# Supplementary Online Content

Evans IVR, Phillips GS, Alpern ER, et al. Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis. *JAMA.* doi:10.1001/jama.2018.9071

This supplementary material has been provided by the authors to give readers additional information about their work.

## eMethods

### A. Sepsis identification strategies across New York State hospitals

New York hospitals were instructed to identify severe sepsis and septic shock cases using protocols with criteria suggested by Goldstein et al[1], and the American College of Critical Care Medicine[2]. In the case report form, three categories were used to categorize how cases were identified at each facility.

**1. Positive sepsis screening from clinical assessment**

- This category indicates that the facility used some form of screening of ED patients or inpatients, and the result was positive for sepsis/severe sepsis/septic shock
- For many facilities, the sepsis screen tool will utilize an assessment for at least 2 of the 4 SIRS criteria (temp, heart rate, respiratory rate, WBC's) **and** a suspected/confirmed infection
- This screening process can also incorporate clinical assessments for blood pressure/hypotension, altered mental status, etc.
- Laboratory values (e.g. WBCs, serum lactate levels, creatinine, bilirubin, etc.) may also contribute to a positive screening, but for this category, lab values are **not always** necessary to reach a positive screening result

**2. Positive sepsis screen from clinical assessment AND abnormal laboratory values**

- This category includes the components of the previous category **plus** laboratory values
- In some facilities when the initial screening of a patient comes back as positive for possible sepsis, immediate laboratory tests are ordered. The clinician then used the laboratory values in deciding whether or not to initiate their protocol
- For this category, any laboratory value can be used that supports the sepsis assessment qualifies (WBC counts, % of band cells, platelet counts, serum lactate, blood glucose, creatinine, bilirubin, C-reactive protein, procalcitonin, coagulation abnormalities-INR/aPTT, blood gases)

**3. Positive sepsis screen from clinical assessment AND code sepsis**

- This category includes a positive sepsis screen by clinical assessment
- However, it identifies patients in whom a code sepsis or rapid response team call initiates the case identification

### B. Statistical methods for the development of the propensity score matching analysis

We generated a propensity score (logit) using logistic regression and then matched 286 patients out of a possible 294 on a 1:1 basis for those that completed the one-hour bundle within one hour compared to those 286 patients that did not complete the one-hour bundle within one hour based on a random seed, nearest neighbor, without replacement, and a caliper of 0.10 (approximately 10% of the standard deviation of the logits)[3].

The starting model included all available patient demographics and clinical comorbidities to maximize patient similarity across one-hour bundle completion status. Variables were removed from the model if their inclusion decreased the number of matched cases by more than 10. Variables were removed from the model if their standard errors were greater than 0.1 to ensure that the model was not over-fit. Additionally, variance inflation factors (VIF) were generated to confirm that there was no collinearity among the independent variables. If the VIF of an independent variable was greater than 10, this variable was removed from the model.

Model calibration and discrimination were not calculated because the goal was to match the patients as closely as possible across bundle completion status instead of predicting bundle completion. An in-hospital mortality odds ratio was generated across bundle completion status using an unadjusted logistic regression model restricted to the 286 propensity score matched subjects (total N = 572). Propensity score generation and matching were run using Stata 14.2 (Stata Corporation, College Station, Texas).

### C. Statistical methods for the development of the inverse probability weighted risk-adjusted regression analysis

The average treatment effect (ATE) for in-hospital mortality across 1-hour bundle completion status was generated using inverse probability weighted risk adjusted regression[4]. This statistical method simultaneously fits two regression models – one for the prediction of the outcome of in-hospital mortality and one for the prediction of the risk factor (one-hour bundle status). Since both the outcome and risk factor are binary, logistic regression was used in both models. Additionally, an independent variable could be in both regression models or in only one of the models.

The starting basis for the in-hospital mortality logistic regression model was the same model used in the primary analysis of the manuscript. The starting model for one-hour bundle completion included all available patient demographics and clinical comorbidities in order to minimize confounding by indication. Variables were removed from the starting analysis if their inclusion precluded model convergence since inverse probability models have a tendency to be unstable.

Each variable was then checked to determine the percent change in the ATE odds ratio, in light of the other independents variables in the model, when it was included compared to when it was not included in the model. If the ATE odds ratio changed by more than 15% in either direction the variable was removed from the model since its inclusion caused the inverse probability weighting to become excessively large for some of the subjects.

In other words, the probability generated for each subject in the analysis is that of being in the group that completed the 1-hour bundle within one hour. Therefore, if a subject has a very small probability but is in the group that completed the bundle or has a very large probability but is in the group that did not complete the bundle, then the inverse probability weighting is very large and can have an overdue influence on the ATE odds ratio. All analyses were run using Stata 14.2 (Stata Corporation, College Station, Texas).

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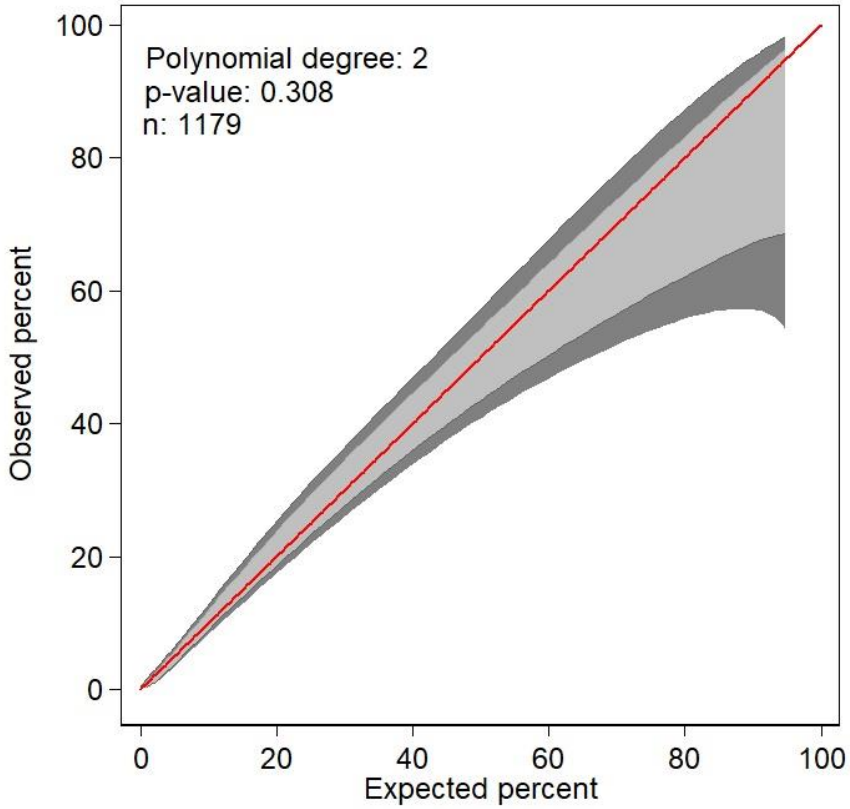
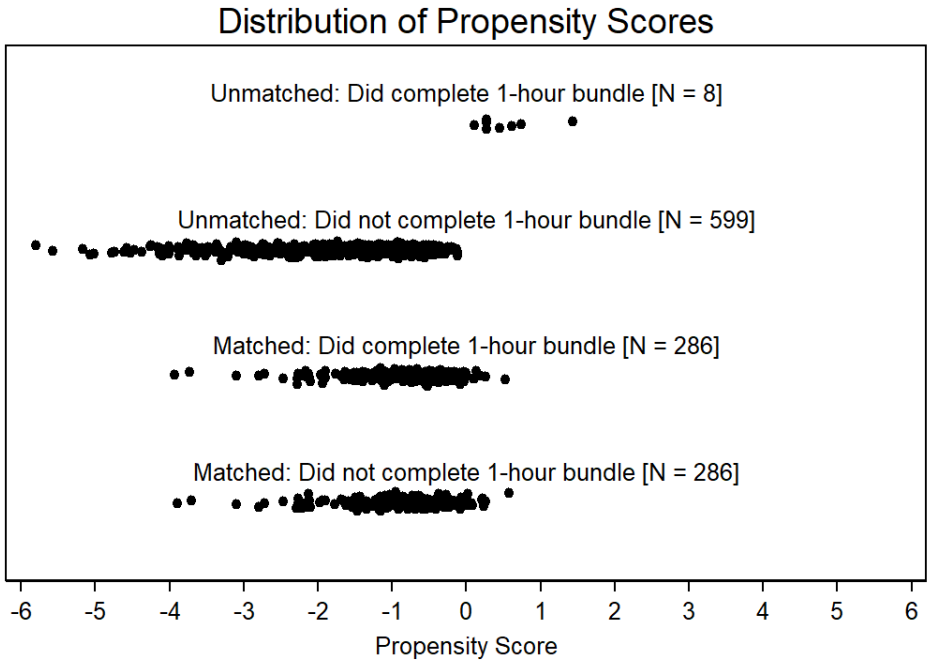
**eFigure 1.** Calibration Belt Showing Observed In-Hospital Mortality (y axis) Compared to Model-Based Estimates of Expected In-Hospital Mortality (x axis).

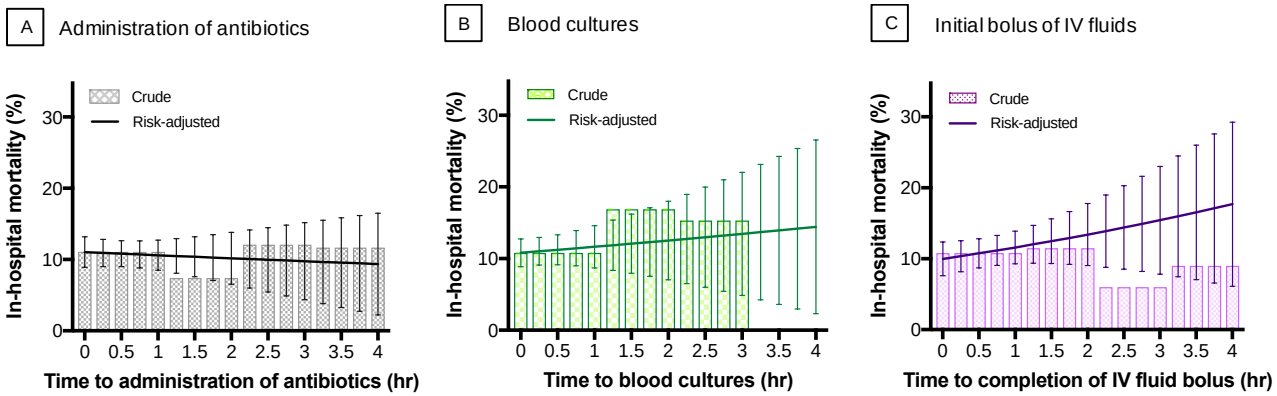



The calibration belt shows the 80% confidence interval (shaded light gray) and 95% confidence interval (shaded dark gray), around the observed rates, which upper and lower bounds do not cross the red line over the range of expected probabilities. The belt and the Hosmer-Lemeshow statistic confirm adequate calibration for the risk-adjustment model.

**eFigure 2.** Distribution of Propensity Scores for Completing the One-Hour Bundle Within One Hour Among Matched (N = 572) and Unmatched (N = 607) Patients.

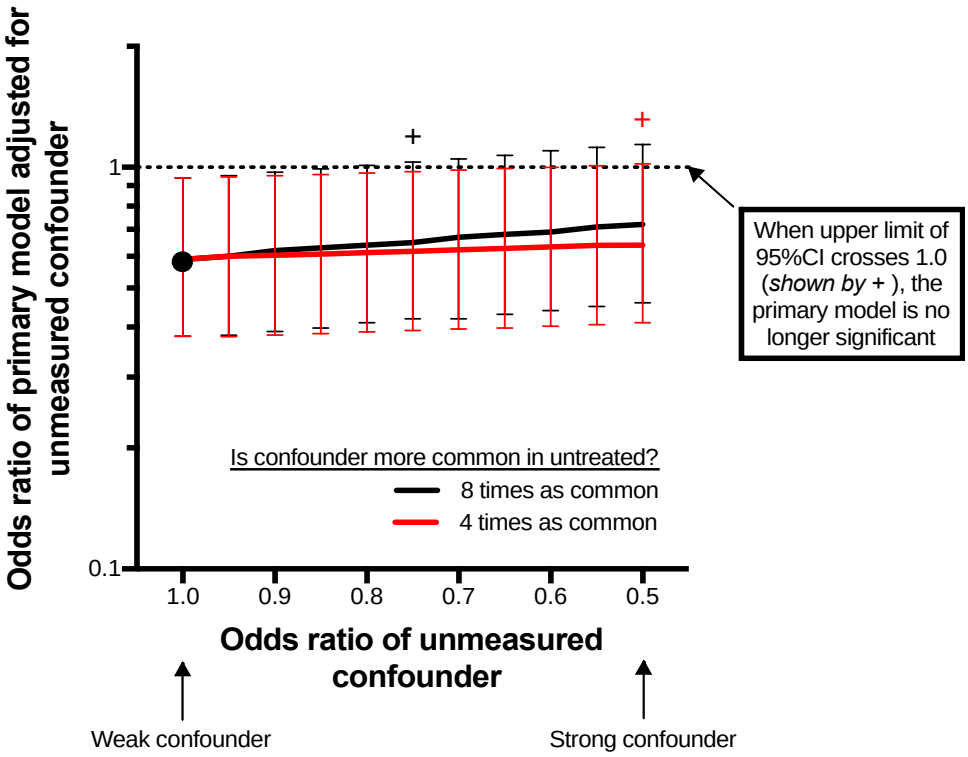


**eFigure 3.** Crude In-Hospital Mortality and Predicted Risks of In-Hospital Death, With Adjustment for Covariates Up to Four Hours After Protocol Initiation, for the Administration of Antibiotics (*panel A*), Blood Cultures (*panel B*), and Completing the Initial Bolus of Intravenous Fluids (*panel C*) in a Typical Pediatric Patient. Solid line is the predicted risk from the adjusted model margins with 95% confidence intervals, and shaded bars are crude mortality rates.




No deaths occurred among patients completing the blood cultures between hours 3 to 4, and thus bars for crude in-hospital mortality are omitted. Predicted risks derive from model adjusted for age category, payer, protocol initiation site, diagnosis of septic shock, site of infection, platelet count < 150,000/mm$^3$ at protocol initiation, chronic renal disease or liver failure, diabetes, acute respiratory failure requiring mechanical ventilation, serum lactate, and transfer status across four hours after protocol initiation for the completion of the one-hour bundle of sepsis care.

**eFigure 4.** *In silico* Quantitative Bias Analysis of a Hypothetical Unmeasured Confounder



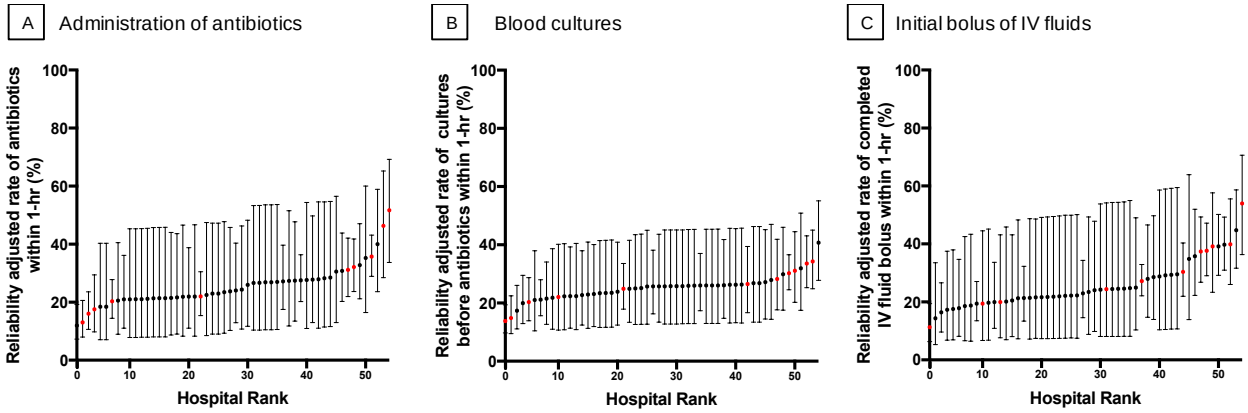

The plot has two important features, i.) the univariate odds ratios of confounder with in-hospital mortality over a plausible range – this corresponds to the strength of the unmeasured confounder "on its own.", ranging from OR=1.0 or weak confounder with no effect to a strong confounder with OR=0.5, ii.) the prevalence of the hypothetical confounder among patients who did not complete the bundle in two scenarios, when it is 8 times as common as in the exposed group (black curve) and when it is 4 times as common (red curve). The y axis is the odds ratio of in-hospital mortality from our primary model for completing the one-hour bundle *if the hypothetical confounder was included* on the log scale. This is the primary simulation read-out, and corresponds to how the primary model would change if the confounder was "added in." The (+) symbol corresponds to scenarios when the primary model is no longer significant, as the upper limit of the 95% confidence interval has crossed 1.0 (on the vertical axis).

The model had the following base assumptions:

- Prevalence of unmeasured confounder among exposed (completing one-hour bundle within one hour) is 5%.
- No modification of the effect of time to completing the one-hour bundle by the unmeasured confounder
- Unmeasured confounder uncorrelated with other variables in the model

*Interpretive example:* To find scenarios where the odds ratio for completing the one-hour bundle within one hour from our primary model was no longer significant, the hypothetical unmeasured confounder must be four times as common among unexposed (0.20) vs. exposed patients (0.05), and have an odds ratio for in-hospital mortality that exceeds 0.5. Much stronger, if not implausible, confounders are required if the prevalence among the unexposed is lower.[5]

**eFigure 5.** Reliability-Adjusted Rate for Each Hospital for Completion of Individual Bundle Elements Within One Hour.




The 54 study hospitals were ranked form lowest to highest, with higher ranks (x axis) indicating a greater predicted likelihood of completing antibiotics (panel A), blood cultures before antibiotics (panel B), and the initial IV fluids bolus (panel C) in a typical pediatric patient within one hour. Bars represents 95% confidence intervals. Red circles correspond to hospitals with pediatric intensive care and cardiac surgery services (Level I PICU). Risk and reliability adjustment accounts for both patient-level risk factors that may influence outcome and statistical variation attributed to small sample sizes at the level of the hospital. These adjustments allow for accurate comparisons between hospitals of different patient volume and case mix.

**eTable 1.** Comparison of Clinical Characteristics Before and After Propensity Score Matching

| Variable[1] | Matching | Completed 1-hour bundle within 1 hour | | Standardized % bias | Percent reduction in bias | *t*-test | |
|---|---|---|---|---|---|---|---|
| | | Yes | No | | | t-statistic | P value |
| Male | Before | 0.54762 | 0.54011 | 1.5 | | 0.2 | 0.82 |
| | After | 0.53846 | 0.54895 | -2.1 | -39.7 | -0.3 | 0.80 |
| Hispanic Origin | Before | 0.20068 | 0.19887 | 0.5 | | 0.1 | 0.95 |
| | After | 0.2028 | 0.18881 | 3.5 | -672.6 | 0.4 | 0.68 |
| Unknown ethnicity | Before | 0.13265 | 0.14802 | -4.4 | | -0.7 | 0.52 |
| | After | 0.13287 | 0.16434 | -9.1 | -104.7 | -1.1 | 0.29 |
| 1 month of age | Before | 0.09524 | 0.09153 | 1.3 | | 0.2 | 0.85 |
| | After | 0.0979 | 0.1014 | -1.2 | 5.8 | -0.1 | 0.89 |
| > 1 month to < 1 year of age | Before | 0.13605 | 0.14124 | -1.5 | | -0.2 | 0.82 |
| | After | 0.13636 | 0.13287 | 1.0 | 32.6 | 0.1 | 0.90 |
| 1 to < 2 years of age | Before | 0.09184 | 0.07684 | 5.4 | | 0.8 | 0.41 |
| | After | 0.09091 | 0.06993 | 7.5 | -39.9 | 0.9 | 0.36 |
| 2 to < 5 years of age | Before | 0.18027 | 0.14915 | 8.4 | | 1.3 | 0.20 |
| | After | 0.16783 | 0.12937 | 10.4 | -23.6 | 1.3 | 0.20 |
| 5 to < 11 years of age | Before | 0.18707 | 0.20113 | -3.6 | | -0.5 | 0.60 |
| | After | 0.19231 | 0.2028 | -2.6 | 25.4 | -0.3 | 0.75 |
| Medicare | Before | 0.0034 | 0.0226 | -17.0 | | -2.2 | 0.03 |
| | After | 0.0035 | 0.00699 | -3.1 | 81.8 | -0.6 | 0.56 |
| Medicaid | Before | 0.44218 | 0.42825 | 2.8 | | 0.4 | 0.68 |
| | After | 0.44755 | 0.45455 | -1.4 | 49.8 | -0.2 | 0.87 |
| Self-pay | Before | 0.02381 | 0.01469 | 6.6 | | 1.1 | 0.29 |
| | After | 0.01399 | 0.02797 | -10.2 | -53.4 | -1.2 | 0.24 |
| Other payer | Before | 0.06122 | 0.06667 | -2.2 | | -0.3 | 0.74 |

| Variable[1] | Matching | Completed 1-hour bundle within 1 hour | | Standardized % bias | Percent reduction in bias | *t*-test | |
|---|---|---|---|---|---|---|---|
| | | Yes | No | | | t-statistic | P value |
| | After | 0.06294 | 0.05245 | 4.3 | -92.7 | 0.5 | 0.59 |
| Prior admission for sepsis | Before | 0.09524 | 0.05989 | 13.2 | | 2.1 | 0.04 |
| | After | 0.07692 | 0.08741 | -3.9 | 70.3 | -0.5 | 0.65 |
| Protocol initiated in the floor | Before | 0.11224 | 0.16158 | -14.4 | | -2.1 | 0.04 |
| | After | 0.11538 | 0.11189 | 1.0 | 92.9 | 0.1 | 0.89 |
| Protocol initiated in the ICU | Before | 0.19388 | 0.30621 | -26.1 | | -3.7 | < 0.001 |
| | After | 0.1993 | 0.1993 | 0.0 | 100.0 | 0.0 | > 0.99 |
| Septic shock diagnosis | Before | 0.70408 | 0.68249 | 4.7 | | 0.7 | 0.49 |
| | After | 0.7028 | 0.69231 | 2.3 | 51.4 | 0.3 | 0.78 |
| Chronic renal failure | Before | 0.0102 | 0.01808 | -6.7 | | -0.9 | 0.35 |
| | After | 0.01049 | 0.00699 | 3.0 | 55.6 | 0.5 | 0.65 |
| Platelet count | Before | 0.2415 | 0.32203 | -18.0 | | -2.6 | 0.009 |
| | After | 0.24126 | 0.23077 | 2.3 | 87.0 | 0.3 | 0.77 |
| Infection etiology | Before | 0.03741 | 0.10508 | -26.5 | | -3.6 | < 0.001 |
| | After | 0.03846 | 0.03147 | 2.7 | 89.7 | 0.5 | 0.65 |
| Unknown infection etiology | Before | 0.04082 | 0.12881 | -32.0 | | -4.3 | < 0.001 |
| | After | 0.04196 | 0.04545 | -1.3 | 96.0 | -0.2 | 0.84 |
| Altered mental status | Before | 0.34014 | 0.25198 | 19.4 | | 2.9 | 0.003 |
| | After | 0.32517 | 0.33566 | -2.3 | 88.1 | -0.3 | 0.79 |
| Malignancy | Before | 0.09524 | 0.14124 | -14.3 | | -2.0 | 0.04 |
| | After | 0.0979 | 0.1049 | -2.2 | 84.8 | -0.3 | 0.78 |
| Immunologic modifier | Before | 0.22109 | 0.23051 | -2.3 | | -0.3 | 0.74 |
| | After | 0.21329 | 0.21678 | -0.8 | 62.9 | -0.1 | 0.92 |
| Congestive heart failure | Before | 0.08844 | 0.1322 | -14.0 | | -2.0 | 0.05 |
| | After | 0.09091 | 0.06643 | 7.8 | 44.1 | 1.1 | 0.28 |
| Acute | Before | 0.1224 | 0.1887 | -18.3 | | -2.6 | 0.009 |

| Variable[1] | Matching | Completed 1-hour bundle within 1 hour | | Standardized % bias | Percent reduction in bias | *t*-test | |
|---|---|---|---|---|---|---|---|
| | | Yes | No | | | t-statistic | P value |
| respiratory failure requiring mechanical ventilation prior to protocol initiation | | 5 | | | | | |
| | After | 0.12587 | 0.12238 | 1.0 | 94.7 | 0.1 | 0.90 |
| Gram negative pathogen | Before | 0.09184 | 0.08701 | 1.7 | | 0.3 | 0.80 |
| | After | 0.09091 | 0.09441 | -1.2 | 27.6 | -0.1 | 0.89 |
| Other/missing pathogen | Before | 0.01361 | 0.09379 | -36.1 | | -4.6 | < 0.001 |
| | After | 0.01399 | 0.00699 | 3.2 | 91.3 | 0.8 | 0.41 |
| No pathogen reported | Before | 0.73469 | 0.71525 | 4.3 | | 0.6 | 0.52 |
| | After | 0.74126 | 0.75524 | -3.1 | 28.1 | -0.4 | 0.70 |
| Lactate reported | Before | 0.87755 | 0.81921 | 16.3 | | 2.3 | 0.02 |
| | After | 0.87413 | 0.88112 | -2.0 | 88.0 | -0.3 | 0.80 |
| Lactated was not ordered | Before | 0.09524 | 0.10169 | -2.2 | | -0.3 | 0.75 |
| | After | 0.0979 | 0.09091 | 2.3 | -8.3 | 0.3 | 0.77 |
| Any comorbidity reported | Before | 0.93537 | 0.95932 | -10.7 | | -1.7 | 0.09 |
| | After | 0.94056 | 0.93706 | 1.6 | 85.4 | 0.2 | 0.86 |

[1]Referent group not shown

**eTable 2.** Sensitivity and Subgroup Analyses for the Primary Model

| Analyses | Completed one-hour bundle in one hour | | Did not complete one-hour bundle in one hour | | Risk difference from adjusted model (95% CI) | Odds Ratio (95% CI) |
|---|---|---|---|---|---|---|
| | No. With Outcome / Total No. (%) | Risk adjusted In-hospital Mortality (95% CI) | No. With Outcome / Total No. (%) | Risk adjusted In-hospital Mortality (95% CI) | | |
| Primary logistic regression | 22 / 294 | 8.7% (5.4, 12.0%) | 117 / 885 | 12.7% (10.5, 14.7%) | 4.0% (0.9, 7.0%) | 0.59 (0.38, 0.93) |
| **Sensitivity analyses** | | | | | | |
| Excluding patients who were transferred | 14 / 254 | 6.3% (2.6, 10.0%) | 77 / 700 | 10.5% (8.7, 12.5%) | 4.3% (1.0, 7.7%) | 0.52 (0.27, 0.99) |
| Including hospice discharges as in-hospital deaths | 22 / 294 | 8.6% (5.4, 11.8%) | 122 / 885 | 13.2% (11.0, 15.4%) | 4.6% (1.6, 7.6%) | 0.56 (0.36, 0.86) |
| Including “prior admission for sepsis” as confounder | 22 / 294 | 8.4% (4.8, 12.0%) | 117 / 885 | 12.8% (10.6, 14.9%) | 4.4% (1.1, 7.6%) | 0.56 (0.34, 0.92) |
| Excluding patients who never completed the one-hour bundle | 22 / 294 | 8.6% (5.5, 11.8%) | 69 / 598 | 10.8% (8.4, 13.2%) | 2.2% (-0.7, 5.1%) | 0.73 (0.47, 1.13) |
| Two element bundle (blood culture and antibiotics) | 46 / 523 | 9.7% (6.9, 12.5%) | 93 / 656 | 13.2% (11.0, 15.4% | 3.5% (0.6, 6.4% | 0.65 (0.44, 0.96) |
| Including all organ dysfunction and comorbidity for risk adjustment | 22 / 294 | 8.3% (4.6, 11.9%) | 117 / 885 | 12.8% (10.5, 15.0%) | 4.5% (1.4, 7.7%) | 0.54 (0.33, 0.90) |
| **Subgroups**[a] | | | | | | |
| Location of protocol initiation | | | | | | |
| Emergency department | 12 / 204 | 8.0% (2.6, 13.3%) | 36 / 471 | 10.4% (7.7, 13.1%) | 2.4% (-3.4, 8.3%) | 0.70 (0.28, 1.77) |
| Ward | 2 / 33 | 10.0% (0.0, 20.5%) | 26 / 143 | 18.8% (12.2, 25.4%) | 8.8% (-3.5, 21.2%) | 0.40 (0.09, 1.76) |
| Intensive care unit | 8 / 57 | 8.2% (3.1, 13.2%) | 55 / 271 | 13.1% (9.3, 16.8%) | 4.9% (-2.1, 11.9%) | 0.53 (0.20, 1.42) |
| Age | | | | | | |
| ≤ 1 month | 1 / 28 | 5.2% (0.0, 14.1%) | 13 / 81 | 14.8% (7.1, 22.3%) | 9.6% (-2.6, 21.9%) | 0.25 (0.03, 2.45) |
| > 1 month - < 1 year | 4 / 40 | 12.1% (3.4, 20.7%) | 21 / 125 | 15.5% (6.9, 24.0%) | 3.4% (-9.8, 16.6%) | 0.70 (0.17, 2.87) |
| 1 - < 2 years | 5 / 27 | 17.8% (10.5, 25.2%) | 14 / 68 | 18.2% (11.3, 25.1%) | 0.4% (-8.7, 9.5%) | 0.97 (0.44, 2.12) |

| Analyses | Completed one-hour bundle in one hour | | Did not complete one-hour bundle in one hour | | Risk difference from adjusted model (95% CI) | Odds Ratio (95% CI) |
|---|---|---|---|---|---|---|
| | No. With Outcome / Total No. (%) | Risk adjusted In-hospital Mortality (95% CI) | No. With Outcome / Total No. (%) | Risk adjusted In-hospital Mortality (95% CI) | | |
| Age, continued | | | | | | |
| 2 – 5 years | 2 / 53 | 3.2% (0.0, 10.0%) | 17 / 132 | 10.4% (5.1, 15.8%) | 7.2% (-0.7, 15.1%) | 0.23 (0.02, 2.65) |
| 6 – 11 years | 4 / 55 | 9.0% (3.2, 14.8%) | 27 / 178 | 14.7% (10.6, 18.9%) | 5.7% (-2.3, 13.6%) | 0.51 (0.18, 1.40) |
| 12 – 17 years | 6 / 91 | 8.3% (3.7, 12.8%) | 25 / 301 | 9.2% (6.4, 12.1%) | 1.0% (-5.4, 7.3%) | 0.87 (0.33, 2.28) |
| Septic shock | | | | | | |
| No | 1 / 57 | 0.9% (0.0, 4.3%) | 18 / 281 | 7.1% (3.8, 10.5%) | 6.2% (1.5, 10.9%) | 0.09 (0.00, 5.76) |
| Yes | 21 / 207 | 11.5% (6.7, 16.3%) | 99 / 604 | 14.8% (12.0, 17.6%) | 3.3% (-0.6, 7.2%) | 0.70 (0.44, 1.11) |
| Hospital with pediatric intensive care unit | | | | | | |
| No | 3 / 36 | 17.3% (13.1, 21.5%) | 9 / 112 | 13.4% (8.3, 18.5%) | -3.9% (-8.4, 0.6%) | 1.47 (0.92, 2.36) |
| Yes | 19 / 258 | 8.0% (4.9, 11.1%) | 108 / 773 | 12.6% (10.4, 14.8%) | 4.6% (1.4, 7.8%) | 0.54 (0.33, 0.85) |

[a]Likelihood ratio tests for effect modification were not significant for location (p = 0.77), age (p = 0.68), shock (p = 0.07), and hospital with pediatric intensive care (p=0.34)

**eTable 3.** Risk Adjustment Model Variable Coefficients With 95% Confidence Interval for In-Hospital Mortality

| Variable | | Coefficient (95% CI) | P-value |
|---|---|---|---|
| Age | | | |
| | ≤ 1 month | 0.44 (-0.38, 1.27) | 0.29 |
| | > 1 month - < 1 year | 0.67 (-0.12, 1.46) | 0.10 |
| | 1 - < 2 years | 0.98 (0.31, 1.65) | 0.004 |
| | 2 – 5 years | -0.03 (-0.91, 0.85) | 0.95 |
| | 6 – 11 years | 0.56 (0.12, 1.01) | 0.01 |
| | 12 – 17 years | *ref* | |
| Payer | | | |
| | Medicare | 1.28 (-0.28, 2.84) | 0.11 |
| | Medicaid | 0.33 (-0.20, 0.86) | 0.22 |
| | Private, HMO | *ref* | |
| | Self-pay | 1.01 (0.46, 1.56) | <0.001 |
| | Other | 0.82 (0.11, 1.54) | 0.02 |
| Protocol initiation site | | | |
| | ER | *ref* | |
| | Floor | 0.83 (0.23, 1.44) | 0.007 |
| | ICU | 0.31 (-0.17, 0.79) | 0.20 |
| Septic shock | | | |
| | No | *ref* | |
| | Yes | 1.13 (0.34, 1.86) | 0.003 |
| Site of infection | | | |
| | Urinary | *ref* | |
| | Respiratory | 2.30 (0.83, 3.76) | 0.002 |
| | Gastrointestinal | 2.13 (0.62, 3.63) | 0.006 |
| | Skin | 1.91 (0.16, 3.66) | 0.03 |
| | CNS | 1.95 (0.07, 3.83) | 0.04 |
| | Other | 2.36 (0.91, 3.81) | 0.001 |
| | Unknown | 2.39 (1.02, 3.77) | 0.001 |
| Platelet count < 150,000/mm$^3$ at protocol initiation | | | |
| | No | *ref* | |
| | Yes | 0.91 (0.42, 1.40) | <0.001 |
| Chronic renal failure or liver disease | | | |
| | No | *ref* | |
| | Yes | 1.41 (0.74, 2.08) | <0.001 |
| Diabetes | | | |
| | No | *ref* | |
| | Yes | 0.91 (-0.06, 1.88) | 0.07 |
| Acute respiratory failure requiring mechanical ventilation at protocol initiation | | | |
| | No | *ref* | |
| | Yes | 0.88 (0.29, 1.47) | 0.004 |
| Serum lactate (mmol/L) | | 0.18 (0.11, 0.25) | <0.001 |
| Transferred patient | | | |
| | No | *ref* | 0.01 |
| | Yes | 0.52 (0.10, 0.93) | |

**eTable 4.** Results of Unadjusted Regression in the Propensity Matched Cohort (N=572) and the Inverse Probability Weighted Risk-Adjusted Regression Analysis (N=1,179) for In-Hospital Mortality.

| Analysis | N | Odds ratio (95% CI) | P value |
|---|---|---|---|
| Primary logistic regression | 1,179 | 0.59 (0.38, 0.93) | 0.02 |
| Unadjusted logistic regression in propensity matched cohort | 572 | 0.53 (0.30, 0.94) | 0.03 |
| | | **Average treatment effect (95% CI)** | |
| Inverse probability weighted risk-adjusted regression analysis | 1,179 | 0.958 (0.924, 0.994) | 0.02 |

**eTable 5.** Adjusted Hospital Length of Stay for Entire Cohort, Decedents, and Survivors From Poisson Regression Models and Linear Regression With Logarithmic Transformation of Outcome Models

| **Poisson regression** | **N** | **Incidence rate ratio (95% CI)** | **P value** |
|---|---|---|---|
| All patients | 1,179 | 0.76 (0.64, 0.89) | 0.001 |
| Decedents | 139 | 1.09 (0.71, 1.69) | 0.68 |
| Survivors | 1,040 | 0.71 (0.60, 0.84) | < 0.001 |
| **Linear regression with logarithmic transformation** | | **Ratio of geometric means (95% CI)** | |
| All patients | 1,179 | 0.83 (0.74, 0.92) | 0.001 |
| Decedents | 139 | 1.34 (0.77, 2.34) | 0.30 |
| Survivors | 1,040 | 0.78 (0.69, 0.87) | < 0.001 |

**eTable 6.** Variable Coefficients With 95% Confidence Interval From Poisson Regression Model for Hospital Length of Stay

| Variable | Coefficient (95% CI) | P-value |
|---|---|---|
| Completion of 1-hour bundle within 1 hour | | |
| No | *ref* | |
| Yes | -0.278 (-0.445, -0.111) | 0.001 |
| Age | | |
| ≤ 1 month | -0.389 (-0.664, -0.115) | 0.005 |
| > 1 month - < 1 year | 0.206 (-0.022, 0.434) | 0.08 |
| 1 - < 2 years | 0.020 (-0.344, 0.384) | 0.91 |
| 2 – 5 years | -0.041 (-0.312, 0.231) | 0.77 |
| 6 – 11 years | -0.351 (-0.608, -0.094) | 0.007 |
| 12 – 17 years | *ref* | |
| Payer | | |
| Medicare | 0.050 (-0.653, 0.752) | 0.89 |
| Medicaid | 0.122 (-0.140, 0.365) | 0.38 |
| Private, HMO | *ref* | |
| Self-pay | 0.278 (-0.168, 0.724) | 0.22 |
| Other | 0.213 (-0.161, 0.586) | 0.26 |
| Protocol initiation site | | |
| Emergency department | *ref* | |
| Floor | 0.784 (0.537, 1.031) | < 0.001 |
| Intensive care unit | 0.405 (0.136, 0.675) | 0.003 |
| Septic shock | | |
| No | *ref* | |
| Yes | 0.163 (-0.052, 0.378) | 0.14 |
| Site of infection | | |
| Urinary | *ref* | |
| Respiratory | 0.441 (0.064, 0.818) | 0.02 |
| Gastrointestinal | 0.471 (0.025, 0.916) | 0.04 |
| Skin | 0.202 (-0.237, 0.641) | 0.37 |
| CNS | 1.007 (0.460, 1.555) | < 0.001 |
| Other | 0.448 (0.073, 0.824) | 0.02 |
| Unknown | 0.272 (-0.161, 0.706) | 0.22 |
| Platelet count < 150,000/$mm^3$ at protocol initiation | | |
| No | *ref* | |
| Yes | 0.384 (0.056, 0.712) | 0.02 |
| Chronic renal failure or liver disease | | |
| No | *ref* | |
| Yes | 0.029 (-0.398, 0.455) | 0.89 |
| Diabetes | | |
| No | *ref* | |
| Yes | -0.136 (-0.505, 0.232) | 0.47 |
| Acute respiratory failure requiring mechanical ventilation at protocol initiation | | |
| No | *ref* | |
| Yes | 0.387 (0.105, 0.669) | 0.007 |
| Serum lactate - mmol/L | | |
| Patient transferred from another hospital | 0.044 (0.012, 0.076) | 0.008 |
| No | *ref* | |
| Yes | 0.048 (-0.099, 0.195) | 0.52 |

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