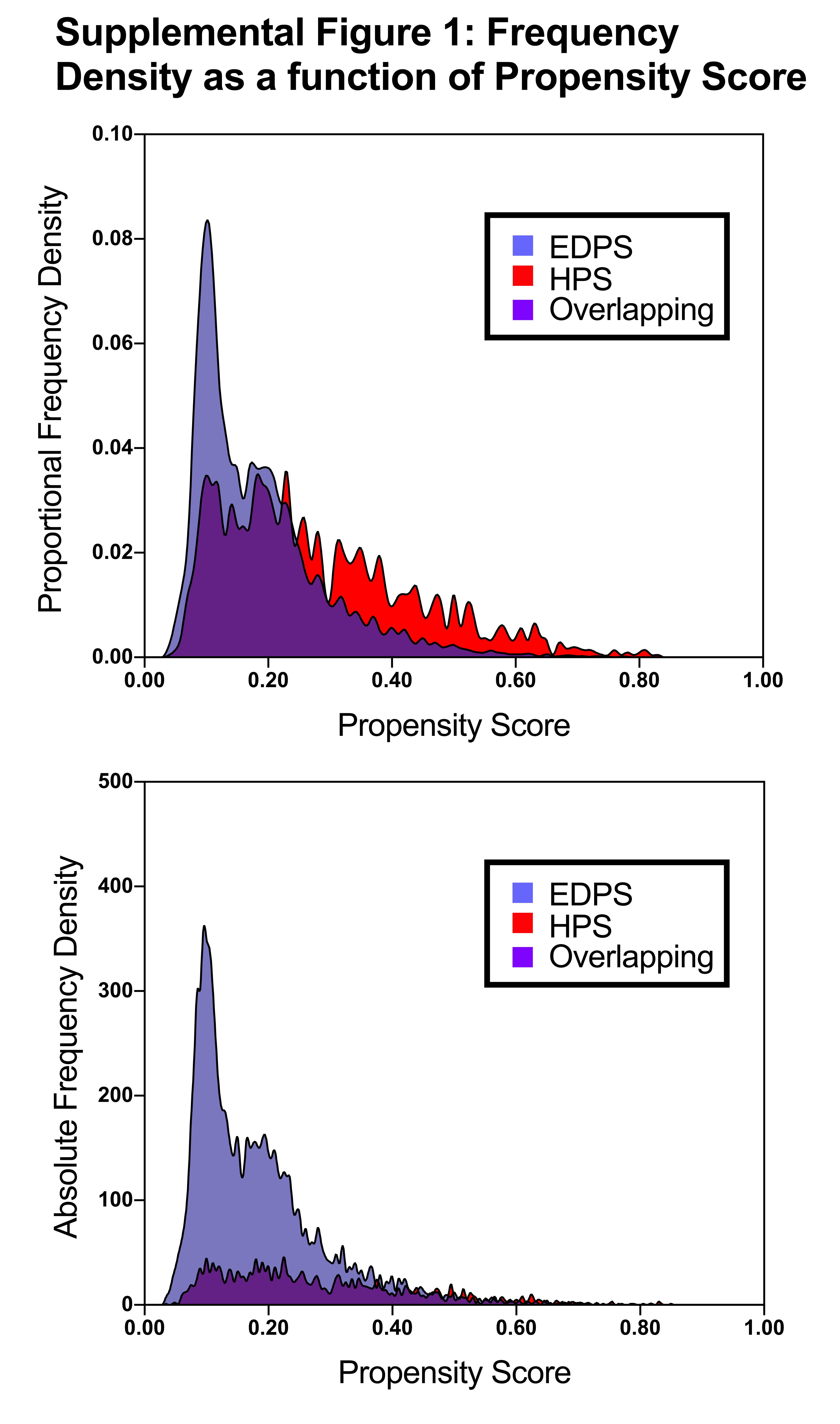
**Supplemental Material:**

Sepsis in Hospitals vs. Emergency Departments

Leisman et al.



**Supplemental Figure 1:**

Shows the proportional and absolute frequency densities as a function of the calculated propensity score for HPS vs. EDPS, where a propensity-score of 1.0 corresponds to 100% probability of being an HPS patient. Frequency curves were generated by smoothing to 2 neighbors and using a 2nd order polynomial function. Abbreviations: HPS – hospital presenting sepsis, EDPS – emergency department presenting sepsis.

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| **Supplemental Table 1: Organ Dysfunction Criteria for Study Inclusion** | |
| **Organ Dysfunction Criteria** a | **Definition** |
| 1. Elevated Lactate | Serum lactate >2.1 mmol/L |
| 2. Hypotension | Systolic blood pressure < 90 mmHg or a mean arterial pressure < 65 mmHg. |
| 3. Acute Kidney Injury | Serum creatinine >2.0 mg/dL or 50% increase from known baseline in the absence of chronic kidney disease |
| 4. Thrombocytopenia | Platelet count < 150,000 cells/μm3 |
| 5. Coagulopathy | International normalized ratio >1.5, activated partial thromboplastin time >30 seconds, or partial thromboplastin time >60 seconds, not otherwise explained by medical history |
| 6. Elevated Bilirubin | Serum bilirubin > 2.0 mg/dL in the absence of pre-existing liver failure |
| 7. Acute Altered Mental Status | New altered mentation unrelated to the patient’s prior medical history |
| 8. Altered Gas Exchange | New increased O2 requirement to maintain SaO2 > 90% or a PaO2/FiO2 ratio < 300 |
| 9. ≥2 “Super-SIRS” Criteria at Triage | Locally developed consensus-criteria, where meeting ≥2 criteria at triage was a “time-zero” entry point for 3-hour bundle care. “Super-SIRS” criteria were:   1. Heart rate greater ≥ 120 2. Respiratory rate ≥ 24 3. Systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg 4. Temperature ≥ 38.0° C (101.0° F) or ≤ 36.0° C (96.8° F) 5. Acutely altered mental status |
| a All patients included in this study had a source of infection, met at least 2 SIRS criteria, and met at least one of the above organ dysfunction criteria. All organ dysfunction criteria was new, acute, and not explainable by the patients past medical history alone. | |

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| **Supplemental Table 2: Three-Hour Sepsis Bundle Interventions** | |
| **Domain** | **Required Interventions** |
| **Local Sepsis Bundle at Study Institutions** a |  |
| Antibiotics | Administer Broad-Spectrum, Source-Directed, Empiric Antibiotics within 180 minutes of suspected sepsis meeting 2 SIRS criteria, or within 60 minutes of meeting objective sepsis organ dysfunction criteria (Time-Zero), whichever is earlier.  Inpatients already receiving broad-spectrum intravenous antibiotics were exempt from this requirement and their care was considered compliant. |
| Blood Cultures | Draw 2 sets of blood cultures prior to the administration of antibiotics |
| Intravenous Fluids | *Initiate* a bolus administration (20-30mL/kg at 500mL/15 min) of intravenous crystalloid *within 30 minutes* of Time-Zero.  Patients whose care did not meet this goal were exempt and considered fluid compliant if they had either acute decompensated heart failure and a left ventricular assist device, or dialysis-dependent end-stage renal failure with clinical evidence of volume overload, were exempt from the fluid requirement. The bundle goal was intended to be met for all other patients. |
| Lactate Measurement | Order lactate measurement and obtain result within 90 minutes of order time. |
| **Surviving Sepsis Campaign 3-hour Bundle** |  |
| Antibiotics | Administer Broad-Spectrum, Source-Directed, Empiric Antibiotics within 60 minutes of Time-Zero |
| Blood Cultures | Draw 2 sets of blood cultures prior to the administration of antibiotics |
| Intravenous Fluids | *Complete* a bolus administration (30mL/kg) of intravenous crystalloid within *3 hours* of Time-Zero. |
| Lactate Measurement | Measure lactate level within 180 minutes. |
| a Full bundle compliance was considered to be adherence to all four bundle elements. The local sepsis bundle was used for the main analysis as this reflected standard of care at the study sites. | |

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| **Supplemental Table 3: Baseline Variables in Unmatched and Matched Cohorts** | | | | | |
|  | **Entire (Unmatched) Cohort** | | | **Matched Cohort** | |
| **Variable** | **All Subjects** | **EDPS** | **(All) HPS** | **EDPS** | **(All) HPS** |
| **N** | **11,182** | **8,673 (77.6%)** | **2,509 (22.4%)** | **1,942 (50.0%)** | **1,942 (50.0%)** |
| **Demographics** |  |  |  |  |  |
| Age\* - median(IQR) | 74 (62, 85) | 75 (62, 85) | 73 (62, 83) | 73 (61-84) | 74 (62-84) |
| Male Sex\* | 5,740 (51.3%) | 4,436 (51.1%) | 1,304 (52.0%) | 1,025, (52.8%) | 1,021, (52.6%) |
| Tertiary Care Hospital\* | 8,069 (72%) | 6,171 (71%) | 1,898 (76%) | 1,441 (74.2%) | 1,451 (74.7%) |
| Body Mass Index | 27.1 (7.0) | 26.9 (7.0) | 27.5 (7.0) | 26.9 (7.0) | 27.5 (7.0) |
| Admitted from a SNF | 2,477 (22.2%) | 2,211 (24.5%) | 356 (14.2%) | 488 (25.1%) | 268 (13.8%) |
| **Comorbiditiesa** |  |  |  |  |  |
| Heart Failure\* | 1,647 (14.7%) | 1,171 (13.5%) | 476 (19.0%) | 322 (16.6%) | 351 (18.1%) |
| Renal Failure\* | 1,161 (10.4%) | 754 (8.7%) | 407 (16.2%) | 278 (14.3%) | 284 (14.6%) |
| COPD\* | 793 (7.1%) | 666 (7.7%) | 127 (5.1%) | 96 (4.9%) | 100 (5.1%) |
| Diabetes\* | 3,631 (32.5%) | 2,815 (32.5%) | 816 (32.5%) | 587 (30.2%) | 617 (31.8%) |
| Liver Failure\* | 173 (1.5%) | 124 (1.4%) | 49 (2.0%) | 41 (2.1%) | 36 (1.9%) |
| Immune modifying medications\* | 2,346 (21.0%) | 1,748 (20.2%) | 598 (23.8%) | 439 (22.6%) | 459 (23.6%) |
| **Presentation and Etiology** |  |  |  |  |  |
| Respiratory Infection Source | 4,460 (39.9%) | 3,456 (39.8%) | 1,004 (40.0%) | 728 (37.5%) | 787 (40.5%) |
| Urinary Infection Source | 2,802 (25.1%) | 2,321 (26.8%) | 481 (19.2%) | 404 (20.8%) | 369 (19.0%) |
| Skin/Soft Tissue Infection Source | 778 (7.0%) | 644 (7.4%) | 134 (5.3%) | 154 (7.9%) | 92 (4.7%) |
| Gastrointestinal Infection Source | 1,071 (9.6%) | 734 (8.5%) | 337 (13.4%) | 202 (10.4%) | 268 (13.8%) |
| Other/Unknown Infection Source | 2,071 (18.5%) | 1,518 (17.5%) | 553 (22.0%) | 454 (23.4%) | 426 (21.9%) |
| Confirmed Nosocomial Source\* | 1,213 (10.9%) | 705 (8.1%) | 508 (20.3%) | 339 (17.5%) | 332 (17.1%) |
| Tachycardia >90 beats/minute | 8,442 (75.5%) | 6,691 (77.1%) | 1,751 (69.8%) | 1,438 (74.0%) | 1,384 (71.3) |
| Tachypnea >20 breaths/minute | 6,147 (55.0%) | 4,882 (56.3%) | 1,265 (50.4%) | 1,110 (57.1%) | 1,014 (52.2%) |
| Fever\* | 4,040 (36.1%) | 3,334 (38.4%) | 706 (28.1%) | 637 (32.8%) | 553 (28.5%) |
| Hypothermia\* | 1,195 (10.7%) | 871 (10.0%) | 324 (12.9%) | 278 (14.3%) | 236 (12.2%) |
| Leukocytosis | 6,596 (59.0%) | 5,146 (59.3%) | 1,450 (57.8%) | 1,123 (57.8%) | 1,128 (58.1%) |
| Leukocytopenia | 639 (5.7%) | 475 (5.5%) | 164 (6.5%) | 140 (7.2%) | 127 (6.5%) |
| **Severity of Illness** |  |  |  |  |  |
| Initial Lactate (mmol/L) - mean(SD)\* | 3.2 (2.4) | 3.3 (2.3) | 3.1 (2.7) | 3.1 (2.2) | 3.1 (2.7) |
| Lactate >4.0 mmol/L | 2,458 (23.0%) | 1,977 (23.2%) | 481 (22.2%) | 450 (23.2%) | 435 (22.4%) |
| Hypotension\* | 3,714 (33.2%) | 2,551 (29.4%) | 1,163 (46.4%) | 872 (44.9%) | 849 (43.7%) |
| Altered Gas Exchangeb\* | 2,412 (21.6%) | 1,606 (18.5%) | 806 (32.1%) | 604 (31.1%) | 622 (32.0%) |
| Altered Mental Status\* | 2,675 (23.9%) | 2,060 (23.8%) | 615 (24.5%) | 461 (23.7%) | 469 (24.2%) |
| Acute Kidney Injuryc\* | 2,328 (20.8%) | 1,847 (21.3%) | 481 (19.2%) | 380 (19.6%) | 372 (19.2%) |
| Coagulopathyd\* | 637 (5.7%) | 501 (5.8%) | 136 (5.4%) | 114 (5.9%) | 264 (13.6%) |
| Thrombocytopeniae\* | 1,240 (11.1%) | 910 (10.5%) | 330 (13.2%) | 323 (16.6%) | 356 (18.3%) |
| All data presented as frequency (percentage) unless otherwise indicated.  \* Indicates variable was used in generating propensity score for matching.  a Comorbidities reflect status at time zero, and would not reflect conditions developing subsequently during hospital stay.  b Altered Gas Exchange defined as PaO2 /FiO2 <300 or an increased O2 requirement to maintain SaO2 >90%.  c Acute Kidney Injury defined as creatinine >2.0 or 50% increase from a known baseline.  d Coagulopathy defined as international normalized ratio >1.5 or partial thromboplastin time >60 seconds.  eThrombocytopenia defined as platelet count <150,000 cells/µm3  Abbreviations: COPD, chronic obstructive pulmonary disease; EDPS, emergency department-presenting sepsis; HPS, hospital-presenting sepsis, ICU, intensive care unit; IQR, interquartile range; SNF, skilled nursing facility; SD, standard deviation. | | | | | |

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| **Supplemental Table 4: Propensity Model for Community-Acquired vs. Any Hospital-Acquired Sepsis (Primary Analysis)** | | | |
| **Variable** | **(β) Propensity Coefficient** | **Odds Ratio** | **95% CI** |
| Age | 0.005 | 1.01 | 1.00, 1.01 |
| Male Sex | -0.041 | 0.96 | 0.87, 1.06 |
| Tertiary Care Hospital | -0.014 | 0.99 | 0.88, 1.11 |
| Heart Failure | -0.257 | 0.77 | 0.67, 0.89 |
| Renal Failure | -0.476 | 0.62 | 0.53, 0.72 |
| COPD | 0.703 | 2.02 | 1.62, 2.52 |
| Diabetes | 0.027 | 1.03 | 0.92, 1.15 |
| Liver Failure | -0.044 | 0.96 | 0.66, 1.40 |
| Immunocompromise | -0.072 | 0.93 | 0.83, 1.05 |
| *Infection Source (vs. Respiratory)* |  |  |  |
| Urinary | 0.044 | 1.05 | 0.91, 1.20 |
| Skin/Soft-Tissue | 0.199 | 1.22 | 0.97, 1.54 |
| Gastrointestinal | -0.686 | 0.50 | 0.43, 0.60 |
| Other/Unknown | -0.393 | 0.68 | 0.59, 0.78 |
| Temperature | -0.282 | 0.75 | 0.70, 0.82 |
| Hospital Acquired Infection | -0.905 | 0.41 | 0.35, 0.47 |
| Serum Lactate Level (per mmol/L) | 0.057 | 1.06 | 1.04, 1.08 |
| Initial Hypotension | -0.591 | 0.55 | 0.50, 0.61 |
| Altered Gas Exchange | -0.845 | 0.43 | 0.38 0.48 |
| Altered Mental Status | 0.128 | 1.14 | 1.01, 1.28 |
| Acute Kidney Injury | 0.202 | 1.22 | 1.08, 1.39 |
| Coagulopathy | -0.208 | 0.81 | 0.71, 0.93 |
| Hosmer-Lemeshow: χ2 = 9.5, p=0.30 |  |  |  |
| Model displays maximum likelihood estimates and exponentiated coefficient values with confidence intervals. The dependent variable is community-acquired vs. non-ICU hospital-hospital acquired sepsis, where positive estimates (and odds ratios >1.0) indicate greater propensity for community-acquired. | | | |

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| **Supplemental Table 5: Propensity Model for Community-Acquired vs. Non-ICU Hospital-Acquired Sepsis (Sensitivity Analysis)** | | | |
| **Variable** | **(β) Propensity Coefficient** | **Odds Ratio** | **95% CI** |
| Age | 0.001 | 1.00 | 1.00, 1.01 |
| Male Sex | -0.009 | 0.99 | 0.88, 1.12 |
| Tertiary Care Hospital | 0.001 | 1.00 | 0.88, 1.15 |
| Heart Failure | -0.195 | 0.82 | 0.70, 0.97 |
| Renal Failure | -0.460 | 0.63 | 0.53, 0.76 |
| COPD | 0.708 | 2.03 | 1.55, 2.66 |
| Diabetes | 0.113 | 1.12 | 0.98, 1.28 |
| Liver Failure | -0.126 | 0.88 | 0.56, 1.39 |
| Immunocompromise | 0.245 | 1.28 | 1.07, 1.53 |
| *Infection Source (vs. Respiratory)* |  |  |  |
| Urinary | -0.052 | 0.95 | 0.81, 1.12 |
| Skin/Soft-Tissue | -0.068 | 0.94 | 0.72, 1.21 |
| Gastrointestinal | -0.766 | 0.47 | 0.38, 0.57 |
| Other/Unknown | -0.410 | 0.66 | 0.56, 0.78 |
| Temperature | -0.222 | 0.80 | 0.73, 0.88 |
| Hospital Acquired Infection | -0.905 | 0.41 | 0.35, 0.47 |
| Serum Lactate Level (per mmol/L) | 0.082 | 1.09 | 1.06, 1.12 |
| Initial Hypotension | -0.443 | 0.64 | 0.57, 0.73 |
| Altered Gas Exchange | -0.777 | 0.46 | 0.40 0.53 |
| Altered Mental Status | 0.105 | 1.11 | 0.96, 1.28 |
| Acute Kidney Injury | 0.267 | 1.31 | 1.12, 1.52 |
| Coagulopathy | -0.175 | 0.84 | 0.72, 0.98 |
| Hosmer-Lemeshow: χ2 = 11.0, p=0.20 |  |  |  |
| Model displays maximum likelihood estimates and exponentiated coefficient values with confidence intervals. The dependent variable is community-acquired vs. non-ICU hospital-hospital acquired sepsis, where positive estimates (and odds ratios >1.0) indicate greater propensity for community-acquired. | | | |

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| **Supplemental Table 6: Process and Patient Outcomes in Unmatched and Matched Cohorts** | | | | | |
|  | **Entire (Unmatched) Cohort** | | | **Matched Cohort** | |
| **Variable** | **All Subjects** | **EDPS** | **(All) HPS** | **EDPS** | **(All) HPS** |
| **N** | **11,182** | **8,673 (77.6%)** | **2,509 (22.4%)** | **1,942 (50.0%)** | **1,942 (50.0%)** |
| **Process Outcomes** |  |  |  |  |  |
| Full 3h-bundle compliance (local) | 3,056 (27.3%) | 2,696 (31.1%) | 360 (14.3%) | 588 (30.3%) | 330 (17.0%) |
| Full 3h-bundle compliance (SSC) | 5,854 (52.4%) | 5,127 (59.1%) | 727 (29.0%) | 1,114 (57.4%) | 591 (30.4%) |
| Antibiotics within 1 h | 5,399 (48.3%) | 4,317 (49.8%) | 1,082 (43.1%) | 935 (48.1%) | 879 (45.3%) |
| Antibiotics within 3 h | 9,040 (80.8%) | 7,437 (85.7%) | 1,603 (63.9%) | 1,628 (83.8%) | 1,285 (66.2%) |
| Antibiotics within 6 h | 9,987 (89.3%) | 8,111 (93.5%) | 1,876 (74.8%) | 1,796 (92.5%) | 1,496 (77.0%) |
| Time to Antibiotics-mean (SD) | 91 (132) | 83 (110) | 117 (187) | 87 (115) | 108 (185) |
| Blood Cultures Before Antibiotics | 7,350 (67.3%) | 6,170 (71.1%) | 1,360 (54.2%) | 1,350 (69.5%) | 1,036 (53.3%) |
| Fluids Initiated within 2 h | 7,724 (69.1%) | 6,774 (78.1%) | 950 (37.9%) | 1,506 (77.5%) | 790 (40.7%) |
| Time to Fluid Initiation-mean (SD) | 118 (149) | 86 (128) | 220 (160) | 89 (129) | 210 (166) |
| Fluid Volume (mL/kg) - mean (SD) | 22.9 (18.7) | 25.4 (18.4) | 14.1 (16.9) | 26.0 (18.8) | 15.4 (17.2) |
| Lactate Result within 90 minutes | 9,318 (83.3%) | 7,443 (85.8%) | 1,875 (74.7%) | 1,709 (88.9%) | 1,671 (88.7%) |
| Repeat Lactate Obtained | 5,976 (53.4%) | 4,617 (53.2%) | 1,359 (54.2%) | 1,054 (54.3%) | 1,211 (62.4%) |
| **Patient Outcomes** |  |  |  |  |  |
| In-Hospital Mortality | 2,241 (20.0%) | 1,456 (16.8%) | 785 (31.3%) | 374 (19.3%) | 605 (31.2%) |
| Mechanical Ventilation | 3,265 (29.2%) | 2,024 (23.3%) | 1,241 (49.5%) | 532 (27.4%) | 1,000 (51.5%) |
| ICU Admission (excluding ICU admit before sepsis onset) | 5,185 (46.4%) | 3,423 (39.5%) | 973 (58.5%) | 903 (46.5%) | 775 (60.6%) |
| ICU Days [95% CI] (ICU admit only) | 6 [5.7-6.3] | 5 [4.8-5.2] | 10 [9.2-10.8] | 5 [4.6-5.5] | 10 [9.0-11.0] |
| Hospital Days [95% CI] | 9.0 [8.8-9.2] | 8 [7.8-8.2] | 17 [16.1-17.9] | 8 [7.6-8.4] | 17 [15.9-18.0] |
| All data presented as frequency (percentage) unless otherwise indicated.  Abbreviations: EDPS, emergency department-presenting sepsis; HPS, hospital-presenting sepsis; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; SSC, Surviving Sepsis Campaign. | | | | | |

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| **Supplemental Table 7: Interaction Coefficients for the Association of Hospital vs. ED Sepsis Presentation with Outcomes by Bundle Intervention.** | | | | |
|  | All Hospital Presenting Sepsis | | Non-ICU Hospital Presenting Sepsis | |
| Phenotype | Interaction Term [95%CI] | p(interaction) | Interaction Term [95%CI] | p(interaction) |
| ***Hospital Mortality*** |  |  |  |  |
| Hours to Antibiotics | 0.99 [0.92-1.06] | 0.75 | 0.96 [0.88-1.05] | 0.40 |
| Hours to Crystalloid Initiation | 0.96 [0.89-1.03] | 0.21 | 1.02 [0.93-1.11] | 0.69 |
| Volume of Initial Crystalloid (per 10 mL/kg) | 0.89 [0.82-0.97] | 0.007\* | 0.85 [0.76-0.94] | 0.002\* |
| Blood Cultures Before Antibiotics | 0.81 [0.59-1.11] | 0.18 | 0.97 [0.65-1.45] | 0.87 |
| Lactate Result in 90 minutes | 2.66 [1.67-4.26] | < 0.001\* | 1.46 [0.80-2.62] | 0.23 |
| Repeat Lactate Obtained | 1.27 [0.93-1.73] | 0.13 | 1.18 [0.80-1.74 | 0.41 |
| Full Bundle Compliance (Local Bundle) | 1.18 [0.79-1.76] | 0.43 | 1.31 [0.80-2.15] | 0.28 |
| Full Bundle Compliance (SSC Bundle) | 0.94 [0.66-1.33] | 0.97 | 1.28 [0.82-2.00] | 0.27 |
| Definitions: ED – emergency department, CI – confidence interval, SSC – Surviving Sepsis Campaign.  The tabulated values are the interaction coefficients with 95% confidence intervals and p-interaction values from the multivariable models. The interaction coefficient is the ratio of odds-ratios for Hospital vs. ED-presenting sepsis at the different levels of the bundle exposure. An interaction coefficient >1.0 indicates that the association of Hospital-presenting sepsis is quantitatively larger (greater differential effect) when the bundle element was present compared to when it was not, and visa-versa. For example, the significant interaction between hospital presentation and initial crystalloid volume indicates that as the volume of crystalloid increased (per 10 mL/kg), the strength of association between hospital sepsis presentation (vs. ED) and risk of in-hospital death significantly decreased (by a factor of 0.89). | | | | |