**Supplemental Material**

*Enrollment criteria*

Patients were included if they were adults (age >18 years), had a urine and/or blood culture positive for at least one gram-negative organism obtained at any time during hospitalization, and underwent antibiotic treatment on the day index culture was drawn, which continued for >3 consecutive days. To identify cUTI patients we developed an ICD-9-CM based algorithm, which is available in Table 1.

Patients were excluded if they were <18 years, had a hospital LOS <2 days, were transferred from another acute care facility, or if the cUTI episode was a repeat bout during the index hospitalization (as evidenced by a >3-day hiatus in UTI-specific antimicrobial regimen administration and a new positive culture). In order to increase the likelihood that the identified gram-negative organism originated in the urine rather than another site, we excluded all patients who fit the definition for complicated intra-abdominal infection (Table 2).

*Microbiology and treatment variables and definitions*

In addition to growing at least one gram-negative organism for inclusion in the cohort, a patient has to grow out a qualifying organism in the urine and/or blood in order to be considered culture-positive. Gram-negative organisms of particular interest were: *Pseudomonas aeruginosa, Acinetobacter bamannii*, *Stenotrophomonas maltophilia* (assumed always to be CR)*,* and Enterobacteriaceae, as listed in Table 3.

Organisms were classified as carbapenem S (susceptible), I (intermediate) or R (resistant). For the purposes of the current analyses, I and R were grouped together as resistant. CR was defined as any organism with an I or R in the susceptibility category to one of the four carbapenems – imipenem, meropenem, ertapenem or doripenem. CS was defined as any organism with a S in the susceptibility category to either any carbapenem tested or to any third generation cephalosporin (Table 4) tested. First detection of a CR organism served as the index culture; if there was no CR organism detected, then the first culture growing out one of the organisms of interest served as the index culture.

**Table 1. Selection algorithm for complicated urinary tract infection (cUTI, catheter-associated UTI [CAUTI] analyzed as a subgroup of cUTI)**

|  |  |
| --- | --- |
| **Algorithm CAUTI = Any Group A OR (At least one group B + At least one group C) cUTI = (At least one group B + At least one group D) OR (At least one group B + At least one group E)** | |
| **Code** | **Description** |
|  | **Group A** |
|  |  |
| 996.64 | Infection and inflammatory reaction due to indwelling urinary catheter |
|  |  |
|  | **Group B** |
|  | Pyelonephritis |
| 590.1x | Acute pyelonephritis |
| 590.0x | Chronic pyelonephritis |
| 590.8 | Unspecified pyelonephritis |
| 590.3 | Pyeloureteritis cystica |
|  |  |
|  | **Group C** |
|  | Urinary Catheter |
| 57.94 | Insertion of indwelling urinary catheter |
| 57.95 | Replacement of indwelling urinary catheter |
| 96.48 | Irrigation of indwelling urinary catheter |
| V53.6 | Urinary catheter |
| V55.6 | Attention to other artificial opening of urinary tract |
|  |  |
|  | **Group D** |
|  | Urinary Tract Obstruction or other abnormality |
| 593.7x | Vesicoureteral reflux |
| 592.x | Nephrolithiasis or ureteric calculi |
| 753.2x | Obstructive defect of renal pelvis and ureter |
| 599.6x | Urinary obstruction |
| 600.x | Prostate hyperplasia |
| 596.0 | Bladder neck obstruction |
| 591 | Hydronephrosis |
| 788.2x | Retention of urine |
|  |  |
|  | **Group E** |
|  | Immunocompromised |
| V 58.1 | Encounter for chemotherapy and immunotherapy for neoplastic conditions |
| V 15.3 | Personal history of irradiation |
| V 42 | Organ or tissue replaced by transplant |
|  | Received ≥ 5mg prednisone equivalent |

**Table 2. cIAI identification algorithm\***

|  |  |
| --- | --- |
| **cIAI = at least 1 diagnosis code + at least 1 procedure code** | |
|  |  |
| ***Code*** | ***Diagnosis*** |
| 531.1X, 531.5X | Gastric ulcer with perforation |
| 531.2X, 531.6X | Gastric ulcer with hemorrhage and perforation |
| 532.1X, 532.5X | Duodenal ulcer with perforation |
| 532.2X, 532.6X | Duodenal ulcer with hemorrhage and perforation |
| 533.1X, 533.5X | Peptic ulcer with perforation |
| 533.2X, 533.6X | Peptic ulcer with hemorrhage and perforation |
| 534.1X, 534.5X | Gastrojejunal ulcer with perforation |
| 534.2X, 534.6X | Gastrojejunal ulcer with hemorrhage and perforation |
| 540.0 | Acute appendicitis with generalized peritonitis |
| 540.1 | Acute appendicitis with peritoneal abscess |
| 567.X | Peritonitis |
| 569.5 | Abscess of intestine |
| 569.81 | Fistula of intestine, excl. rectum and anus |
| 569.82 | Ulceration of intestine |
| 569.83 | Perforation of intestine |
| 572.0 | Abscess of liver |
| 575.4 plus 574.0, 574.3, 574.6, 574.8, or 575.0 | Acute cholecystitis |
|  |  |
| ***Code*** | ***Procedure*** |
| 43.5X-43.9X | Laparotomy/laparoscopy |
| 44.40-44.42 |  |
| 44.61 |  |
| 45.6X-46.13 |  |
| 46.20-46.23 |  |
| 46.7X |  |
| 46.80-46.82 |  |
| 46.91-46.94 |  |
| 46.99 |  |
| 47.XX |  |
| 50.0X |  |
| 50.12-50.69 |  |
| 51.02-51.04 |  |
| 51.13 |  |
| 51.2X |  |
| 51.3X |  |
| 51.4X-51.5X |  |
| 51.61-51.63 |  |
| 51.61-51.63 |  |
| 51.61-51.63 |  |
| 51.61-51.63 |  |
| 51.61-51.63 |  |
| 51.61-51.63 |  |
| 51.61-51.63 |  |
| 51.61-51.63 |  |
| 51.69 |  |
| 51.7X |  |
| 51.81-51.83 |  |
| 51.89 |  |
| 51.91-51.95 |  |
| 51.99 |  |
| 52.01 |  |
| 52.09 |  |
| 52.12 |  |
| 52.22 |  |
| 52.3X-52.83 |  |
| 52.92 |  |
| 52.95 |  |
| 52.96 |  |
| 52.99 |  |
| 54.1X |  |
| 54.21 |  |
| 54.4X |  |
| 54.5X |  |
| 54.92-54.95 |  |

\*In ICD-9-CM, "X" denotes a wildcard that includes a missing digit as well as the range of digits that span from 0 to 9 (Reference #18 and personal communication with G. Oster re: laparotomy/laparoscopy codes)

**Table 3. Enterobacteriaceae included in the analysis**

|  |  |
| --- | --- |
| *E. coli* | *Proteus spp.* |
| *K. pneumoniae* | *S. marcesens* |
| *K. oxytoca* | *C. freundii* |
| *E. cloacae* | *M. morganii* |
| *E. aerogenes* | *Providencia spp.* |
| *P. mirabilis* |  |

**Table 4. Third generation cephalosporins**

|  |  |
| --- | --- |
| Ceftibuten | Cefixime |
| Ceftriaxone | Cefditoren |
| Cefotaxime | Ceftizoxime |
| Cefpodoxime | Cefoperazone |
| Cefdinir | Ceftazidime |

**Table 5. Baseline characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **CR (N = 1,357)** | | **CS (N = 23,928 )** | |  |
|  | N | % | N | % | P-value |
| Mean age, years (SD) | 64.1 (17.9) |  | 64.0 (18.7) |  | 0.86 |
| Gender: male | 855 | 63.01% | 10,526 | 43.99% | <0.001 |
| Race |  |  |  |  |  |
| White | 966 | 71.19% | 17,260 | 72.13% | 0.011 |
| Black | 245 | 18.05% | 3,576 | 14.94% |
| Hispanic | 16 | 1.18% | 323 | 1.35% |
| Other | 127 | 9.36% | 2,713 | 11.34% |
| Unknown | 3 | 0.22% | 56 | 0.23% |
| Admission Source |  |  |  |  |  |
| Non-healthcare facility (including from home) | 962 | 70.89% | 17,284 | 72.23% | <0.001 |
| Clinic | 47 | 3.46% | 932 | 3.90% |
| Transfer from ECF | 179 | 13.19% | 1,829 | 7.64% |
| Transfer from another non-acute care facility | 0 | 0.00% | 3 | 0.01% |
| Emergency Department | 139 | 10.24% | 3,152 | 13.17% |
| Other | 30 | 2.21% | 728 | 3.04% |
| Admission type |  |  |  |  |  |
| Medical | 1,160 | 85.48% | 20,469 | 85.54% | 0.950 |
| Surgical | 197 | 14.52% | 3,459 | 14.46% |  |
| Neurologic | 37 | 2.73% | 669 | 2.80% | 0.880 |
| Trauma | 38 | 2.80% | 766 | 3.20% | 0.413 |
| Elixhauser Comorbidities |  |  |  |  |  |
| Congestive heart failure | 244 | 17.98% | 3,646 | 15.24% | 0.006 |
| Valvular disease | 67 | 4.94% | 1,302 | 5.44% | 0.425 |
| Pulmonary circulation disease | 40 | 2.95% | 646 | 2.70% | 0.584 |
| Peripheral vascular disease | 142 | 10.46% | 1,759 | 7.35% | <0.001 |
| Paralysis | 455 | 33.53% | 3,796 | 15.86% | <0.001 |
| Other neurological disorders | 338 | 24.91% | 4,485 | 18.74% | <0.001 |
| Chronic pulmonary disease | 288 | 21.22% | 4,973 | 20.78% | 0.698 |
| Diabetes without chronic complications | 495 | 36.48% | 8,484 | 35.46% | 0.444 |
| Diabetes with chronic complications | 113 | 8.33% | 2,221 | 9.28% | 0.237 |
| Hypothyroidism | 220 | 16.21% | 3,668 | 15.33% | 0.380 |
| Renal failure | 372 | 27.41% | 5,600 | 23.40% | 0.001 |
| Liver disease | 46 | 3.39% | 788 | 3.29% | 0.846 |
| Peptic ulcer disease with bleeding | 1 | 0.07% | 32 | 0.13% | 1.000 |
| AIDS | 3 | 0.22% | 32 | 0.13% | 0.434 |
| Lymphoma | 24 | 1.77% | 173 | 0.72% | <0.001 |
| Metastatic cancer | 47 | 3.46% | 665 | 2.78% | 0.138 |
| Solid tumor without metastasis | 46 | 3.39% | 713 | 2.98% | 0.389 |
| Rheumatoid arthritis/collagen vascular | 59 | 4.35% | 1,072 | 4.48% | 0.819 |
| Coagulopathy | 88 | 6.48% | 1,972 | 8.24% | 0.021 |
| Obesity | 200 | 14.74% | 3,857 | 16.12% | 0.178 |
| Weight loss | 246 | 18.13% | 2,512 | 10.50% | <0.001 |
| Fluid and electrolyte disorders | 604 | 44.51% | 10,681 | 44.64% | 0.926 |
| Chronic blood loss anemia | 25 | 1.84% | 399 | 1.67% | 0.626 |
| Deficiency anemia | 545 | 40.16% | 8,009 | 33.47% | <0.001 |
| Alcohol abuse | 23 | 1.69% | 481 | 2.01% | 0.419 |
| Drug abuse | 58 | 4.27% | 646 | 2.70% | 0.001 |
| Psychosis | 70 | 5.16% | 1,254 | 5.24% | 0.895 |
| Depression | 289 | 21.30% | 3,862 | 16.14% | <0.001 |
| Hypertension | 631 | 46.50% | 11,887 | 49.68% | 0.023 |
| Charlson Comoribidity Score |  |  |  |  |  |
| 0 | 151 | 11.13% | 5,484 | 22.92% | <0.001 |
| 1 | 184 | 13.56% | 4,266 | 17.83% |
| 2 | 333 | 24.54% | 4,957 | 20.72% |
| 3 | 254 | 18.72% | 3,474 | 14.52% |
| 4 | 179 | 13.19% | 2,416 | 10.10% |
| 5+ | 256 | 18.87% | 3,331 | 13.92% |
| Mean (SD) | 2.9 (2.2) |  | 2.3 (2.2) |  |  |
| Median [IQR] | 3 [2,4] |  | 2 [1,3] |  |  |
| Hospital Characteristics |  |  |  |  |  |
| Census region |  |  |  |  |  |
| Midwest | 350 | 25.79% | 5,884 | 24.59% | 0.004 |
| Northeast | 209 | 15.40% | 3,934 | 16.44% |
| South | 525 | 38.69% | 10,081 | 42.13% |
| West | 273 | 20.12% | 4,029 | 16.84% |
| Number of Beds |  |  |  |  |  |
| <100 | 41 | 3.02% | 712 | 2.98% | <0.001 |
| 100 to 199 | 133 | 9.80% | 3,092 | 12.92% |
| 200 to 299 | 356 | 26.23% | 5,233 | 21.87% |
| 300 to 399 | 185 | 13.63% | 4,255 | 17.78% |
| 400 to 499 | 213 | 15.70% | 3,385 | 14.15% |
| 500+ | 429 | 31.61% | 7,251 | 30.30% |
| Teaching | 591 | 43.55% | 10,813 | 45.19% | 0.238 |
| Urban | 1,248 | 91.97% | 21,624 | 90.37% | 0.052 |
| CR Rate at Hospital Level |  |  |  |  |  |
| Mean (SD) | 4.7% (4.2) |  |  |  |  |
| Median [IQR] | 4.0% [1.6%, 6.6%] |  |  |  |  |

CR = carbapenem resistant; CS = carbapenem susceptible; SD = standard deviation; ECF = extended care facility; AIDS = acquired immune deficiency syndrome; IQR = interquartile range

**Table 6. Hospitalization events**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **CR (N = 1,357)** | | **CS (N = 23,928 )** | |  |
|  | N | % | N | % | P-value |
| Infection subtype |  |  |  |  |  |
| cUTI | 326 | 24.02% | 12,730 | 53.20% | <0.001 |
| CAUTI | 1031 | 75.98% | 11,198 | 46.80% |
| Risk factors for CR |  |  |  |  |  |
| Hospital Onset (HO) | 106 | 7.81% | 1,710 | 7.15% |  |
| Community Onset (CO) | 1,251 | 92.19% | 22,218 | 92.85% | 0.356 |
| Community Acquired CO (CA-CO) | 439 | 32.35% | 10,976 | 45.87% |  |
| Health Care Associated CO (HCA-CO) | 812 | 59.84% | 11,242 | 46.98% | <0.001 |
| Antibiotics within 90 days prior to admission | 682 | 50.26% | 6,247 | 26.11% | <0.001 |
| CR organism within 90 days prior to admission | 160 | 11.79% | 216 | 0.90% | <0.001 |
| Time to infection onset from admission, days |  |  |  |  |  |
| cUTI |  |  |  |  |  |
| Mean (SD) | 1.6 (2.5) |  | 1.2 (2.0) |  | 0.001 |
| Median [IQR] | 1 [1,1] |  | 1 [1,1] |  | 0.003 |
| CAUTI |  |  |  |  |  |
| Mean (SD) | 1.8 (4.4) |  | 2.0 (3.6) |  | 0.049 |
| Median [IQR] | 1 [1,1] |  | 1 [1,1] |  | 0.130 |
| Illness severity at infection onset |  |  |  |  |  |
| ICU admission | 289 | 21.30% | 4,887 | 20.42% | 0.438 |
| Mechanical ventilation | 118 | 8.70% | 1,325 | 5.54% | <0.001 |
| Vasopressors | 67 | 4.94% | 1,805 | 7.54% | <0.001 |
| Dialysis | 44 | 3.24% | 531 | 2.22% | 0.014 |
| Severe sepsis | 251 | 18.50% | 4,416 | 18.46% | 0.970 |
| Septic shock | 144 | 10.61% | 2,602 | 10.87% | 0.762 |
| Mean (SD) time to cUTI treatment, days | 1.1 (0.5) |  | 1.2 (1.2) |  | <0.001 |

CR = carbapenem resistant; CS = carbapenem susceptible; cUTI = complicated urinary tract infection; CAUTI = cathater-associated urinary tract infection; HO = hospital-onset; CO = community-onset; CA = community-acquired; HCA = healthcare associated; SD = standard deviation; IQR = interquartile range; ICU = intensive care unit;

**Table 7. Microbiology and empiric treatment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **CR (N = 1,357)** | | **CS (N = 23,928 )** | |  |
|  | N | % | N | % | P-value |
| cUTI organism |  |  |  |  |  |
| *Klebsiella pneumoniae* | 232 | 17.10% | 3,499 | 14.62% | 0.012 |
| *Proteus mirabilis* | 179 | 13.19% | 3,186 | 13.31% | 0.896 |
| *Escherichia coli* | 156 | 11.50% | 13,559 | 56.67% | <0.001 |
| *Enterobacter cloacae* | 35 | 2.58% | 643 | 2.69% | 0.811 |
| *Providencia spp* | 48 | 3.54% | 535 | 2.24% | 0.002 |
| *Serratia marcescens* | 21 | 1.55% | 337 | 1.41% | 0.673 |
| *Morganella morganii* | 59 | 4.35% | 452 | 1.89% | <0.001 |
| *Enterobacter aerogenes* | 16 | 1.18% | 289 | 1.21% | 0.925 |
| *Proteus spp.* | 187 | 13.78% | 3,292 | 13.76% | 0.981 |
| *Citrobacter freundii* | 20 | 1.47% | 435 | 1.82% | 0.354 |
| *Klebsiella oxytoca* | 13 | 0.96% | 475 | 1.99% | 0.007 |
| *Enterobacter other* | 21 | 1.55% | 327 | 1.37% | 0.578 |
| *Citrobacter other* | 12 | 0.88% | 257 | 1.07% | 0.507 |
| *Serratia other* | 3 | 0.22% | 31 | 0.13% | 0.428 |
| *Klebsiella other* | 4 | 0.29% | 61 | 0.25% | 0.779 |
| *Pseudomonas aeruginosa* | 740 | 54.53% | 3,216 | 13.44% | <0.001 |
| *Acinetobacter baumannii* | 77 | 5.67% | 129 | 0.54% | <0.001 |
| *Stenotrophomonas maltophilia* | 168 | 12.38% | 0 | 0.00% | <0.001 |
| Empiric antibiotics |  |  |  |  |  |
| Antipseudomonal penicillins with beta-lactamase inhibitor | 463 | 34.12% | 7,188 | 30.04% | 0.001 |
| Extended spectrum cephalosporins | 658 | 48.49% | 13,746 | 57.45% | <0.001 |
| Antipseudomonal floroquinolones | 459 | 33.82% | 10,067 | 42.07% | <0.001 |
| Antipseudomonal carbapenems | 257 | 18.94% | 3,051 | 12.75% | 0.186 |
| Aminoglycosides | 180 | 13.26% | 2,411 | 10.08% | <0.001 |
| Penicillins with beta-lactamase inhibitors | 25 | 1.84% | 405 | 1.69% | 0.678 |
| Tetracyclines | 24 | 1.77% | 249 | 1.04% | 0.012 |
| Folate pathway inhibitors | 40 | 2.95% | 619 | 2.59% | 0.417 |
| Polymyxins | 5 | 0.37% | 29 | 0.12% | 0.016 |
| Antipseudomonal cephalosporins | 330 | 24.32% | 3,620 | 15.13% | <0.001 |
| Aztreonam | 62 | 4.57% | 900 | 3.76% | 0.130 |
| Fosfomycin | 4 | 0.29% | 28 | 0.12% | 0.073 |
| Tigecycline | 54 | 3.98% | 193 | 0.81% | <0.001 |
| 3rd generation cephalosporin | 483 | 35.59% | 12,187 | 50.93% | <0.001 |
| Empiric treatment appropriateness |  |  |  |  |  |
| Non-IET | 515 | 37.95% | 17,918 | 74.88% | <0.001 |
| IET | 467 | 34.41% | 2,688 | 11.23% |  |
| Indeterminate | 375 | 27.63% | 3,322 | 13.88% |  |

CR = carbapenem resistant; CS = carbapenem susceptible; cUTI = complicated urinary tract infection; IET = inappropriate empiric therapy