited range of motion
   c. Antibiotic/antiviral/antifungal/antifungal treatment initiated/recommended for suspected infection
   d. Any one of the following (i-iv)
      i. Synovial fluid WBC ≥ 30,000/mm³
      ii. Synovial fluid WBC ≥ 60,000/mm³ with > 75% PMNs
      iii. Skin lesions, tenosynovitis, or urethral/cervical/rectal Gram stain or culture suggestive of *Neisseria gonorrhoeae*
      iv. Any indication of the following in the synovial fluid: needle-like crystals, CPPD crystals, uric acid.
4. Positive bone biopsy [at least one of the following (a-c)]:
   a. Positive culture for any organism
   b. Positive gram stain
5. Imaging and indirect features *[at least two of the following (a-c)]:
   a. Consistent imaging [at least one of the following (i-iv)]:
      i. Plain X-ray read by a radiologist as suggestive of osteomyelitis
      ii. CT Scan read by a radiologist as suggestive of osteomyelitis
      iii. MRI read by a radiologist as suggestive of osteomyelitis
      iv. Bone scan or WBC scan read as suggestive of osteomyelitis
   b. Suggestive indirect features *[at least one of the following (i-viii)]:
      i. Temperature > 100.4°F (38°C)
      ii. Bony pain or tenderness or erythema over bone suspected to be infected
      iii. Draining soft tissue sinus over bone suspected to be infected
      iv. Positive “probe to bone” (or visible bone in deep ulcer at suspected site)
      v. Blood culture positive for *S. aureus*
      vi. ESR ≥ 75 mm/hour
      vii. Intravenous drug use or indwelling catheter
      viii. Inflammation on imaging associated with an orthopedic prosthesis
   c. Positive culture for any organism form wound sample over the bone suspected of infection
   d. Antibiotic/antiviral/antifungal treatment for suspected infection
VIII. References

1. Grijalva CG, Chung CP, Stein CM, et al. Computerized definitions showed high positive predictive values for identifying hospitalizations for congestive heart failure and selected infections in Medicaid enrollees with rheumatoid arthritis. Pharmacoepidemiology and drug safety 2008; 17(9): 890-5.
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3. Patkar NM, Curtis JR, Teng GG, et al. Administrative codes combined with medical records based criteria accurately identified bacterial infections among rheumatoid arthritis patients. Journal of clinical epidemiology 2009; 62(3): 321-7, 7.e1-7.