**Supplementary Table 1- Characteristics of patients with sepsis upon admission or with nosocomial sepsis, Shamir (Assaf Harofeh) Medical Center, 2016.**

|  |  |  |
| --- | --- | --- |
|  | **Sepsis upon admission** | **Nosocomial sepsis** |
| **Parameter** | **Frequency** | **Valid percent**1 | **Frequency** | **Valid percent** |
| Population (number of patients enrolled) | 1,536 | 802 |
| **Demographics** |
| Age (years) mean ± SD | 62 ± 22 | 77 (18-103) |
| Female gender | 869 | 56.6 | 367 | 45.8 |
| Elderly (> 65 years old) | 827 | 53.8 | 618 | 77.1 |
| **Exposure to healthcare environments or procedures** |
| Recent (<3 months) hospitalization | 387 | 25.2 | 313 | 39 |
| LTCF resident | 162 | 10.5 | 151 | 18.8 |
| Recent (<3 months) LTCF stay prior to hospitalization  | 490 | 31.9 | 176 | 21.9 |
| Regular visits (at least weekly) to outpatient clinics | 79 | 5.1 | 120 | 15 |
| Hemodialysis | 41 | 2.7 | 43 | 5.4 |
| Advanced nursing or intravenous therapy administered at home | 23 | 1.5 |  |  |
| Antibiotic course (≥2 days duration) in the preceding 3 months | 601 | 40.7 | 611 | 76.2 |
| Invasive procedure in the preceding 6 months | 234 | 15.2 | 380 | 47.4 |
| Permanent device1 | 173 | 11.3 | 187 | 23.3 |
| ICU stay in the preceding 3 months | 13 | 0.8 | 23 | 8 |
| MDRO2 carrier from the preceding 2 years | 183 | 11.9 | 265 | 33 |
| **Background medical status and conditions** |
| Functionally dependent | 540 | 35.2 |  |  |
| Chronic skin ulcers |  |  | 212 | 26.4 |
| Altered consciousness / cognition | 276 | 18 | 251 | 31.3 |
| Ischemic heart disease | 323 | 21 | 288 | 35.9 |
| Congestive heart failure | 208 | 13.5 | 318 | 39.7 |
| Diabetes mellitus | 486 | 31.6 | 360 | 44.9 |
| Chronic kidney disease | 249 | 16.2 | 205 | 25.6 |
| Chronic lung disease | 277 | 18 | 297 | 37 |
| Active malignancy | 142 | 9.2 | 164 | 20.4 |
| AIDS | 3 | 0.2 | 1 | 0.1 |
| Immunosuppression3  | 220 | 14.3 | 237 | 29.6 |
| Charlson's scores, mean ± standard deviation | Weighted Index Comorbidity | 2.1 ± 2.4 | 5.2 ± 3.1 |
| Combined Condition Score | 4.2 ± 3.5 | 8± 3.8 |
| 10 Year Survival, percent | 7.3 ± 6.8 | 1 (0-98) |
| **Acute illness indices** |
| Severe sepsis, septic shock, multi-organ failure (previous sepsis severity classification) | 444 | 28.9 | 319 | 39.8 |
| In ICU at culture date | 121 | 7.9 | 321 | 40.1 |
| Mechanically ventilated | 119 | 7.7 | 107 | 17.8 |
| Acute kidney injury | 329 | 22.1 | 222 | 29.2 |
| Altered consciousness at culture date | 380 | 24.7 | 438 | 54.6 |
| Rapidly fatal McCabe score | 167 | 10.9 | 104 | 62.7 |
| Pitt score, median (IQR) | 1 (0-1) | 2 (0-14) |
| Clinical syndrome | Urinary tract infection | 374 | 24.3 | 151 | 18.8 |
| Pneumonia and upper respiratory tract infection | 552 | 35.9 | 343 | 42.8 |
| Skin or soft tissue infection | 217 | 14.1 | 92 | 11.5 |
| Intra-abdominal infection | 185 | 12 | 50 | 6.2 |
| Endocarditis | 11 | 0.7 | 3 | 0.4 |
| Primary blood stream infection | 17 | 1.1 | 96 | 12 |
| Central nervous system infection | 22 | 1.4 | 2 | 0.2 |
| Bacteremia without determined focus | 39 | 2.5 | 64 | 8 |
| Gynecologic / pelvic infection | 119 | 7.7 | 1 | 0.1 |
| Hospitalization division  | Medicine (including advanced-care rooms) | 976 | 63.5 | 327 | 41 |
| Surgery | 157 | 10.2 | 148 | 18 |
| Obstetrics-Gynecology | 201 | 13.1 | 8 | 1 |
| ICU or ICCU  | 132 | 8.6 | 319 | 40 |
| Emergency Room | 70 | 4.6 | NA | NA |
| **Antimicrobial therapy** |
| Days to initiation of appropriate therapy, median (range) | 0 (0-2) | 1 (0-12) |
| ≥ 48 hours delay in initiating appropriate therapy | 130 | 26.4 | 63 | 22.2 |
| **Outcomes** |
| Length of stay from infection to discharge, after excluding the dead, days, median (IQR) | 5 (3-8) | 22 (5-669) |
| Died during current hospitalization | 142 | 9.2 | 287 | 35.8 |
| Died during 14 days after culture date | 105 | 7 | 223 | 27.8 |
| Died during 90 days after culture date  | 217 | 16.5 | 363 | 45.3 |
| Among survivors of index hospitalization | Functional status deterioration at discharge | 140 | 10 | 255 | 50 |
| Discharge to LTCF (only patients admitted from home) | 60 | 4.7 | 176 | 39 |
| *Clostridium difficile* infection in 90 days | 7 | 0.9 |  |  |
| Additional hospitalization in the following 3 months | 348 | 29.6 | 158 | 35.6 |

1 data is presented as valid percent- unknown data was removed from statistics.

2 MDRO- multi-drug resistant organisms included pathogens that were resistant to the first empiric antibiotic line: Methicillin-resistant *Staphylococcus aureus* (MRSA); Ampicillin and/or vancomycin resistant Enterococcus; Penicillin and/or ceftriaxone non-susceptible *Streptococcus pneumoniae*; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*; Enterobacteriaceae non-susceptible to ≥1 3rd generation cephalosporin (e.g., ceftriaxone, ceftazidime, cefotaxime); *Stenotrophomonas maltophilia*.

3 Immunosuppression include either of the following situations: neutropenia (<500 neutrophils) present at day of culture; Glucocorticoid use for >48 hours in the month previous to culture day; chemotherapy or radiotherapy in the 3 months previous to culture day; carrier of Human Immunodeficiency Virus; Patient has had a bone marrow or solid organ transplantation; Anti-Tumor Necrosis Factor of Anti-tyrosine kinase therapy in past 3 months

SD – standard deviation; LTFC – Long Term Care Facility; S/P – stats post; CABG – coronary artery bypass graft; CVA - cerebrovascular accident; TIA - Transient Ischemic Attack; AIDS - Acquired Immune Deficiency Syndrome; SIRS - Systemic Inflammatory Response Syndrome; ICU - intensive care unit; ICCU - Intensive Cardiac-Care Unit. Ob/Gyn- Obstetrics or Gynecology; IQR – inter quartile range.

**Supplementary Table 2 – Characteristics and features of the validation datasets included in the study**.

|  |  |
| --- | --- |
| Validation datasets of the MDR upon admission score | Validation datasets of the nosocomial XDR score |
| Dataset name | PI | Pt. No. | Period | Description | Dataset name | PI | Pt. No. | Period | Description |
| SMC MDR1 | Gil Marcus | 426 | 1/12/2014 – 4/25/2014 | SMC, patients with MDR BSI vs. patients with non-MDR BSI | DMC CRE1 | Violet Libman | 182 | 2007-2010 | DMC, patients with CRE BSI vs. patients with ESBL BSI |
| SMC MDR2 | Mor Broide | 199 | 7/1/2012 - 6/30/2013 | SMC, patients with ESBL-producing Enterobacterales infections vs. patients with non-ESBL-producing Enterobacterales infections | SMC XDR1 | Matar Yekutiel | 257 | 1/1/2013- 2/28/2013 | SMC, patients with XDR BSI vs. patients with non-XDR BSI |
| SMC MDR3 | Eyal Taleb | 311 | 1/1/2013- 7/31/2013 | SMC, patients with MDR infections vs. patients with non-MDR infections | SMC XDR2 | Dana Leveat | 162 | 1/1/2013- 7/31/2013 | SMC, patients with nosocomial BSI vs. patients with community-onset (i.e., both community-acquired and healthcare-associated) BSI |
|  |  |  |  |  | SMC XDR3 | Itzhak Vitkon-Barkay | 239 | 1/1/2007- 5/31/2012 | SMC, patients with XDR infections vs. patients with MDR infections |

PI= primary investigator; Pt= patient; No= number; MDR= multi-drug resistant; XDR= extensively drug resistant; SMC= Shamir Medical Center; BSI= bloodstream infection; DMC= Detroit Medical Center; CRE= carbapenem-resistant Enterobacterales; ESBL= extended-spectrum beta-lactamase producing Enterobacterales.

**Supplementary Table 3 - Frequencies of pathogens in the developing cohorts, Shamir (Assaf Harofeh) Medical Center, 2016**.

|  |  |  |
| --- | --- | --- |
|  | **MDRO upon-admission** | **Nosocomial XDRO**  |
|  | **Frequency** | **Valid percent1** | **Frequency** | **Valid percent1** |
| **Blood bacteria isolation** |
| Bacteremia | 19.3 | 296 | 201 | 40 |
| Polymicrobial isolations | 11.7 | 35 | 176 | 35 |
| **Representative organisms’ group/type** |
| Aerobic Gram positive bacteria | 148 | 29.5 | 78 | 15.5 |
| Aerobic Gram negative bacteria | 351 | 70.1 | 370 | 73.5 |
| **Organism type** | **Organism's full name** | **Frequency** | **Valid percent1** | **Frequency** | **Valid percent1** |
| Aerobic GPC | *Enterococcus* spp. | 27 | 5.4 | 35 | 7.8 |
| *Staphylococcus aureus* | 53 | 10.6 | 36 | 8 |
| Coagulase negative staphylococci | 66 | 13.2 | 6 | 1.3 |
| *Lactobacillus* spp. | 1 | 0.2 | 0 |  |
| *Listeria monocytogenes* | 1 | 0.2 | 0 |  |
| *Corynebacterium* spp. | 1 | 0.2 | 0 |  |
| Viridans streptococci | 62 | 12.4 | 1 | 0.2 |
| Aerobic GNB | *Achromobacter xylosoxidans* | 2 | 0.4 | 2 | 0.4 |
| *Acinetobacter baumannii* | 7 | 1.4 | 108 | 24 |
| *Acinetobacter haemolyticus* | 1 | 0.2 |  |  |
| *Acinetobacter junii* | 0 |  | 1 | 0.2 |
| *Acinetobacter lwoffii* | 0 |  | 2 | 0.4 |
| *Burkholderia cepacia* | 0 |  | 1 | 0.2 |
| *Salmonella* spp. | 4 | 0.8 |  |  |
| *Citrobacter* spp. | 7 | 1.4 | 3 | 0.6 |
| *Enterobacter* spp. | 11 | 2.2 | 20 | 4.4 |
| *Moraxella catarrhalis* | 4 | 0.8 | 0 |  |
| *Mycoplasma hominis* | 1 | 0.2 | 0 |  |
| *Escherichia coli* | 152 | 30.3 | 50 | 11.2 |
| *Haemophilus influenzae* | 8 | 1.6 | 3 | 0.7 |
| *Klebsiella pneumoniae* | 59 | 11.8 | 58 | 12.9 |
| *Morganella morganii* | 6 | 1.2 | 5 | 1.1 |
| *Pantoea agglomerans* | 1 | 0.2 | 1 | 0.2 |
| *Proteus mirabilis* | 16 | 3.1 | 24 | 5.3 |
| *Proteus penneri* |  |  | 1 | 0.2 |
| *Providencia stuartii* | 3 | 0.6 | 4 | 0.9 |
| *Pseudomonas aeruginosa* | 40 | 8 | 57 | 12.7 |
| Other *Pseudomonas* spp. | 5 | 1 |  |  |
| *Serratia* spp | 4 | 0.8 | 4 | 0.9 |
| *Shigella* spp. | 7 | 1.4 | 0 |  |
| *Sphingomonas paucimobilis* | 2 | 0.4 | 1 | 0.2 |
| *Stenotrophomonas maltophilia* | 7 | 1.4 | 25 | 5.6 |
| Mycobacteria | *Mycobacterium tuberculosis* | 2 | 0.4 | 0 |  |
| **MDRO** |
| Gram positives | *Staphylococcus aureus* | 12 | 7.3 |  |  |
| *Enterococcus faecalis* | 2 | 1.2 |  |  |
| *Enterococcus faecium* | 2 | 1.2 |  |  |
| Gram negatives | *Escherichia coli* | 45 | 27.3 |  |  |
| *Pseudomonas aeruginosa* | 41 | 24.8 |  |  |
| *Klebsiella pneumoniae* | 28 | 17 |  |  |
| *Proteus mirabilis* | 10 | 6.1 |  |  |
| *Acinetobacter baumannii* | 7 | 4.2 |  |  |
| *Stenotrophomonas maltophilia* | 7 | 4.2 |  |  |
| *Morganella morganii* | 3 | 1.8 |  |  |
| *Providencia stuartii* | 3 | 1.8 |  |  |
| *Achromobacter xylosoxidans* | 1 | 0.6 |  |  |
| *Enterobacter aerogenes* | 1 | 0.6 |  |  |
| *Enterobacter asburiae* | 1 | 0.6 |  |  |
| *Pseudomonas alcaligenes* | 1 | 0.6 |  |  |
| *Sphingomonas paucimobilis* | 1 | 0.6 |  |  |
| **XDRO group/type** |
| GPC |  |  | 2 | 1.2 |
| GNB |  |  | 165 | 98.8 |
| **XDRO type** | **XDRO's full name** |  |  |  |  |
| Aerobic GPC | VRE |  |  | 2 | 0.2 |
| Aerobic GNB | *Achromobacter xylosoxidans* |  |  | 1 | 0.1 |
| CRAB |  |  | 100 | 12.5 |
| *Burkholderia cepacia* |  |  | 1 | 0.1 |
| CRE | *Enterobacter aerogenes* |  |  | 1 | 0.1 |
| *Enterobacter cloacae* |  |  | 1 | 0.1 |
| *Escherichia coli* |  |  | 1 | 0.1 |
| *Klebsiella pneumoniae* |  |  | 16 | 2.1 |
| CRPA |  |  | 19 | 2.4 |
| *Stenotrophomonas maltophilia* |  |  | 25 | 3.1 |

1 Valid percent represents the frequency percent after exclusion of items for which data was missing (those were subtracted from the denominator).

MDRO- multi-drug resistance organisms; XDRO- extensively drug-resistant organisms; CRAB – carbapenem-resistant *Acinetobacter baumannii*; CRE – carbapenem -resistant enterobacteriaceæ; CRPA – carbapenem-resistant *Pseudomonas aeruginosa*; GNB – Gram-negative bacilli; VRE- vancomycin-resistant *Enterococcus*; GPC- Gram positive cocci.