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Patient and physician predictors of patient receipt of therapies recommended by a computerized decision support system when initially prescribed broad-spectrum antibiotics: a cohort study

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ABSTRACT

Objective Antibiotic computerized decision support systems (CDSSs) were developed to guide antibiotic decisions, yet prescriptions of CDSS-recommended antibiotics have remained low. Our aim was to identify predictors of patients' receipt of empiric antibiotic therapies recommended by a CDSS when the prescribing physician had an initial preference for using broad-spectrum antibiotics.

Methods We conducted a prospective cohort study in a 1 500-bed tertiary-care hospital in Singapore. We included all patients admitted from October 1, 2011 through September 30, 2012, who were prescribed piperacillin-tazobactam or carbapenem for empiric therapy and auto-triggered to receive antibiotic recommendations by the in-house antibiotic CDSS. Relevant data on the patient, prescribing and attending physicians were collected via electronic linkages of medical records and administrative databases. To account for clustering, we used multilevel logistic regression models to explore factors associated with receipt of CDSS-recommended antibiotic therapy.

Results One-quarter of the 1 886 patients received CDSS-recommended antibiotics. More patients treated for pneumonia (33.2%) than sepsis (12.1%) and urinary tract infections (7.1%) received CDSS-recommended antibiotic therapies. The prescribing physician – but not the attending physician or clinical specialty – accounted for some (13.3%) of the variation. Prior hospitalization (odds ratio [OR] 1.32, 95% CI, 1.01-1.71), presumed pneumonia (OR 6.77, 95% CI, 3.28-13.99), intensive care unit (ICU) admission (OR 0.38, 95% CI, 0.21-0.66), and renal impairment (OR 0.70, 95% CI, 0.52-0.93) were factors associated with patients' receipt of CDSS-recommended antibiotic therapies.

Conclusions We observed that ICU admission and renal impairment were negative predictors of patients' receipt of CDSS-recommended antibiotic therapies. Patients admitted to ICU and those with renal impairment might have more complex clinical conditions that require a physician's assessment in addition to antibiotic CDSS.

Keywords: antibiotic resistance, decision support system, patient factors, physician factors, antibiotic prescribing, empiric therapy

RESEARCH AND APPLICATIONS

INTRODUCTION

Antimicrobial resistance is now regarded as a serious threat to public health[1] and antibiotic use is the key driver.[2,3] The intensity of antibiotic use in hospitals is high and utilization has increased substantially over the years.[4,5] However, 41–91% of all antibiotics prescribed in hospitals worldwide are considered inappropriate.[6] Antimicrobial stewardship programs have been established in many hospitals to facilitate the optimal use of antibiotics.[4,7–10] Furthermore, antibiotic computerized decision support systems (CDSS) are developed to improve antibiotic decision making through the accessibility of patient-specific clinical data and local antibiotic guidelines at the point of prescribing.[11–16]

Antibiotic CDSS are particularly useful for antibiotic selection for empiric therapy, as optimal selection is complex when the causative pathogen is unknown.[17,18] The appropriate empiric treatment is crucial for the resolution of infection and reduction of mortality.[19] In line with growing evidence on factors that influence CDSS use,[20] many systems have been developed with active feedback from physicians, designed with user-centric features, and integrated into workflows.[21] Yet, physicians have prescribed CDSS-recommended antibiotics in only about one-half of medication orders.[11]

Antibiotic CDSSs have been shown to improve antibiotic prescribing and patient clinical outcomes including the reduction of mortality.[4,11,12,22–24] Patients' and physicians' characteristics associated with physicians' adherence to recommendations by hospital antimicrobial guidelines have been well explored.[18,19,25–30] However, there is limited information on factors influencing physicians' acceptance or patients' receipt of CDSS-recommended antibiotics. Understanding these factors can guide strategies to improve patients' receipt of antibiotic therapies recommended by CDSSs and enhance clinical care.

OBJECTIVE

We conducted a prospective cohort study to evaluate the extent to which hospitalized patients received antibiotics as recommended by our in-house antibiotic CDSS, Antimicrobial Resistance Utilization and Surveillance Control (ARUSC), and to identify patient and physician factors associated with patients' receipt of empiric antibiotic therapies recommended by ARUSC when the prescribing physician had an initial preference for using broad-spectrum antibiotics and targets for improvement.

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METHODS

Study setting and population

The study was conducted in Tan Tock Seng Hospital, a 1 500-bed tertiary-care academic medical center that serves a diverse ethnic, adult medical and surgical population in Singapore. Singapore is a tropical island city-state in Southeast Asia, located just north of the equator at latitude 1.5°N and longitude 104°E. It had a population of 5.3 million in 2012.

In 2009, the hospital launched its in-house antibiotic CDSS, ARUSC, which integrates antimicrobial stewardship with the hospital's computerized physician order entry (CPOE) system and provides patient-specific evidence-based antibiotic recommendations at the point of prescribing[16] (Figure 1). All medication orders in the hospital are made via the CPOE. From September 12, 2011, whenever a physician makes an electronic prescription of piperacillin-tazobactam or a carbapenem for an inpatient, the prescription automatically triggers the launch of ARUSC. Piperacillin-tazobactam and carbapenems are antibiotics of last resort for many bacterial infections, particularly those caused by multidrug-resistant pathogens. Hence, it is crucial to ensure the judicious use of these antibiotics. Using a rules-based algorithm, ARUSC provides guidance on antibiotic selection and dosing, based on guidelines developed by the hospital's antimicrobial stewardship committee, which recommends the narrowest-spectrum antibiotic appropriate for common organisms responsible for the diagnosed infection taking into account the local epidemiology of infectious diseases, local microbiology and antibiotic susceptibility patterns in the hospital in the prior 5 years, and incorporating evidence-based international guidelines including the Infectious Diseases Society of America's Practice Guidelines and Australia's Therapeutic Guidelines: Antibiotics. Hospital-wide consultations and consensus from all clinical departments were sought in the development of the guidelines, which were endorsed by the hospital's medical board. Data from individual patients' electronic medical records including medication history and drug allergies, as well as laboratory results such as creatinine levels are also pulled into ARUSC and included in the algorithm. A prescription can be made for empiric, prophylactic, or definitive therapy. Empiric therapy is the initiation of antibiotic treatment prior to the identification of the infection-causing microorganism. ARUSC recommends the most appropriate antibiotic for the patient, taking into account the patient's antibiotic allergies and renal function. The prescribing physician can either accept or reject ARUSC-recommended antibiotics, which are assumed to be always appropriate. To promote the acceptance of ARUSC, monthly educational campaigns on ARUSC are done, particularly for new physicians joining the hospital, as well as one-on-one education on a specific prescribing problem with individual prescribers by physicians on the hospital's antimicrobial stewardship program (ASP) team, and quarterly emails by the ASP team actively seeking feedback from physicians on ARUSC are carried out. Piperacillin-tazobactam is recommended in the institutional empiric antibiotic guidelines for healthcare-associated pneumonia and nosocomial intra-abdominal infections. Anticipating that prescribing physicians might "game" the system to generate a recommendation of broad-spectrum antibiotics for empiric therapy, ARUSC was designed with several features to dissuade such behavior. For example, ARUSC will alert the prescribing physician, if the chest X-ray was reported to be normal for a patient diagnosed with pneumonia. Additionally, ARUSC would remind physicians that documentation on ARUSC constituted medicolegal medical records and that they should not falsify information. If nosocomial pneumonia was selected within the first two days of hospital admission, ARUSC would alert physicians that the diagnosis might not be correct. Furthermore, all piperacillin-tazobactam and carbapenem prescriptions were reviewed by the hospital's ASP team, who would recommend antibiotic changes if the prescribed antibiotics were found to be inappropriate for the patient.

All patients admitted to the hospital, from October 1, 2011 through September 30, 2012, who were prescribed piperacillin-tazobactam or a carbapenem for empiric therapy and auto-triggered to receive antibiotic therapies recommended by ARUSC were included in the study. Prescriptions for prophylactic or definitive therapy were excluded. We chose to focus our study on empiric therapy, as empiric antibiotic prescriptions have been found to be the least concordant with recommended antibiotic guidelines.[18] Furthermore, empiric antibiotics are usually the first antibiotics received by a patient in an infective episode; appropriate empiric antibiotics is a critical determinant of clinical outcomes.[19]

Study design

We assembled a prospective observational cohort comprising eligible inpatients based on the inclusion criteria described above, starting from the automatically triggered launch of ARUSC at the point of antibiotic prescribing up to 30 days post-discharge from the hospital (Figure 2).

Outcome variable

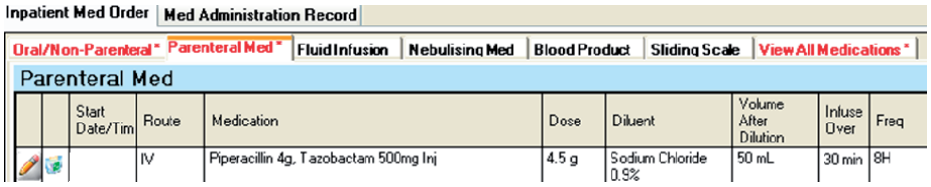
Patients' receipt of antibiotics recommended by ARUSC was determined by electronically matching antibiotics prescribed in the institutional CPOE with those recommended by ARUSC. A patient was classified as having received antibiotic therapies recommended by ARUSC if the antibiotics matched exactly the drug prescribed, including dose, route, and frequency of administration. A match in antibiotics would mean that antibiotics recommended by ARUSC were found to be prescribed precisely as recommended by ARUSC and no additional antibiotics were prescribed to treat the infection that initially triggered ARUSC, in the first 24–48 h of the empiric treatment of the infection, until the causative pathogen with its antibiotic sensitivities was identified. Empiric therapy is commonly defined as treatment given within 24–48 h of clinical management of an infection when the causative organism has not been identified.[31]

Predictor variables

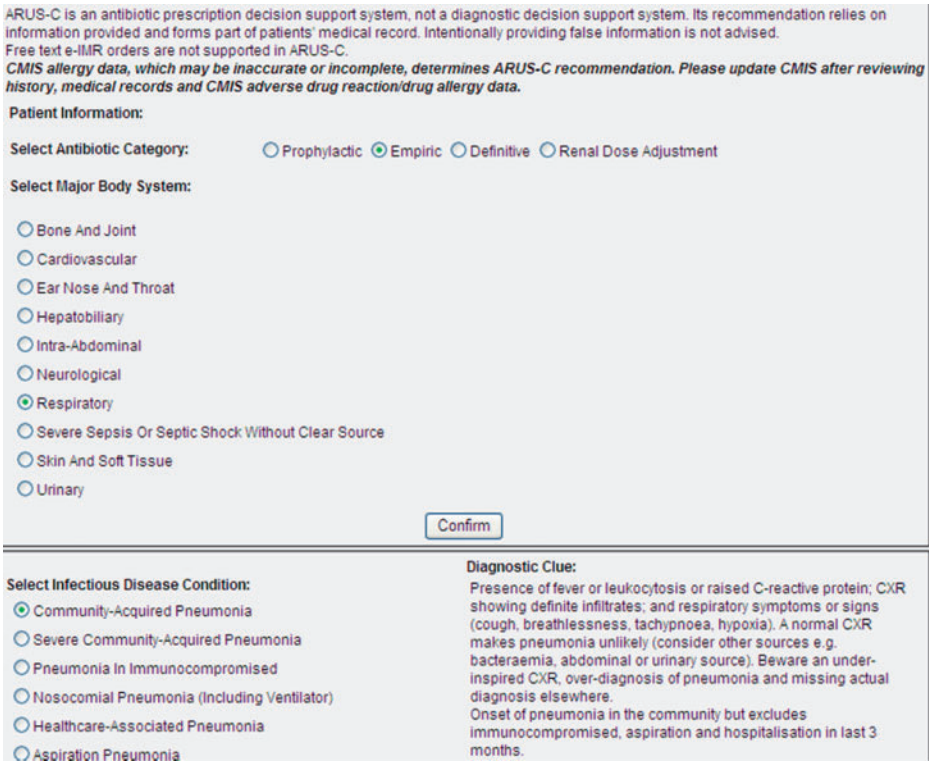
Relevant patients' characteristics included socio-demographic data (age, gender, ethnicity, resident status, and ward class status), co-morbidity (diabetes mellitus, cardiovascular disease, liver disease, renal disease, neoplasm, central nervous system disease, and chronic pulmonary disease), illness severity, admission to an ICU at the time of prescribing, prior antibiotic exposures in the 180 days preceding current prescription, prior hospitalization in the 90 days preceding current admission, diagnosed infection for current antibiotic therapy, and the time and day of the week when the prescription was made.

Ward class status (private or subsidized) was based on whether a patient was admitted to a private room for which the patient bore 80–100% of the hospitalization costs or to a subsidized room for which the government funded 65–80% of the costs. We used ward class as a surrogate measure of the patient's socioeconomic status. We defined co-morbidities as follows: diabetes mellitus was a diagnosis of diabetes with or without complications; cardiovascular disease was coronary artery disease or congestive heart failure; liver disease was liver disease of any severity; renal disease was moderate to severe renal disease; neoplasm was solid malignant tumor, leukemia, lymphoma, or any metastasis; central nervous system disease was cerebrovascular disease, dementia; and chronic pulmonary disease was chronic obstructive pulmonary disease. Charlson's co-morbidity index (CCI)[32] was derived from electronic medical records using

Figure 1: (**A–F**) Antimicrobial Resistance Utilization and Surveillance Control (ARUSC) system. (**A**) Screenshot of the hospital's CPOE system. When piperacillin-tazobactam is ordered on the CPOE, it will automatically launch ARUSC. (**B**) Screenshot of the first page of ARUSC when launched. As the patient's microbiologic results are pending and the patient is being treated empirically for the infection, the prescribing physician selects "empiric" as the antibiotic category and "community-acquired pneumonia" as the infectious disease condition. Educational clues on diagnosis are also provided (bottom right of screenshot). (**C**) Next, the system prompts the prescribing physician to enter the patient's weight, which is used in the auto-calculation of creatinine clearance. As the reported drug allergy information lacks details on severity, the prescriber is requested to confirm the absence or presence of severe penicillin allergy precluding beta-lactam use. CURB-65 is used to stratify into non-severe or severe community-acquired pneumonia. Serum urea is auto-populated from the laboratory information system. Clicking on the "Submit" button returns ARUSC's antibiotic recommendations within 5–10 s. (**D**) Patient's administrative details (Patient Name, Patient NRIC, Admission Date), demographic (Date of Birth, Gender), laboratory (Creatinine, White Blood Cell Count, Urea, C-Reactive Protein), radiologic (X-Ray Result), and drug allergy (CMIS Reported ADR/DA) data pulled from electronic medical records are integrated with the physician-entered information (Antibiotic Category Selected, Major Body System and ID Condition Selected, Severe Penicillin Allergy) and summarized on this ARUSC page. Intravenous amoxicillin-clavulanate and oral clarithromycin are recommended for the patient with non-severe community-acquired pneumonia. Antibiotic doses will automatically be adjusted by ARUSC (if necessary) based on the calculated creatinine clearance. Chest radiograph (X-Ray Result) will be flagged as normal or abnormal. (**E**) Educational advice on suggested investigations, treatment, and criteria for oral antibiotic step-down is further provided on the next page. Explanation was provided on efficacy of penicillin in pneumococcal pneumonia in absence of pneumococcal penicillin MIC >8 mg/l, and reminder to consider tuberculosis in unexplained prolonged cough given prevalence of tuberculosis in the local setting. In this case, the doctor was alerted to the absence of a recent chest X-ray and reminded to order one to support the diagnosis of pneumonia. (**F**) Option is provided for the prescribing physician to override ARUSC's recommendations. If the prescriber accepts the recommendations, clicking on the "Save" button will auto-populate the recommended antibiotics back into the CPOE within 5–10 s.

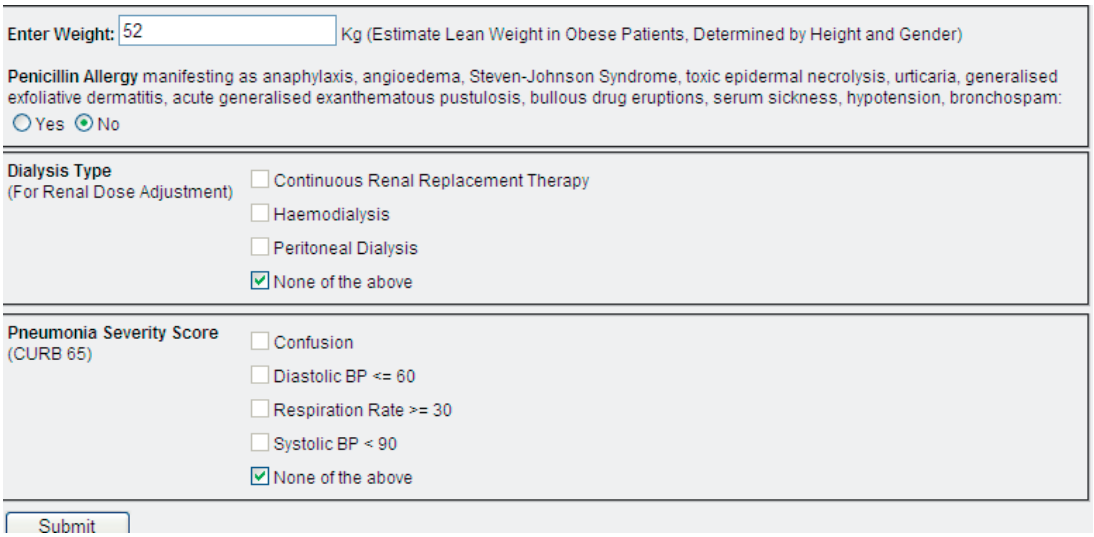


A. Screenshot of the hospital's CPOE system. When piperacillin-tazobactam is ordered on the CPOE, it will automatically launch ARUSC.



B. Screenshot of the first page of ARUSC when launched. As the patient's microbiologic results are pending and the patient is being treated empirically for the infection, the prescribing physician selects "empiric" as the antibiotic category and "community-acquired pneumonia" as the infectious disease condition. Educational clues on diagnosis are also provided (bottom right of screenshot).

Figure 1: Continued



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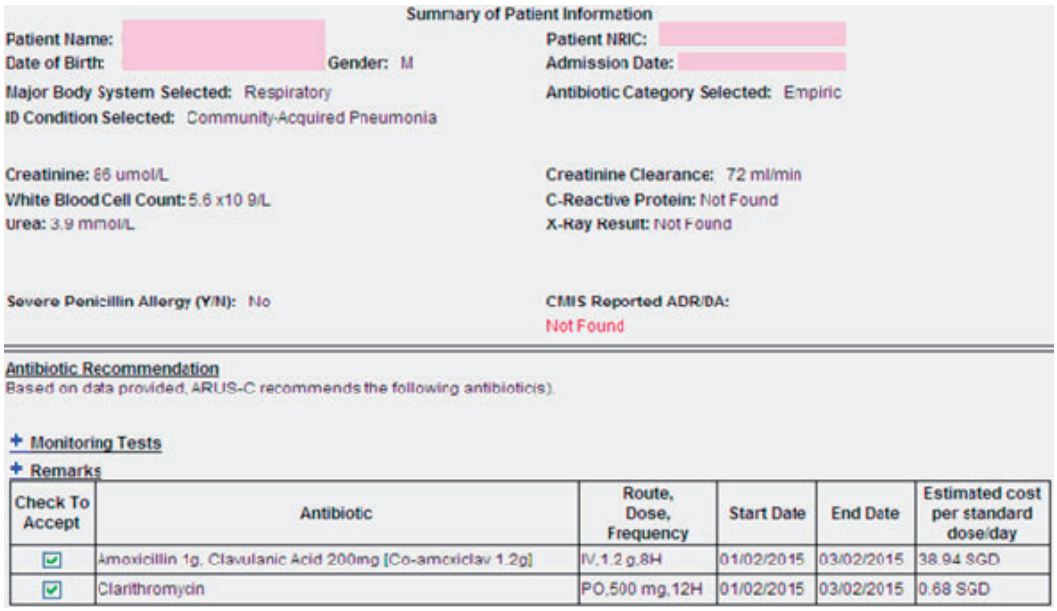

D. Patient's administrative details (Patient Name, Patient NRIC, Admission Date), demographic (Date of Birth, Gender), laboratory (Creatinine, White Blood Cell Count, Urea, C-Reactive Protein), radiologic (X-Ray Result), and drug allergy (CMIS Reported ADR/DA) data pulled from electronic medical records are integrated with the physician-entered information (Antibiotic Category Selected, Major Body System and ID Condition Selected, Severe Penicillin Allergy) and summarized on this ARUSC page. Intravenous amoxicillin-clavulanate and oral clarithromycin are recommended for the

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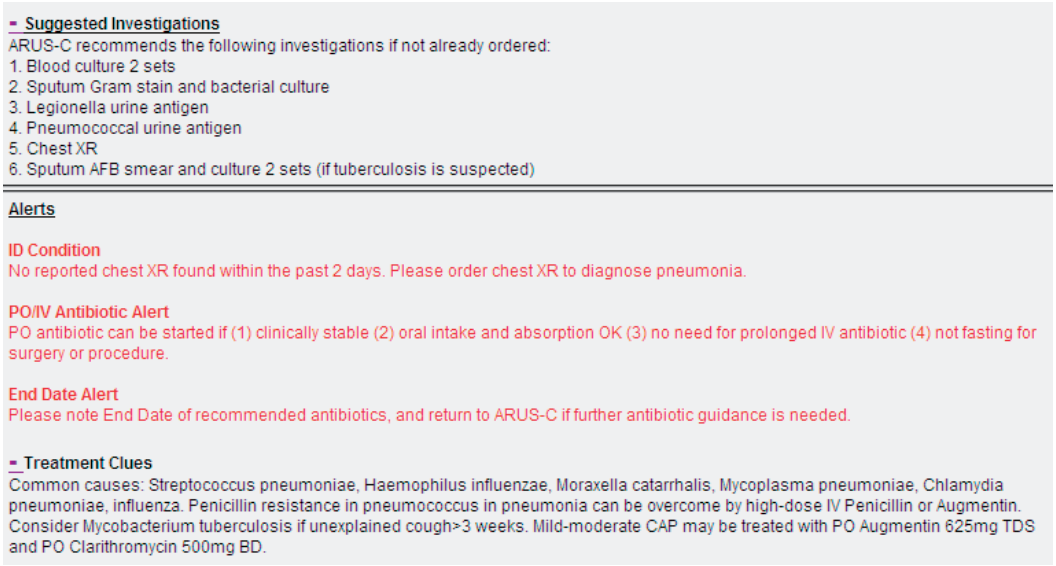

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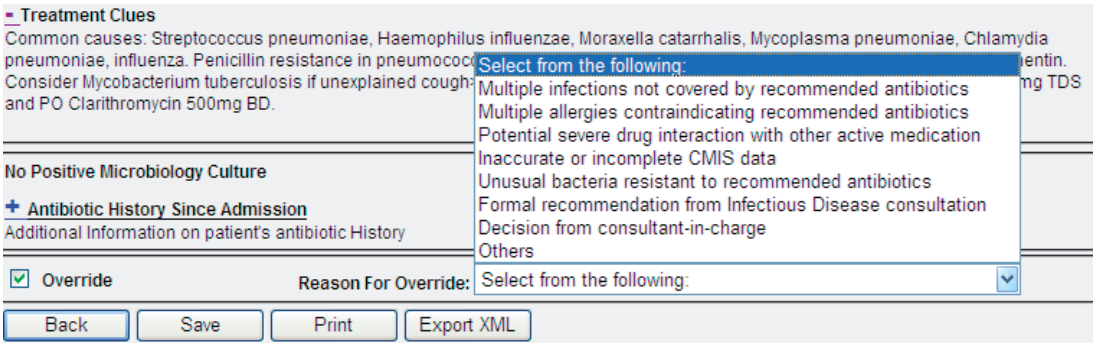
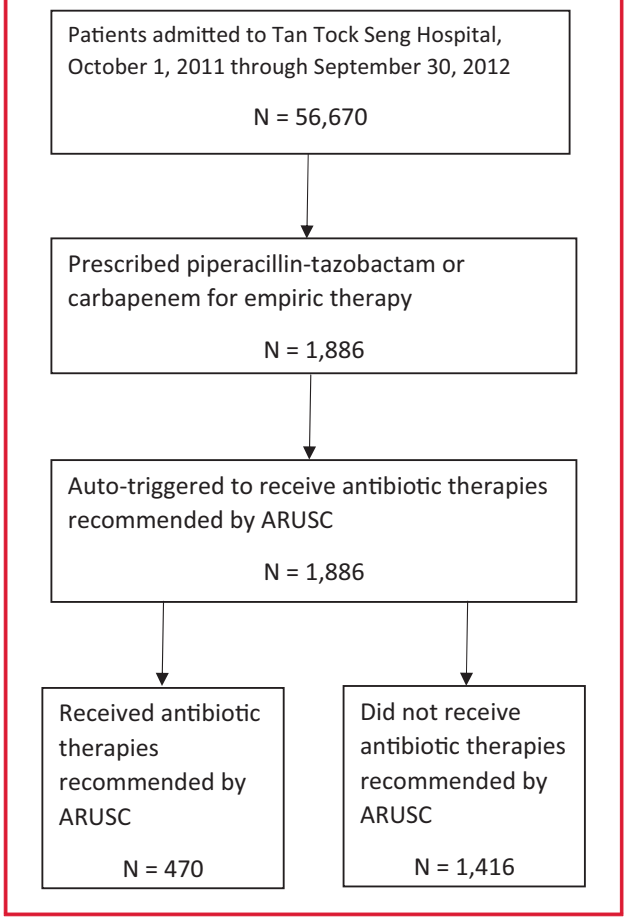


F. Option is provided for the prescribing physician to override ARUSC's recommendations. If the prescriber accepts the recommendations, clicking on the "Save" button will auto-populate the recommended antibiotics back into the CPOE within 5-10 seconds.

coding algorithms developed by Quan H et al.[33] CCI was then dichotomized into ≤ 5 and >5, representing good and poor chronic health status. Illness severity was determined using biochemical markers measured within 7 days of the prescription. We used C-reactive protein >100 mg/l and leukocyte count <4 or $>12 \times 10^9$/l as proxies for severe infection, and serum creatinine >130 μmol/l as a proxy for renal impairment.[25] Data were obtained electronically from ARUSC, institutional electronic medical and pharmacy records, and admission and discharge databases.

The prescribing physician was the physician who initiated the empiric antibiotic prescription that auto-triggered ARUSC. The attending physician was the physician who was primarily responsible for the patient's clinical care and outcome for the hospitalization episode. Physicians' characteristics collected included the prescribing physician's seniority, and the attending physician's ethnicity and clinical specialty. Prescribing physicians' seniority was determined by their designation. Interns and residents were classified as juniors, whereas fellows and attending were seniors. Data on physicians' designation

Figure 2: Study Cohort.



and ethnicity were obtained from institutional human resource database and matched to the identity and clinical specialty data in ARUSC.

Statistical analysis

First, we used appropriate descriptive statistics to summarize patients' characteristics and their respective prescribing and attending physicians and clinical specialties by receipt of ARUSC-recommended antibiotic therapies. Next, we explored the relationships between the various patients' and physicians' characteristics and receipt of ARUSC-recommended antibiotic therapies, using multilevel logistic regression models with random intercepts. We fitted two types of such models: model 1 involved nesting of patients within their prescribing physicians, and model 2 nested patients within their attending physicians who in turn were nested with their clinical specialties, to account for clustering within prescribing physicians and clustering within attending physicians and clinical specialties, respectively. Finally, we constructed two multivariable multilevel logistic regression models to assess independent factors associated with receipt of ARUSC-recommended antibiotic therapies. We included variables decided a prior as effects to be tested based on prior knowledge of factors associated with adherence to antibiotic guidelines in general (though not specific for antibiotic CDSS). Collinearity among predictor variables was assessed by means of the Pearson's correlation coefficient. Strongly correlated variables were excluded from the multivariable models. Statistical interactions between variables were explored and product terms included in the models where appropriate. We estimated the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for each association. The percentages of the total outcome variances that could be explained by differences between prescribing physicians, attending physicians, and clinical specialties, respectively, were computed.[34] The chi-square goodness-of-fit test was used to evaluate the adequacy of the models. The Akaike information criterion (AIC), the Bayesian information criterion (BIC), and the log-likelihood ratio statistic were used to compare between models and to guide the final model selection. All analyses were performed using SAS version 9.3 (SAS Institute Inc., NC, USA).

Ethical approval for the study was obtained from the National Healthcare Group's Domain Specific Research Board and UCLA Institutional Review Boards.

RESULTS

During the 1-year study period, about one-quarter (24.9%) of the 1 886 inpatients automatically-triggered into ARUSC for prescriptions of piperacillin-tazobactam and carbapenems for empiric therapy received ARUSC-recommended antibiotics. Patients who received ARUSC-recommended antibiotic therapies were older (mean 74.8 years [SD 14.5] vs 71.8 [15.9]) and tended to have a better chronic health status (CCI $>$5 11.5% vs 14.2%) than those who did not. They were also more likely to have a recent hospitalization (45.1% vs 38.1%) and be diagnosed with pneumonia (85.7% vs 57.2%), but less likely to have an ICU admission (7.9% vs 12.8%) than patients who did not receive the antibiotic therapies recommended by ARUSC. The characteristics of prescribing and attending physicians of the two patient groups appeared similar. However, more patients who received ARUSC-recommended antibiotic therapies were managed by medical specialties (83.2% vs 73.0%).

Data on patient demographics, co-morbidities, illness severity, diagnosed infection, and clinical outcomes, and prescribing and attending physician characteristics are presented in Table 1.

Univariate analysis

Univariate patient factors associated with receipt of ARUSC-recommended antibiotics are similar in both models (Table 2). Age (Model 1: OR 1.01, 95% CI, 1.01-1.02; Model 2: OR 1.01, 95% CI, 1.00-1.02), cardiovascular disease (Model 1: OR 1.42, 95% CI, 1.06-1.91; Model 2: OR 1.38, 95% CI, 1.05-1.82), chronic pulmonary disease (Model 1: OR 1.38, 95% CI, 0.93-2.06; Model 2: OR 1.48, 95% CI, 1.01-2.16), prior hospitalization (Model 1: OR 1.28, 95% CI, 1.01-1.61; Model 2: OR 1.29, 95% CI, 1.04-1.61), prescription at night (Model 1: OR 1.34, 95% CI, 1.06-1.69; Model 2: OR 1.28, 95% CI, 1.03-1.59), and pneumonia (Model 1: OR 7.20, 95% CI, 3.51-14.75; Model 2: OR 6.28, 95% CI, 3.12-12.61) were positively associated with receipt. In contrast, ICU admission (Model 1: OR 0.57, 95% CI, 0.38-0.87; Model 2: OR 0.68, 95% CI, 0.46-1.01) and renal impairment (Model 1: 0.69, 95% CI, 0.53-0.91; Model 2: OR 0.68, 95% CI, 0.54-0.88) decreased patients' receipt of antibiotic therapies recommended by ARUSC (Table 2).

The prescribing physician accounted for 16.5% of the variation in patient receipt of ARUSC-recommended antibiotic therapies ($P < 0.001$). The attending physician (0.4%) and clinical specialty (2.3%) contributed to a much lesser extent. The prescribing physician's seniority and the attending physician's ethnicity were respectively not associated with patients' receipt of ARUSC-recommended antibiotic therapies. At the clinical specialty level, patients managed by a medical service were 1.7

Table 1: Characteristics of 1 886 patients and their prescribing and attending physicians, by receipt of CDSS-recommended antibiotic therapy

Characteristics	Receipt of CDSS-recommended antibiotic therapy	Non-receipt of CDSS-recommended antibiotic therapy
Total, *N*	470	1 416
Demographic data		
Age, mean (SD)	74.8 (14.5)	71.8 (15.9)
Males, *N* (%)	261 (55.5)	793 (56.0)
Ethnicity, *N* (%)		
Chinese	379 (80.6)	1 083 (76.5)
Malay	45 (9.6)	148 (10.5)
Indian	25 (5.3)	109 (7.7)
Other	21 (4.5)	76 (5.4)
Singapore residents, *N* (%)	453 (96.4)	1 347 (95.1)
Private ward class, *N* (%)	34 (7.2)	138 (9.7)
Medical history		
Co-morbidities, *N* (%)		
Diabetes mellitus	161 (34.3)	449 (31.7)
Cardiovascular disease	104 (22.1)	235 (16.6)
Liver disease	16 (3.4)	52 (3.7)
Renal disease	91 (19.4)	298 (21.1)
Neoplasia	70 (14.9)	225 (15.9)
Central nervous system disease	92 (19.6)	302 (21.3)
Chronic pulmonary disease	50 (10.6)	109 (7.7)
Charlson's comorbidity index >5, *N* (%)	54 (11.5)	201 (14.2)
Prior hospitalization (90 days), *N* (%)	212 (45.1)	539 (38.1)
Prior antibiotics (180 days), *N* (%)	370 (78.7)	1 106 (78.1)
Current Admission		
Length of stay prior to antibiotics, mean (SD)	8.1 (16.8)	9.6 (27.7)
Day of antibiotic prescription, *N* (%)		
Weekend or Public Holiday	129 (27.5)	407 (28.7)
Weekday	341 (72.6)	1 009 (71.3)
Time of antibiotic prescription, *N* (%)		
Night[a]	197 (41.9)	502 (35.5)
Day	273 (58.1)	914 (64.5)
Diagnosed infection, *N* (%)		
Pneumonia	403 (85.7)	810 (57.2)
Sepsis	26 (5.5)	189 (13.4)
Urinary tract infection	13 (2.8)	169 (11.9)
Hepatobiliary or Intra-abdominal	19 (4.0)	128 (9.0)
Other	9 (1.9)	120 (8.5)
Illness severity, *N* (%)		
C-reactive protein[b] >100 mg/l	168 (39.0)	497 (40.1)
Leukocyte count <4 or >12 $\times 10^9$/l	232 (49.4)	724 (51.1)
Serum creatinine[c] >130 μmol/l	105 (22.4)	401 (28.5)
Intensive care unit admission, *N* (%)	37 (7.9)	181 (12.8)

(continued)

Table 1: Continued

Characteristics	Receipt of CDSS-recommended antibiotic therapy	Non-receipt of CDSS-recommended antibiotic therapy
Prescribing physician, *N* (%)		
Senior	48 (10.2)	143 (10.1)
Junior	422 (89.8)	1 273 (89.9)
Attending physician, *N* (%)		
Ethnic Chinese	341 (72.6)	1 041 (73.5)
Ethnic Indian	92 (19.6)	284 (20.1)
Other Ethnicity	37 (7.9)	91 (6.4)
Clinical specialties, *N* (%)		
Medical		
Internal Medicine	151 (32.1)	359 (25.4)
Geriatric Medicine	76 (16.2)	149 (10.5)
Neurology	50 (10.6)	144 (10.2)
Respiratory Medicine	38 (8.1)	112 (7.9)
Cardiology	31 (6.6)	80 (5.7)
Infectious Disease	11 (2.3)	42 (3.0)
Hematology and Oncology	8 (1.7)	41 (2.9)
Gastroenterology	10 (2.1)	34 (2.4)
Rehabilitation Medicine	5 (1.1)	20 (1.4)
Palliative Medicine	5 (1.1)	15 (1.1)
Renal Medicine	4 (0.9)	15 (1.1)
Rheumatology, Allergy, and Immunology	1 (0.2)	17 (1.2)
Dermatology	0 (0.0)	5 (0.4)
Psychological Medicine	1 (0.2)	1 (0.1)
Surgical		
General Surgery	38 (8.1)	212 (15.0)
Neurosurgery	20 (4.3)	75 (5.3)
Orthopedic Surgery	14 (3.0)	70 (4.9)
Urology	7 (1.5)	15 (1.1)
Otolaryngology	0 (0.0)	10 (0.7)
Clinical outcomes, *N* (%)		
30-day Infection-related mortality	61 (13.0)	151 (10.7)
30-day All-cause mortality	97 (20.6)	264 (18.6)

[a]Night is defined as physician on-call hours from 1730 hours to 0730 hours.
[b]Missing values in receipt (39/470 = 8.3%) vs non-receipt (177/1416 = 12.5%) of CDSS-recommended antibiotic therapy groups.
[c]Missing values in receipt (2/470 = 0.4%) vs non-receipt (8/1416 = 0.6%) of CDSS-recommended antibiotic therapy groups.

times as likely as those managed by a surgical service to receive ARUSC-recommended antibiotics (OR 1.71, 95% CI, 1.19-2.46).

Multivariable analysis

The independent factors associated with patients' receipt of ARUSC-recommended antibiotic therapies were all patient-related (Table 3). Although prescribing physicians' preference accounted for 13.3% of the variation in receipt of ARUSC-recommended antibiotic therapies, physicians' seniority was not found to be an independent factor. There was no difference in patient receipt of ARUSC-recommended antibiotic therapies between attending physicians and clinical specialties. Both the 2-level and 3-level models yielded very similar results. We selected the 2-level model (Model 1: prescribing physician, patient) as the final multivariable model, as only the effect of prescribing physicians needed to be taken into account and the model provided a better fit. Interactions between co-morbidities, illness severity, and diagnosed infection were assessed. ICU admission was found to interact positively with cardiovascular disease and the product term was included in the final model.

After adjusting for the prescribing physicians' preference and seniority, the patient's socio-demographic factors, CCI > 5, prior antibiotic exposure, length of stay prior to antibiotic therapy, and time of

Table 2: Univariate analysis of factors associated with receipt of CDSS-recommended antibiotic therapy (Model 1: 2-level logistic regression analysis of data on 1 886 patients seen by 575 prescribing physicians; Model 2: 3-level logistic regression analysis of data on 1886 patients seen by 220 attending physicians in 19 clinical specialties)

	Model 1		Model 2	
Factor	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Patient Factors				
Age (years)	**1.01 (1.01-1.02)**	**.0011**	**1.01 (1.00-1.02)**	**.0103**
Male gender	0.98 (0.78-1.24)	.8869	1.01 (0.82-1.26)	.8998
Ethnicity				
Chinese	1.25 (0.73-2.15)	.4147	1.13 (0.68-1.88)	.6285
Malay	1.07 (0.57-2.03)	.8279	0.99 (0.55-1.80)	.9840
Indian	0.76 (0.37-1.54)	.4437	0.73 (0.38-1.42)	.3523
Other	1.00		1.00	
Singapore resident	1.36 (0.75-2.45)	.3054	1.24 (0.72-2.16)	.4386
Private ward class	0.73 (0.48-1.12)	.1475	0.75 (0.51-1.11)	.1545
Comorbidity				
Diabetes mellitus	1.13 (0.88-1.44)	.3326	1.07 (0.85-1.34)	.5731
Cardiovascular disease	**1.42 (1.06-1.91)**	**.0174**	**1.38 (1.05-1.82)**	**.0218**
Liver disease	0.82 (0.44-1.54)	.5434	0.94 (0.52-1.68)	.8352
Renal disease	0.93 (0.81-1.08)	.3323	0.91 (0.79-1.04)	.1524
Neoplasia	0.99 (0.72-1.37)	.9654	1.10 (0.80-1.50)	.5636
CNS disease	0.88 (0.66-1.18)	.3958	0.81 (0.60-1.08)	.1487
Chronic pulmonary disease	1.38 (0.93-2.06)	.1077	**1.48 (1.01-2.16)**	**.0431**
Charlson's comorbidity index >5	0.83 (0.59-1.19)	.3129	0.87 (0.63-1.21)	.4140
Prior hospitalization (past 90 days)	**1.28 (1.01-1.61)**	**.0411**	**1.29 (1.04-1.61)**	**.0202**
Prior antibiotics (past 180 days)	1.01 (0.76-1.34)	.9462	1.00 (0.77-1.30)	.9894
Length of stay prior to antibiotics	1.00 (0.99-1.00)	.3155	1.00 (0.99-1.00)	.4064
Day of antibiotic prescription (weekend/public holiday vs. weekday)	0.93 (0.72-1.21)	.6003	0.92 (0.73-1.17)	.5048
Time of antibiotic prescription (Night[a] vs. Day)	**1.34 (1.06-1.69)**	**.0161**	**1.28 (1.03-1.59)**	**.0255**
Diagnosed Infection				
Pneumonia	**7.20 (3.51-14.75)**	**<.0001**	**6.28 (3.12-12.61)**	**<.0001**
Sepsis	1.85 (0.81-4.22)	.1457	1.72 (0.77-3.84)	.1826
Urinary tract infection	1.00 (0.40-2.49)	.9962	0.91 (0.37-2.21)	.8283
Hepatobiliary or Intra-abdominal	2.13 (0.89-5.08)	.0879	2.14 (0.92-4.98)	.0785
Other	1.00		1.00	
ICU admission	**0.57 (0.38-0.87)**	**.0081**	**0.68 (0.46-1.01)**	**.0550**
Abnormal C-reactive protein	0.96 (0.75-1.23)	.7282	1.00 (0.95-1.06)	.8752
Abnormal leukocyte count	0.95 (0.75-1.19)	.6306	0.96 (0.78-1.19)	.7390
Renal impairment [b]	**0.69 (0.53-0.91)**	**.0076**	**0.68 (0.53-0.88)**	**.0035**
Prescribing Physician Factor (ICC = 16.5%)				
Seniority level (Junior vs Senior)	0.98 (0.63-1.53)	.9300	–	–
Attending Physician Factor (ICC = 0.4%)				
Ethnic Chinese	–	–	0.87 (0.57-1.33)	.5223
Ethnic Indian	–	–	0.79 (0.56-1.42)	.6230
Other ethnicity	–	–	1.00	
Clinical Specialty Factor (ICC = 2.3%)				
Medical vs Surgical	–	–	**1.71 (1.19-2.46)**	**.0037**

Abbreviations: CNS, central nervous system; ICC, intraclass correlation coefficient; ICU, intensive care unit; OR, odds ratio; CI, confidence interval. Bold values indicate results with $P < 0.05$.

[a]Night is defined as physician on-call hours from 1730 hours to 0730 hours.

[b]Creatinine level >130 μmol/l within 7 days of antibiotic prescription.

Table 3: Multivariable analysis of predictors of receipt of CDSS-recommended antibiotic therapy (Model 1: 2-level logistic regression analysis of data on 1 886 patients seen by 575 prescribing physicians; Model 2: 3-level logistic regression analysis of data on 1 886 patients seen by 220 attending physicians in 19 clinical specialties)

	Model 1*		Model 2*	
Factor	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Patient Factors				
Age (years)	1.00 (0.99-1.01)	.6898	1.00 (0.99-1.01)	.9084
Male gender	0.95 (0.74-1.22)	.7139	0.97 (0.77-1.22)	.7829
Ethnicity				
Chinese	0.86 (0.45-1.65)	.6508	0.84 (0.46-1.54)	.5675
Malay	0.92 (0.44-1.91)	.8265	0.91 (0.46-1.81)	.7948
Indian	0.53 (0.24-1.18)	.1192	0.54 (0.26-1.13)	.1044
Other	1.00		1.00	
Singapore resident	0.77 (0.36-1.63)	.4898	0.79 (0.39-1.60)	.5099
Private ward class	0.71 (0.43-1.18)	.1893	0.72 (0.45-1.15)	.1650
Cardiovascular disease	1.34 (0.96-1.87)	.0900	1.27 (0.93-1.74)	.1319
Charlson's comorbidity index >5	0.81 (0.56-1.17)	.2678	0.80 (0.57-1.14)	.2211
Prior hospitalization (past 90 days)	**1.32 (1.01-1.71)**	**.0399**	**1.36 (1.07-1.74)**	**.0134**
Prior antibiotics (past 180 days)	0.99 (0.72-1.35)	.9345	0.98 (0.73-1.31)	.8747
Length of stay prior to antibiotics	1.00 (0.99-1.00)	.7512	1.00 (0.99-1.00)	.8726
Time of antibiotic prescription (Night[a] vs Day)	1.25 (0.98-1.60)	.0777	1.20 (0.96-1.51)	.1136
Diagnosed infection				
Pneumonia	**6.77 (3.28-13.99)**	**<.0001**	**6.19 (3.04-12.61)**	**<.0001**
Sepsis	1.85 (0.80-4.24)	.1477	1.74 (0.78-3.92)	.1784
Urinary tract infection	0.93 (0.37-2.35)	.8839	0.91 (0.37-2.24)	.8444
Hepatobiliary or Intra-abdominal	2.01 (0.83-4.86)	.1195	2.02 (0.86-4.77)	.1079
Other	1.00		1.00	
Renal impairment[b]	**0.70 (0.52-0.93)**	**.0166**	**0.70 (0.53-0.91)**	**.0090**
ICU admission	**0.38 (0.21-0.66)**	**.0007**	**0.44 (0.26-0.77)**	**.0040**
ICU admission by Cardiovascular disease	**3.97 (1.60-9.81)**	**.0029**	**3.76 (1.60-8.83)**	**.0024**
Prescribing Physician Factor (ICC = 13.3%)				
Seniority level (Junior vs Senior)	0.95 (0.60-1.49)	.8105	–	–
Attending Physician Factor (ICC = 0.3%)	–	–		
Clinical Specialty Factor (ICC = 0.7%)				
Medical vs Surgical	–	–	1.16 (0.78-1.73)	.4595

Abbreviations: ICC, intraclass correlation coefficient; ICU, intensive care unit; OR, odds ratio; CI, confidence interval. Bold values indicate results with $P < 0.05$.

[a]Night is defined as physician on-call hours from 1730 hours to 0730 hours.

[b]Creatinine level >130μmol/l within 7 days of antibiotic prescription.

*Model 1: ROC = 0.8212; Fit statistics (−2 Log Likelihood = 1894.34, AIC = 1940.34, AICC = 1940.34, BIC = 2040.37)
Model 2: ROC = 0.7154; Fit statistics (−2 Log Likelihood = 1911.92, AIC = 1959.92, AICC = 1960.57, BIC = 1982.59)

prescription, hospitalization in the 90 days preceding current admission (OR 1.32, 95% CI, 1.01-1.71), and pneumonia as the diagnosed infection (OR 6.77, 95% CI, 3.28-13.99) were positively associated with receipt of ARUSC-recommended antibiotic therapies. In contrast, ICU admission (OR 0.38, 95% CI, 0.21-0.66) and renal impairment (OR 0.70, 95% CI, 0.52-0.93) were negatively associated. Although cardiovascular disease was marginally associated with receipt of ARUSC-recommended antibiotic therapies (OR 1.34, 95% CI, 0.96-1.87), the interaction between ICU admission and cardiovascular disease had a much larger positive effect (OR 3.97, 95% CI, 1.60-9.81).

The finding that only one-quarter of patients who were prescribed piperacillin-tazobactam or a carbapenem for empiric therapy received antibiotics according to ARUSC-recommended antibiotic therapies showed that there was room for improvement in the quality of care for

patients with infections. We had applied the strict criterion of exact match of antibiotics, as it was crucial for optimal clinical outcomes. The patients in this study represented a population with poor chronic health status (13.5% CCI $>$ 5) and who were more severely ill (11.6% ICU admission, 19.1% 30-day all-cause mortality). The use of antibiotic therapies containing broad-spectrum antibiotics such as piperacillin-tazobactam, imipenem, or meropenem have been observed to be associated with non-adherence with local written guidelines for empiric therapy.[30] Therefore, it is not surprising that adherence to recommendations by the antibiotic CDSS was low for our patient population. Piperacillin-tazobactam and carbapenems are generally used to treat more aggressive infections where the attending physicians' inputs might influence prescribing choice. The adherence rate in our study was comparable to the findings in medium-sized Dutch hospitals where empiric antibiotics prescribed according to national guidelines ranged from 5 to 59%.[26] Qualitative studies have suggested that physicians tended to consider their patients to be outside the boundaries of local evidence-based antibiotic guidelines and policies.[35]

We did not identify any physician demographic or clinical specialty factor that was associated with patient receipt of ARUSC-recommended antibiotic therapies. We examined the effect of the attending physician's ethnicity on patients' receipt of ARUSC-recommended antibiotic therapies, but did not observe any effects. Some studies have suggested associations between physician ethnicity and clinical practice including antibiotic prescribing.[36,37] The use of a decision support algorithm based on patients' clinical parameters could have removed the effect of physicians' antibiotic preferences influenced by their ethnicities and cultures. We also did not identify any differences in patient receipt of ARUSC-recommended antibiotic therapies between the seniority levels of prescribing physicians and clinical specialties of attending physicians, after adjusting for differences in patient characteristics and clinical factors. Differences in adherence rates with antimicrobial guidelines by physicians from different clinical specialties and seniority levels were observed in previous studies on guidelines.[10,18,29] A recent psychosocial study observed that physicians' willingness to consult an antibiotic CDSS determined physicians' acceptance of the CDSS recommendations.[38]

Several patient factors were identified to be associated with the receipt of antibiotic therapies recommended by ARUSC. Patients who were hospitalized in the preceding 90 days were 30% more likely to receive ARUSC-recommended antibiotic therapies. This finding has not been reported in previous studies on adherence with antibiotic guidelines. It is likely that patients with recent hospitalizations were more likely to be treated empirically for possible nosocomial infections and ARUSC recommendations for such infections included more broad-spectrum antibiotics, which physicians were more likely to accept.

A diagnosis of pneumonia was highly associated with the receipt of ARUSC-recommended antibiotic therapies. Other studies have reported similar findings with adherence to hospital antimicrobial guidelines.[18,25] ARUSC-recommended antibiotic regimens for nosocomial pneumonia included piperacillin-tazobactam, which was the antibiotic prescribed by the physicians. Patients with cardiovascular disease were 1.3 times as likely as those without cardiovascular disease to receive ARUSC-recommended antibiotic therapies. Menendez et al.[29] reported similar findings for adherence to the Spanish guidelines for the empiric treatment of community-acquired pneumonia. Interestingly, patients with cardiovascular disease admitted to ICU were even more likely to receive antibiotic therapies recommended by ARUSC. They tended to be admitted to the coronary ICU, which had a higher acceptance of ARUSC-recommended therapies.

We identified several patient factors that could be targeted for enhancement of ARUSC to improve patients' receipt of its recommended antibiotic therapies, namely, patients admitted to ICU and those with renal impairment. We found that ICU patients were 60% less likely to receive ARUSC-recommended antibiotic therapies. Several studies reported a similar decrease in adherence to hospital antibiotic guidelines for ICU patients.[27,29] Physicians have also been observed to choose to exercise their own or clinical team's decision to override antibiotic CDSS recommendations in complex patient situations.[38] It was suggested that the non-adherence might have been driven by the inability of antibiotic guidelines to cover all encountered clinical conditions.[39] It is likely that severely ill patients require additional considerations for their antibiotic therapy needs that were not covered by ARUSC, although it was tailored to incorporate patient-specific data. The complexity of treatment for the ICU patient may have to be considered in addition to the parameters provided for general inpatients. We had assumed that ARUSC's recommendations were always appropriate for the patient, but it might not be so for ICU patients. Likewise, for patients with renal impairment, receipt of ARUSC-recommended antibiotic therapies was observed to be 30% lower than for patients with normal renal function. This could be due to the perceived nephrotoxicity of ARUSC-recommended antibiotics such as the aminoglycosides. ARUSC could be enhanced to provide more detailed information on such antibiotics for physician education and assurance of their safe utilization. The dose adjustments required by patients with renal impairment have already been accounted for in ARUSC's recommendations. Mettler et al. has reported an even higher reduction in empiric guidelines adherence (42%) with renal failure patients. [25,30] As with other studies, the patient's age was not found to be associated with patient receipt of ARUSC-recommended antibiotic therapies.[19,25]

Strengths and Limitations

Our study has several strengths. First, it followed up a cohort of hospitalized patients longitudinally from the initiation of an electronic antibiotic prescription up to 30 days post-discharge from hospital. The unique patient identifier and admission episode number allowed for electronic linkages across medical and pharmacy records, and administrative databases. As such, all data were electronically collated and any measurement error and misclassification of exposures was likely to be minimal. Unlike most studies assessing adherence to antibiotic guidelines, which involved study investigators manually reviewing prescriptions that was error-prone and challenged with inter-rater reliability issues, our study electronically matched antibiotics prescribed on the CPOE system with ARUSC recommendations to determine patient receipt of ARUSC-recommended antibiotic therapies. Hence, outcome measurement was not subject to measurement error or differential misclassification.

Another major strength of the study was the use of multilevel modeling techniques to account for the clustering of patients within prescribing physicians, and within attending physicians and clinical specialties. Many previous studies were not able to do so, and employed standard modeling techniques that were prone to type I error. Our multilevel models have also addressed the concern about multiple testing, via multilevel averaging ("shrinkage") to reduce estimation and testing error.[40,41] Furthermore, we were able to study and estimate the relative effects of prescribing physician, attending physician, and medical specialty on patients' receipt of antibiotic therapies recommended by an antibiotic CDSS.

By restricting our study population to patients who were prescribed either piperacillin-tazobactam or carbapenems, we were able to better

understand the specific factors associated with receipt of ARUSC-recommended antibiotic therapies for this patient group. This is the hospital's primary target population for reduction of broad-spectrum antibiotic use, as they could create selection pressures for the development of extensively drug-resistant bacteria. Our findings are less likely to be biased given the large number of potential confounding variables controlled for in the multivariable adjusted models.

This study is novel as it is the first to assess associations between patient and physician factors and an antibiotic CDSS. Previous studies on such associations were on antibiotic guidelines, which did not provide clinical decision support that was integrated with patient clinical data and prescribing workflow.

Our study may be limited by the inability to study certain patient and physician factors, due to lack of available electronic data. We could not explain the relatively large variation between prescribing physicians as the very characteristics of prescribing physicians that could have explained the differences remained unmeasured and unknown in our study. However, physicians' characteristics may not be amenable barriers to patients' receipt of recommended antibiotics. Focusing on specific patient populations rather than physicians for the enhancement of antibiotic CDSS makes the reduction of patients' non-receipt of its recommended antibiotic therapies more feasible.[19] Our findings may not be generalizable to pediatric populations, but may be applied to other adult tertiary-care centers where antibiotic CDSSs are used.

CONCLUSION

This study gave insights into predictors of patients' receipt of empiric antibiotic therapies recommended by a CDSS when the prescribing physician had an initial preference for using broad-spectrum antibiotics. While the prescribing physician accounted for some of the differences, the attending physician and clinical specialty were not associated with patients' receipt of CDSS-recommended antibiotic therapies. Patients admitted to the ICU or who had renal impairment were less likely to receive CDSS-recommended antibiotics. Enhancements to the antibiotic CDSS can help address some of the unique patient needs, but the more complex clinical conditions (such as multiple infections) and antibiotic needs of such patients may require a physician's assessment in addition to the CDSS recommendations.

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COMPETING INTEREST

The authors have no competing interests to declare.

CONTRIBUTORS

A.C. and D.L. were responsible for the conception and design of the study, and the acquisition of the data. A.C. and O.A. contributed to the analysis of the data. All the authors were involved with the drafting and critical revision of the article, and gave the final approval of the manuscript.

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