**Supplemental Table 2. Representative Case Examples from Each Category of Post-Hoc Likelihood of Bacterial Infection**

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| **Category**  n (%) | **Description of Case** |
| **Definite**  115 (38)  *Compatible clinical syndrome and pathologic diagnosis of infection, or operative recovery of pus, or positive cultures from a normally sterile site, or positive cultures from a normally non-sterile site via a high quality sample consistent with infection* | A middle-aged man with hypertension and hyperlipidemia presented with fevers, leg pain, and redness spreading from his ankle to his thigh over the past 2 days. His temperature was 39 degrees Celsius in the ED. Exam was notable for skin tears, but no obvious wounds or abscesses. WBC count was 9.7 with 82% neutrophils. Ultrasound of his leg was negative for thrombosis. Superficial culture grew rare coagulase-negative Strep. One of four blood cultures in ED grew *Peptostreptococcus* species, but repeat blood cultures were negative. He was admitted to the ward. He underwent surgical incision and drainage of a pocket of purulent fluid without muscle or fascial involvement, and a fluid culture grew Group G Streptococcus. He was treated with vancomycin, cefazolin, and clindamycin, then narrowed to cefazolin after culture results. WBC initially peaked at 16.1, then normalized after surgical drainage. Discharged on hospital day 13. *Definite bacterial infection given operative recovery of pus and culture-proven Group G Streptococcus consistent with skin/soft tissue-infection.* |
| A young woman with obesity presented with nausea, vomiting, diarrhea, abdominal pain, and fevers for two days. She was febrile to 38 degrees Celsius in ED. WBC count was 19.4 (91% neutrophils). CT abdomen and pelvis showed diffuse colitis, not specific for infection vs inflammatory. Blood and urine cultures were negative. Stool culture grew Shigella (fecal leukocytes not checked). She was treated with piperacillin/tazobactam and metronidazole, then ciprofloxacin. Clinically she improved, defervesced, and her WBC normalized after three days of antibiotics. *Definite bacterial infection given stool culture with pathogenic organism along with compatible imaging and clinical syndrome.* |
| An elderly man with history of end-stage renal disease on dialysis via arterio-venous graft in the upper extremity with recent admission for graft revision presented from his dialysis center with pain, redness, and purulent drainage from graft site. He was afebrile with a normal WBC in ED. Frank pus was seen from graft site. He was admitted to the ward and underwent incision and drainage followed by excision of graft site. Cultures from his graft grew MRSA. He received vancomycin at his dialysis center, then ceftazidime and gentamicin in the ED, then was treated with daptomycin per Infectious Disease consult. *Definite bacterial infection given operative recovery of pus and positive tissue culture for MRSA.* |
| **Likely**  81 (27)  *Did not meet criteria for definite bacterial infection but had a compatible clinical syndrome and the patient was treated with antibiotics and improved, no clear alternate etiology was found, and there was no alternate reason for clinical improvement* | An elderly woman with a history of hypothyroidism and recent diverticulitis presented with abdominal pain and constipation. She was hypothermic to 34.4 degrees Celsius in the ED.WBC was 10.7 with 78% neutrophils. She was ill-appearing but with a reassuring abdominal exam. CT of the abdomen and pelvis showed marked dilation of large bowel and circumferential thickening of sigmoid with surrounding stranding, plus abrupt transition in distal sigmoid possibly representing a stricture. She received IV ciprofloxacin and metronidazole in the ED, which was continued throughout her stay. She was admitted to the ward. Work up included negative stool culture, stool ova and parasites, cultures for Yersinia, Vibrio, Giardia, Cryptosporidium, and C diff PCR. She underwent sigmoidoscopy on hospital day 5 with biopsies consistent with colitis. A biopsy culture grew vancomycin-resistant *Enterococcus* for which she never received treatment. Her abdominal pain and distension improved over course of hospitalization, her temperature normalized, and her WBC declined to 7.6. She was discharged on hospital day 6. *Likely bacterial colitis given compatible clinical syndrome and imaging and improvement with antibiotics; did not meet criteria for definite despite positive biopsy culture because she improved despite not receiving treatment for the only organism identified.* |
| A middle-aged woman with ovarian cancer undergoing chemotherapy and recent filgrastim administration presented from home with subjective fevers and fatigue. She was afebrile in the ED. Her WBC count was 30 (72% neutrophils, 3% bands). Urinalysis showed many (>100 per high powered field) WBC and 1+ bacteria, but with squamous cells present. Urine culture ultimately grew >100k *Citrobacter freundii*. Blood cultures were negative. Ultrasound of kidneys was unremarkable. No other source of infection was apparent. She was treated with ceftriaxone and doxycycline in the ED and discharged with doxycycline for five days. She was seen in clinic after completed antibiotics with repeat urinalysis which was negative for WBCs, and culture grew <1k mixed flora. *Likely bacterial urinary tract infection; however, does not meet criteria for definite given presence of squamous cells on urinalysis and did not receive the standard antibiotic course for the presumably causative organism.* |
| An elderly man with history of Alzheimer’s dementia presented from home with worsening agitation for several days after a change in medications by his neurologist and a new “wet” but unproductive cough and fever for one day. He was febrile to 39.6 degrees Celsius in the ED. WBC count was 7.6. Chest X-ray showed a left lower lobe infiltrate potentially consistent with pneumonia or aspiration. Procalcitonin was elevated to 1.48. Sputum gram stain showed rare polys and no organisms; culture grew abundant normal flora and rare MSSA. Blood cultures were negative. He was treated with ceftriaxone and azithromycin in the ED, then completed additional six days of ceftriaxone and doxycycline. He rapidly defervesced and his agitation improved, but he also had several medication changes including discontinuing benzodiazepines and increasing valproic acid. His procalcitonin was not rechecked; WBC remained stable. His hospital course was complicated by NSTEMI and atrial fibrillation. *Likely bacterial infection with respiratory source given clinical syndrome, elevated procalcitonin, and compatible imaging; did not meet criteria for definite infection given sputum had only rare polys on sputum sample and had plausible alternative explanations for his symptoms on presentation (medication changes +/- mild aspiration).* |
| **Unlikely**  55 (18)  *Clinical syndrome potentially consistent with infection and were treated with antibiotics, but had a more likely alternate diagnosis in retrospect and did not meet any of the criteria for definite or likely bacterial infection* | An elderly woman with history notable for polymyalgia rheumatica on chronic low dose prednisone, irritable bowel syndrome, and monoclonal gammopathy of undetermined significance presented with sudden onset severe diarrhea, nausea, and vomiting, as well as subjective fevers, which started hours after eating fish stew. She was febrile to 38.4 in ED. WBC count was elevated to 12.4 with 24% band forms. CT abdomen/pelvis showed fluid-filled small bowel loops without involvement of the large intestine. She received IV ciprofloxacin and IV fluids in ED, with persistent low systolic blood pressures in 80s-90s mmHg, so she was admitted to the ICU for observation but did not require vasopressors. Blood cultures were no growth. Stool culture grew normal flora. Fecal leukocytes, stool ova and parasites, and PCR for C difficile were all negative. She received a total of three days of antibiotics (ciprofloxacin, then ciprofloxacin and metronidazole). Her GI symptoms and fevers resolved and her WBC improved to 9.6 within 12 hours of presentation. *Unlikely bacterial infection given negative bacterial work up and more plausible non-infectious cause-- viral- or toxin-mediated gastroenteritis with hypovolemia, however there was no objective evidence to support this diagnosis (e.g. stool viral PCR).* |
| A young woman with history of anxiety presented with a non-productive of cough and subjective fever for three days. Her young son had a febrile illness six days prior to presentation which resolved without treatment. She saw her PCP on the day prior to ED visit, at which time she had a chest X-ray performed which was normal. She was febrile to 39.3 degrees Celsius in the ED. Her WBC was 4.7 (75 % neutrophils). Repeat chest X-ray showed mild hazy, interstitial opacities in the right middle lobe and lingula. PCR for influenza A and B were negative. No additional testing was done including no respiratory culture, viral panel, or urine Strep pneumo or Legionella antigens. She was treated with ceftriaxone and doxycycline in the ED and discharged with amoxicillin/clavulanic acid and doxycycline for one week. She was seen by her PCP four days later with resolution of fever and respiratory symptoms but new muscle pains, felt related to the antibiotics. She was switched to levofloxacin which was discontinued one day later due to continued muscle pains and resolution of infectious symptoms. In total, she received about seven days of antibiotics. *Unlikely bacterial infection due to absence of objective evidence (culture or highly suggestive imaging) for bacterial pneumonia; history and imaging most consistent with viral pneumonia, however there was no objective evidence for viral infection either.* |
| An elderly woman with severe dementia dependent for all ADLs and cared for at home by family presented with agitation and fever intermittently for over one week. She had been diagnosed with a urinary tract infection by her PCP one week ago and prescribed Macrobid for 7 days, of which she had completed 5 days at time of ED presentation. Urinalysis in PCP office had shown no leukocyte esterase or nitrites and a culture grew 10-50k E coli sensitive to Macrobid and 10-50k mixed organisms; no sediment from that sample was sent. In the ED, she was febrile to 38.3 degrees Celsius and severely agitated requiring Haldol. Her WBC 11.4. Chest X-ray was unremarkable. Urinalysis in ED was negative for leukesterase or nitrites; sediment showed <1 WBC, <1 squamous cell, and no bacteria. She received one dose of ceftriaxone. Family declined admission and she was discharged without additional antibiotics, but had several presentations to ED and Urgent Care over the next week during which she had negative urinalyses and urine cultures and received additional single doses of antibiotics. *Unlikely bacterial infection given absence of suggestive urinalysis or urine culture from good quality specimen despite repeated samples; had received adequate treatment for only organism identified without improvement in symptoms; however, no clear alternative explanation for presentation was evident.* |
| **Definitely None**  49 (16)  *Clear non-infectious diagnosis that accounted for the patient’s clinical syndrome and no evidence of a concurrent bacterial process* | A middle-aged woman with a history of obesity status post Roux-en-Y Gastric Bypass, peripheral neuropathy, and non-alcoholic fatty liver disease without known cirrhosis presented with confusion, disorientation, and odd affect for days. She was afebrile with normal WBC (10.8) in the ED. She was treated with ceftriaxone once in ED, but did not receive any further antibiotics. Chest X-ray was unremarkable. Blood cultures were negative. Urinalysis was unremarkable. She was admitted to ward and underwent extensive neurologic and metabolic work up. She was treated empirically for Wilson’s disease with zinc and chelation; Wernicke’s encephalopathy with high dose thiamine; and hepatic encephalopathy with lactulose and rifaximin. Neurologic symptoms improved slowly, and the patient was discharged near her baseline on hospital day 37. *Definitely no bacterial infection given absence of culture or imaging data to suggest bacterial source; alternative diagnosis per discharge and consultants’ documentation most likely Wilson’s Disease versus less likely Wernicke’s encephalopathy.* |
| A middle-aged man without previous medical history presented with decreased alertness, agitation, headache, and ataxia for one day. He was febrile to 38.3 in the ED. WBC 4.5 (57% neutrophils). Procalcitonin was normal at 0.05. Chest X-ray showed questionable hazy opacities without consolidation. An attempt at lumbar puncture (LP) was unsuccessful in the ED. He was intubated for airway protection. He received ceftriaxone, ampicillin, vancomycin, oseltamivir, and acyclovir in the ED. LP was performed by interventional radiology; CSF was clear with 7 WBC (80% lymphocytes), elevated protein (95), normal glucose (66); all CSF micro studies were negative including HSV, cryptococcus, CMV, enterovirus, influenza, H flu, HHV6, VZV, and cultures. EEG showed temporal delta slowing consistent with HSV encephalitis. He completed six days IV acyclovir followed by eight days of PO valacyclovir; he did not receive prolonged anti-bacterials. Clinically he improved. *Definitely no bacterial infection given absence of CSF or other studies consistent with bacterial infection and alternative diagnosis of VZV encephalitis based upon characteristic EEG findings.* |
| An elderly woman with history of recently-diagnosed advanced ovarian carcinoma complicated by abdominal carcinomatosis and large right-sided pleural effusion who had not yet begun treatment for her malignancy presented to the ED with worsening shortness of breath and non-productive cough over days, as well as worsening chronic fatigue and poor appetite over weeks. In the ED she was afebrile but lethargic. A chest X-ray showed the known large right pleural effusion and could not rule out pneumonia. CT pulmonary embolism protocol showed subsegmental pulmonary emboli without evidence of pneumonia. She received levofloxacin and low molecular weight heparin in the ED. A thoracentesis was done which was exudative by Light’s criteria with a pH >7.8. Culture of pleural fluid grew two colonies of coagulase-negative Staphylococcus (different organisms), thought likely contaminants. Antibiotics were not continued. She was admitted to the ward and started on chemotherapy during the admission; she remained afebrile without new signs or symptoms of infection. She was discharged to subacute rehab and died soon after due to progressive malignancy. *Definitely no bacterial infection given absence of culture or imaging evidence; positive pleural culture grew common contaminant; improved without course of antibiotics; alternative explanation for presentation evident—new subsegmental pulmonary emboli and progressive known malignancy.* |