Supplemental Table 1: Definitions of drug resistant organisms used in the study.

|  |  |
| --- | --- |
| Organism | Definition |
| ESBL *Enterobacteriaceae* CDC | *K. pneumoniae, K. oxytoca,* or *E. coli* with ceftazidime, aztreonam, cefotaxime, or ceftriaxone MIC of ≥2 µg/mL |
| ESBL *Enterobacteriaceae* | Any species from the *Enterobacteriaceae* Family with ceftazidime, aztreonam, cefotaxime, or ceftriaxone MIC of ≥2 µg/mL |
| MDR *Enterobacteriaceae* 30 | Any species from the *Enterobacteriaceae* Family non-susceptible to ≥1 agent in ≥3 of the following antimicrobial categories to which there was no species intrinsic resistance: aminoglycosides, anti-MRSA cephalosporins (only for *K. pneumoniae, K. oxytoca,* or *E. coli*), antipseudomonal penicillins + β-lactamase inhibitors, carbapenems, non-extended spectrum cephalosporins; 1st and 2nd generation cephalosporins, cephamycins, fluoroquinolones, folate pathway inhibitors, glycylcyclines, monobactams, penicillins, penicillins + β-lactamase inhibitors, phenicols, phosphonic acids, polymyxins, tetracyclines |
| HDR *Enterobacteriaceae* 28 | Any species from the *Enterobacteriaceae* Family non-susceptible to ≥1 agent in all 5 of the following antimicrobial categories: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin-tazobactam |
| CRE 29 | *K. pneumoniae, K. oxytoca,* *Escherichia coli*, or *Enterobacter* spp. resistant to imipenem, meropenem, doripenem, or ertapenem by standard susceptibility testing methods |
| MDR *Acinetobacter* 29 | Any *Acinetobacter* species non-susceptible to ≥1 agent in ≥3 of the following antimicrobial categories: aminoglycosides, carbapenems, fluoroquinolones, β-lactam/β-lactam β-lactamase inhibitor combination, cephalosporins, sulbactam |
| MDR *Acinetobacter* 30 | Any *Acinetobacter* species non-susceptible to ≥1 agent in ≥3 of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal penicillins + β-lactamase inhibitors, extended-spectrum cephalosporins, folate pathway inhibitors, penicillins + β-lactamase inhibitors, polymyxins, tetracyclines |
| XDR *Acinetobacter* 30 | Any *Acinetobacter* species non-susceptible to ≥1 agent in all but ≤2 of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal penicillins + β-lactamase inhibitors, extended-spectrum cephalosporins, folate pathway inhibitors, penicillins + β-lactamase inhibitors, polymyxins, tetracyclines |
| HDR *Acinetobacter* 28 | *A. baumannii* non-susceptible to ≥1 agent in all 6 of the following antimicrobial categories: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin or piperacillin-tazobactam, ampicillin/sulbactam |
| Carbapenem resistant *Acinetobacter* 28 | *A. baumannii* non-susceptible to antipseudomonal carbapenems |
| Colistin resistant *Acinetobacter* 28 | *A. baumannii* non-susceptible to colistin/polymyxin B |
| MRSA 29 | *S. aureus* oxacillin, cefoxitin, or methicillin resistant by standard susceptibility testing or an FDA-approved laboratory test for MRSA detection |
| MDR *S. aureus* 30 | *S. aureus* that is MRSA (as above row) or non-susceptible to ≥1 agent in ≥3 of the following antimicrobial categories: aminoglycosides, ansamycins, anti-MRSA cephalosporins, anti-staphylococcal β-lactams, fluoroquinolones, folate pathway inhibitors, fucidanes, glycopeptides, glycylcyclines, lincosamides, lipopeptides, macrolides, oxazolidinones, phenicols, phosphonic acids, streptogramins, tetracyclines |
| VISA | *S. aureus* vancomycin MIC of 4 or 8 µg/mL |
| VRE 29 | *E. faecalis*, *E. faecium*, or *Enterococcus* species unspecified (those not identified to species level) that is resistant to vancomycin by standard susceptibility testing methods |
| MDR *E. faecalis* 30 | *E. faecalis* non-susceptible to ≥1 agent in ≥3 of the following antimicrobial categories: aminoglycosides (except streptomycin), streptomycin, carbapenems, fluoroquinolones, glycopeptides, glycylcyclines, lipopeptides, oxazolidinones, penicillins, tetracyclines |
| MDR *E. faecium* 30 | *E. faecium* non-susceptible to ≥1 agent in ≥3 of the following antimicrobial categories: aminoglycosides (except streptomycin), streptomycin, fluoroquinolones, glycopeptides, glycylcyclines, lipopeptides, oxazolidinones, penicillins, tetracyclines, streptogramins |
| MDR *P. aeruginosa* 30 | *P. aeruginosa* non-susceptible to ≥1 agent in ≥3 of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal cephalosporins, antipseudomonal fluoroquinolones, antipseudomonal penicillins + β-lactamase inhibitors, monobactams, phosphonic acids, polymyxins |
| XDR *P. aeruginosa* 30 | *P. aeruginosa* non-susceptible to ≥1 agent in ≤2 of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal cephalosporins, antipseudomonal fluoroquinolones, antipseudomonal penicillins + β-lactamase inhibitors, monobactams, phosphonic acids, polymyxins |
| HDR *P. aeruginosa* 28 | *P. aeruginosa* non-susceptible to ≥1 agent in all 5 of the following antimicrobial categories: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin or piperacillin-tazobactam |
| Carbapenem resistant *P. aeruginosa* 28 | *P. aeruginosa* non-susceptible to antipseudomonal carbapenems |
| Colistin resistant *P. aeruginosa* 28 | *P. aeruginosa* non-susceptible to colistin/polymyxin B |

CRE: carbapenem-resistant *Enterobacteriaceae*. ESBL: Extended-spectrum beta lactamase. HDR: Highly drug resistant. MIC: minimum inhibitory concentration. MDR: Multidrug resistant. MRSA: Methicillin-resistant *S. aureus*. VISA: vancomycin intermediate *S. aureus*. VRE: vancomycin resistant enterococci. XDR: Extensively drug resistant.

Supplemental Table 2: Interaction terms tested for multivariate Cox proportional hazards models.

|  |  |
| --- | --- |
| **Interaction tested** | *p* value |
| Index ICU stay\*CHF | 0.93 |
| Index ICU stay\*cirrhosis | 0.94 |
| Index ICU stay\*chronic respiratory failure | 0.85 |
| Index ICU stay\*leukemia | 0.18 |
| Index ICU stay\*lymphoma | 0.17 |
| Index ICU stay\*solid organ malignancy | 0.44 |

CHF: congestive heart failure. ICU: intensive care unit.

Supplemental Table 3: Comparison of patients who died\* during the index MDRO hospitalization versus survivors discharged alive from the index MDRO hospitalization

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | All patients (% of all patients) | Died or discharged on hospice (%) | Survivors (%) | P value |
|  | N = 4429 | N = 976 | N = 3453 |  |
| Age (± SD) | 58.2 ± 16.1 | 61.7 ±15.0 | 57.2 ± 16.3 | **<0.001** |
| Gender, male | 2535 (57.4) | 534 (54.9) | 2001 (58.1) | 0.081 |
| Ethnicity, white | 2954 (66.7) | 687 (70.4) | 2267 (65.7) | **0.006** |
| Bone marrow transplant | 184 (4.2) | 91 (9.3) | 93 (2.7) | **<0.001** |
| Solid organ transplant | 223 (5.0) | 41 (4.2) | 182 (5.3) | 0.199 |
| Cardiovascular disease | 2695 (60.8) | 713 (73.1) | 1982 (57.4) | **<0.001** |
| Congestive heart failure | 1101 (24.9) | 302 (30.9) | 799 (23.1) | **<0.001** |
| Chronic respiratory failure | 1246 (28.1) | 291 (29.8) | 955 (27.7) | 0.185 |
| Diabetes mellitus | 1543 (34.8) | 332 (34.0) | 1211 (35.1) | 0.542 |
| CKD | 1013 (22.9) | 244 (25.0) | 769 (22.3) | 0.074 |
| ESRD | 519 (11.7) | 119 (12.2) | 400 (11.6) | 0.602 |
| Solid organ malignancy | 1025 (23.1) | 284 (29.1) | 741 (21.5) | **<0.001** |
| Leukemia | 555 (12.5) | 198 (20.3) | 357 (10.3) | **<0.001** |
| Lymphoma | 254 (5.7) | 75 (7.7) | 179 (5.2) | **0.004** |
| Cirrhosis | 389 (8.8) | 162 (16.6) | 227 (6.6) | **<0.001** |
| Charlson Comorbidity Score [IQR] | 4 [2-6] | 5 [3-7] | 3 [2-6] | **<0.001** |
| APACHE II score (± SD) | 11.9 ± 5.4 | 14.0 ± 6.0 | 11.3 ± 5.1 | **<0.001** |
| Culture source |  |  |  |  |
| Blood | 3231 (73.0) | 758 (77.7) | 2473 (71.6) | **<0.001** |
| Bronch/BAL | 716 (16.2) | 188 (19.3) | 528 (15.3) | **0.003** |
| Other sterile site | 815 (18.4) | 123 (12.6) | 692 (20.0) | **<0.001** |
| More than one site | 324 (7.3) | 89 (9.1) | 235 (6.8) | **0.014** |
| Index drug-resistant organism+ |  |  |  |  |
| *S. aureus* | 1756 (39.6) | 295 (30.2) | 1461 (42.3) | **<0.001** |
| *Enterococcus* | 851 (19.2) | 268 (31.5) | 583 (16.9) | **<0.001** |
| *Enterobacteriaceae* | 1226 (27.7) | 218 (22.3) | 1008 (29.2) | **<0.001** |
| *Acinetobacter* | 107 (2.4) | 44 (4.5) | 63 (1.8) | **<0.001** |
| *P. aeruginosa* | 204 (4.6) | 54 (5.5) | 150 (4.3) | 0.118 |
| Polymicrobial | 285 (6.4) | 97 (34.0) | 188 (66.0) | **<0.001** |
| Any ICU stay | 2507 (56.6) | 807 (82.7) | 1700 (49.2) | **<0.001** |
| LOS (days) [IQR] | 15.6 [7.7-31.5] | 19.5 [9.5-36.9] | 14.6 [7.3-29.9] | **<0.001** |
| In-hospital mortality or discharge on hospice, % | 976 (22.0) | 976 (100) | 0 |  |

P values obtained via Chi-square test or Fisher’s exact where appropriate for categorical values. Mann-Whitney U or t-test was used where appropriate for continuous variables. APACHE-II: Acute Physiology and Chronic Health Evaluation. BAL: bronchoalveolar lavage. CKD: Chronic kidney disease. ESRD: End-stage renal disease. ICU: intensive care unit. IQR: interquartile range. LOS: length of stay. SD: standard deviation.

\*Individuals discharged on hospice were included as having died during the index MDRO hospitalization.

+Drug-resistance was defined according to the definitions in Supplemental Table 1.

Supplemental Table 4: Relative risk of in-hospital mortality or discharge on hospice from index MDRO hospitalization

|  |  |  |
| --- | --- | --- |
| **Index drug-resistant pathogen** | **Relative risk (95% confidence intervals)** | **p value** |
| *S. aureus* | reference | reference |
| *Enterobacteriaceae* | 1.06 (0.90-1.24) | 0.48 |
| *P. aeruginosa* | 1.58 (1.23-2.03) | 0.0004 |
| *Enterococcus* | 1.87 (1.62-2.16) | <0.0001 |
| Polymicrobial infection | 2.03 (1.67-2.46) | <0.0001 |
| *Acinetobacter* | 2.45 (1.91-3.14) | <0.0001 |

MDRO: multidrug resistant organism

Supplemental Table 5: Comparison of index hospitalization characteristics by drug-resistant index pathogen group

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Index admission characteristics | *S. aureus* n (%) | *Enterococcus* n (%) | *Enterobacteriaceae* n (%) | *Acinetobacter* n (%) | *Pseudomonas* n (%) | Polymicrobial n (%) |
|  | 1756 | 851 | 1226 | 107 | 204 | 285 |
| Age | 58.0 ± 16.6 | 58.8 ± 15.7 | 59.3 ± 15.4 | 57.6 ± 16.6 | 52.2 ± 16.6 | 56.9 ± 15.8 |
| Gender, male | 1018 (58.0) | 466 (55.1) | 695 (56.8) | 49 (45.8) | 134 (65.7) | 173 (60.7) |
| Ethnicity, white | 1115 (63.5) | 581 (68.3) | 846 (69.0) | 66 (61.7) | 158 (77.5) | 188 (66.0) |
| Any ICU stay during index | 877 (49.9) | 491 (57.8) | 686 (56.0) | 79 (73.8) | 163 (79.9) | 211 (74.0) |
| Receipt of bone marrow transplant (ever) | 24 (1.4) | 91 (10.7) | 46 (3.8) | 3 (2.8) | 6 (2.9) | 14 (4.9) |
| Receipt of a solid organ transplant (ever) | 46 (2.6) | 41 (4.8) | 75 (6.1) | 4 (3.7) | 35 (17.2) | 22 (7.7) |
| Cardiovascular disease | 1070 (60.9) | 534 (62.7) | 694 (56.6) | 71 (66.4) | 130 (63.7) | 196 (68.8) |
| Congestive heart failure | 503 (28.8) | 198 (23.3) | 253 (20.6) | 22 (20.6) | 52 (25.5) | 73 (25.6) |
| Chronic respiratory failure | 552 (31.4) | 206 (24.2) | 261 (21.3) | 35 (32.7) | 99 (48.5) | 93 (32.6) |
| Diabetes mellitus | 672 (38.3) | 281(33.0) | 383 (31.2) | 36 (33.6) | 67 (32.8) | 104 (36.5) |
| CKD | 469 (26.7) | 180 (21.2) | 218 (17.8) | 28 (26.2) | 46 (22.5) | 72(25.3) |
| ESRD | 242 (13.8) | 97 (11.4) | 99 (8.1) | 21 (19.6) | 23 (11.3) | 37 (13.0) |
| Solid organ malignancy | 375 (21.4) | 160 (18.8) | 370 (30.2) | 23 (21.5) | 37 (18.1) | 60 (21.1) |
| Leukemia | 102 (5.8) | 251 (29.5) | 141 (11.5) | 10 (9.3) | 19 (9.3) | 32 (11.2) |
| Lymphoma | 81 (4.6) | 71 (8.3) | 75 (6.1) | 4 (3.7) | 9 (4.4) | 14 (4.9) |
| Cirrhosis | 118 (6.7) | 84 (9.9) | 116 (9.5) | 13 (12.1) | 16 (7.8) | 42 (14.7) |
| Charlson Comorbidity Score | 4 [2-6] | 4 [2-6] | 3 [2-6] | 4 [2-6] | 3 [2-5] | 4 [2-6] |
| APACHE II score | 11.7 ± 5.3 | 11.6 ± 5.1 | 11.9 ± 5.6 | 13.9 ± 6.3 | 11.7 ± 5.4 | 13.1 ± 5.4 |
| Culture source, % (n) |  |  |  |  |  |  |
| Blood | 1225 (69.8) | 787 (92.5) | 886 (72.3) | 69 (64.5) | 56 (27.5) | 208 (73.0) |
| Bronch/BAL | 295 (16.8) | 1 (0.1) | 185 (15.1) | 34 (31.8) | 122 (59.8) | 79 (27.7) |
| Other sterile | 407 (23.2) | 86 (10.1) | 196 (16.0) | 10 (9.3) | 40 (19.6) | 76 (26.7) |
| More than one site | 168 (9.6) | 23 (2.7) | 40 (3.3) | 6 (5.6) | 14 (6.9) | 73 (25.6) |
| Index LOS (days) | 12.6 [7.1-22.9] | 23.1 [10.8-40.1] | 12.9 [5.9-26.9] | 22.1 [9.5-36.6] | 30.5 [12.9-55.1] | 30.9 [16.4-55.0] |
| In-hospital mortality or discharge on hospice, % | 294 (16.7) | 267 (31.4) | 216 (17.6) | 44 (41.1) | 51 (25.0) | 96 (33.7) |
| Number of patients discharged from the index hospitalization alive but lost to follow up before 1 year (%) | 236 (16.2) | 76 (13.0) | 133 (13.2) | 9 (14.3) | 20 (13.3) | 26 (13.8) |

P values were obtained using Chi-square for categorical variables, Kruskal-Wallis for continuous variables. APACHE-II: Acute Physiology and Chronic Health Evaluation. BAL: bronchoalveolar lavage. CKD: Chronic kidney disease. ESRD: End-stage renal disease. ICU: intensive care unit. LOS: length of stay.

Supplemental Table 6: Comparison of survivors readmitted within 1 year and did not have an MDRO infection during a readmission to those who were readmitted within 1 year and had an MDRO infection during a readmission

|  |  |  |  |
| --- | --- | --- | --- |
| Index admission characteristics | Survivors, readmitted without MDRO n (%) | Survivors, readmitted with MDRO infection n (%) | P value |
|  | 1615 | 512 |  |
| Age | 56.9 ± 16.1 | 56.1 ± 14.7 | 0.701 |
| Gender, male | 923 (57.2) | 307 (60.0) | 0.136 |
| Ethnicity, white | 1047 (64.8) | 301 (58.8) | **0.014** |
| Any ICU stay during index | 731 (45.3) | 235 (45.9) | 0.494 |
| Bone marrow transplant | 49 (3.0) | 25 (4.9) | **0.004** |
| Solid organ transplant | 90 (5.6) | 36 (7.0) | 0.343 |
| Cardiovascular disease | 905 (56.0) | 304 (59.4) | 0.081 |
| Congestive heart failure | 363 (22.5) | 125 (24.4) | 0.157 |
| Chronic respiratory failure | 421 (26.1) | 140 (27.3) | 0.434 |
| Diabetes mellitus | 563 (34.9) | 195 (38.1) | 0.181 |
| CKD | 370 (22.9) | 136 (26.6) | 0.065 |
| ESRD | 186 (11.5) | 88 (17.2) | **0.001** |
| Solid organ malignancy | 384 (23.8) | 87 (17.0) | **0.038** |
| Leukemia | 196 (12.1) | 78 (15.2) | 0.075 |
| Lymphoma | 83 (5.1) | 37 (7.2) | **0.030** |
| Cirrhosis | 117 (7.2) | 32 (6.3) | 0.631 |
| Charlson Comorbidity Score | 4 [2-6] | 4 [2-6] | 0.132 |
| APACHE II score | 11.0 ± 4.8 | 11.5 ± 5.3 | 0.062 |
| Culture source, % (n) |  |  |  |
| Blood | 1174 (72.7) | 391 (76.4) | 0.100 |
| Bronch/BAL | 210 (13.0) | 72 (14.1) | 0.538 |
| Other sterile | 330 (20.4) | 92 (18.0) | 0.223 |
| More than one site | 97 (6.0) | 41 (8.0) | 0.109 |
| Index drug-resistant organism |  |  |  |
| *S. aureus* | 658 (40.7) | 215 (42.0) | 0.617 |
| *Enterococcus* | 292 (18.1) | 110 (21.5) | 0.086 |
| *Enterobacteriaceae* | 495 (30.7) | 110 (21.5) | **<0.001** |
| *Acinetobacter* | 23 (1.4) | 11 (2.1) | 0.255 |
| *P. aeruginosa* | 64 (4.0) | 31 (6.1) | **0.046** |
| Polymicrobial | 83 (5.1) | 35 (6.8) | 0.144 |
| Discharge disposition |  |  | 0.366 |
| Left hospital against medical advice | 6 (0.4) | 3 (0.6) | 0.539 |
| Home | 1004 (62.2) | 297 (58.0) | **0.011** |
| SNF/LTACH/Rehab/NH | 580 (35.9) | 203 (39.6) | **0.018** |
| Other hospital | 25 (1.5) | 9 (1.8) | 0.652 |
| LOS (days) | 13.7 [6.8-30.0] | 14.7 [8.0-30.8] | **0.011** |

P values were obtained using univariate Cox-regression. APACHE-II: Acute Physiology and Chronic Health Evaluation. BAL: bronchoalveolar lavage. CKD: Chronic kidney disease. ESRD: End-stage renal disease. ICU: intensive care unit. LTACH: long-term acute care hospital. LOS: length of stay. NH: nursing home. SNF: skilled nursing facility.

Supplemental Figure 1:MDROs isolated during a readmission by index pathogen group.