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Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia: a cohort study

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Key Words: Pneumonia, healthcare-associated, antibiotic, antimicrobial stewardship, antibiotic resistance

Summary sentence: Despite propensity-based, weighted balancing including providers, and adjustment for multiple patient-level confounders, broad-spectrum antibiotics appear to be associated with increased mortality and other poor outcomes in community-onset pneumonia.

Abstract:

Question

Is broad-spectrum antibiotic use associated with poor outcomes in community-onset pneumonia after adjusting for confounders?

Methods

Retrospective, observational cohort study of 1,995 adults with pneumonia admitted from 4 United States hospital emergency departments. We used multivariable regressions to investigate the effect of broad-spectrum antibiotics on 30-day mortality, length of stay, cost, and *Clostridioides difficile* infection. To address indication bias, we developed a propensity score using multilevel (individual provider) generalized linear mixed models to perform inverse-probability of treatment weighting (IPTW) to estimate the average treatment effect in the treated (ATT). We also manually reviewed a sample of mortality cases for antibiotic-associated adverse events.

Results

39.7% of patients received broad-spectrum antibiotics, but drug-resistant pathogens were recovered in only 3%. Broad-spectrum antibiotics were associated with increased mortality in both the unweighted multivariable model (*OR* 3.8, *CI* 2.5 to 5.9, $p<0.001$) and IPTW analysis (*OR* 4.6, *CI* 2.9 to 7.5, $p<0.001$). Broad-spectrum antibiotic use by either analysis was also associated with longer hospital stay, greater costs, and increased *C. difficile* infection. Healthcare- associated pneumonia (HCAP) was not associated with mortality independent of broad-spectrum antibiotic use. In manual review we identified antibiotic-associated events in 17.5% of mortality cases.

Conclusion

Broad-spectrum antibiotics appear to be associated with increased mortality and other poor outcomes in community-onset pneumonia.

Introduction

Antibiotic selection is an important contributor to outcomes in community-onset pneumonia. In patients without risk factors for drug-resistant pathogens (DRP), treatment with a narrow-spectrum beta-lactam plus a macrolide is associated with decreased mortality.[1] However, it is less clear how best to identify and treat patients at high risk of DRP. Since publication of the healthcare-associated pneumonia (HCAP) [2] and the surviving sepsis guidelines,[3] utilization of broad-spectrum antibiotics such as vancomycin and piperacillin-tazobactam has doubled, yet the incidence of DRP and overall outcomes remain stable.[4, 5] Higher mortality has been observed in patients meeting at least one HCAP criterion,[6, 7] although it remains unclear whether this effect is due to severity, comorbidities, and poor functional reserve.[7, 8] Two large propensity-adjusted studies have associated broad-spectrum antibiotic use with increased mortality in HCAP.[9, 10] In this study, we sought to clarify these important clinical questions: 1) Is broad-spectrum antibiotic use associated with poor outcomes in community-onset pneumonia after controlling for known contributors of mortality, and 2) after adjusting for antibiotic selection, does HCAP remain associated with mortality risk?

Methods

Design and Population

We performed a retrospective observational cohort analysis of patients >18 years of age admitted to the hospital with community-onset pneumonia from four Utah, United States emergency departments (ED) from December 2011 through November 2012[6] and from November 2014 through September 2015.[11] Data were gathered through queries of Intermountain Healthcare's enterprise data warehouse. Cases were identified using ICD-9 pneumonia codes and/or ED physician completion of an electronic pneumonia clinical decision support tool and then radiographically confirmed manually through review of ED chest imaging reports by study

investigators. Except for Charlson Comorbidity Index (Charlson), rare missing data (e.g. mental status in the ED not recorded during initial nurse exam) were located by manual review of provider notes. We excluded patients with more than one episode of pneumonia within 12 months and immunocompromised patients with HIV or active solid and hematologic cancers. Because the regression analyses adjusted for provider variability, we also excluded patients seen by providers who saw fewer than six patients. We also excluded patients with missing Charlson data.

All antibiotics administered within the first 12 hours after ED registration were included for analysis, thereby capturing empiric antibiotics administered in the ED as well as during the initial hospital admission. Broad-spectrum antibiotics were defined as receipt of any agent during that window with activity against either methicillin-resistant *Staphylococcus aureus* (MRSA), such as vancomycin or linezolid, or *Pseudomonas aeruginosa*, such as piperacillin-tazobactam, imipenem-cilastin, meropenem, cefepime, ceftazidime or aztreonam, but excluding fluoroquinolones as they are recommended monotherapy for CAP.[12] Inadequate spectrum was defined as any initial antibiotic regimen not active against the pathogen ultimately identified.

All microbiology results were reviewed manually by the infectious disease author. Positive results included organisms compatible with respiratory pathogens[13] recovered from cultures of blood, sputum, tracheal aspirate, bronchoalveolar lavage or pleural fluid, as well as urine antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* and polymerase chain reaction assays for *Mycoplasma pneumoniae* and *Chlamydophilia pneumoniae.* Drug-resistant pathogens were defined as organisms falling outside the spectrum of antibiotics recommended for treatment of CAP, e.g. ceftriaxone and azithromycin or respiratory fluoroquinolones, and included MRSA, *P. aeruginosa*, extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, and other gram negative bacilli resistant to 3rd generation cephalosporins or fluoroquinolones. *Clostridioides difficile* infection (CDI) was defined by diagnosis more than 72 hours after admission and within 30 days of hospital-discharge. Cost was calculated as total variable costs, excluding indirect facility costs, in $USD.

Approval for the study was granted by the Intermountain Healthcare institutional review board.

Statistical Analysis

Simple, two-way comparisons used $\chi 2$ or Fisher's exact test for categorical variables and the unpaired *t*-test or Mann-Whitney *U* for continuous variables depending on distributional assumption. Hypothesis tests were two-tailed and considered statistically significant if $p<0.05$.

The primary outcome was 30-day all-cause mortality, and we chose the following covariate adjusters: age, gender, HCAP, Charlson, electronic CURB-65 (eCURB)[14], PaO2/FiO2 [15], intubation status, receipt of vasopressors, number of severe community-acquired pneumonia minor criteria [16] (sCAP), bacteremia, length of stay (LOS), inadequate antibiotic spectrum, and admitting provider. Secondary outcomes included LOS, cost, and 30-day incidence of CDI. Covariate adjusters for LOS and cost were age, HCAP, Charlson, eCURB, intubation status, receipt of vasopressors, number of sCAP criteria, and provider. Because we observed only 27 cases of CDI (1.4%), we adjusted only for length of stay to avoid overfitting.

To measure the effect of broad-spectrum antibiotic use on binary outcomes (30-day mortality, CDI), we fit unweighted multivariable regressions with logit link functions. For gamma-distributed outcomes (LOS and cost), we fit unweighted multivariable regressions with log link functions. Effect estimates are reported as exponentiated beta-coefficients ($\exp\{\beta\}$), interpreted as odds ratios (OR) for binary outcomes and as multipliers for gamma-distributed outcomes.

Because the decision to prescribe broad-spectrum antibiotics varies by an individual provider's assessment of both severity of illness and likelihood of a drug-resistant pathogen, we recognized the possibility of indication bias in estimating the causal effect of broad-spectrum antibiotics on outcomes. To mitigate this bias, we conducted sensitivity analyses to measure the average treatment effect on the treated (ATT) by inverse-probability of treatment weighting

(IPTW).[17-19] To do this, we developed a propensity score using multilevel generalized linear mixed models (GLMM) with provider-level random intercepts and the following covariates: age, gender, eCURB, PaO2/FiO2, number of sCAP criteria, intubation status, receipt of vasopressors, Charlson, HCAP, diabetes mellitus, moderate-to-severe liver disease, paraplegia and hemiplegia, congestive heart failure, and cancer. Lastly, to address the possibility that some patients may not have received care commensurate with severity due to goals of care decisions, we also conducted identical sub-group analysis in a cohort restricted only to patients admitted to the intensive care unit (ICU).

We conducted statistical model diagnostics using calibration plots and discrimination via receiver operator characteristic curves for all binary outcome models and de-trended quantile-quantile plots for continuous outcome variables.[20] See *Supplementary Materials* for detailed summary of model diagnostics. To assess the impact of IPTW on balancing variables between the broad-spectrum and non-broad-spectrum groups, we plotted the unweighted and the IPTW standardized differences and variance ratio between treatment groups for each covariate in the primary model.[19] Statistical analyses were conducted in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 22.1 (IBM, Armonk NY).

Finally, to investigate unmeasured variables and real-world biological plausibility of observations noted during analysis, the infectious disease physician investigator (BW) performed a standardized manual review of 20% of randomly selected mortality cases. Cases were annotated when any of the following were considered to directly contribute to demise: 1) comorbidities and in-hospital complications, including acute kidney injury, blood disorders, cardiac events, chronic pulmonary disease, falls/injury, hypersensitivity, metastatic malignancy, neurological/cognitive and thrombosis; 2) change of goals of care leading to palliative management or withdrawal of care; 3) advanced age (>75 years); 4) severity (referring to hemodynamic and/or respiratory compromise attributable to pneumonia); 5) adverse events attributable to broad-spectrum antibiotic and not to any other more obvious cause, including the following: acute kidney injury, anaphylaxis, CDI,

cytopenia, encephalopathy, hepatotoxicity, hypersensitivity (non-anaphylactic), skin/mucosal reaction (e.g. Stevens-Johnson or similar disorders).

Results

We identified 2,198 patients who met our eligibility criteria. We excluded 37 patients cared for by low-volume providers (see methods), and another 166 patients with missing Charlson data. The final cohort for analysis included 1,995 patients.

Median age was 67 and 51.5% were female (see Table 1). Median Charlson comorbidity index was 3 and mean eCURB-predicted 30-day mortality was 6.1%. A bacterial pathogen was identified in 14.2% of cases; the incidence of identified DRP was 3% but 39.7% of cases received initial empiric broad-spectrum antibiotics. Clinical and demographic data by broad-spectrum antibiotic use are displayed in Table 1. Patients in the broad-spectrum group more frequently met HCAP criteria (36.4% versus 7.4%). The broad-spectrum group also had higher eCURB predicted mortality (8.1% vs. 5.0%), lower Pa02/FiO2 ratio (248.2 vs. 269.5), and more sCAP criteria (2 vs. 1). Intubation (13.3% vs. 2.8%) and vasopressor use (13% vs. 1.7%) were more common in the broad-spectrum group. Bacterial pathogens were recovered more often in this group (21.2% vs. 9.9%), as were drug resistant pathogens (7.3% vs. 0.6%). Inadequate empiric antibiotic spectrum was not significantly different in the broad-spectrum group (1.4% vs 0.6%, p=0.1). Observed 30-day mortality was 18.3% vs 4.4%.

Unweighted multivariable regressions

In the unweighted multivariable regressions (Table 2, *Unweighted Regression*), broad-spectrum antibiotic use was associated with increased mortality risk (*OR* 3.8, *CI* 2.5 to 5.9, p<0.001). HCAP was not associated with mortality (*OR* 1.2, *CI* 0.76 to 1.9). We also observed significant increases in LOS (exp{β}1.7, *CI* 1.5 to 1.8, p<0.001), cost (exp{β}1.8, *CI* 1.7 to 2.0, p<0.001), and CDI (*OR* 3.9, *CI* 1.6 to 10.9, p=0.008) associated with broad-spectrum antibiotic use (See Table 3). In the

ICU subgroup, broad-spectrum antibiotic use remained associated with increased mortality risk (*OR* 3.4, *CI* 1.8 to 6.3, *p*<0.001).

Average treatment effect on the treated using IPTW multivariable regressions

In sensitivity analyses using IPTW, the ATT for broad-spectrum antibiotic use was associated with increased mortality (*OR* 4.6, *CI* 2.92 to 7.45, *p*<0.001, Table *2*), LOS (exp{β}1.52, *CI* 1.4 to 1.6, *p*<0.001), cost (exp{β} 1.7, *CI* 1.6 to 2.8, *p*<0.001) and CDI (*OR* 5.8, *CI* 1.9 to 27.5, *p*=0.008, Table *3*). By IPTW-ATT, HCAP remained without mortality association (*OR* 1.3, *CI* 0.8 to 1.9). As depicted in Figure 1, IPTW improved the covariate balance between treatment groups. In the IPTW-ATT analysis for the ICU subgroup, the ATT for broad-spectrum antibiotic use was associated with increased mortality (*OR* 4.0, *CI* 2.2 to 7.7, *p*<0.001).

In the manual review of mortality cases, n=40, 26 (65%) received broad-spectrum antibiotics. Mortality occurred prior to hospital discharge in 21 cases (53%). Comorbidities and complications were major contributors to mortality in 37 patients (92.5%); of these the most common were neurological/cognitive 9 (22.5%), chronic pulmonary 9 (22.5%), metastatic malignancy 8 (20%), acute kidney injury 8 (20%), and cardiac events 4 (10%). Palliative goals of care led to withdrawal of care or discharge to hospice in 21 (52.5%) cases. Advanced age (>75 years) contributed to mortality in 18 cases (45%), and severity of illness in 18 (45%). Consequences of broad-spectrum antibiotics contributed to mortality in 7 cases (17.5%); of these, acute kidney injury attributable to concomitant vancomycin and piperacillin-tazobactam was identified in 3 (7.5%), vancomycin alone 2 (5%), CDI in 2 patients (5%) and one case of cefepime-associated encephalopathy (2.5%). One patient treated with ceftriaxone/azithromycin developed CDI associated with mortality.

Discussion

This is the first study to simultaneously evaluate the relative effects of broad-spectrum antibiotic use and HCAP status on outcomes in a community-onset pneumonia cohort that includes

both community-acquired pneumonia and HCAP patients, and patient-level microbiology data. Demographics and comorbidities were generally similar between patients receiving broad-spectrum antibiotics and those who did not. Interestingly, we observed only modest differences between groups in objective severity measures such as PaO2/FiO2, eCURB predicted 30-day mortality and sCAP criteria, but more pronounced differences in process measures including vasopressor use or mechanical ventilation. This supported our *a priori* hypothesis that both outcomes and antibiotic prescribing are influenced by provider and our consequent choice to adjust for baseline provider variability in our primary analysis. In both the primary and the IPTW multivariable regression models, broad-spectrum antibiotic use remained associated with mortality, while HCAP status did not.

The finding that HCAP status itself contributes less to overall mortality than do severity of illness, comorbidities, antibiotic selection and goals of care aligns with the conclusion of a meta-analysis by Chalmers et al.[8] In a large healthcare database study, Rothberg et al. reported persistently increased case fatality rate in HCAP compared to CAP despite adjustment for demographic, comorbidity and severity data.[7] However, neither of these studies included adjustment for broad-spectrum or inadequate initial antibiotic spectrum.

One strength of this study was the use of a multilevel propensity score model to account for some provider variability and confounders, as well as inverse-probability of treatment weighting which, in principle, balances treatment and non-treatment groups to theoretically simulate results from a randomized controlled trial.[19] After IPTW adjustment, the average effect on mortality and other outcomes in patients treated with broad spectrum antibiotics not only persisted, but was amplified, suggesting that the association is robust.

This observation that empiric broad-spectrum antibiotics may be associated with worsened outcomes is intriguing and merits further investigation. Previously, Attridge et al. showed that guideline-concordant broad-spectrum antibiotics were associated with increased 30-day mortality (OR 2.1 95% CI 1.86-2.55) after propensity score adjustment in a U.S. Veterans Affairs cohort of

15,071 non-critically ill HCAP patients. Similarly, Rothberg et al. found that broad-spectrum antibiotic use remained associated with increased odds (OR 1.39 95% CI 1.32-1.47) of inpatient mortality after adjustment for a large set of clinical and demographic features, and propensity adjustment in 85,097 patients in an administrative database. Neither study adjusted for microbiology, and both studies acknowledged that their observations may have been influenced by unmeasured confounders unavailable in administrative databases.

Antibiotics are associated with multiple consequences that could potentially impact outcomes, including hypersensitivity, gastrointestinal disturbances, encephalopathy, cytopenias, disruption of the microbiome, and *Clostridium difficile* infection.[21-25] Broad-spectrum regimens are also associated with increased length of stay, which could also increase cumulative exposure to other nosocomial insults that impact outcomes. Adverse drug events complicate up to 15% of hospital admissions,[26] and antibiotics are among the most common culprits.[24] In pneumonia, antibiotic-associated adverse drug events are associated with longer LOS.[27] Among adverse drug effects, acute kidney injury is most relevant to broad-spectrum agents. Recently it has been identified that the most common broad-spectrum regimen used in pneumonia, vancomycin plus piperacillin-tazobactam, is associated with significant risk of nephrotoxicity.[28-33] A meta-analysis including nearly 25,000 patients indicated that the rate of acute kidney injury with this regimen is over 21% and more than twice as likely compared with vancomycin alone or in combination with other beta-lactams with a number needed to harm of only 11.[34] Acute kidney injury (AKI) is a known contributor to mortality in pneumonia.[35] Considering that vancomycin and piperacillin-tazobactam use has doubled in the last decade,[4, 36] this observation is important.

Clostridioides difficile infection is more likely with broad spectrum regimens that include more than one antibiotic class.[21] Indeed, in our study, odds of CDI were 4-fold greater for those receiving broad-spectrum regimens. Like AKI, CDI is also associated with increased mortality in pneumonia.[37] Similarly, impact of antibiotics on the microbiome could worsen outcomes in ways

more difficult to identify. Secondary or subsequent infections are more common in patients exposed to antibiotics, especially those with the greatest activity against components of the microbiome.[38] Baggs et al. recently showed that the risk of 90-day readmission with sepsis or septic shock was 65% higher in patients who had received broad-spectrum antibiotics.[22]

In that context, results from our manual review of mortality cases are particularly interesting. While comorbidities and complications, palliative goals of care, advanced age and severity were the most commonly identified contributors to demise, antibiotic side effects, including encephalopathy, AKI, and CDI, were identified as having a plausible contribution to mortality in 17.5% of cases. This suggests that outcomes noted in our statistical analyses may have real-world basis.

Prescription of broad-spectrum antibiotics far exceeds rates of DRP recovery in pneumonia. The lack of improved outcomes with widespread use of broad-spectrum regimens[5] supports the notion that most culture-negative pneumonia is not due to occult DRP, even in patients with epidemiological risk of resistance.[5] Clinical decision support tools to guide appropriate selection of broad-spectrum regimens in patients with risk factors for drug-resistant bacteria are important,[39] as are rapid methods of excluding the presence of resistant pathogens.[40] The pendulum may now be swinging back towards more narrow empiric antibiotic prescribing for community-onset pneumonia.

This study is limited by its observational design. Despite the inclusion of a large set of well-recognized confounder variables and use of inverse-probability of treatment weighting to balance treatment groups in an effort to mitigate indication bias, it is possible that the propensity model was not well specified, due perhaps to poor model assumptions or unmeasured variables. Two such variables identified in our manual review include complications of hospitalization and palliative goals of care, which are known predictors of mortality. However, these variables could only introduce bias if they are associated with the decision to prescribe initial empiric broad-spectrum antibiotics, which

seems unlikely for these variables. Another possible limitation was the inability to accurately capture “do not intubate/do not resuscitate” status. While goals of care certainly contribute to mortality, code status does not uniformly determine the level of care provided and reflects a dynamic decision that may change during the course of a hospital admission. For example, in our hospitals, patients with DNR status are regularly admitted for aggressive care in the ICU, while some patients with no code status on admission change to do not intubate or palliative status later in their course. For this reason, we conducted the ICU subgroup analysis. We were unable to accurately report the cause of mortality in all cases, and in this cohort, vasopressor use was used as a surrogate for septic shock. It is also possible that the manual chart review was prone to some bias because it was conducted by a single, non-blinded investigator. A strength of this study was the pragmatic real-world design that permitted the inclusion of severely ill patients and those with decreased level of consciousness, yielding a study population more representative of ED pneumonia patients than prospective cohorts that require individual consent.

Conclusion

Whether analyzed by unweighted multivariable regression or by inverse-probability of treatment weighting, use of broad-spectrum antibiotics in community-onset pneumonia was associated with higher mortality, longer hospital stay, higher costs and increased risk of *Clostridioides difficile* infection. These results lend additional support for more judicious use of broad-spectrum antibiotics in community-onset pneumonia. Accurate methods to better identify the small proportion of pneumonia patients who require broad-spectrum antibiotics are needed.

Acknowledgment Section

Author Contributions:

Dr. Webb had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Webb, Dean.
Acquisition, analysis or interpretation of data: All authors
Drafting of the Manuscript: Webb, Sorensen, Dean.
Critical review of the manuscript for important intellectual content: All authors
Statistical Analysis: Sorensen, Webb

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study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1: Baseline characteristics stratified by receipt of any broad-spectrum antibiotic

Variable	Any broad-spectrum antibiotic (n=731)	No broad-spectrum antibiotic (n=1264)
Age (years, median)	67 (IQI 54-79)	67 (IQI 52.8-79)
Female, %	50.5% (n=369)	52.1% (n=658)
Charlson Comorbidity Index, median	3 (IQI 2-5)	3 (IQI 1-4)
Diabetes mellitus, %	45.3% (n=331)	37.6% (n=475)
Chronic Pulmonary Disease, %	67.4% (n=493)	67.3% (n=851)
Congestive Heart Failure, %	44.5% (n=325)	33.1% (n=418)
Dementia, %	6.2% (n=45)	5% (n=63)
Renal Disease, %	35% (n=256)	25.9% (n=327)
eCURB, mean	8.1 (SD 11.0)	5.0 (SD 7.1)
Vasopressors, %	13% (n=95)	1.7% (n=22)
Intubation, %	13.3% (n=97)	2.8% (n=36)
sCAP Minor Criteria, median	2 (IQI 1-3)	1 (IQI 1-2)
PaO2:FiO2 Ratio, median	248.2 (IQI 188.6-303.8)	269.5 (IQI 220.9-319.1)
Multilobar Infiltrates, %	51.3% (n=375)	43.7% (n=552)
Confusion, %	17.6% (n=129)	5.2% (n=66)
BUN >19 mg/dL, %	58.3% (n=426)	47.2% (n=597)
White Blood Cell count <4,000 cells/mm^3, %	4.0% (n=29)	2.4% (n=30)
Platelets <100,000 cells/mm^3	6.3% (n=46)	3.5% (n=44)
Tachypnea, %	15.2% (n=111)	8.7% (n=110)
Temperature <36 C°, %	13.5% (n=98)	9.1% (n=115)
Systolic Blood Pressure <90 mmHg, %	8.9% (n=65)	2.8% (n=36)
Corticosteroids on admission, %	26% (n=189)	23% (n=292)
Pleural Effusion, %	33.9% (n=248)	20.5% (n=259)
HCAP %	36.4% (n=266)	7.4% (n=94)

Bacterial Pathogen identified, %	21.6% (n=158)	9.9% (n=125)
Bacteremia, %	5.9% (n=43)	2.8% (n=35)
Drug Resistant Pathogen, %	7.3% (n=53)	0.55% (n=7)
Methicillin-resistant *Staphylococcus aureus*)	4.0% (n=29)	0% (n=0)
Antibiotic resistant gram negative bacilli	3.7% (n=27)	0.55% (n=7)
Inadequate antibiotic therapy	1.4% (n=10)	0.6% (n=7)
Length of Stay (hours), median	101 (IQI 64.5-188)	63.5 (IQI 41-92)
Cost (1,000 $USD), median	12.2 (IQI 6.9-22.8)	6 (IQI 4.2-9)
Clostridioides difficile Infection, %	2.9% (n=21)	0.5% (n=6)
30-day Mortality, %	18.3% (n=134)	4.4% (n=55)

Abbreviations: IQI – 25%-75% Interquartile Interval, eCURB: electronic CURB-65 predicted 30-day mortality, sCAP: severe CAP minor criteria from 2007 IDSA/ATS guidelines, BUN: Blood Urea Nitrogen, HCAP: Healthcare-associated pneumonia

Table 2. Unweighted and IPTW multivariable regression effects of broad spectrum antibiotics on 30-day mortality

Variable	Primary Regression (OR)	*p*	IPTW-ATT (OR)	*p*
(Intercept)	0.04 (0 to 0.38)	0.012	0.01 (0 to 0.27)	0.008
Broad-Spectrum Antibiotics	3.82 (2.48 to 5.92)	<0.001	4.61 (2.92 to 7.46)	<0.001
Age*	2.16 (1.68 to 2.82)	<0.001	2.51 (1.9 to 3.38)	<0.001
Female	1.13 (0.78 to 1.63)	0.522	1.11 (0.74 to 1.67)	0.608
eCURB*	1.15 (0.97 to 1.36)	0.107	1.16 (0.97 to 1.38)	0.103
PaO2:FiO2*	0.99 (0.79 to 1.22)	0.902	1.02 (0.8 to 1.28)	0.889
sCAP	1.7 (1.41 to 2.05)	<0.001	1.74 (1.42 to 2.14)	<0.001
Intubation	1.22 (0.62 to 2.37)	0.559	1.4 (0.7 to 2.75)	0.335
Vasopressors	2.53 (1.29 to 5.01)	0.007	2.55 (1.31 to 5)	0.006
Inadequate Antibiotics	5.34 (1.1 to 23.19)	0.03	5.56 (1.11 to 24.92)	0.029
Bacteremia	1.53 (0.68 to 3.27)	0.291	1.54 (0.68 to 3.34)	0.282
Length of Stay*	0.82 (0.66 to 0.99)	0.045	0.7 (0.56 to 0.86)	0.001
Charlson comorbidity index	0.99 (0.91 to 1.09)	0.91	0.92 (0.83 to 1.01)	0.088
HCAP	1.19 (0.76 to 1.85)	0.449	1.24 (0.8 to 1.93)	0.332

Abbreviations: OR: Odds Ratio, IPTW: Inverse-probability treatment weighting, ATT: Average treatment effects in the treated, eCURB: electronic CURB-65 30-day mortality probability, sCAP: severe CAP minor criteria from 2007 IDSA/ATS guidelines, HCAP: Healthcare-associated pneumonia

*Continuous variables results are reported as exponentiated beta coefficients, interpreted as multipliers

Table 3. Unweighted and IPTW multivariable regression effects of broad spectrum antibiotics on secondary outcomes.

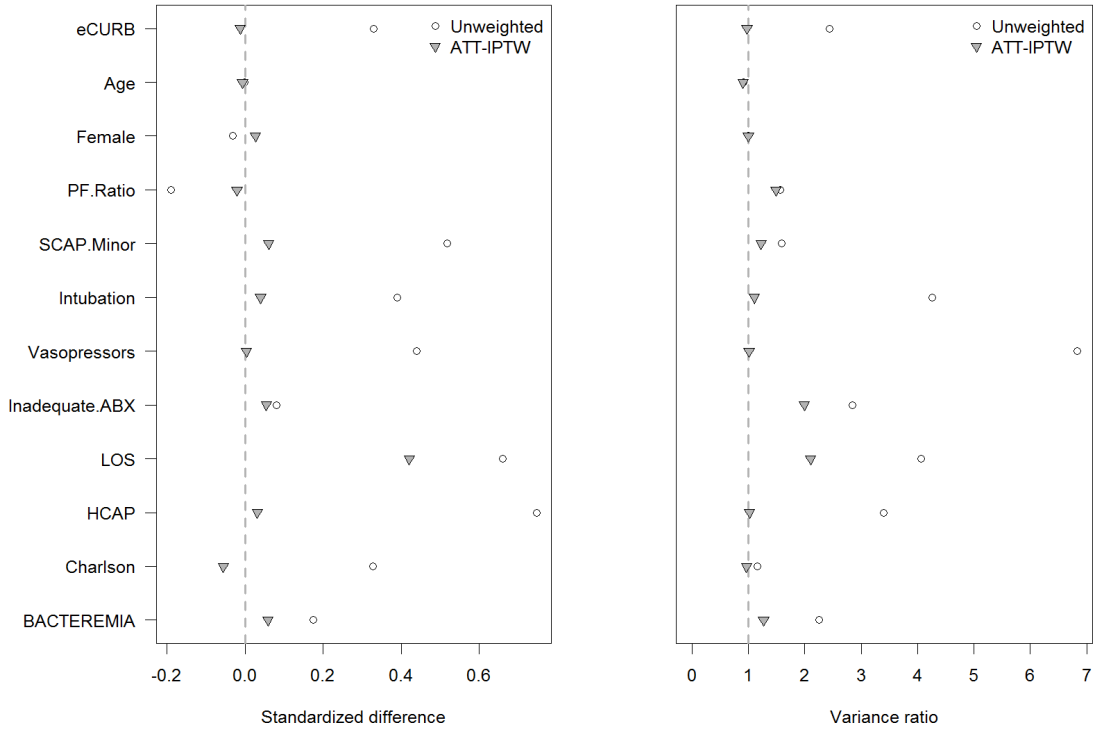
Outcome	Unweighted Regression (exp{β})*	*p*	IPTW-ATT (exp{β})*	*p*
Length of Stay	1.66 (1.53 to 1.8)	<0.001	1.52 (1.41 to 1.63)	<0.001

Cost	1.83 (1.68 to 2.01)	<0.001	1.7 (1.57 to 1.84)	<0.001
CDI	3.85 (1.55 to 10.93)	0.006	5.79 (1.86 to 27.51)	0.008

Abbreviations: IPTW: Inverse-probability treatment weighting, ATT: Average treatment, CDI: *Clostridioides difficile* infection.

*Exponentiated beta coefficients (exp{β}) are interpreted as multipliers for gamma-distributed variables (LOS and Cost) and as odds ratios for binary outcomes (CDI)

Figure 1. Balance diagnostics for inverse-probability of treatment weighting (IPTW).



In principle, IPTW should shrink the standardize difference (of the first central moment) toward zero and the variance ratio (of the second central moment) toward 1. Observing both panels, we see that the IPTW tended to improve balance between broad-spectrum antibiotic use across all covariates.

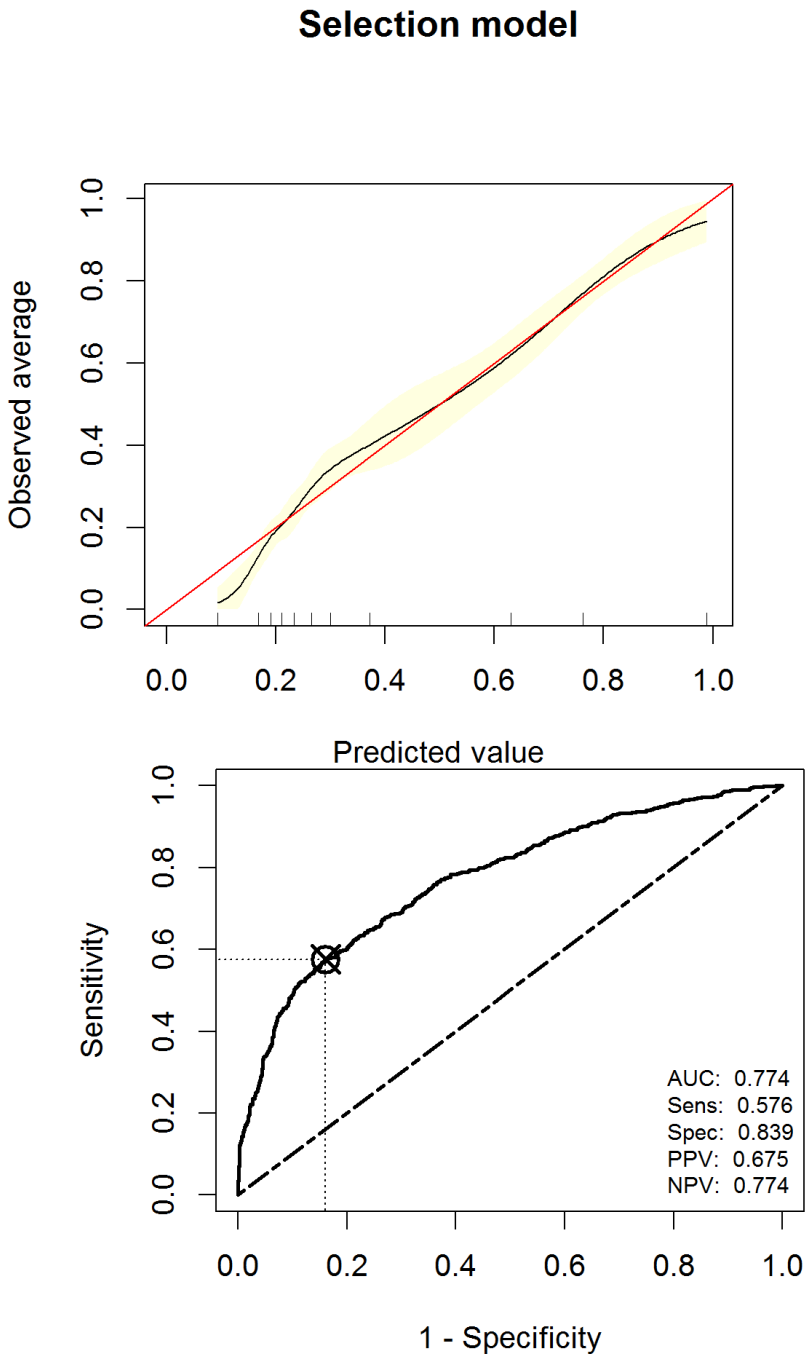
Supplementary Electronic Materials

eAppendix A, Methods for model diagnostics

Model diagnostics assessed calibration and discrimination for all binary outcome models (Mortality, CDI, broad-spectrum antibiotic use "selection model") using calibration plots and receiver operating characteristic curves, respectively.[1, 2] Diagnostics for LOS and Cost used de-trended quantile-quantile plots, which plot standardized deviance residuals as a function of their theoretical quantiles.[3] To assess the impact of IPTW on covariate balance, we plotted for each covariate in the primary model, both the unweighted and the ATT-IPTW standardized differences (ie, first central moment) and variance ratio (ie, second central moment).[4]

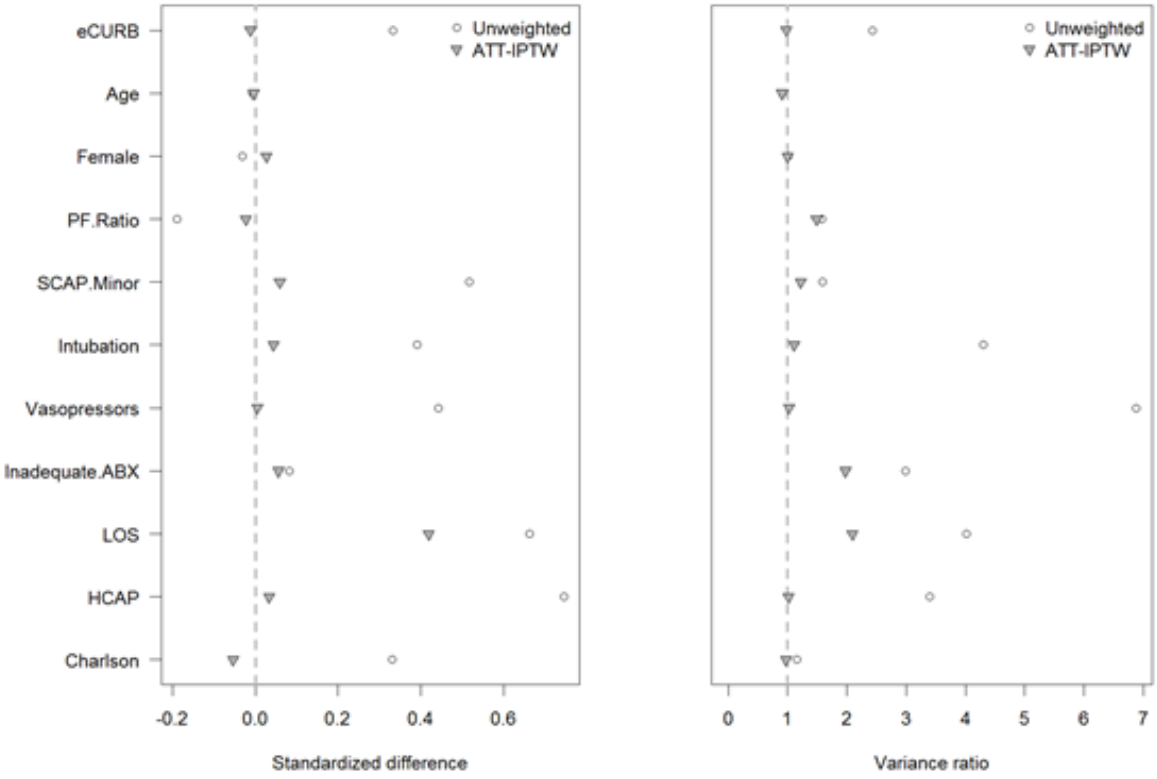
eAppendix B, Results for model diagnostics

Model diagnostics of the propensity score selection model (eFigure 1) indicated good calibration and discrimination (AUC=0.77). The ATT-IPTW improved the covariate standardized differences and variance ratios (eFigure 2). Diagnostics of multivariable regressions on mortality (eFigure 3) suggested reasonable calibration for both the unweighted and ATT-IPTW models as well as good discrimination, each with AUC >0.85. Though calibration of both unweighted and ATT IPTW-regressions on CDI (eFigure 4) did not demonstrate statistically significant poor calibration, the observed event rate was small (n=27) and the calibration assessment might have been underpowered. The de-trended Q-Q plots of residuals for multivariable regression of LOS and Cost (eFigure 5) indicated that both unweighted models had low residual variance, and the Cost model had positive residual skewness. The effect of the ATT-IPTW, however, appeared to trade some of the positive residual skewness for leptokurtotic residuals, meaning that the tails of the ATT-IPTW models' fitted distributions were too light.[5]

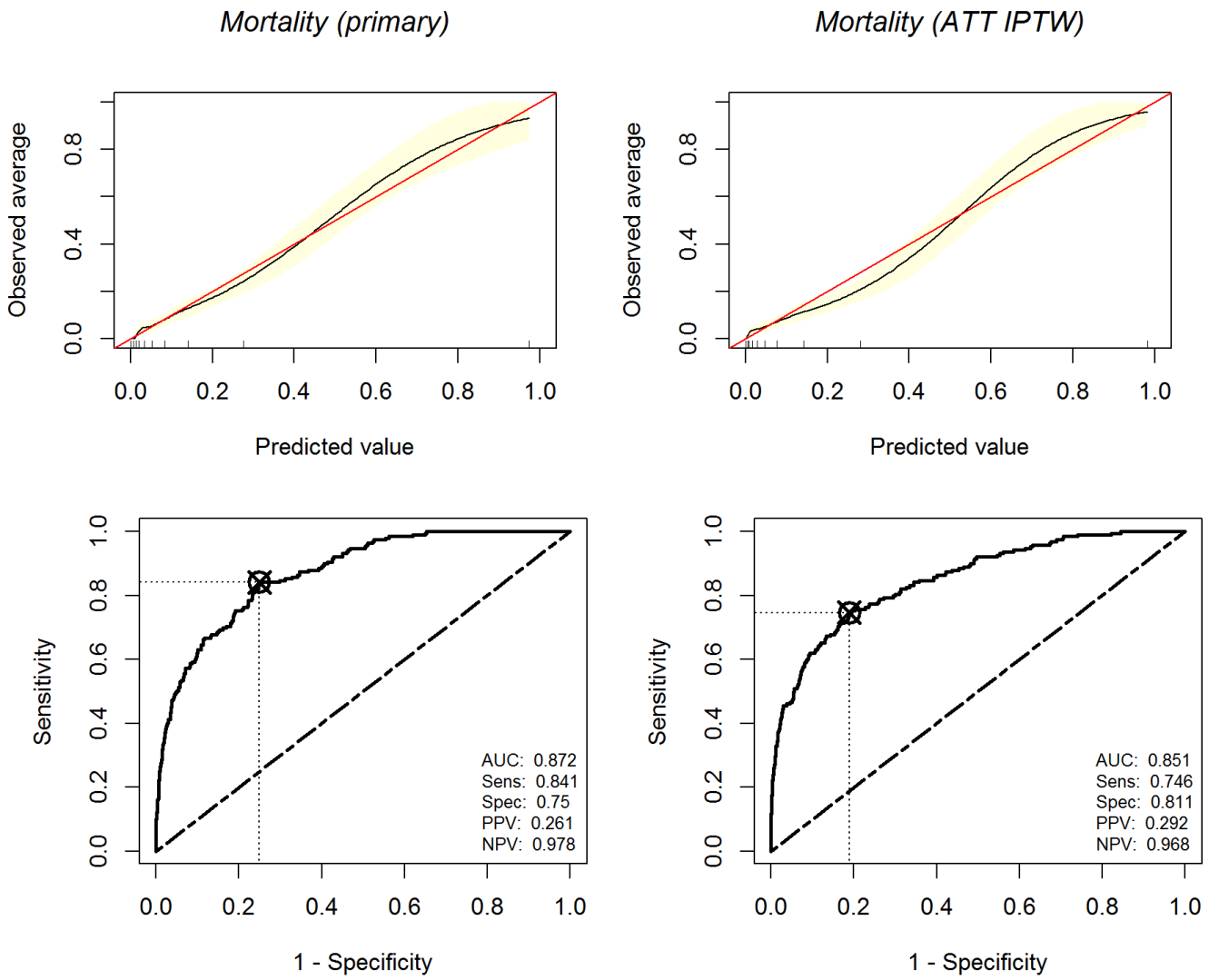


eFigure 1, Calibration and discrimination of propensity score "selection model" predicting receipt of any broad-spectrum antibiotics. The top panel displays calibration by fitting a natural, cubic spline of the observed average rate of broad-spectrum antibiotic administration as a function of the predicted probability. The bottom panel displays model discrimination using the receiver operating characteristic curve.

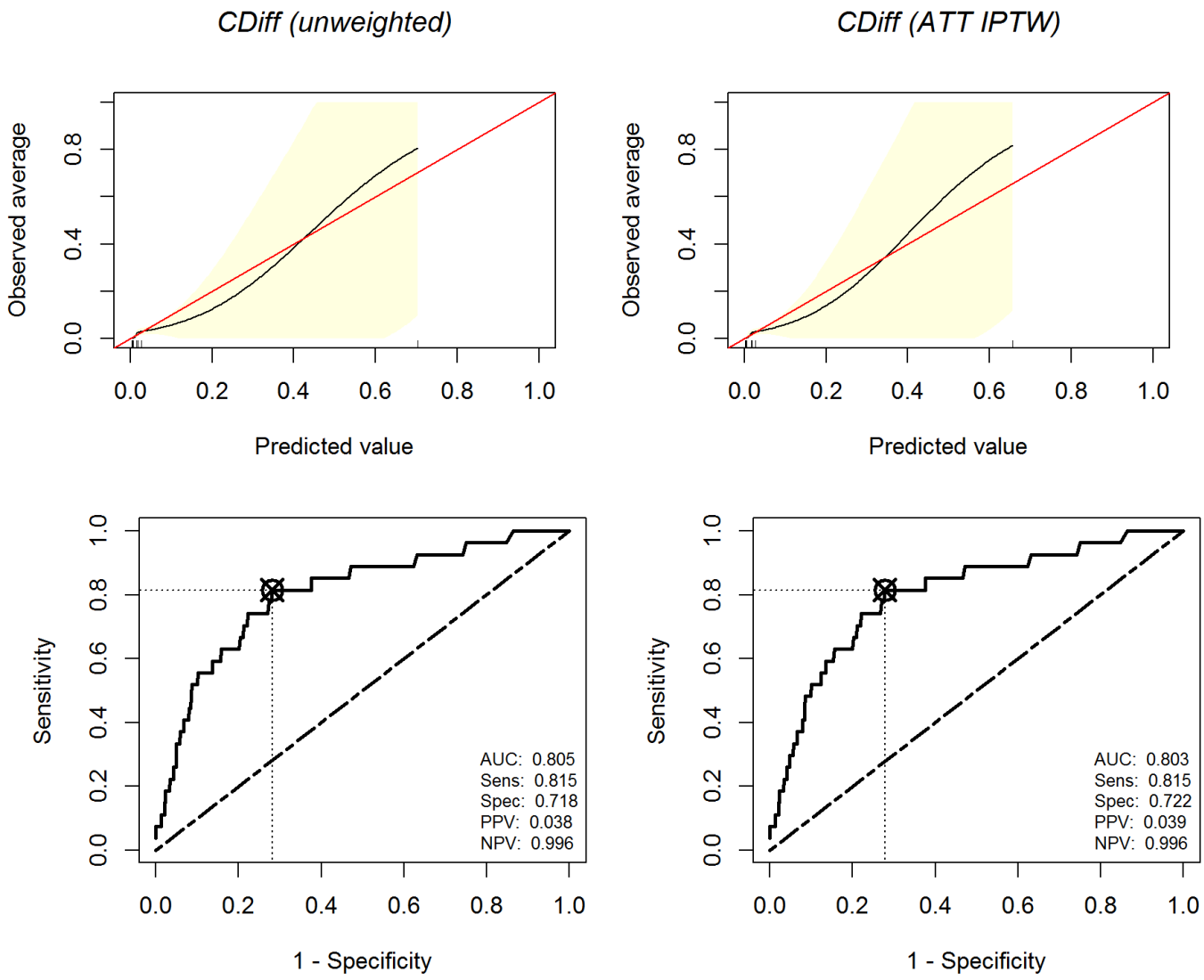
eFigure 2, Balance diagnostics for inverse-probability of treatment weighting (IPTW). In principle, IPTW should shrink the standardize difference (the first central moment) toward zero and the variance ratio (the second central moment) toward 1. Observing both panels, we see that the IPTW tended to improve balance across all covariates.



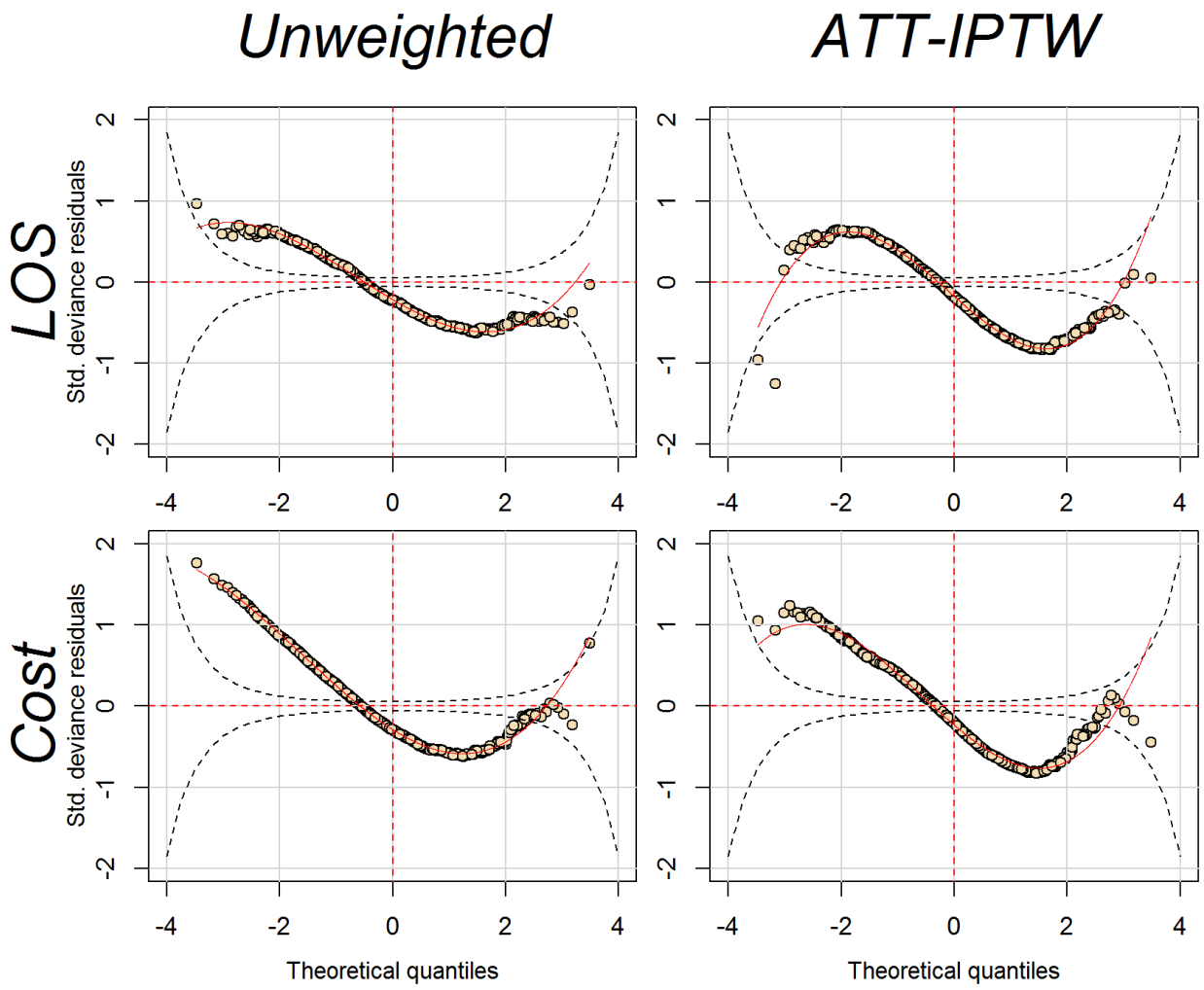
eFigure 3, Calibration and discrimination for primary outcome model along with corresponding sensitivity analysis using ATT IPTW. The top panel displays calibration by fitting a natural, cubic spline of the observed average rate of broad-spectrum antibiotic administration as a function of the predicted probability. The bottom panel displays model discrimination using the receiver operating characteristic curve.



eFigure 4, Calibration and discrimination for secondary outcome model (CDI) along with corresponding sensitivity analysis using ATT IPTW. The top panel displays calibration by fitting a natural, cubic spline of the observed average rate of broad-spectrum antibiotic administration as a function of the predicted probability. The bottom panel displays model discrimination using the receiver operating characteristic curve.



eFigure 5, De-trended quantile-quantile (Q-Q) plots for Gamma-distributed secondary outcomes, Cost and LOS. Ideally, the plotted residuals should mostly lie between the dashed, back lines. The solid, red lines are a lowess smooth of the plotted residuals.



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