

Supplemental Table 2: Healthcare resource utilization and unit costs (per jurisdiction)

Cost Categories	Natural Units	Unit Cost	Total Cost	Source
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<p>Study-related drugs</p> <ul style="list-style-type: none"> • probiotics (<i>Lactobacillus rhamnosus GG</i>) □ antibiotics: <ul style="list-style-type: none"> ○ piperacillin-tazobactam ○ ceftriaxone ○ ceftazidime ○ azithromycin ○ vancomycin ○ metronidazole <ul style="list-style-type: none"> ○ levofloxacin ○ imipenem ○ meropenem ○ amoxicillin-clavulin ○ cefuroxime ○ linezolid ○ cefazolin ○ cloxacillin ○ ciprofloxacin ○ gentamicin ○ trimethoprim-sulfamethoxazole • steroids <ul style="list-style-type: none"> ○ dexamethasone ○ methylprednisone ○ hydrocortisone ○ prednisone • stress ulcer prophylaxis <ul style="list-style-type: none"> ○ cimetidine ○ ranitidine ○ famotidine ○ nizatidine ○ lansoprazole ○ dexlansoprazole ○ pantoprazole ○ esomeprazole ○ omeprazole ○ rabeprazole • laxatives/motility agents <ul style="list-style-type: none"> ○ domperidone ○ metoclopramide ○ erythromycin ○ senna ○ dulcolax ○ golytely ○ glycerin ○ lactulose 				
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<ul style="list-style-type: none"> ○ colace ○ citromag ○ PegLyte ○ pancreatic enzymes ○ enema □ opiates ○ morphine ○ hydromorphone ○ demerol ○ fentanyl ○ oxycodone ○ percocets 				
<p>Laboratory testing</p> <ul style="list-style-type: none"> • complete blood count • creatinine • arterial blood gas • lactate • albumin • blood cultures • urine cultures • sputum/tracheal aspirate/bronchoalveolar lavage cultures • <i>C. difficile</i> polymerase chain reaction (PCR), toxin assays, ELISA, cell culture, LAMP • other aerobic/anaerobic cultures ○ thoracentesis ○ paracentesis 				
<p>Personnel (<i>per diem</i> or <i>hourly wage</i>)</p> <ul style="list-style-type: none"> • most responsible physician ○ ICU ○ Hospital • consultation physicians • nursing • pharmacist • respiratory therapist • physical therapist • social work • ICU administrative and/or clerical staffing 				

<p>Radiology</p> <ul style="list-style-type: none">• portable chest or abdominal radiographs• computerized tomography (CT) scan: chest, abdomen, pelvis, sinusitis, head• MRI: head, chest, joint				
<p><input type="checkbox"/> abdominal ultrasound</p>				

<p>Procedural costs:</p> <ul style="list-style-type: none"> • central venous catheter, peripherally inserted central catheter, arterial lines • chest tube • naso- or oro-gastric tube • percutaneous endoscopic gastrostomy (PEG) tube • tube feed • fiber • protein supplement • ventilator circuit changes • endotracheal tubes (with or without subglottic suction) • invasive ventilation (ventilator days) <ul style="list-style-type: none"> ○ heat moisture exchange ○ heated humidifier • non-invasive positive pressure ventilation • high-flow nasal cannula • vasopressor/inotropic agents • VAP prevention bundles <ul style="list-style-type: none"> ○ chlorhexidine usage ○ bacterial filters ○ oral decontamination ○ gut decontamination ○ oral antibiotic paste • colonoscopy (cautery, epinephrine injection) • echocardiograms (transthoracic/transesophageal) • bronchoscopy • thoracostomy • tracheostomy • interventional radiology drain • intermittent hemodialysis • continuous renal replacement therapy • fecal management device 				
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Operative costs <ul style="list-style-type: none"> • laparotomy (toxic megacolon, bowel perforation) • colectomy • thoracotomy • open abdominal wound (vacuum-assisted closure (VAC) devices) 				
<input type="checkbox"/> surgeon <input type="checkbox"/> surgical assistant <input type="checkbox"/> anesthesiology <input type="checkbox"/> nursing				
Overhead costs <ul style="list-style-type: none"> <input type="checkbox"/> ICU days <input type="checkbox"/> ward days 				

CT = computerized tomography; ELISA = enzyme-linked immunosorbent assay; ICU = intensive care unit; LAMP = loop-mediated isothermal amplification; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia;

Supplemental Table 2: Health economic evaluation assumptions

Assumption	Rationale
<p>Prophylactic and therapeutic probiotic administration outside the ICU</p> <ul style="list-style-type: none"> • If no prophylactic/therapeutic probiotics was used prior to trial enrollment, we will assume study product (<i>Lactobacillus rhamnosus</i> GG prophylaxis or placebo) will be used for duration of stay in the ICU with no other probiotic co-administration; • If open label probiotics were used in the ICU, we will assume study product (<i>Lactobacillus rhamnosus</i> GG prophylaxis or placebo) will still be used for duration of stay in the ICU (coadministered); • After the duration of ICU stay (transfer to the ward), we assume that there will be no further probiotic administration 	<p>Ward-based/pre-admission ICU prophylactic and therapeutic probiotic administration was not directly measured</p>
<p>Variability in investigations and treatment practice of disease/illness</p> <ul style="list-style-type: none"> • Based on variability in incidence of disease/illness, we will investigate the incidence of each illness severity, and average resource utilization for a particular illness. • We will utilize the mean costs for a particular illness (we will attempt to directly derive this variability from the case report forms) For patients who undergo multiple investigations, treatment (medications/procedures/surgeries) for a particular disease/illness, we will assume the lowest number of potential interventions to treat the disease/illness, as well as mean resource utilization for such events from PROSPECT 	<p>Various clinical diagnoses will have variability in severity, and therefore, variability in the way they are investigated and treated (i.e. <i>C. difficile</i> could be investigated/treated with only culture assay, abdominal x-ray and antibiotics to colectomy). Based on prior scoping reviews for VAP/CDAD, there will be variability in the resource utilization of each treatment/test based on illness severity, which may drive differences in resource utilization</p>

<p>Investigations of other infectious outcomes</p> <ul style="list-style-type: none"> • For those illnesses that are only investigated if positive or indeterminate cultures are detected (i.e. endocarditis), we will assume there is a potential minimum and maximal resource utilization that would be used to investigate/treat a specific diagnosis • Certain assumptions will need to be made for healthcare resource utilization for certain services, investigations, procedures/surgeries, as they may not be explicitly captured in PROSPECT, but can be gleaned indirectly from the case report forms • For example: <ul style="list-style-type: none"> ○ central-line blood stream infections would be assumed to warrant a replacement or previous venous or arterial catheters; ○ broncho-alveolar lavage (BAL) cultures were assumed to have a bronchoscopy procedure to perform them ○ CDAD was assumed to have an abdominal x-ray (at a minimum) for radiological investigation <ul style="list-style-type: none"> ▪ At a maximum, a proportion of patients would receive at CT abdo, colonoscopy/flexible sigmoidoscopy, laparotomy, colectomy, fecal transplant, vacuum-assisted closure device ○ empyema/lung abscess would be assumed to be diagnosed by CT chest, and treated with a chest tube (with a proportion of patients with tissue plasminogen activator into the pleural cavity, or VATS thoracotomy with decortication and irrigation and debridement) ○ abdominal x-rays can be used to count the number of abdominal drains inserted <ul style="list-style-type: none"> ▪ a proportion of patients were assumed to receive an abdominal ultrasound, CT abdo, MRI abdo ○ we will assume that a positive blood culture with specific organisms (known to cause endocarditis) would warrant a transthoracic echocardiogram ± transesophageal echocardiogram; ○ confirmed endocarditis would be investigated with a transthoracic echocardiogram ± transesophageal echocardiogram ○ mediastinitis would be assumed to be 	<p>There are certain investigations or interventions that would be expected to be associated with various disease state suspicions (and given correct circumstances, we would assume these would be tested/treated in these ways)</p>
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diagnosed by CT or MRI chest

- at a maximum, they would receive an thoracotomy/sternotomy for an I&D and potential VAC dressing
- initiation (on the first day) of intermittent hemodialysis or continuous renal replacement therapy would incur a cost of central venous hemodialysis line placement
- suspected meningitis/encephalitis case would warrant a lumbar puncture ± CT or MRI head;
- osteomyelitis would warrant a NM scan or MRI;
- biliary tract infections would be assumed to have at minimum an abdominal ultrasound;
 - At a maximum, a proportion of patients would receive at CT abdo, ERCP, percutaneous transhepatic cholecystostomy (PTC) tube, cholecystectomy
- pancreatic infections would be assumed to have at minimum an abdominal ultrasound;
 - At a maximum, a proportion of patients would receive at CT abdo, MRI abdo, abdominal drain or aspiration
- typhilitis would be assumed to have at minimum an abdo X-ray;
 - At a maximum, a proportion of patients would receive at CT abdo
- toxic megacolon would be assumed to have at minimum an abdo X-ray;
 - At a maximum, a proportion of patients would receive at CT abdo
- urinary tract infection would be assumed to have at a urinalysis and urine culture
- sinusitis would be assumed to have investigations at baseline
 - At a maximum, a proportion of patients would receive at CT head
- septic arthritis would be assumed to have an aspiration culture at a minimum
 - At a maximum, a proportion of patients would receive an orthopedic surgery for I&D

<ul style="list-style-type: none"> ○ PEG tube insertion would be assumed to be placed when 1st record on the daily data form of PEG tube utilization (Daily Form 4.2 of 3) ○ Tracheostomy insertion would be assumed to be placed when 1st record on the daily 	
<p>data form (Daily Form 4.1 of 3 – Mechanical airway in place today)</p>	
<p>Imputation of missing data</p> <ul style="list-style-type: none"> □ For those patients with missing data from a clinical outcomes perspective, multiple imputation methods will be utilized – including generalized estimating equations (GEEs) □ For missing unit costs (which are not attainable from public jurisdiction databases or trial site specific inquiries), we will utilize costing -ratio methodology 	<p>We will utilize standard multiple imputation methods to handle missing clinical outcome data, or costing-ratio methodology for missing unit costs</p>

BAL = broncho-alveolar lavage; CDAD = C. Difficile-associated diarrhea; CT = computerized tomography; CXR = chest x-ray; ERCP = endoscopic retrograde cholangio-pancreatography; ICU = intensive care unit; I&D: irrigation & debridement; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal

Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia; VATS = video-assisted thoroscopic surgery