Title
Clinical Epidemiology and Comparative Effectiveness of Computerized Antibiotic Stewardship on Patient Infection Resolution, Clostridium difficile Infection, and Mortality

Author
Chow, Angela Li Ping

Publication Date
2014

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Clinical Epidemiology and Comparative Effectiveness of Computerized Antibiotic Stewardship on Patient Infection Resolution, *Clostridium difficile* Infection, and Mortality

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Epidemiology

by

Angela Li Ping Chow

2014

ABSTRACT OF THE DISSERTATION

Clinical Epidemiology and Comparative Effectiveness of
Computerized Antibiotic Stewardship on Patient Infection Resolution,
Clostridium difficile Infection, and Mortality

by

Angela Li Ping Chow
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2014
Professor Onyebuchi A. Arah, Chair

Antibiotic resistance is a serious global public health threat and antibiotic prescribing is the key driver. Computerized antibiotic stewardship interventions have been implemented to facilitate physicians' decision making and promote optimal antibiotic selection at the point of prescribing. However, predictors of patient receipt of computerized antibiotic stewardship interventions have not been studied, and the clinical benefits of such interventions to individual patients remain unclear. This dissertation investigated physician and patient factors associated with physicians' acceptance or patients' receipt of computerized antibiotic stewardship intervention, the comparative effectiveness of computerized antibiotic stewardship intervention on individual patients' clinical outcomes, and the modification of these effects by patient factors.

We followed up an inpatient cohort in a 1500-bed tertiary care hospital in Singapore, with its homegrown antibiotic computerized decision support system (CDSS) that integrates antibiotic stewardship with electronic prescribing. In addition, we conducted a mixed methods study on physicians, to determine the psychosocial factors associated with physicians' acceptance of CDSS recommendations.

We observed that physicians' willingness to consult the antibiotic CDSS determined acceptance of its recommendations, and that physicians would choose to exercise their own or clinical team's decision over the CDSS recommendations in complex patient situations when the antibiotic prescribing needs were not met. The prescribing physician —but not the attending physician or clinical specialty— accounted for some (13.3%) of the variation in patients' receipt of CDSS recommendations. Patients requiring intensive care (OR 0.38, 95% CI 0.21-0.66) and those with renal impairment (OR 0.70, 95% CI 0.52-0.93) were less likely to receive the intervention, as their complex clinical conditions might require a physician's assessment in addition to antibiotic CDSS.

We further observed that patients' receipt of CDSS recommendations halved the odds of mortality in patients (OR 0.54, 95% CI 0.26-1.10), with patients aged <= 65 years having a greater mortality benefit (OR 0.45, 95% CI 0.20-1.00). No appreciable increase in infection-related readmission (OR 1.16, 95% CI 0.48-2.79) was found in survivors.

Our findings can help healthcare institutions in the design of new antibiotic CDSSs and enhancements of existing ones to promote the optimal use of antibiotics in the global battle against antibiotic resistance.

The dissertation of Angela Li Ping Chow is approved.

Beate Ritz

Frank J. Sorvillo

Abdelmonem A. Afifi

Onyebuchi A. Arah, Committee Chair

University of California, Los Angeles

2014

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LIST OF ABBREVIATIONS

ARUSC	Antimicrobial Resistance Utilization and Surveillance Control
CCI	Charlson's comorbidity index
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CDSS	Computerized decision support system
CI	Confidence interval
CNS	Central nervous system
CPOE	Computerized physician order entry
FGD	Focus group discussion
ICC	Intraclass correlation coefficient
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
MDRO	Multidrug resistant organism
OR	Odds ratio
PS	Propensity score
RR	Risk ratio
SHEA	Society for Healthcare Epidemiology of America
TTSH	Tan Tock Seng Hospital Singapore
US	United States
WHO	World Health Organization

ACKNOWLEDGEMENTS

I would like to express my heartfelt thanks to all my friends and instructors at UCLA. I am indebted to my dissertation committee chair and advisor Onyebuchi Arah who had not only provided me with the once-in-a-lifetime opportunity to pursue my PhD studies at UCLA but had also believed in me and stretched me to my fullest, and mentored me through many challenging periods during the journey. Special thanks also to my dissertation committee members: Beate Ritz, Frank Sorvillo, and Abdelmonem Afifi, who provided me with invaluable guidance for this dissertation.

This work was supported by a scholarship from Tan Tock Seng Hospital Singapore.

VITA

EDUCATION & PROFESSIONAL EXPERIENCE

1995	Bachelor of Medicine, Bachelor of Surgery National University of Singapore
2000	Master of Medicine in Public Health National University of Singapore
2001-2006	Public Health Physician Ministry of Health Singapore
2007-2010	Consultant Department of Clinical Epidemiology Tan Tock Seng Hospital Singapore
2010-2011	Special Reader Department of Epidemiology University of California, Los Angeles
2011	Master of Science in Epidemiology University of California, Los Angeles
2012-2014	Senior Consultant Department of Clinical Epidemiology Institute of Infectious Diseases & Epidemiology Tan Tock Seng Hospital Singapore

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1. INTRODUCTION

The discovery of antibiotics is among the most important of public health interventions in the 20th century (1). Antibiotics, along with improved sanitation and vaccination, have brought about substantial reduction in infectious mortality. However, soon after the widespread use of antibiotics, bacteria expressing antibiotic resistance emerged. Over the years, inappropriate antibiotic use has driven the rapid increase in antibiotic resistance, and with the drying up of the pipeline of new antibiotics, a post-antibiotic era is imminent (2–4). The Centers for Disease Control and Prevention estimates that at least 2 million people in the United States (US) become infected with antibiotic-resistant bacteria each year, and at least 23,000 people die each year as a direct result of these infections (5). In the US, the number of hospitalizations attributable to antibiotic-resistant infections increased by 359% from 37,000 in 1997 to almost 170,000 in 2006 (6). A survey of 22 US academic centers found a substantial increase in total antibiotic use from a mean of 798 to 855 days of therapy per 1000 patient days, between 2002 and 2006 (7).

Antibiotic stewardship programs were introduced to optimize antibiotic therapy and clinical outcomes, while minimizing the unintended consequences of antibiotic use, including the selection of pathogenic organisms such as *Clostridium difficile*. Although antibiotic stewardship has been in existence for many years, evaluations of stewardship interventions to date have focused primarily on successes achieved with process measures such as the optimization of antibiotic use and cost savings (8). Limited research have been on patient outcomes. Even more limited research have been on the effect of computerized decision support systems (CDSSs) (9). Antibiotic CDSSs have been developed to support antibiotic stewardship and enhance prescribing, providing guidance on antibiotic selection at the point of prescribing. Results of outcome studies are often limited by the ecologic study design and uncontrolled confounding (10). More research on the comparative effectiveness of antibiotic stewardship interventions on

individual patient clinical outcomes is urgently needed (8). At issue is whether using appropriate antibiotics for the right patients at the right dose, at the right time, and for the right duration, matters for patient outcomes such as infection resolution and survival.

This dissertation aims to address knowledge gaps in Clinical Epidemiology and the Comparative Effectiveness of Computerized Antibiotic Stewardship Intervention on Patient Clinical Outcomes. Using an observational cohort comprising inpatients from Tan Tock Seng Hospital Singapore exposed to a computerized antibiotic stewardship intervention, starting from the initiation of the intervention up to 180 days post-intervention or 30-days post-discharge from hospital, we propose to first determine patient and physician predictors for patient receipt of the computerized antibiotic stewardship intervention, then investigate the comparative effectiveness of the intervention on three important patient outcomes: infection resolution, incident *Clostridium difficile* infection, and mortality, and finally to investigate for the heterogeneity of the effects of intervention on patient subgroups. To better understand the psychosocial factors associated with physicians' acceptance of antibiotic recommendations from the CDSS, we further conducted a mixed methods study on physicians from the hospital.

The proposed research will help in the identification of patient and physician factors which can be targeted to improve the acceptance of computerized antibiotic stewardship intervention, enhance the understanding of the effects of computerized antibiotic stewardship intervention on patients and in subgroups of patients, and identify those who may benefit the most from the intervention and on whom intervention efforts should be focused.

2. BACKGROUND

2.1 Antibiotic Discovery and Antibiotic Resistance

Antibiotics have transformed the practice of medicine. Sir Alexander Fleming's accidental discovery and isolation of penicillin in September 1928 marks the start of modern antibiotics. Countless lives have been enhanced and saved with antibiotic use. However, Sir Fleming also observed very early on that bacteria developed antibiotic resistance whenever too little penicillin was used or when it was used for too short a period (11).

2.2 Antibiotic Resistance: a global public health problem and emerging crisis

Antibiotic resistance is a major global public health problem. In Europe, it was estimated that approximately 25,000 patients died from infections due to antibiotic-resistant organisms in 2007 (12). In contrast, each year, about 48,000 persons were killed in a road accident. In the United States, it is estimated that at least 2 million people become infected with antibiotic-resistant bacteria each year, and at least 23,000 people die each year as a direct result of these infections (5). The number of hospitalizations attributable to antibiotic-resistant infections increased by 359% from 37,000 in 1997 to almost 170,000 in 2006 (6). On World Health Day 2011, the World Health Organization (WHO) highlighted this pressing issue with the slogan: "Antimicrobial resistance: no action today, no cure tomorrow" (13). In April 2014, the WHO released its first global report on the surveillance of antimicrobial resistance, “Antimicrobial resistance: global report on surveillance 2014”, and warned of the imminence of a post-antibiotic era – in which common infections and minor injuries can kill (4).

2.3 Antibiotic Stewardship to curb the rising tide

Inappropriate antibiotic use drives antibiotic resistance. An estimated 50% of all antibiotic use (14,15), and 20-50% of antibiotic use in empiric therapy is deemed to be inappropriate (16–19). In hospitals, the intensity of antibiotic use is high and utilization has increased substantially over the years (7,9). A survey of 22 US academic centers found a substantial increase in total antibiotic use from a mean of 798 to 855 days of therapy per 1000 patient days, between 2002 and 2006 (7). However, 41-91% of all antibiotics prescribed in hospitals worldwide are inappropriate (20).

The rapid rise in antibiotic resistance, coupled with the dwindling pipeline of effective antibiotic armamentarium, has raised tremendous concern about the emergence of the doomsday organism. Soon, the Centers for Medicare and Medicaid Services may require the physician to justify the rationale for any antibiotic requested in the hospital (21). Major efforts have been spearheaded by the Centers for Disease Control and Prevention (CDC) and the Society for Healthcare Epidemiology of America (SHEA), to encourage the judicious use of antibiotics. The creation of SHEA's Antimicrobial Stewardship Taskforce and the launch of CDC's "Get Smart for Healthcare" campaign marked the beginning of a new era of nationally coordinated efforts to promote inpatient antibiotic stewardship in the United States (22). Similar efforts have also been made in Singapore (23).

The Infectious Diseases Society of America (IDSA) and SHEA 2007 guidelines have identified formulary restriction and prospective audit with intervention and feedback as the key evidence-based strategies for stewardship programs (24). The ultimate goal of antibiotic stewardship is to optimize antibiotic therapy and clinical outcomes, while minimizing the unintended consequences

of antibiotic use, including the selection of pathogenic organisms such as *Clostridium difficile* (10,24).

Antibiotic stewardship programs have been shown to have positive effects on the optimization of antibiotic use, reduction of bacterial resistance, and on cost savings (25,26). However, few studies have shown improvement in patient outcomes and only a handful were from outside of North America and Europe (9). Results of such studies are also limited by the quasi-experimental study design and confounded by the lack of control for co-interventions (10). There is an urgent need for more research on the effect of antibiotic stewardship programs on patient clinical outcomes (8). Antibiotic stewardship should aid physicians in selecting the appropriate antibiotic to improve outcomes. In the future, measuring the effect of stewardship on clinical outcomes will become part of ongoing processes of healthcare, and not merely a research tool (27). At issue is whether using appropriate antibiotics for the right patients at the right dose, at the right time, and for the right duration, matters for clinical outcomes such as infection resolution and survival. Studies demonstrating improvement of patient outcomes can lead to an increased acceptance of antibiotic stewardship by physicians, and enhance appropriate antibiotic use (10).

2.4 Computerized Clinical Decision Support System to enhance antibiotic stewardship

Adherence to antibiotic guidelines has generally been poor, with non-adherence rates ranging from 30 to 82% (28,29). Several barriers to adherence to guidelines have been identified, including insufficient updating or involvement of senior physicians in the development of antibiotic guidelines (30). Adherence with guidelines could be improved by as much as 15% with periodic updating, close collaboration with prescribing physicians, and active dissemination (31). Physicians' adherence could also be improved with feedback on antibiotic utilization and active

communications to prescribing physicians on local patient profiles and pathogen epidemiology (32,33).

Computerized clinical decision support systems are developed to address the above issues, to increase the effectiveness of antibiotic stewardship programs in hospitals (34–36). They provide patient-specific data and antibiotic suggestions to physicians to prescribe patients with the most appropriate antibiotics, at the point of care (28,37). These computerized systems can educate physicians on the appropriate use of antibiotics, restrict prescription of targeted antibiotics, and review antibiotic prescribing patterns with active feedback to physicians. Patients who receive antibiotics recommended by antibiotic computerized decision support systems (CDSSs) can have better clinical outcomes, through their physicians' improved antibiotic prescribing practices (38–42).

Worldwide, only a handful of hospitals have successfully implemented CDSSs for antibiotic stewardship (16,23,36,38–44). Whilst many studies have shown that computerized clinical decision support systems improve physician performance, their effects on patient outcomes remain understudied and when studied, findings have been inconsistent (45). Few studies have evaluated CDSSs in routine clinical settings (46,47). To date, there has been only one study assessing patient and physician factors associated with the physicians' adoption of an antibiotic CDSS but none on patient and physician factors influencing physicians' acceptance of recommendations from computerized antibiotic stewardship interventions. As more hospitals develop and implement such systems, understanding these factors is crucial for the success of antibiotic stewardship programs in terms of effective and safe antibiotic prescribing (6).

2.5 Computerized Antibiotic Stewardship Intervention and Predictors for Acceptance

In general, junior physicians have been observed to be more likely than senior physicians to accept prescribing recommendations by clinical decision support systems (48–50). However, their prescribing practices were often highly influenced by senior physicians. Senior physicians were the decision makers, yet it was the junior physicians who interact with the computerized systems to enter medication orders. Clinical decision support systems have been seen to fail to target physicians who were making the prescribing decisions on ward rounds (49).

User-centered antibiotic CDSSs, developed in close collaboration with users using a "bottom-up" approach, have been shown to improve physician engagement and increase adoption of antibiotic recommendations (51). Compared to passive and didactic educational approaches, antibiotic CDSSs have elicited greater behavioral change in prescribing practices among physicians, regardless of seniority (41). They seem to be able to overcome the habitual prescribing preferences of senior physicians.

Certain patient and physician characteristics have been observed to influence adherence to antibiotic guidelines (29–33), but few studies have examined these factors at the individual patient level (29). For empiric antibiotic therapy, adherence was poor for sepsis and urinary tract infections, but high for pneumonia (29,30,33). Predisposing illnesses and active malignancies were also associated with more adherent prescribing, whilst renal impairment was associated with less adherent prescribing (33). Among clinical specialties, surgeons, urologists, pulmonologists, and geriatricians have been observed to be less adherent with antibiotic recommendations (29). However, the influence of these factors on the acceptance of computerized antibiotic stewardship interventions has yet to be studied.

It has been suggested that if physicians find the CDSS to be easier to use than the methods they had been using for ordering antibiotics, antibiotic recommendations tend to be followed (27). However, the psychosocial determinants of physicians' acceptance of recommendations by antibiotic CDSSs have remained poorly understood.

2.6 Computerized Antibiotic Stewardship Intervention and Infection Resolution

Although the primary goal of antibiotic stewardship is to optimize antibiotics to treat a patient's infection, few studies have actually evaluated the effect of antibiotic stewardship on infection resolution. Readmission is a surrogate measure for infection resolution. A recent publication suggested that the reduction of readmissions may become antibiotic stewardship programs' new "low-hanging" fruit - the most obtainable target with limited resources (26). A study in Singapore based on manual reviews of inpatient clinical charts reported a reduction in 30-day readmission due to infection in patients whose physicians accepted the antibiotic stewardship intervention, compared to patients whose physicians did not (intervention group 10.1% (53/523) vs. no intervention 12.6% (18/143)) (52). Other studies have observed an increase in hospital readmissions associated with antimicrobial stewardship interventions intended to decrease excessive prescribing (combined risk ratio 1.26, 95% CI 1.02-1.57, P = 0.03), but did not observe a difference between intervention and control groups for infection-related readmissions (9). However, there has been no published literature on the effect of computerized antibiotic stewardship intervention on readmissions.

2.7 Computerized Antibiotic Stewardship Intervention and *Clostridium difficile* infection

To date, studies on the effects of antibiotic stewardship interventions on the incidence of *Clostridium difficile* infection (CDI) have been ecologic studies with interrupted time-series analyses (53–55). Two quasi-experimental studies in the United Kingdom observed a reduction in the incidence CDI following the implementation of revised antibiotic guidelines (incidence rate ratio 0.34, 95% CI 0.20-0.58) (53) and the restriction of broad-spectrum antibiotic use (incidence rate ratio 0.35, 95% CI 0.17-0.73) (54). A 7-year study on a hospital-wide broad-based antibiotic control program reported a reduction of CDI from 2.2 per 1,000 patient-days in the one-year pre-implementation to 1.4 per 1,000 patient-days in the first year as well as the following five years post-implementation (55). In all studies (53–55), the detection of CDI was based solely on a positive test for *Clostridium difficile* toxin, which has a low sensitivity of 36% (56–59). The effect of antibiotic stewardship intervention on the reduction in CDI incidence has yet to be assessed at the individual patient level, nor for high-risk patients in intensive care units (60). Although decreases in CDI have been reported in studies on antibiotic restriction and stewardship policies, the effect of antibiotic CDSSs on the incidence of CDI has not been studied (9,55,61).

2.8 Computerized Antibiotic Stewardship Intervention and Mortality

Most studies on the effect of antibiotic stewardship were ecologic quasi-experimental studies, which evaluated mortality rates pre- and post-implementation of stewardship programs. No study detected an increase in mortality due to antibiotic stewardship, in spite of reduced duration of antibiotic therapies (60,62). A recent meta-analysis on the effect of antimicrobial stewardship interventions intended to increase appropriate antimicrobial therapy for all infections reported no increase in mortality (combined risk ratio 0.91, 95% CI 0.81-1.06, P = 0.25)(9). In the limited

studies on the clinical effects of antibiotic CDSS in hospitals in the US, Europe, and Australia, no difference was observed in the pooled 30-day mortality (17,35,63), although an European study on the effectiveness of TREAT, a CDSS established in three medical centers in Germany, Israel, and Italy, found that inappropriate empiric antibiotic therapy was associated with a 1.58 times (OR 1.58, 95% CI 0.99-2.54) increased risk for 30-day all-cause mortality in medical inpatients (18). A more recent study in Germany on ICU patients with sepsis found that low adherence to CDSS recommendations was found to be associated with increased risk of ICU mortality (OR 2.43, 95%CI 1.13-5.24, P = 0.02)(39).

Antibiotic CDSS presents a promising future for optimizing antibiotic selection and improving clinical outcomes (27,64). However, few studies have been conducted on the effect of antibiotic CDSS and very few were from outside of the US. More studies are needed in different settings, including Asia (64). Furthermore, none of the previous studies has explored the modifying effects of patient factors on clinical outcomes. Investigating the effect of antibiotic CDSS on subgroups of patients would help identify those who may benefit the most from the intervention and on whom intervention efforts should be focused.

3. METHODS

3.1 Data Sources

ARUSC Database

Tan Tock Seng Hospital Singapore (TTSH)'s Antimicrobial Resistance Utilization and Surveillance Control (ARUSC) system was established in 2009. ARUSC 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 (Appendix I) (65) . ARUSC provides guidance on antibiotic prescribing, based on guidelines developed by the hospital's antimicrobial stewardship committee, which took into account the local epidemiology of infectious diseases, microbiologic resistance patterns, and incorporated evidenced-based international guidelines. Inputs from all clinical departments were sought and considered in the development of guidelines, which were endorsed by the hospital's medical board.

All medication orders in the hospital are made via the CPOE system. ARUSC contains data on all inpatient prescriptions of piperacillin-tazobactam and carbapenems, which are antibiotics on the hospital's restricted formulary list. Piperacillin-tazobactam is a broad-spectrum antibiotic that is effective against many bacteria including *Pseudomonas aeruginosa* which is naturally resistant to a wide range of antibiotics. Carbapenems are antibiotics of last resort for many bacterial infections. Hence, it is crucial to ensure the judicious use of these antibiotics. The recent identification and global spread of carbapenem-resistant bacterial infections due to the production of New Delhi metallo-β-lactamase-1, NDM-1, is worrisome. Carbapenem-resistant bacteria respond to very few (if any) antibiotics.

From September 12, 2011, every inpatient prescription of piperacillin-tazobactam or a carbapenem antibiotic will automatically trigger a clinical decision support algorithm on ARUSC. Using a rules-based algorithm, ARUSC provides guidance on antibiotic selection and dosing, based on guidelines developed by the hospital's antimicrobial stewardship committee and data from individual patients' electronic medical records including medication history and drug allergies, as well as laboratory results such as creatinine levels pulled into ARUSC and included in the algorithm. A prescription can be made for the purpose of empiric, prophylactic, or definitive therapy. ARUSC recommends the narrowest-spectrum antibiotic appropriate for common organisms responsible for the diagnosed infection, based on the local epidemiology and antibiotic susceptibility patterns, taking into account the patient's antibiotic allergies. The prescribing physician can either accept or reject ARUSC's antibiotic recommendations.

At the patient level, there is one record for every inpatient prescription. Hence, one individual may contribution to multiple observations. Only the first prescription for empiric therapy per patient during the study period was included in the study. At the physician level, data on the identity and seniority of the prescribing physician, the identity of the attending physician, and their clinical specialties are available in ARUSC.

Focus Groups and Questionnaire Survey

Transcripts from the focus group discussions with junior and senior physicians in TTSH conducted in February 2013 were included in the physician study. Furthermore, data collected from a cross-sectional questionnaire survey in April 2013 on physicians involved with inpatient care at TTSH were also evaluated (Appendix II).

3.2 Study Setting

The three studies were conducted in TTSH, a 1500-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 has a population of 5.3 million in 2012.

3.3 Study Population

ARUSC Patient Cohort

The study group comprised all inpatients at TTSH who met the following inclusion criteria:

(1) prescribed piperacillin-tazobactam or a carbapenem antibiotic for empiric therapy,

(2) auto-triggered to receive antibiotic stewardship intervention on the antibiotic CDSS, ARUSC, and

(3) the initiation of antibiotics was from Oct 1, 2011 through Sep 30, 2012.

Inpatients who were prescribed piperacillin-tazobactam or a carbapenem for prophylactic or definitive therapy, inpatients who were prescribed other antibiotics for empiric therapy, inpatients who received antibiotic stewardship intervention but were not auto-triggered on ARUSC, and outpatients, were excluded from the study population.

Empiric therapy is the initiation of antibiotic treatment prior to the identification of the specific microorganism causing the infection. We chose to focus on empiric therapy, as antibiotic prescriptions for such therapies have been found to be least concordant with recommended antibiotic guidelines (29). Furthermore, appropriate empiric antibiotics is a critical determinant of clinical outcomes (66). Antibiotics prescribed for empiric therapy tend to be the first antibiotics

received by patients in the course of the infection episode and hence the association between the antibiotic stewardship intervention and the outcomes of interest would less likely be confounded by time-varying confounding variables. Prophylactic therapy was excluded from our analyses, as patients who receive such therapies are a special group of inpatients who are well and healthy, and are receiving antibiotics to prevent infections from surgical procedures.

From Oct 1, 2011 through Sep 30, 2012, there were 1886 patients who fulfilled the inclusion criteria.

Physician Cohort

A cross-sectional questionnaire survey was conducted on all physicians involved with inpatient care at TTSH, from April 1 through April 26, 2013. Prior to this, focus group discussions (FGDs), separately with junior and senior physicians purposively sampled from all clinical specialties were conducted in February 2013.

3.4 Study Design

ARUSC Patient Cohort

We assembled and followed up an observational cohort comprising eligible inpatients based on the inclusion criteria described above, starting from the initiation of the computerized antibiotic stewardship intervention up to 180 days from the initiation date or 30 days post-discharge from hospital, whichever was later. In addition to the data available from ARUSC, data were merged from various hospital systems including the Hospital Admission and Discharge database (SAP), Clinical Information System (PanFlu), Electronic Pharmacy Records (eIMR), Laboratory Information System (LIS), the Infection Control database (ICESS), and the hospital's Human Resource database.

Physician Cohort

A mixed methods study was conducted, with a qualitative phase followed by a dominant quantitative phase. Themes derived from the qualitative study were used to inform the quantitative survey. Two FGDs, separately for junior and senior physicians, purposively sampled from all clinical specialties in the hospital, were conducted in February 2013. The discussions used the same set of semi-structured questions, and were audio-recorded and transcribed verbatim.

Following that, a cross-sectional questionnaire survey was conducted on all physicians involved with inpatient care at TTSH, from April 1 through April 26, 2013. A survey instrument was developed, comprising questions on the situations for use, the perceived credibility and usefulness, and the desired useful features of ARUSC for empiric antibiotic therapy. A five-point Likert scale ranging from 1 ("Strongly disagree") to 5 ("Strongly agree") was used for each response. The survey instrument incorporated themes and subthemes that emerge from the FGDs. Physicians were informed of the study via email, one week prior to the study. Survey questionnaire were distributed to all physicians via their departments. In addition, physicians were individually approached in the inpatient wards and invited to participate in the survey.

3.5 Statistical software

All statistical analyses were conducted in SAS version 9.3 (SAS Institute Inc., Cary, NC).

4. PSYCHOSOCIAL DETERMINANTS OF PHYSICIANS' ACCEPTANCE OF RECOMMENDATIONS BY ANTIBIOTIC COMPUTERIZED DECISION SUPPORT SYSTEMS

4.1 ABSTRACT

Introduction

Antibiotic computerized decision support systems (CDSSs) were developed to facilitate optimal prescribing, but acceptance of their recommendations has remained low. This study aimed to evaluate physicians' perceptions and attitudes toward antibiotic CDSSs, and to determine psychosocial factors associated with acceptance of CDSS recommendations for empiric therapy.

Methods

We conducted a mixed methods study in a 1500-bed tertiary-care hospital in Singapore, with its in-house antibiotic CDSS that integrates antimicrobial stewardship with electronic prescribing. Focus group discussions were conducted among purposively sampled physicians and data analyzed using the framework approach. Emerging themes were included in the questionnaire with newly developed scales for the subsequent cross-sectional survey involving all physicians. Principal components analysis was performed to derive the latent factor structure that was later applied in multivariable analyses.

Results

Physicians expressed confidence in the credibility of CDSS recommendations. Junior physicians accepted CDSS recommendations most of the time, while senior physicians acknowledged overriding recommendations in complex patients with multiple infections or allergies. Willingness to consult CDSS for common and complex infections (OR 1.68; 95%CI 1.16–2.44) and preference for personal or team decision (OR 0.61; 95%CI 0.43–0.85) were associated with acceptance of

CDSS recommendations. Cronbach's alpha for scales measuring physicians' attitudes and perceptions toward acceptance of CDSS recommendations ranged from 0.64 to 0.88.

Conclusion

Physicians' willingness to consult an antibiotic CDSS determined the acceptance of its recommendations. Physicians would choose to exercise their own or clinical team's decision over the CDSS recommendations in complex patient situations when the antibiotic prescribing needs were not met.

4.2 INTRODUCTION

The rapid emergence and unimpeded increase in antibiotic resistance has raised serious concerns about the public health threat of a post-antibiotic era (4). Antibiotic prescribing is regarded as the key driver of antibiotic resistance (8,67,68), and prescriber involvement in antibiotic stewardship efforts is paramount (69).

Attempts have been made to understand physician and patient factors influencing antibiotic prescribing. Physician attitudes such as fear of future complications and of losing the patient, and patient-related factors including the patient's clinical status and antibiotic allergies were identified as major factors associated with inappropriate antibiotic prescribing (70,71). In the limited studies on physicians working in adult acute-care hospitals, specific barriers to optimal antibiotic prescribing included the lack of confidence in antibiotic guidelines, inertia of current practice, and the lack of independence in decision making (30,72).

Clinical decision support systems have been developed to improve clinical practice, but one-third

have not managed to succeed (45,73). Features of such systems deemed critical for improving clinical practice included decision support provided automatically within the clinical workflow, given at the time and location of decision making, and that is computer-generated (73). Antibiotic computerized decision support systems (CDSSs) incorporating these critical features have been developed to facilitate optimal antibiotic prescribing (9,16,23,35,44). Antibiotic CDSSs are particularly useful for antibiotic selection for empiric therapy, as optimal selection is complex when the causative pathogen is as yet unknown and it is when the greatest discordance with recommended antibiotic guidelines occurs (29,74).

Although such systems were developed with active feedback from physicians (51), less than half of antibiotic CDSS recommendations were accepted (44). Physicians' negative perceptions of clinical decision support systems can affect their use (75). To date, there is no validated scale available for measuring physicians' perceptions of CDSS (76,77). Some studies have attempted to understand the relationship between physicians' perceptions and the adoption of antibiotic CDSS (77). However, the psychosocial determinants for physicians' acceptance of antibiotic recommendations by antibiotic CDSS have remained poorly understood. Qualitative methods have been increasingly recognized as an important complement to quantitative methods for gaining better insights into clinical practices and behaviors, and are becoming more widely accepted in medical research (71,78,79).

We, therefore, sought to evaluate physicians' perceptions and attitudes toward a tertiary hospital's antibiotic CDSS, Antimicrobial Resistance Utilization and Surveillance Control (ARUSC) (65), and to determine the psychosocial factors associated with physicians' acceptance of antibiotic recommendations for empiric therapy by the system, using a mixed methods study design.

4.3 METHODS

A mixed methods design was employed, with a qualitative phase followed by a dominant quantitative phase. Themes derived from the qualitative study were used to inform the quantitative survey.

Study setting

Both studies were conducted in Tan Tock Seng Hospital Singapore, a 1500-bed adult tertiary-care center. In 2009, the hospital launched its in-house ARUSC, which integrates antibiotic stewardship with its computerized physician order entry system and provides patient-specific evidence-based antibiotic recommendations at the point of prescribing (Appendix I) (65). Inputs from all clinical departments were considered in ARUSC's development. However, acceptance of ARUSC's antibiotic recommendations has remained at 67% [unpublished data].

Qualitative Study

Focus groups

We conducted two focus group discussions (FGDs), separately with junior and senior physicians purposively sampled from all clinical specialties in February 2013. FGDs were facilitated by a junior attending physician who was respected by junior physicians and well regarded by senior physicians, but not directly involved with the hospital's antimicrobial stewardship program.

The discussions used the same set of semi-structured questions, and were audio-recorded and transcribed verbatim. We referred to participants by study numbers (S1-6 and J1-5), and strict confidentiality of their identities was maintained.

Quantitative Study

Study population

We then conducted a cross-sectional questionnaire survey, from April 1 through April 26, 2013. All physicians involved with inpatient care were included in the study.

Survey questionnaire

A survey instrument was developed, which comprised 20 questions on the situations for use, the perceived credibility and usefulness, and the desired useful features of ARUSC for empiric antibiotic therapy. A five-point Likert scale ranging from 1 ("Strongly disagree") to 5 ("Strongly agree") was used for each response. In addition, the survey instrument included a Yes/No question on the physician's preference for obtaining ARUSC's recommendations via a mobile application and an item requesting the physician to rank from 1 ("Most preferred") to 6 ("Least preferred") on the likelihood of acceptance of recommendations from six information sources including ARUSC and consultation with an infectious disease physician. Information on the physician's designation, clinical specialty, and length of practice in the clinical department and hospital respectively were collected.

The initial survey instrument was enhanced to incorporate two questions on the use of ARUSC for renal dose adjustment and when on-call, as these were sub-themes that emerged strongly

from FGDs. The improved questionnaire was piloted on ten junior and five senior physicians, who provided useful feedback on the construct of three questions. These were revised for the final questionnaire (Appendix II).

Conduct of survey

Physicians were informed of the study via email, one week prior to the study. Survey questionnaire were distributed to all physicians via their departments. Additionally, physicians were individually approached in the inpatient wards and invited to participate. The questionnaire did not contain any identifiers and could not be traced to the participating physician.

Ethical approval for both studies was obtained from the Domain Specific Research Board, National Healthcare Group, and UCLA Institutional Review Board.

Data analysis

Qualitative analysis

We analyzed data from the FGDs using the framework approach (80). We categorized emerging themes according to the perceived facilitators and barriers associated with the acceptance of ARUSC antibiotic recommendations.

Quantitative analysis

Means (standard deviations) and medians (lower and upper quartiles) were computed for each question, and compared between junior and senior physicians and between medical and surgical

specialties. Student's t-test was used to compare the differences in means between groups. The acceptance of recommendations from ARUSC and consultation with an infectious disease physician was defined as having a ranking of 1 to 3 respectively, for the most preferred information source. Odds ratios (OR) and 95% confidence intervals (CI) were derived from the univariate analysis of the association between the 20 question items and the acceptance of ARUSC's recommendations and preference for obtaining ARUSC recommendations via a mobile application respectively. We performed principal components analysis with varimax rotation to derive the latent factor structure that was later applied in the multivariable analyses. Reliability of the survey scales was measured using Cronbach's alpha co-efficient. All statistical analyses were conducted in SAS version 9.3 (SAS Institute Inc., Cary, NC).

4.4 RESULTS

Qualitative Analysis

Eleven physicians (6 senior and 5 junior) participated in the FGDs. The majority held positive views for ARUSC, with junior physicians using ARUSC more than seniors. All 5 junior physicians unanimously agreed that ARUSC was their most preferred source of antibiotic recommendations, and that they would like ARUSC on a mobile application. In contrast, senior physicians preferred recommendations from infectious disease physicians to those from ARUSC, as they felt that ARUSC could not fully account for the patient's clinical condition (Table 4.1).

Willingness to accept ARUSC's recommendations

Junior physicians accepted ARUSC's recommendations most of the time, while senior physicians were willing to accept its recommendations if source of infection in the patient was unknown [S1].

Trust in ARUSC's recommendations

Junior physicians trusted the credibility of ARUSC's recommendations, and would use them as "confidence booster" and to "cross-reference" their antibiotic choices [J3, J5]. Senior physicians would often advise their juniors to refer to ARUSC when in doubt [S2, S5].

Usefulness of ARUSC's recommendations

Junior physicians found ARUSC to be particularly useful when on-call [J3, J5]. Colleagues from other hospitals have also requested for hard copies of ARUSC recommendations that were unique to the hospital. Both junior and senior physicians found ARUSC recommendations for renal dose adjustments to be useful [J5, S1, S3]. Although senior physicians (who were more experienced with antibiotic prescribing) were less likely to appreciate ARUSC recommendations for common infections, they found ARUSC useful for patients with unknown or unfamiliar infection sources [S1, S3, S4].

Personal or team preference

Junior physicians were inclined to accept ARUSC recommendations most of the time, but had to override its recommendations when senior colleagues decided on a different antibiotic [J2-3]. Senior physicians acknowledged that they tended to have personal preferences for antibiotics and that they would "ignore" ARUSC recommendations in situations when they needed to be "aggressive" with therapy based on their prior experiences with similar patients [S3-4].

Patient factors

Both junior and senior physicians felt that ARUSC recommendations were inadequate in addressing the antibiotic needs of patients with multiple infections and allergies [J3-5, S2, S5].

Quantitative Analysis

A total of 265 physicians participated in the study. Fifty-seven percent were junior physicians, and 82% were from medical specialties. Participants were representative of the physician population and ARUSC users in the hospital (Table 4.2). About 30% preferred to accept antibiotic recommendations from ARUSC. Slightly more junior (75%) than senior physicians (70%) liked ARUSC's recommendations on a mobile application.

Using the scree method, we determined the number of factors to be included in the principal components analysis to be five (Figure 4.1). Principal components analysis revealed the following latent factors on the perceptions and attitudes toward ARUSC recommendations: i) willingness to accept ARUSC recommendations, ii) personal or team decision over ARUSC recommendations, iii) desired useful features for ARUSC, iv) perceived useful features of ARUSC, and v) perceived useful situations for ARUSC recommendations. The five factors accounted for 63% of the total variance (Table 4.3). Junior physicians were more likely than senior physicians to consult ARUSC before prescribing antibiotics for patients with complex infections (P=0.0030), and to follow their team's clinical discretion, even if it required them to override ARUSC's recommendations for both patients with common (P=0.0008) and complex infections (P=0.0114) (Table 4.4). Junior physicians were more likely to find ARUSC's recommendations useful when on-call (P=0.0004)

and for renal dose adjustment (P=0.0005). Psychosocial factors were not different between surgical and medical specialties (Table 4.5).

Reliability of scales

All the scales demonstrated construct validity and good reliability, with Cronbach's alpha coefficient ranging from 0.64 to 0.88. The scale on willingness to accept ARUSC recommendations had the highest reliability (Cronbach's alpha 0.88). Scales on the perceived useful features (Cronbach's alpha 0.75) and desired features of ARUSC (Cronbach's alpha 0.72), and the perceived useful situations for ARUSC recommendations (Cronbach's alpha 0.72) also had good reliability. Cronbach's alpha of the scale on preference for personal or team decision over ARUSC's recommendations was 0.64.

Acceptance of ARUSC recommendations

After accounting for seniority and clinical specialty, the physician's willingness to consult ARUSC for common and complex infections was positively associated with acceptance of ARUSC's recommendation (OR 1.68; 95%CI 1.16–2.44). Physicians who preferred personal or team decision were 40% less likely to accept ARUSC's recommendations (OR 0.61; 95%CI 0.43–0.85) (Table 4.6).

Preference for ARUSC recommendations via mobile application

After adjusting for seniority and clinical specialty, the physician's willingness to consult ARUSC for common and complex infections (OR 1.44; 95%CI 1.02–2.02), expression of desired features

for ARUSC (OR 1.63; 95%CI 1.15–2.31), acknowledgement of useful features of ARUSC (OR 1.86; 95%CI 1.32–2.64), and perceived usefulness of ARUSC in various situations (OR 1.77; 95%CI 1.24–2.51) were factors positively associated with the physician's preference for obtaining ARUSC's recommendations via a mobile application (Table 4.7).

Sensitivity analyses

Sensitivity analyses carried out replacing seniority as classified by the physician's designation with the length of practice in the clinical department and hospital respectively in the multiple logistic regression models produced the same conclusions. On evaluation of factors associated with physicians' preference for antibiotic recommendations from infectious disease physicians, multivariable analysis revealed that the preference for personal or team decision was positively associated (OR 1.69; 95%CI 1.11–2.55) and the willingness to consult ARUSC for antibiotic recommendations negatively associated (OR 0.63; 95% CI 0.39–1.00) with the preference for such recommendations. Furthermore, correlational analysis of the five derived scales for empiric therapy showed that they were highly correlated with the corresponding items for definitive therapy in the questionnaire.

Table 4.1. Themes arising from Focus Group Discussions with Junior and Senior Physicians

Themes	Examples of relevant abstracts from Junior Physicians	Examples of relevant abstracts from Senior Physicians
Facilitators for accepting ARUSC recommendations		
1. Willingness to accept ARUSC recommendations	"All the time (for antibiotic dosage for renal impairment)" [J1]	".. If we don't really have a source, or we just want the best antibiotic to start with" [S1]
	"I actually use it quite often. One, when I'm not sure what antibiotic I should use, especially for empirical.." [J5]	"Personally, I try not to override ARUSC's recommendations… unless there's some justification for it" [S3]
2. Trust in ARUSC recommendations	"When we write our plans, we'd say 'suggested by ARUSC' "[J3]	"..it's (ARUSC) quite reliable.." [S2]
	"...you can back it up if the next day the next team asks you why it's like that, then you say "ARUSC recommended", so in that way, you're covered." [J5]	"… your (antibiotic) selection may not be superior to ARUSC..It's probably better to use ARUSC" [S3]
	"use it as a guide to boost your confidence when prescribing an antibiotic" [J3]	"I think as long as they (junior physicians) know that ARUSC is there as an option for guidance, there is some reassurance (when on-call at night)" [S5]

Table 4.1. (Continued)

Themes	Examples of relevant abstracts from Junior Physicians	Examples of relevant abstracts from Senior Physicians
	"I already know what I want to use but I want to cross-reference to see what they recommend, and when it's different, I'll think about why it's different" [J5]	".. Sometimes when we've lost touch for a while, we don't know what's the latest, then I'll probably refer (to ARUSC)" [S5]
	"...it's just very accurate (for renal dosing)" [J3]	"….I ask my MOs (medical officers) and HOs (house officers) to use it (ARUSC). To start off on the correct antibiotic, because by the next morning it's already on antibiotics and I want it to be the right antibiotics." [S2]
3. Usefulness of ARUSC recommendations	"I use quite often because at night when you really don't know what's going on…" [J3]	"Most of the time, I find that the problem is the overnight, that's why I ask my MOs (medical officers) and HOs (house officers) to use it (ARUSC)." [S2]
	"It's good when it's at night and you don't feel like thinking…" [J5]	"I don't really use it that often, because I find the information is the same. I tend to encourage my junior staff to use it" [S2]
	"There are friends outside (this hospital)…they say that ARUSC is just so good. In the far West, they don't have this system and they actually ask us 'Can you email me the guidelines?' " [J3]	".. Our organisms are almost always skin organism…the day-to-day impact (of ARUSC) is less because it's just the common antibiotics that we use" [S4]

Table 4.1. (Continued)

Themes	Examples of relevant abstracts from Junior Physicians	Examples of relevant abstracts from Senior Physicians
	"Renal dosing is very good" [J5]	"I would use the renal dose adjustment" [S1]
	"We use it for empirical (therapy)" [J1]	".. If we don't really have a source, or we just want the best antibiotic to start with" [S1]
	"I want to know what organisms I should be thinking about when I'm treating community-acquired UTI, rather than 'Bactrim' " [J3]	"I think if the infection is somewhere you're not very familiar with, then ARUSC is useful" [S3]
Barriers to accepting ARUSC recommendations		
1. Personal or team preference	"Sometimes they (senior physicians) want to give pip-tazo, regardless of whatever ARUSC recommends." [J2]	"Patients we know who have had an infection before, or patients that we know are at very high risk of getting an MRSA or a bad joint infection…we tend to be very aggressive (in antibiotic therapy). That's when we would possibly ignore the recommendations..." [S4]
	"Sometimes it's the consultant's decision and we have to fill up all these (reasons for overriding ARUSC's recommendations)." [J3]	"I think part of the challenge is that we all have our personal preferences" [S3]

Table 4.1. (Continued)

Themes	Examples of relevant abstracts from Junior Physicians	Examples of relevant abstracts from Senior Physicians
	".. The consultants make the decision. I don't think they would wait for you to check ARUSC" [J2]	"I think ARUSC's antibiotic recommendations is too limited" [S3]
2. Patient factors	"… the patient may have more than one infection… we can only key-in one option" [J2]	"When there are a few infections, when you think that they had recent admission or prior admission when they had certain microorganism in their cultures, then it's very hard to use ARUSC…. ARUSC doesn't account for these" [S2]
	"… when patients come from nursing home.. and are already on particular antibiotics, and that antibiotic does not agitate the patient.." [J4]	"ARUSC just doesn't take into account enough of the patient's (medical) history… and patients that don't follow the clinical course (improvement) given that antibiotic recommended"[S2]
	"… when cases are complex, differs from the norm…" [J5]	" …whether or not you want to stop or step-down the antibiotics depends on the patient's clinical situation" [S1]
	"… you may have a patient with allergies, you're stuck…" [J3]	"The only problem is that if patient is allergic to penicillin, they (ARUSC) don't have any other recommendation" [S5]

Table 4.2. Characteristics of Respondents to the Physician Questionnaire Survey and Outcome variables

Characteristics	Junior physician (n=150)		Senior physician (n=115)		All (n=265)	
	N	**%**	**N**	**%**	**N**	%
Clinical specialty						
All Medical specialties	*111*	*74.00*	*106*	*92.17*	*217*	*81.89*
Anesthesia	4	2.67	8	6.96	12	4.53
Cardiology	4	2.67	7	6.09	11	4.15
Endocrinology	2	1.33	9	7.83	11	4.15
Gastroenterology and Hepatology	1	0.67	5	4.35	6	2.26
General Medicine	43	28.67	15	13.04	58	21.89
Geriatric Medicine	13	8.67	8	6.96	21	7.93
Hematology	1	0.67	8	6.96	9	3.40
Infectious Disease	4	2.67	4	3.48	8	3.02
Neurology	12	8.00	9	7.83	21	7.92
Palliative Medicine	5	3.21	6	5.13	11	4.03
Psychological Medicine	1	0.67	0	0.00	1	0.38
Renal Medicine	8	5.33	8	6.96	16	6.04
Respiratory Medicine	13	8.67	13	11.30	26	9.81
Rheumatology, Allergy & Immunology	0	0.00	6	5.22	6	2.26
All Surgical specialties	*39*	*26.00*	*9*	*7.83*	*48*	*18.11*
General Surgery	20	13.33	0	0.00	20	7.55
Neurosurgery	2	1.33	0	0.00	2	0.75
Orthopedic Surgery	9	6.00	0	0.00	9	3.40
Otorhinolaryngology	1	0.67	1	0.87	2	0.75
Urology	7	4.67	8	6.96	15	5.66
Length of practice in clinical department						
<3 months	40	26.67	1	0.87	41	15.47
3-6 months	60	40.00	6	5.22	66	24.91
6-12 months	27	18.00	11	9.57	38	14.34
1-5 years	23	15.33	58	50.43	81	30.57
>5 years	0	0.00	39	33.91	39	14.72

Table 4.2. (Continued)

Characteristics	Junior physician (n=150)		Senior physician (n=115)		All (n=265)	
	N	%	N	%	N	%
Length of practice in hospital						
<3 months	15	10.00	0	0.00	15	5.66
3-6 months	34	22.67	5	4.35	39	14.72
6-12 months	47	31.33	4	3.48	51	19.25
1-5 years	54	36.00	51	44.35	105	39.62
>5 years	0	0.00	55	47.83	55	20.75
Outcomes						
Prefer to accept ARUSC recommendation	44	30.14	35	31.25	79	30.62
Prefer to accept infectious disease physician's recommendation	120	82.19	96	85.71	216	83.72
Would like ARUSC recommendation via mobile application	113	75.33	78	70.27	191	73.18

Table 4.3. Rotated Factor Analysis of Response Variables from Survey Questionnaire

	Factor Loadings					Communality	Specificity
Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	h_i^2	u_i^2
1. Will consult ARUSC before prescribing (Common infections)	0.509	0.007	-0.059	0.377	0.287	0.487	0.513
2. ARUSC is useful for de-escalation (Common infections)	0.776	0.026	0.009	0.207	0.157	0.670	0.330
3. ARUSC is useful for IV-to-Oral conversion (Common infections)	0.809	0.034	0.027	0.184	0.061	0.693	0.307
4. Will exercise own clinical discretion when accepting ARUSC recommendation (Common infections)	0.101	0.728	0.064	0.258	-0.068	0.616	0.384
5. Will follow team clinical discretion when accepting ARUSC recommendation (Common infections)	0.007	0.768	-0.037	-0.213	0.106	0.647	0.353
6. Will consult ARUSC before prescribing (Complex infections)	0.662	0.106	0.147	0.032	0.263	0.542	0.458
7. ARUSC is useful for de-escalation (Complex infections)	0.867	0.116	0.195	0.102	0.030	0.815	0.185
8. ARUSC is useful for IV-to-Oral conversion (Complex	0.869	0.094	0.185	0.100	0.001	0.809	0.191
9. Will exercise own clinical discretion when accepting ARUSC recommendation (Complex infections)	0.188	0.725	0.139	0.217	-0.164	0.653	0.347
10. Will follow team clinical discretion when accepting ARUSC recommendation (Complex infections)	0.011	0.815	0.036	-0.060	0.091	0.678	0.322
11. Finds ARUSC useful for the microbiology results	0.153	0.132	0.033	0.848	0.201	0.801	0.199
12. Finds ARUSC useful for the current laboratory parameters	0.311	-0.050	0.217	0.717	0.093	0.669	0.331
13. Finds ARUSC useful for the drug allergies	0.307	0.066	0.396	0.423	-0.173	0.464	0.536
14. Would like ARUSC to include current clinical status	0.057	-0.047	0.748	0.019	0.156	0.590	0.410
15. Would like ARUSC to include previous admissions' microbiology results	0.017	0.100	0.689	0.301	0.062	0.579	0.421
16. Would like ARUSC to include past medical history	0.243	0.048	0.755	-0.019	0.131	0.648	0.352
17. Would like ARUSC to include rationale for recommendation	0.046	0.311	0.469	0.054	0.394	0.477	0.523
18. Refers to ARUSC often when on-call	0.259	-0.051	0.218	0.003	0.696	0.602	0.398
19. Refers to ARUSC for educational information	0.454	0.011	0.097	0.393	0.318	0.471	0.529
20. Refers to ARUSC for renal dose adjustment	0.167	0.005	0.160	0.336	0.720	0.685	0.315
Variance explained	4.088	2.483	2.235	2.176	1.615	$\sum h_i^2$= 12.596	$\sum u_i^2$= 7.404
Percentage	20.4	12.4	11.2	10.9	8.1	63.0	37.0

Table 4.4. Factors associated with ARUSC Use, Junior and Senior Physicians

	Junior physician					Senior physician					t-test
Latent Psychosocial Factors	**Mean**	**SD**	**Median**	**LQ**	**UQ**	**Mean**	**SD**	**Median**	**LQ**	**UQ**	***P* Value**
Willingness to consult ARUSC for common and complex infections											
Will consult ARUSC before prescribing (Common infections)	3.65	1.03	4	3	4	3.43	1.14	4	2.5	4	0.1100
ARUSC is useful for de-escalation (Common infections)	3.64	0.92	4	3	4	3.50	1.00	4	3	4	0.2544
ARUSC is useful for IV-to-Oral conversion (Common infections)	3.38	0.98	4	3	4	3.32	0.98	3	3	4	0.6186
Will consult ARUSC before prescribing (Complex infections)	4.26	0.87	4	4	5	3.90	1.04	4	4	5	**0.0030**
ARUSC is useful for de-escalation (Complex infections)	3.88	0.89	4	3.5	4	3.67	1.09	4	3	4	0.0959
ARUSC is useful for IV-to-Oral conversion (Complex infections)	3.63	0.94	4	3	4	3.59	1.03	4	3	4	0.7622
Composite Index 1 (Sum of all component variables)	22.42	4.35	23	20	25	21.36	5.13	22	18	24	0.0800
Factor Score 1	0.05	0.99	0.19	-0.50	0.68	-0.08	1.02	0.16	-0.75	0.62	0.3310
Personal or team decision over ARUSC recommendations											
Will exercise own clinical discretion when accepting ARUSC recommendation (Common infections)	4.31	0.59	4	4	5	4.33	0.61	4	4	5	0.8199
Will follow team clinical discretion when accepting ARUSC recommendation (Common infections)	4.43	0.57	4	4	5	4.13	0.76	4	4	5	**0.0008**
Will exercise own clinical discretion when accepting ARUSC recommendation (Complex infections)	4.34	0.64	4	4	5	4.34	0.62	4	4	5	0.9928

Table 4.4. (Continued)

Latent Psychosocial Factors	Junior physician					Senior physician					t-test *P* Value
	Mean	SD	Median	LQ	UQ	Mean	SD	Median	LQ	UQ	
Will follow team clinical discretion when accepting ARUSC recommendation (Complex infections)	4.38	0.66	4	4	5	4.15	0.75	4	4	5	**0.0114**
Composite Index 2 (Sum of all component variables)	17.49	1.74	18	16	19	16.97	2.14	16	16	19	**0.0405**
Factor Score 2	0.06	0.93	0.12	-0.68	0.79	-0.09	1.10	-0.44	-0.76	1.12	0.2685
Desired useful features for ARUSC											
Would like ARUSC to include current clinical status	3.86	0.85	4	4	4	3.89	0.95	4	3	5	0.8434
Would like ARUSC to include previous admission's microbiology results	4.19	0.72	4	4	5	4.14	0.76	4	4	5	0.6028
Would like ARUSC to include past medical history	3.70	0.92	4	3	4	3.77	0.93	4	3	4	0.5712
Would like ARUSC to include rationale for recommendation	4.42	0.58	4	4	5	4.37	0.69	4	4	5	0.5667
Composite Index 3 (Sum of all component variables)	16.17	2.23	16	15	17	16.15	2.56	16	15	18	0.9475
Factor Score 3	-0.08	1.02	-0.07	-0.56	0.54	0.12	0.97	0.00	-0.49	0.92	0.1356
Perceived useful features of ARUSC											
Finds ARUSC useful for the microbiology results	4.19	0.69	4	4	5	4.18	0.66	4	4	5	0.8466
Finds ARUSC useful for the current laboratory parameters	3.90	0.84	4	3	4	3.81	0.91	4	3	4	0.4302
Finds ARUSC useful for the drug allergies	4.13	0.89	4	4	5	4.10	0.92	4	4	5	0.7375
Composite Index 4 (Sum of all component variables)	12.23	1.95	12	12	13	12.09	2.03	12	11	13	0.5733
Factor Score 4	-0.01	0.99	-0.04	-0.44	0.81	0.02	1.02	0.00	-0.45	0.68	0.8480

Table 4.4. (Continued)

	Junior physician					Senior physician					t-test
Latent Psychosocial Factors	**Mean**	**SD**	**Median**	**LQ**	**UQ**	**Mean**	**SD**	**Median**	**LQ**	**UQ**	***P* Value**
Perceived useful situations for ARUSC recommendations											
Refers to ARUSC often when on-call	3.87	1.02	4	3	5	3.39	1.08	3	3	4	**0.0004**
Refers to ARUSC for educational information	3.82	0.88	4	3	4	3.80	0.87	4	3	4	0.8415
Refers to ARUSC for renal dose adjustment	4.34	0.80	4	4	5	3.90	1.09	4	3.5	5	**0.0005**
Composite Index 5 (Sum of all component variables)	12.02	2.08	12	11	13	11.18	2.26	11	10	12	**0.0032**
Factor Score 5	0.22	0.91	0.24	-0.28	0.82	-0.32	1.05	-0.18	-0.79	0.35	**<.0001**

Abbreviations: SD, standard deviation; LQ, lower quartile; UQ, upper quartile

Table 4.5. Factors associated with ARUSC Use, Surgical and Medical Specialties

	Surgical specialty					Medical specialty					t-test
Latent Psychosocial Factors	**Mean**	**SD**	**Median**	**LQ**	**UQ**	**Mean**	**SD**	**Median**	**LQ**	**UQ**	***P* Value**
Willingness to consult ARUSC for common and complex infections											
Will consult ARUSC before prescribing (Common infections)	3.65	1.00	4	3	4	3.53	1.11	4	3	4	0.5086
ARUSC is useful for de-escalation (Common infections)	3.70	0.98	4	3	4	3.56	0.95	4	3	4	0.3467
ARUSC is useful for IV-to-Oral conversion (Common infections)	3.38	1.14	3	2.5	4	3.35	0.94	4	3	4	0.8852
Will consult ARUSC before prescribing (Complex infections)	4.27	1.07	5	4	5	4.07	0.93	4	4	5	0.1838
ARUSC is useful for de-escalation (Complex infections)	3.98	0.98	4	3.5	5	3.74	0.98	4	3	4	0.1351
ARUSC is useful for IV-to-Oral conversion (Complex infections)	3.79	1.05	4	3	5	3.57	0.96	4	3	4	0.1609
Composite Index 1 (Sum of all component variables)	22.64	4.80	23	21	25	21.81	4.70	22	19	24	0.2806
Factor Score 1	0.07	1.10	0.14	-0.36	0.74	-0.02	0.98	0.20	-0.72	0.64	0.6329
Personal or team decision over ARUSC recommendations											
Will exercise own clinical discretion when accepting ARUSC recommendation (Common infections)	4.35	0.67	4	4	5	4.31	0.58	4	4	5	0.6675
Will follow team clinical discretion when accepting ARUSC recommendation (Common infections)	4.38	0.76	4.5	4	5	4.28	0.65	4	4	5	0.3984
Will exercise own clinical discretion when accepting ARUSC recommendation (Complex infections)	4.44	0.62	4.5	4	5	4.32	0.64	4	4	5	0.2374

Table 4.5. (Continued)

Latent Psychosocial Factors	Surgical specialty					Medical specialty					t-test *P* Value
	Mean	SD	Median	LQ	UQ	Mean	SD	Median	LQ	UQ	
Will follow team clinical discretion when accepting ARUSC recommendation (Complex infections)	4.29	0.82	4	4	5	4.28	0.68	4	4	5	0.9102
Composite Index 2 (Sum of all component variables)	17.46	2.25	18	16	20	17.23	1.85	17	16	19	0.4694
Factor Score 2	0.03	1.18	0.16	-0.77	1.00	-0.01	0.96	-0.21	-0.72	0.77	0.8065
Desired useful features for ARUSC											
Would like ARUSC to include current clinical status	3.94	0.93	4	4	5	3.86	0.89	4	4	4	0.5916
Would like ARUSC to include previous admission's microbiology results	4.33	0.69	4	4	5	4.13	0.74	4	4	5	0.0815
Would like ARUSC to include past medical history	3.83	0.84	4	3	4	3.71	0.94	4	3	4	0.4265
Would like ARUSC to include rationale for recommendation	4.42	0.61	4	4	5	4.40	0.64	4	4	5	0.8405
Composite Index 3 (Sum of all component variables)	16.49	2.39	16	15	18	16.09	2.37	16	15	17	0.2971
Factor Score 3	0.17	0.94	0.00	-0.33	0.72	-0.04	1.01	-0.06	-0.62	0.62	0.2106
Perceived useful features of ARUSC											
Finds ARUSC useful for the microbiology results	4.35	0.64	4	4	5	4.15	0.68	4	4	5	0.0571
Finds ARUSC useful for the current laboratory parameters	4.06	0.76	4	4	5	3.82	0.89	4	3	4	0.0796
Finds ARUSC useful for the drug allergies	4.26	0.82	4	4	5	4.09	0.92	4	4	5	0.2500
Composite Index 4 (Sum of all component variables)	12.68	1.82	12	12	15	12.06	2.00	12	11	13	0.0501
Factor Score 4	0.14	0.88	0.21	-0.38	0.81	-0.03	1.03	-0.05	-0.47	0.74	0.3316

Table 4.5. (Continued)

Latent Psychosocial Factors	Surgical specialty					Medical specialty					t-test *P* Value
	Mean	SD	Median	LQ	UQ	Mean	SD	Median	LQ	UQ	
Perceived useful situations for ARUSC recommendations											
Refers to ARUSC often when on-call	3.70	1.12	4	3	5	3.66	1.06	4	3	4.5	0.8231
Refers to ARUSC for educational information	3.81	0.89	4	3	4	3.81	0.87	4	3	4	0.9868
Refers to ARUSC for renal dose adjustment	4.30	0.99	5	4	5	4.12	0.95	4	4	5	0.2305
Composite Index 5 (Sum of all component variables)	11.78	2.47	12	11	13	11.65	2.13	12	10	13	0.7172
Factor Score 5	0.00	1.05	0.03	-0.57	0.60	0.00	0.99	0.02	-0.52	0.71	0.9976

Abbreviations: SD, standard deviation; LQ, lower quartile; UQ, upper quartile

Table 4.6. Univariate and Multivariable Analyses of Factors associated with Acceptance of ARUSC Recommendations

	Univariate Analysis	
	Odds Ratio (95% CI)	*P* Value
Clinical Specialty		
Medical (vs Surgical)	1.50 (0.72 - 3.14)	0.2786
Designation		
Senior (vs Junior)	1.05 (0.62 - 1.80)	0.8474
Length of practice in clinical department		
<3 months	0.71 (0.28 - 1.80)	0.4715
3-6 months	0.59 (0.25 - 1.37)	0.2182
6-12 months	1.00 (0.40 - 2.51)	1.0000
1-5 years	0.48 (0.21 - 1.10)	0.0826
>5 years	Ref Ref Ref	Ref
Length of practice in hospital		
<3 months	1.45 (0.45 - 4.73)	0.5369
3-6 months	0.89 (0.36 - 2.20)	0.7948
6-12 months	1.09 (0.48 - 2.47)	0.8394
1-5 years	0.85 (0.41 - 1.74)	0.6505
>5 years	Ref Ref Ref	Ref
Willingness to consult ARUSC for common and complex infections		
Will consult ARUSC before prescribing (Common infections)	**1.45 (1.11 - 1.89)**	**0.0072**
ARUSC is useful for de-escalation (Common infections)	**1.48 (1.08 - 2.02)**	**0.0134**
ARUSC is useful for IV-to-Oral conversion (Common infections)	**1.35 (1.01 - 1.80)**	**0.0415**
Will consult ARUSC before prescribing (Complex infections)	**1.39 (1.02 - 1.90)**	**0.0392**
ARUSC is useful for de-escalation (Complex infections)	**1.39 (1.04 - 1.87)**	**0.0289**
ARUSC is useful for IV-to-Oral conversion (Complex infections)	1.26 (0.95 - 1.68)	0.1055
Factor 1	**1.53 (1.10 - 2.12)**	**0.0118**
Personal or team decision over ARUSC recommendations		
Will exercise own clinical discretion when accepting ARUSC recommendation (Common infections)	0.80 (0.50 - 1.29)	0.3621
Will follow team clinical discretion when accepting ARUSC recommendation (Common infections)	**0.47 (0.31 - 0.72)**	**0.0005**

Table 4.6. (Continued)

	Univariate Analysis	
	Odds Ratio (95% CI)	*P* Value
Will exercise own clinical discretion when accepting ARUSC recommendation (Complex infections)	0.91 (0.58 - 1.42)	0.6782
Will follow team clinical discretion when accepting ARUSC recommendation (Complex infections)	0.70 (0.48 - 1.02)	0.0638
Factor 2	**0.67 (0.50 - 0.91)**	**0.0112**
Desired useful features for ARUSC		
Would like ARUSC to include current clinical status	1.04 (0.77 - 1.40)	0.8129
Would like ARUSC to include previous admissions' microbiology results	1.15 (0.80 - 1.67)	0.4472
Would like ARUSC to include past medical history	1.32 (0.98 - 1.79)	0.0691
Would like ARUSC to include rationale for recommendation	1.02 (0.67 - 1.55)	0.9220
Factor 3	1.18 (0.88 - 1.59)	0.2730
Perceived useful features of ARUSC		
Finds ARUSC useful for the microbiology results	1.28 (0.84 - 1.94)	0.2511
Finds ARUSC useful for the current laboratory parameters	**1.45 (1.04 - 2.03)**	**0.0304**
Finds ARUSC useful for the drug allergies	1.12 (0.82 - 1.54)	0.4740
Factor 4	1.31 (0.95 - 1.80)	0.0979
Perceived useful situations for ARUSC recommendations		
Refers to ARUSC often when on-call	1.15 (0.88 - 1.51)	0.2960
Refers to ARUSC for educational information	1.34 (0.97 - 1.86)	0.0739
Refers to ARUSC for renal dose adjustment	1.15 (0.86 - 1.54)	0.3635
Factor 5	1.04 (0.77 - 1.41)	0.7822
	Multivariable Analysis	
	Odds Ratio (95% CI)	*P* Value
Medical (vs Surgical) specialty	1.67 (0.71 - 3.89)	0.2386
Senior (vs Junior) physician	0.71 (0.36 - 1.41)	0.3248
Willingness to consult ARUSC for common and complex infections	**1.68 (1.16 - 2.44)**	**0.0064**
Personal or team decision over ARUSC recommendations	**0.61 (0.43 - 0.85)**	**0.0040**
Desired useful features for ARUSC	1.25 (0.91 - 1.72)	0.1715
Perceived useful features of ARUSC	1.32 (0.95 - 1.82)	0.1011
Perceived useful situations for ARUSC recommendations	1.04 (0.72 - 1.50)	0.8240

Abbreviations: CI, confidence interval

Table 4.7. Univariate and Multivariable Analyses of Factors associated with Preference for ARUSC on a Mobile Application

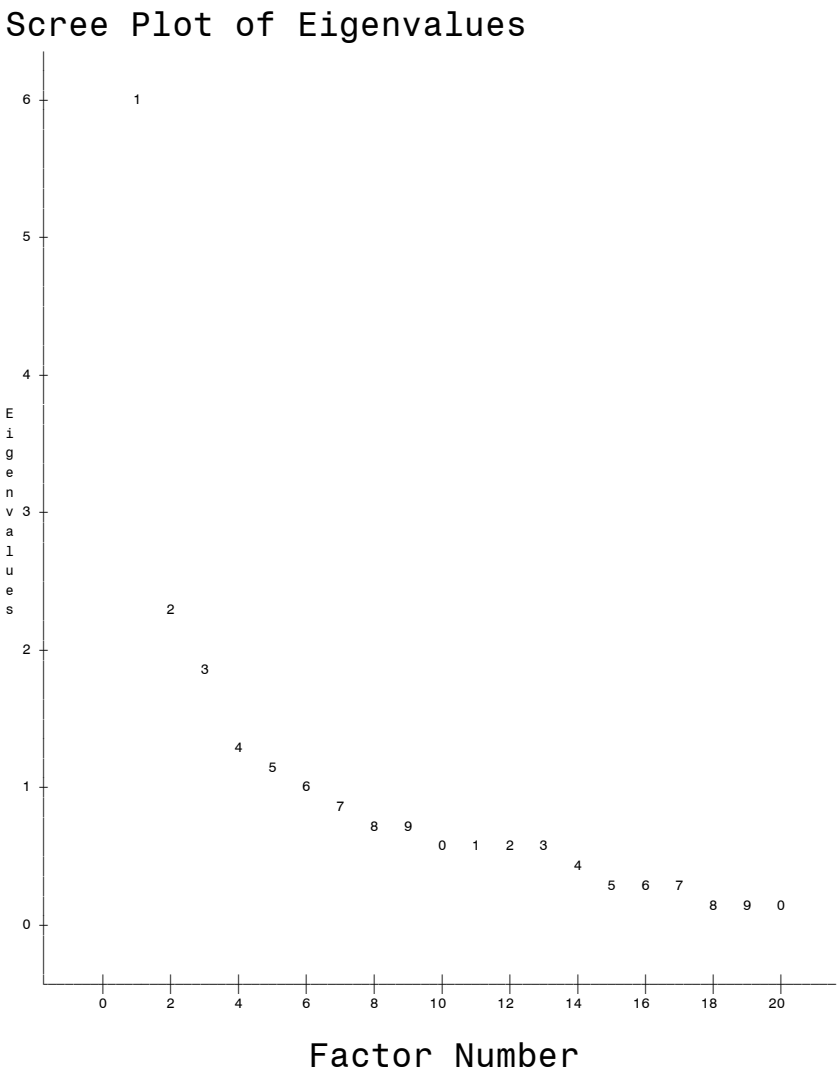
	Univariate Analysis	
	Odds Ratio (95% CI)	*P* Value
Clinical Specialty		
Medical (vs Surgical)	0.67 (0.32 - 1.43)	0.3025
Designation		
Senior (vs Junior)	0.77 (0.45 - 1.34)	0.3619
Length of practice in clinical department		
<3 months	0.64 (0.25 - 1.63)	0.3468
3-6 months	1.51 (0.61 - 3.78)	0.3756
6-12 months	2.11 (0.69 - 6.46)	0.1930
1-5 years	0.99 (0.42 - 2.33)	0.9852
>5 years	Ref Ref Ref	Ref
Length of practice in hospital		
<3 months	1.46 (0.41 - 5.23)	0.5649
3-6 months	1.19 (0.49 - 2.90)	0.6994
6-12 months	**2.85 (1.10 - 7.33)**	**0.0304**
1-5 years	1.44 (0.70 - 2.94)	0.3217
>5 years	Ref Ref Ref	Ref
Willingness to consult ARUSC for common and complex infections		
Will consult ARUSC before prescribing (Common infections)	**1.83 (1.40 - 2.38)**	**<.0001**
ARUSC is useful for de-escalation (Common infections)	**1.62 (1.21 - 2.17)**	**0.0011**
ARUSC is useful for IV-to-Oral conversion (Common infections)	**1.53 (1.15 - 2.04)**	**0.0038**
Will consult ARUSC before prescribing (Complex infections)	**1.53 (1.16 - 2.02)**	**0.0027**
ARUSC is useful for de-escalation (Complex infections)	**1.69 (1.28 - 2.24)**	**0.0003**
ARUSC is useful for IV-to-Oral conversion (Complex infections)	**1.58 (1.19 - 2.11)**	**0.0017**
Factor 1	**1.35 (1.00 - 1.81)**	**0.0482**
Personal or team decision over ARUSC recommendations		
Will exercise own clinical discretion when accepting ARUSC recommendation (Common infections)	1.40 (0.89 - 2.20)	0.1493
Will follow team clinical discretion when accepting ARUSC recommendation (Common infections)	0.69 (0.44 - 1.08)	0.1020
Will exercise own clinical discretion when accepting ARUSC recommendation (Complex infections)	**1.65 (1.07 - 2.54)**	**0.0231**

Table 4.7. (Continued)

	Univariate Analysis	
	Odds Ratio (95% CI)	*P* Value
Will follow team clinical discretion when accepting ARUSC recommendation (Complex infections)	1.00 (0.67 - 1.48)	0.9803
Factor 2	1.02 (0.76 - 1.38)	0.8915
Desired useful features for ARUSC		
Would like ARUSC to include current clinical status	**1.38 (1.03 - 1.87)**	**0.0340**
Would like ARUSC to include previous admission microbiology results	**1.60 (1.10 - 2.31)**	**0.0138**
Would like ARUSC to include past medical history	**1.73 (1.27 - 2.35)**	**0.0004**
Would like ARUSC to include rationale for recommendation	**1.60 (1.04 - 2.44)**	**0.0314**
Factor 3	**1.49 (1.09 - 2.02)**	**0.0121**
Perceived useful features of ARUSC		
Finds ARUSC useful for the microbiology results	**2.60 (1.67 - 4.04)**	**<.0001**
Finds ARUSC useful for the current laboratory parameters	**2.08 (1.49 - 2.88)**	**<.0001**
Finds ARUSC useful for the drug allergies	**1.60 (1.19 - 2.15)**	**0.0017**
Factor 4	**1.73 (1.26 - 2.36)**	**0.0007**
Perceived useful situations for ARUSC's recommendations		
Refers to ARUSC often when on-call	**1.46 (1.11 - 1.91)**	**0.0061**
Refers to ARUSC for educational information	**2.16 (1.55 - 3.01)**	**<.0001**
Refers to ARUSC for renal dose adjustment	**1.88 (1.41 - 2.51)**	**<.0001**
Factor 5	**1.69 (1.24 - 2.31)**	**0.0009**
	Multivariable Analysis	
	Odds Ratio (95% CI)	*P* Value
Medical (vs Surgical) specialty	0.87 (0.34 - 2.20)	0.7676
Senior (vs Junior) physician	0.90 (0.44 - 1.88)	0.7873
Willingness to consult ARUSC for common and complex infections	**1.44 (1.02 - 2.02)**	**0.0369**
Personal or team decision over ARUSC recommendations	1.09 (0.78 - 1.52)	0.6191
Desired useful features for ARUSC	**1.63 (1.15 - 2.31)**	**0.0056**
Perceived useful features of ARUSC	**1.86 (1.32 - 2.64)**	**0.0004**
Perceived useful situations for ARUSC recommendations	**1.77 (1.24 - 2.51)**	**0.0015**

Abbreviations: CI, confidence interval

Figure 4.1. Scree Plot of Eigenvalues and Factor Numbers



4.5 DISCUSSION

This study identified two psychosocial factors that were independently associated with the physicians' acceptance of antibiotic recommendations for empiric therapy by the hospital's antibiotic CDSS. Regardless of seniority and clinical specialty, a physician who was willing to consult ARUSC for common and complex infections was 1.7 times as likely as an unwilling physician to accept an ARUSC antibiotic recommendation. In contrast, a physician preferring personal or team decision over ARUSC was 40% less likely to accept an antibiotic recommendation by ARUSC.

Physicians' willingness to consult ARUSC was indicative of their trust in ARUSC's credibility and hence the increased likelihood of acceptance of its antibiotic recommendations. Junior physicians consulted ARUSC to "use it as a guide to boost your confidence when prescribing an antibiotic", and senior physicians acknowledged that "your (antibiotic) selection may not be superior to ARUSC. It's probably better to use ARUSC". Our findings are consistent with previous qualitative studies which observed that barriers to adherence to antibiotic guidelines included doubt of guidelines' credibility and physicians' negative attitudes toward the guidelines (30,72). While those previous studies have qualitatively identified negative attitudes as barriers to antibiotic guidelines adherence, our study has been able to quantitatively assess the effect of physicians' positive attitudes on acceptance of antibiotic recommendations.

In situations where physicians preferred personal or team decision over ARUSC, the non-acceptance of ARUSC's recommendations was likely to be due to the decision of senior physicians in complex patient situations rather than doubts about the credibility of ARUSC

recommendations. In the FGDs, both senior and junior physicians unanimously expressed great confidence in the reliability of ARUSC.

Although junior physicians interacted much more with ARUSC than senior physicians, antibiotic decisions were often made by senior physicians (49), Junior physicians in the hospital have encountered situations when they did not adhere to ARUSC recommendations, due to their senior colleagues' decision on a different antibiotic.

> "Sometimes it’s the consultant’s decision and we have to fill up all these (reasons for overriding ARUSC's recommendations)."

A recent qualitative study in the United Kingdom identified "prescribing etiquette" as a key determinant of antibiotic prescribing (81). Hospital policies aimed at influencing the antibiotic prescribing behaviors of junior physicians had limited effectiveness because of the social norm of adhering to the "prescribing etiquette" set by one's seniors. Understanding the reasons and context for non-acceptance of antibiotic guidelines by senior physicians was crucial for the enhancement of antibiotic CDSS. In our FGD, senior physicians shared that they had to override ARUSC's recommendations in situations when there was a need for more "aggressive" therapy at the outset, when ARUSC's recommendations were inadequate in addressing the antibiotic needs of patients with multiple infections or antibiotic allergies, and when ARUSC could not take the medical history and clinical course of the patient into consideration. Enhancing ARUSC to address these prescribing needs would be necessary to improve the acceptance of its recommendations.

The majority (73%) of physicians were supportive of obtaining ARUSC recommendations via a mobile application. The strong physician support for a mobile application was indicative of physicians' positive perceptions of ARUSC. We identified four psychosocial factors associated with preference for a mobile application, including the perceived usefulness of ARUSC in various situations. Junior physicians found ARUSC to be particularly useful for antibiotic selection for empiric therapy when they were on-call and did not have ready access to senior colleagues. Similar preferences for availability of guidelines to improve antibiotic prescribing were observed among junior physicians in France and Scotland (82). On the other hand, senior physicians found ARUSC useful in situations when the patient had an unfamiliar or unknown infection source. Increasing ARUSC accessibility via a mobile application would improve antibiotic prescribing. The hospital's information technology infrastructure would have to be reviewed to assure robust network connectivity (83).

Strengths and Limitations

Our study has several strengths. First, it used a balanced study design — a mixed methods study design that triangulated data from qualitative FGDs and a quantitative study — to evaluate physicians' perceptions and attitudes toward a tertiary hospital's antibiotic CDSS. To date, studies on antibiotic prescribing behavior have been either qualitative or quantitative in nature (70,71). Second, it is the first attempt at describing the psychosocial determinants of physicians' acceptance of recommendations by an antibiotic CDSS. Previous studies have reported determinants of physicians' adoption of antibiotic CDSS (77), but not of acceptance of recommendations by such systems. Understanding these factors would help in the design of new systems and the enhancement of existing ones. Third, we developed a new instrument that demonstrated acceptable to very good reliability (Cronbach's alpha ranging from 0.64 to 0.88) for

the measurement of physicians' attitudes and perceptions toward acceptance of CDSS recommendations. To date, there is no such validated scale available. The tools developed and validated in this study would facilitate similar studies in other hospital settings. Furthermore, sensitivity analyses revealed expectedly opposite findings on factors associated with physicians' preference for antibiotic recommendations from infectious disease physicians, demonstrating internal consistency of our findings.

Our study may have been limited by the small number of physicians who were included in the FGDs. Nonetheless, participants were purposively sampled to provide the required contextual information. As discussions were conducted in a non-confrontational setting, with physicians' identities kept strictly confidential, and with junior and senior physicians in separate groups, we believe that the information gathered was authentic. Furthermore, we deliberately selected a junior attending physician who was not directly involved with the hospital's antimicrobial stewardship program, to facilitate both FGDs. The themes that arose from FGDs were also corroborated by results from the quantitative study involving 265 physicians.

Psychosocial factors determining physicians' acceptance of empiric antibiotic recommendations by a computerized decision support system did not differ between junior and senior physicians, or among clinical specialties. Physicians' willingness to consult an antibiotic CDSS determined the acceptance of its recommendations. Physicians would choose to exercise their own or clinical team's decision over the CDSS recommendations in complex patient situations when antibiotic prescribing needs were not met. Further studies are needed to explore these and related issues about physicians' acceptance of recommendations by antibiotic CDSS in other hospital settings.

5. PATIENT AND PHYSICIAN PREDICTORS OF PATIENT RECEIPT OF ANTIBIOTIC COMPUTERIZED DECISION SUPPORT SYSTEM RECOMMENDATIONS

5.1 ABSTRACT

Introduction

Antibiotic computerized decision support systems (CDSS) 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 antibiotic CDSS recommendations.

Methods

We conducted a prospective cohort study in a 1500-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 recommendations.

Results

One-quarter of the 1886 patients received CDSS-recommended antibiotics. More patients treated for pneumonia (33.2%) than sepsis (12.1%) and urinary tract infection (7.1%) received CDSS recommendations. The prescribing physician —but not the attending physician or clinical specialty— accounted for some (13.3%) of the variation. Prior hospitalization (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 recommendations.

Conclusion

We observed that ICU admission and renal impairment were negative predictors of patients' receipt of CDSS recommendations. 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.

5.2 INTRODUCTION

Antibiotic resistance is now regarded as a serious threat to public health (4) and antibiotic use is the key driver (67,68). The intensity of antibiotic use in hospitals is high and utilization has increased substantially over the years (7,9). However, 41-91% of all antibiotics prescribed in hospitals worldwide are considered inappropriate (20). Antimicrobial stewardship programs have been established in many hospitals to facilitate the optimal use of antibiotics (9,23,61,84,85). Furthermore, antibiotic computerized decision support systems (CDSSs) are developed to improve antibiotic decision making through the accessibility of patient-specific clinical data and local antibiotic guidelines, at the point of prescribing (17,42–44,65,77).

Antibiotic CDSSs are particularly useful for antibiotic selection for empiric therapy, as optimal selection is complex when the causative pathogen is unknown (29,74). The appropriate empiric treatment is crucial for the resolution of infection and the reduction of mortality (66). Although such systems have been developed with active feedback from physicians and designed with user-centric features (51), physicians have prescribed CDSS-recommended antibiotics in only 46-67% of medication orders (44).

Antibiotic CDSSs have been shown to improve antibiotic prescribing and patient clinical outcomes including the reduction of mortality (9,17,44,86). Patient and physician characteristics associated with physicians' adherence to recommendations by hospital antimicrobial guidelines have been well explored (29,33,66,87–91). 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 CDSS recommendations and enhance clinical care.

We conducted a prospective cohort study to evaluate the extent to which hospitalized patients received antibiotics as recommended by a tertiary-care hospital's in-house antibiotic CDSS, Antimicrobial Resistance Utilization and Surveillance Control (ARUSC) (Appendix I), and to identify patient and physician factors associated with patients' receipt of antibiotics recommended by ARUSC and targets for improvement.

5.3 METHODS

Study setting and population

The study was conducted in Tan Tock Seng Hospital, a 1500-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 1.5^0N and longitude 104^0E. 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 (65). All medication orders in the hospital are made via the CPOE system. 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 took into account the local epidemiology of infectious diseases, microbiologic resistance patterns, and incorporated evidence-based international guidelines. 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. Inputs from all clinical departments were considered in the development of the guidelines, which were endorsed by the hospital's medical board. 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 narrowest-spectrum antibiotic appropriate for common organisms responsible for the diagnosed infection, based on the local epidemiology and antibiotic susceptibility patterns, taking into account the patient's antibiotic allergies. The prescribing physician can either accept or reject ARUSC's antibiotic recommendations.

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 recommendations 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 (29). 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 (66).

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 hospital.

Outcome variable

Patients' receipt of antibiotics recommended by ARUSC was determined by electronically matching antibiotics prescribed in the institutional CPOE system with those recommended by ARUSC. A patient was classified as having received ARUSC recommendations if the antibiotics matched exactly on the drug prescribed, including dose, route, and frequency of administration.

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 (CNS) disease, and chronic pulmonary disease), illness severity, admission to an intensive care unit (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 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: a diagnosis of diabetes with or without complications. Cardiovascular disease: coronary artery disease or congestive heart failure. Liver disease: liver disease of any severity. Renal disease: moderate to severe renal disease. Neoplasm: solid malignant tumor, leukemia, lymphoma, or any metastasis. CNS disease: cerebrovascular disease, dementia. Chronic pulmonary disease: chronic obstructive pulmonary disease. Charlson's comorbidity index (CCI) (92) was derived from electronic medical records using coding algorithms developed by Quan H *et al* (93). 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 >100mg/l and leukocyte count <4 or >12x10^9/l as proxies for severe infection, and serum creatinine >130µmol/l as proxy for renal impairment (33). 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 as seniors. Data on physicians' designation 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 recommendations. Next, we explored the relationships between the various patients' and physicians' characteristics and receipt of ARUSC recommendations 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 recommendations. 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 (OR) and corresponding 95% confidence intervals (CI) 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 (94). Intraclass correlation coefficients (ICC) were

respectively derived by dividing the variance between prescribing physicians (level 2 variance) by the total variance in model 1, and the variance between attending physicians (level 2 variance) and clinical specialties (level 3 variance) by the total variance in model 2. For the logistic distribution, level 1 variance was estimated to be 3.29 (94). We further estimated risk ratios (RR) using multilevel log-binomial and Poisson regression models, as the outcome was not rare (95). The chi-squared goodness-of-fit test was used to evaluate the adequacy of the models. Akaike information criterion (AIC), 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).

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

5.4 RESULTS

During the one-year study period, a total of 1886 hospitalized patients at Tan Tock Seng Hospital were auto-triggered to receive antibiotic recommendations on ARUSC from a prescription for piperacillin-tazobactam or a carbapenem for empiric therapy. One-quarter (24.9%) of the patients received antibiotics recommended by ARUSC. A higher proportion of patients treated for pneumonia (33.2%) received ARUSC-recommended antibiotics, compared with sepsis (12.1%) and urinary tract infection (7.1%). Patients who received ARUSC recommendations 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 more likely to have a recent hospitalization (45.1% vs. 38.1%) but less likely to have an ICU admission (7.9% vs. 12.8%) than patients who did not receive ARUSC recommendations. The characteristics of prescribing and

attending physicians of the two patient groups appeared similar. However, more patients who received ARUSC recommendations were managed by medical specialties (83.2% vs. 73.0%).

Data on patient demographics, comorbidities, illness severity, diagnosed infection, and clinical outcomes, and prescribing and attending physician characteristics are presented in Table 5.1.

Univariate analysis

Patient factors univariately associated with receipt of ARUSC-recommended antibiotics are similar in both models (Table 5.2). 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 ARUSC antibiotic recommendations (Table 5.2).

The prescribing physician accounted for 16.5% of the variation in patient receipt of ARUSC recommendations ($p<0.001$). 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

recommendations. At the clinical specialty level, patients managed by a medical service were 1.7 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 recommendations were all patient-related (Table 5.3). Although prescribing physicians' preference accounted for 13.3% of the variation in receipt of ARUSC recommendations, physicians' seniority was not found to be an independent factor. There was no difference in ARUSC recommendations receipt 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, time of 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 the patient's receipt of ARUSC recommendations. 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 recommendations (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).

Sensitivity analysis

Our findings were qualitatively unchanged in the multilevel log-binomial and Poisson regression analyses (Tables 5.4 and 5.5). Due to convergence problems with the 3-level log-binomial regression model, only results from the Poisson regression analysis could be assessed. The adjusted risk ratios for factors associated with ARUSC recommendations of the best-fit model (2-level log-binomial model) were as follows: prior hospitalization in the 90 days preceding current admission (RR 1.21, 95% CI 1.03-1.43), pneumonia as the diagnosed infection (RR 4.42, 95% CI 2.33-8.38), ICU admission (OR 0.50, 95% CI 0.32-0.78), renal impairment (OR 0.80, 95% CI 0.66-0.97), and ICU admission by cardiovascular disease (OR 2.46, 95% CI 1.35-4.51).

Table 5.1. Characteristics of 1886 patients and their prescribing and attending physicians, by receipt of antibiotic CDSS recommendations

Characteristics	Receipt of CDSS recommendations		Non-receipt of CDSS recommendations	
Total, N	470		1416	
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)	1083	(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)	1347	(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)	1106	(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)	1009	(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)

Table 5.1. (Continued)

Characteristics	Receipt of CDSS recommendations		Non-receipt of CDSS recommendations	
Hepatobiliary or Intra-abdominal	19	(4.0)	128	(9.0)
Other	9	(1.9)	120	(8.5)
Illness severity, N (%)				
C-reactive protein[b] >100mg/l	168	(39.0)	497	(40.1)
Leukocyte count <4 or >12x10^9/l	232	(49.4)	724	(51.1)
Serum creatinine[c] >130µmol/l	105	(22.4)	401	(28.5)
Intensive care unit admission, N (%)	37	(7.9)	181	(12.8)
Prescribing physician, N (%)				
Senior	48	(10.2)	143	(10.1)
Junior	422	(89.8)	1273	(89.9)
Attending physician, N(%)				
Ethnic Chinese	341	(72.6)	1041	(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 & 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, & 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)

Table 5.1. (Continued)

Characteristics	Receipt of CDSS recommendations		Non-receipt of CDSS recommendations	
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 CDSS recommendations receipt (39/470=8.3%) vs non-receipt (177/1416=12.5%) groups
[c] Missing values in CDSS recommendations receipt (2/470=0.4%) vs non-receipt (8/1416=0.6%) groups

Table 5.2. Univariate analysis of factors associated with receipt of antibiotic CDSS recommendations (Model 1: 2-level logistic regression analysis of data on 1886 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)

Factor	Model 1			Model 2		
	OR	(95% CI)	*P* value	OR	(95% CI)	*P* value
Patient Factors						
Age (years)	**1.01**	**(1.01 - 1.02)**	**0.0011**	**1.01**	**(1.00 - 1.02)**	**0.0103**
Male gender	0.98	(0.78 - 1.24)	0.8869	1.01	(0.82 - 1.26)	0.8998
Ethnicity						
Chinese	1.25	(0.73 - 2.15)	0.4147	1.13	(0.68 - 1.88)	0.6285
Malay	1.07	(0.57 - 2.03)	0.8279	0.99	(0.55 - 1.80)	0.9840
Indian	0.76	(0.37 - 1.54)	0.4437	0.73	(0.38 - 1.42)	0.3523
Other	1.00	.. ..	..	1.00	.. ..	..
Singapore resident	1.36	(0.75 - 2.45)	0.3054	1.24	(0.72 - 2.16)	0.4386
Private ward class	0.73	(0.48 - 1.12)	0.1475	0.75	(0.51 - 1.11)	0.1545
Comorbidity						
Diabetes mellitus	1.13	(0.88 - 1.44)	0.3326	1.07	(0.85 - 1.34)	0.5731
Cardiovascular disease	1.42	(1.06 - 1.91)	0.0174	1.38	(1.05 - 1.82)	0.0218
Liver disease	0.82	(0.44 - 1.54)	0.5434	0.94	(0.52 - 1.68)	0.8352
Renal disease	0.93	(0.81 - 1.08)	0.3323	0.91	(0.79 - 1.04)	0.1524
Neoplasia	0.99	(0.72 - 1.37)	0.9654	1.10	(0.80 - 1.50)	0.5636
CNS disease	0.88	(0.66 - 1.18)	0.3958	0.81	(0.60 - 1.08)	0.1487
Chronic pulmonary disease	1.38	(0.93 - 2.06)	0.1077	**1.48**	**(1.01 - 2.16)**	**0.0431**
Charlson's comorbidity index >5	0.83	(0.59 - 1.19)	0.3129	0.87	(0.63 - 1.21)	0.4140
Prior hospitalization (past 90 days)	**1.28**	**(1.01 - 1.61)**	**0.0411**	**1.29**	**(1.04 - 1.61)**	**0.0202**

Table 5.2. (Continued)

Factor	Model 1 OR	Model 1 (95% CI)	Model 1 *P* value	Model 2 OR	Model 2 (95% CI)	Model 2 *P* value
Prior antibiotics (past 180 days)	1.01	(0.76 - 1.34)	0.9462	1.00	(0.77 - 1.30)	0.9894
Length of stay prior to antibiotics	1.00	(0.99 - 1.00)	0.3155	1.00	(0.99 - 1.00)	0.4064
Day of antibiotic prescription (weekend/public holiday vs. weekday)	0.93	(0.72 - 1.21)	0.6003	0.92	(0.73 - 1.17)	0.5048
Time of antibiotic prescription (Night[a] vs. Day)	**1.34**	**(1.06 - 1.69)**	**0.0161**	**1.28**	**(1.03 - 1.59)**	**0.0255**
Diagnosed Infection						
Pneumonia	**7.20**	**(3.51 - 14.75)**	**<.0001**	**6.28**	**(3.12 - 12.61)**	**<.0001**
Sepsis	1.85	(0.81 - 4.22)	0.1457	1.72	(0.77 - 3.84)	0.1826
Urinary tract infection	1.00	(0.40 - 2.49)	0.9962	0.91	(0.37 - 2.21)	0.8283
Hepatobiliary or Intra-abdominal	2.13	(0.89 - 5.08)	0.0879	2.14	(0.92 - 4.98)	0.0785
Other	1.00	.. ..	..	1.00	.. ..	..
ICU admission	**0.57**	**(0.38 - 0.87)**	**0.0081**	**0.68**	**(0.46 - 1.01)**	**0.0550**
Abnormal C-reactive protein	0.96	(0.75 - 1.23)	0.7282	1.00	(0.95 - 1.06)	0.8752
Abnormal leukocyte count	0.95	(0.75 - 1.19)	0.6306	0.96	(0.78 - 1.19)	0.7390
Renal impairment[b]	**0.69**	**(0.53 - 0.91)**	**0.0076**	**0.68**	**(0.53 - 0.88)**	**0.0035**

Table 5.2. (Continued)

Factor	Model 1 OR	Model 1 (95% CI)	Model 1 *P* value	Model 2 OR	Model 2 (95% CI)	Model 2 *P* value
Prescribing Physician Factor (ICC=16.5%)						
Seniority level (Junior vs. Senior)	0.98	(0.63 - 1.53)	0.9300	-	-	-
Attending Physician Factor (ICC = 0.4%)						
Ethnic Chinese				0.87	(0.57 - 1.33)	0.5223
Ethnic Indian				0.79	(0.56 - 1.42)	0.6230
Other ethnicity	-	-	-	1.00	..	..
Clinical Specialty Factor (ICC = 2.3%)						
Medical vs. Surgical	-	-	-	**1.71**	**(1.19 - 2.46)**	**0.0037**

Abbreviations: CNS, central nervous system; ICC, intraclass correlation coefficient; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

[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

Table 5.3. Multivariable analysis of predictors of receipt of antibiotic CDSS recommendations (Model 1: 2-level logistic regression analysis of data on 1886 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)

Factor	Model 1*			Model 2*		
	Adjusted OR	(95% CI)	*P* value	Adjusted OR	(95% CI)	*P* value
Patient Factors						
Age (years)	1.00	(0.99 - 1.01)	0.6898	1.00	(0.99 - 1.01)	0.9084
Male gender	0.95	(0.74 - 1.22)	0.7139	0.97	(0.77 - 1.22)	0.7829
Ethnicity						
Chinese	0.86	(0.45 - 1.65)	0.6508	0.84	(0.46 - 1.54)	0.5675
Malay	0.92	(0.44 - 1.91)	0.8265	0.91	(0.46 - 1.81)	0.7948
Indian	0.53	(0.24 - 1.18)	0.1192	0.54	(0.26 - 1.13)	0.1044
Other	1.00	.. ..	..	1.00	.. ..	..
Singapore resident	0.77	(0.36 - 1.63)	0.4898	0.79	(0.39 - 1.60)	0.5099
Private ward class	0.71	(0.43 - 1.18)	0.1893	0.72	(0.45 - 1.15)	0.1650
Cardiovascular disease	1.34	(0.96 - 1.87)	0.0900	1.27	(0.93 - 1.74)	0.1319
Charlson's comorbidity index >5	0.81	(0.56 - 1.17)	0.2678	0.80	(0.57 - 1.14)	0.2211
Prior hospitalization (past 90 days)	**1.32**	**(1.01 - 1.71)**	**0.0399**	**1.36**	**(1.07 - 1.74)**	**0.0134**
Prior antibiotics (past 180 days)	0.99	(0.72 - 1.35)	0.9345	0.98	(0.73 - 1.31)	0.8747
Length of stay prior to antibiotics	1.00	(0.99 - 1.00)	0.7512	1.00	(0.99 - 1.00)	0.8726
Time of antibiotic prescription (Night[a] vs. Day)	1.25	(0.98 - 1.60)	0.0777	1.20	(0.96 - 1.51)	0.1136
Diagnosed infection						
Pneumonia	**6.77**	**(3.28 - 13.99)**	**<.0001**	**6.19**	**(3.04 - 12.61)**	**<.0001**
Sepsis	1.85	(0.80 - 4.24)	0.1477	1.74	(0.78 - 3.92)	0.1784

Table 5.3. (Continued)

Factor	Model 1* Adjusted OR	Model 1* (95% CI)	Model 1* *P* value	Model 2* Adjusted OR	Model 2* (95% CI)	Model 2* *P* value
Urinary tract infection	0.93	(0.37 - 2.35)	0.8839	0.91	(0.37 - 2.24)	0.8444
Hepatobiliary or Intra-abdominal	2.01	(0.83 - 4.86)	0.1195	2.02	(0.86 - 4.77)	0.1079
Other	1.00	.. ..	..	1.00	.. ..	..
Renal impairment [b]	**0.70**	**(0.52 - 0.93)**	**0.0166**	**0.70**	**(0.53 - 0.91)**	**0.0090**
ICU admission	**0.38**	**(0.21 - 0.66)**	**0.0007**	**0.44**	**(0.26 - 0.77)**	**0.0040**
ICU admission by Cardiovascular disease	**3.97**	**(1.60 - 9.81)**	**0.0029**	**3.76**	**(1.60 - 8.83)**	**0.0024**
Prescribing Physician Factor (ICC=13.3%)						
Seniority level (Junior vs. Senior)	0.95	(0.60 - 1.49)	0.8105	-	- -	-
Attending Physician Factor (ICC = 0.3%)	-	- -	-			
Clinical Specialty Factor (ICC = 0.7%)						
Medical vs. Surgical	-	- -	-	1.16	(0.78 - 1.73)	0.4595

Abbreviations: ICC, intraclass correlation coefficient; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

[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)

Table 5.4. Multivariable 2-level regression analysis of predictors of receipt of antibiotic CDSS recommendations (Model 1: 2-level log-binomial regression analysis of data on 1886 patients seen by 575 prescribing physicians; Model 2: 2-level Poisson regression analysis of data on 1886 patients seen by 575 prescribing physicians)

	Model 1*			Model 2*		
Factor	**RR**	**(95% CI)**	***P* value**	**RR**	**(95% CI)**	***P* value**
Patient Factors						
Age (years)	1.00	(1.00 - 1.01)	0.5313	1.00	(0.99 - 1.01)	0.6808
Male gender	0.98	(0.83 - 1.15)	0.7721	0.97	(0.81 - 1.18)	0.7843
Ethnicity						
Chinese	0.89	(0.58 - 1.38)	0.6130	0.88	(0.53 - 1.45)	0.6149
Malay	0.96	(0.60 - 1.55)	0.8731	0.94	(0.54 - 1.65)	0.8387
Indian	0.67	(0.39 - 1.14)	0.1355	0.65	(0.35 - 1.20)	0.1686
Other	1.00	.. ..	..	1.00	.. ..	..
Singapore resident	0.86	(0.51 - 1.44)	0.5656	0.84	(0.46 - 1.52)	0.5614
Private ward class	0.77	(0.54 - 1.09)	0.1400	0.78	(0.52 - 1.16)	0.2140
Cardiovascular disease	1.19	(0.97 - 1.45)	0.1007	1.19	(0.93 - 1.52)	0.1722
Charlson's comorbidity index >5	0.85	(0.66 - 1.09)	0.1868	0.83	(0.62 - 1.11)	0.2030
Prior hospitalisation (past 90 days)	**1.21**	**(1.03 - 1.43)**	**0.0237**	**1.24**	**(1.01 - 1.51)**	**0.0364**
Prior antibiotics (past 180 days)	0.96	(0.79 - 1.18)	0.7053	0.98	(0.77 - 1.25)	0.8953
Length of stay prior to antibiotics	0.999	(0.995 - 1.004)	0.7966	1.000	(0.995 - 1.004)	0.8766
Time of antibiotic prescription (Night[a] vs. Day)	1.15	(0.99 - 1.35)	0.0700	1.14	(0.95 - 1.38)	0.1555

Table 5.4. (Continued)

Factor	Model 1* RR	(95% CI)	*P* value	Model 2* RR	(95% CI)	*P* value
Diagnosed infection						
Pneumonia	**4.42**	**(2.33 - 8.38)**	**<.0001**	**4.54**	**(2.33 - 8.87)**	**<.0001**
Sepsis	1.76	(0.85 - 3.64)	0.1255	1.75	(0.82 - 3.75)	0.1501
Urinary tract infection	0.98	(0.43 - 2.22)	0.9534	0.99	(0.42 - 2.32)	0.9759
Hepatobiliary or Intra-abdominal	1.89	(0.88 - 4.03)	0.1010	1.83	(0.82 - 4.09)	0.1409
Other	1.00	.. ..	..	1.00	.. ..	..
Renal impairment[b]	**0.80**	**(0.66 - 0.97)**	**0.0217**	**0.79**	**(0.63 - 0.99)**	**0.0428**
ICU admission	**0.50**	**(0.32 - 0.78)**	**0.0021**	**0.48**	**(0.30 - 0.78)**	**0.0031**
ICU admission by Cardiovascular disease	**2.46**	**(1.35 - 4.51)**	**0.0035**	**2.75**	**(1.37 - 5.50)**	**0.0043**
Prescribing Physician Factor						
Seniority level (Junior vs. Senior)	0.99	(0.75 - 1.32)	0.9542	1.01	(0.75 - 1.37)	0.9395

Abbreviations: ICU, intensive care unit; RR, risk ratio; CI, confidence interval

[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 0.8008; Fit statistics (-2 Log Pseudo-Likelihood 7677.71); Model 2: ROC 0.7007; Fit statistics (-2 Log Pseudo-Likelihood 7839.79)

Table 5.5. Multivariable 3-level regression analysis of predictors of receipt of antibiotic CDSS recommendations (3-level Poisson regression analysis of data on 1886 patients seen by 220 attending physicians in 19 clinical specialties)

	Model*		
Factor	**RR**	**(95% CI)**	***P* value**
Patient Factors			
Age (years)	1.00	(0.99 - 1.01)	0.6871
Male gender	0.97	(0.81 - 1.18)	0.7900
Ethnicity			
Chinese	0.87	(0.52 - 1.43)	0.5788
Malay	0.93	(0.53 - 1.63)	0.7924
Indian	0.64	(0.34 - 1.19)	0.1552
Other	1.00	.. ..	..
Singapore resident	0.84	(0.46 - 1.51)	0.5535
Private ward class	0.78	(0.52 - 1.16)	0.2196
Cardiovascular disease	1.17	(0.91 - 1.50)	0.2094
Charlson's comorbidity index >5	0.84	(0.63 - 1.13)	0.2529
Prior hospitalisation (past 90 days)	**1.23**	**(1.01 - 1.51)**	**0.0367**
Prior antibiotics (past 180 days)	0.98	(0.77 - 1.24)	0.8421
Length of stay prior to antibiotics	1.000	(0.996 - 1.004)	0.9601
Time of antibiotic prescription (Night[a] vs. Day)	1.14	(0.94 - 1.37)	0.1768

Table 5.5. (Continued)

Factor	Model* RR	(95% CI)	*P* value
Diagnosed infection			
Pneumonia	**4.33**	**(2.21 - 8.49)**	**<.0001**
Sepsis	1.66	(0.77 - 3.57)	0.1950
Urinary tract infection	0.95	(0.40 - 2.24)	0.9092
Hepatobiliary or Intra-abdominal	1.83	(0.82 - 4.10)	0.1395
Other	1.00	.. ..	..
Renal impairment[b]	**0.79**	**(0.63 - 0.99)**	**0.0379**
ICU admission	**0.52**	**(0.32 - 0.86)**	**0.0101**
ICU admission by Cardiovascular disease	**2.64**	**(1.31 - 5.29)**	**0.0065**
Clinical Specialty Factor			
Medical vs. Surgical	1.17	(0.90 - 1.53)	0.2330

Abbreviations: ICU, intensive care unit; RR, risk ratio; CI, confidence interval

[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: ROC 0.7029; Fit statistics (-2 Log Pseudo-Likelihood 7847.79)

5.5 DISCUSSION

The finding that only one-quarter of patients who were prescribed piperacillin-tazobactam or a carbapenem for empiric therapy received antibiotics according to ARUSC recommendations showed that there was room for improvement in the quality of care for patients with infections. The patients in this study represented a population with poorer 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 (91). 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 5-59% (87). Qualitative studies have suggested that physicians tended to consider their patients to be outside the boundaries of local evidence-based antibiotic guidelines and policies (81).

We did not identify any physician or clinical specialty factor that was associated with patient receipt of ARUSC recommendations. We examined the effect of the attending physician's ethnicity on patients' receipt of ARUSC recommendations, but did not observe any. Some studies have suggested associations between physician ethnicity and clinical practice including antibiotic prescribing (96,97). 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 recommendations 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 (29,85,90), but physician characteristics associated with physicians' acceptance or patients' receipt of antibiotic CDSS recommendations have not been reported.

Several patient factors were identified to be associated with receipt of ARUSC antibiotic recommendations. Patients who were hospitalized in the preceding 90 days were 30% more likely to receive ARUSC recommendations. 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 for which physicians were more likely to accept.

A diagnosis of pneumonia was highly associated with the receipt of ARUSC recommendations. Other studies have reported similar findings with adherence to hospital antimicrobial guidelines (29,33). ARUSC-recommended antibiotic regimen for nosocomial pneumonia included piperacillin-tazobactam, which was the antibiotic prescribed by the physician. Patients with cardiovascular disease were 1.3 times as likely as those without to receive ARUSC recommendations. Menendez *et al* reported similar findings for adherence to the Spanish guidelines for the empiric treatment of community-acquired pneumonia (90). Interestingly, patients with cardiovascular disease admitted to the ICU were even more likely to receive ARUSC's antibiotic recommendations.

We identified several patient factors that could be targeted for enhancement of ARUSC, to improve patients' receipt of its recommendations, namely patients admitted to the ICU and those with renal impairment. We found that ICU patients were 60% less likely to receive ARUSC recommendations. Several studies reported similar decrease in adherence to hospital antibiotic guidelines for ICU patients (88,90). It was suggested that non-adherence might have been driven by the inability of guidelines to cover all encountered clinical conditions (98). 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 the ICU patient may have to be considered in addition to the parameters provided for general inpatients. Likewise, for patients with renal impairment, receipt of ARUSC recommendations was observed to be 30% lower than 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 (91). As with other studies, the patient's age was not found to be associated with patient receipt of ARUSC recommendations (33,66).

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's antibiotic recommendations. Hence, the outcome measure was not subject to measurement error or differential misclassification.

Another major strength of the study was the use of multilevel modelling 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 modelling techniques which were prone to type I error. Furthermore, we were able to study and estimate the relative effects of prescribing physician, attending physician, and clinical specialty on patients' receipt of recommendations by an antibiotic CDSS. Further analyses using log-binomial and Poisson regression models to estimate risk ratios yielded expectedly smaller effect sizes, but the results corroborated with our findings with the logistic regression models.

Our study may be limited by the inability to study certain patient and physician factors, due to the non-availability of 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 prevention of patients' non-receipt of its recommendations more feasible (66). Our study population did not include children and our findings could not be generalized to pediatric

populations. Nonetheless, our findings may be applied to other adult tertiary-care centers where antibiotic CDSSs are used.

This study gave insight into predictors of patients' receipt of antibiotic CDSS recommendations. While the prescribing physician accounted for some of the differences, the attending physician and clinical specialty were not associated with patients' receipt of CDSS recommendations. 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 and antibiotic needs of such patients may require a physician's assessment in addition to the CDSS recommendations.

6. COMPARATIVE EFFECTIVENESS AND MODIFIERS OF EFFECT OF ANTIBIOTIC COMPUTERIZED DECISION SUPPORT SYSTEM RECOMMENDATIONS ON PATIENT CLINICAL OUTCOMES AND MORTALITY

6.1 ABSTRACT

Introduction

Antibiotic computerized decision support systems (CDSSs) have been shown to improve antibiotic prescribing, but evidence of beneficial patient outcomes is limited. Physicians are primarily concerned with individual patients' clinical outcomes rather than risk of antibiotic resistance in their antibiotic choices. Providing information on the benefits of improved clinical outcomes is essential to increase physicians' acceptance of antibiotic CDSSs. We aim to evaluate the comparative effectiveness and modifiers of effect of antibiotic CDSSs on clinical outcomes.

Methods

We assembled a prospective inpatient cohort in a 1500-bed tertiary care hospital in Singapore, with its homegrown antibiotic CDSS that integrates antimicrobial stewardship with electronic prescribing, starting from automatically-triggered launch of CDSS at the point of antibiotic prescribing to 30 days post-hospital discharge or 180 days post-antibiotic prescription.

All patients hospitalized from October 1, 2011 through September 30, 2012 and prescribed piperacillin-tazobactam or a carbapenem for empiric therapy resulting in the automatic trigger of the CDSS to receive antibiotic recommendations were included. Receipt of antibiotics recommended by CDSS was determined by matching antibiotics on electronic prescription with CDSS-recommended antibiotics. Primary outcome was 30-day all-cause mortality. Secondary outcomes included incidence of *Clostridium difficile* infection (CDI) and multidrug resistant organism (MDRO) infection, and 30-day infection-related readmission.

Results

One-quarter of 1886 eligible inpatients received CDSS-recommended antibiotics. More patients treated for pneumonia (33.2%) than sepsis (12.1%) and urinary tract infection (7.1%) received CDSS recommendations. Receipt of recommendations seemed to halve all-cause mortality risk among patients (OR 0.54, 95% CI 0.26-1.10, *P* = 0.09). Patients aged 65 years or younger had a greater mortality benefit (OR 0.45, 95% CI 0.20-1.00, *P* = 0.05) than patients older than 65 years (OR 1.28, 95% CI 0.91-1.82, *P* = 0.16). Receiving CDSS recommendations did not affect the incidences of *Clostridium difficile* (OR 1.02, 95% CI 0.34-3.01, *P* = 0.97) and multidrug resistant organism infections (OR 1.06, 95% CI 0.42-2.71, *P* = 0.90). No increase in infection-related readmission (OR 1.16, 95% CI 0.48-2.79, *P* = 0.74) was found in survivors.

Conclusion

Receipt of antibiotic CDSS recommendations reduced mortality risk in patients aged 65 years or younger, and did not increase the risk in older patients. Physicians should be informed of the benefits to patients to increase their acceptance of CDSS recommendations.

6.2 INTRODUCTION

Antibiotics are among the major developments in modern medicine, saving countless lives over the decades (27). They are commonly prescribed in hospitals. Worldwide, hospital antibiotic use has increased substantially (7,9). Approximately 60% of adults admitted to US hospitals received at least one dose of antibiotics during their stay (61). However, some 41 to 91% of antibiotics prescribed in hospitals are considered inappropriate (20).

Overuse and misuse of antibiotics have driven the emergence of antimicrobial resistance (67,68).

Antimicrobial resistance is a serious threat to public health, heralding the approach of a post-antibiotic era (4). Antimicrobial stewardship programs have been established in many hospitals to facilitate the optimal use of antibiotics (9,23,61,84,85). Furthermore, antibiotic computerized decision support systems (CDSS) are developed to improve antibiotic decision making through accessibility of patient-specific clinical data and local antibiotic guidelines, at the point of prescribing (17,42–44,65,77). Antibiotic CDSSs are particularly useful for antibiotic selection for empiric therapy, as optimal selection is complex when the causative pathogen is unknown (29,61,74). Appropriate empiric treatment is crucial for resolution of infection and reduction of morbidity and mortality (61,66).

Antimicrobial stewardship can improve antibiotic prescribing and clinical outcomes in hospital inpatients (9). Antibiotic CDSS could further enhance antibiotic prescribing (17,34), but evidence on CDSS benefits on clinical outcomes is limited (8). While most physicians recognize the emergence of antimicrobial resistance as an important problem, they are primarily concerned with individual patients' clinical outcomes rather than the risk of resistance in their antibiotic choices (84). Understanding the clinical benefits of CDSS is essential to increase physicians' confidence in and acceptance of antibiotic CDSS recommendations.

We conducted a prospective cohort study to evaluate the comparative effectiveness of a tertiary hospital's homegrown antibiotic CDSS, Antimicrobial Resistance Utilization and Surveillance Control (ARUSC) (Appendix I), on mortality, readmission, the incidence of *Clostridium difficile* infection (CDI), and multidrug resistant organism (MDRO) infection, and the modification of these effects by patient factors.

6.3 METHODS

Study setting and population

The study was conducted in Tan Tock Seng Hospital, a 1500-bed tertiary-care academic center that serves a diverse ethnic, adult medical and surgical population in Singapore. In 2009, the hospital launched its in-house antibiotic CDSS, ARUSC, which integrates antimicrobial stewardship with its computerized physician order entry (CPOE) system and provides patient-specific evidence-based antibiotic recommendations at the point of prescribing (65). Inputs from all clinical departments were considered in the development of ARUSC. From September 12, 2011, all inpatient prescriptions of piperacillin-tazobactam or a carbapenem automatically triggered a clinical decision support algorithm in ARUSC. 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, for which ARUSC recommends the narrowest-spectrum antibiotic appropriate for common organisms for the diagnosed infection, based on local epidemiology and antibiotic susceptibility patterns. The prescribing physician can either accept or override ARUSC antibiotic recommendations.

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 automatically triggered to receive antibiotic recommendations 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 were found to be the least concordant with antibiotic guidelines (29). 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 (66) .

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 hospital or 180 days post-antibiotic prescription, whichever was later.

Outcome variables

We selected 30-day all-cause mortality as the primary outcome, since the key benefit of appropriate empiric antibiotic therapy is 30-day survival gain (17). As secondary outcomes, we assessed the incidence of CDI and MDRO infection (>2 days and <=180 days after antibiotic prescription) (99). A CDI was defined as concurrent positive results on fecal samples from parallel testing for *C. difficile* toxin and *C. difficile*-specific enzyme glutamate dehydrogenase antigen using the Techlab *C. difficile* Quik Chek Complete test, without a positive test during the preceding 8 weeks (repeat positive tests during this period suggest recurrence rather than incidence) (100). Whenever there was discordance in the results of the two tests, a confirmatory GeneXpert *C. difficile* polymerase chain reaction test for the presence of *C. difficile* genetic material was carried out. We defined MDRO as a bacterium that is resistant to three or more of five antibiotic classes (101). Additionally, we evaluated the incidence of 30-day infection-related readmission rates among survivors. Readmission within 30 days of hospital discharge was a proxy for non-resolution of the infection. We assessed readmission only in survivors of the hospitalization episode, as non-survivors would not be at risk of readmission.

Exposure variable

Patients' receipt of antibiotics recommended by ARUSC was determined by electronically matching antibiotics prescribed in the institutional CPOE system with those recommended by ARUSC. A patient was classified as having received ARUSC intervention if the antibiotics matched exactly on the drug prescribed, including dose, route, and frequency of administration.

Covariates

Relevant patients' characteristics included socio-demographic data (age, gender, ethnicity, resident status, and ward class), comorbidities, illness severity, admission to an intensive care unit (ICU) at the time of prescribing, prior antibiotic exposure within 180 days and proton pump inhibitor exposure within 90 days preceding current prescription, prior hospitalization within 90 days preceding current admission, diagnosed infection for current antibiotic therapy, and the time and day of week when the prescription was made.

We dichotomized age to <=65 and >65 years, representing younger and older age groups. Ward class was based on admission to a private or subsidized room, and used as a surrogate measure of the patient's socioeconomic status. We defined comorbidities as follows. Diabetes mellitus: a diagnosis of diabetes with or without complications. Cardiovascular disease: coronary artery disease or congestive heart failure. Liver disease: liver disease of any severity. Renal disease: moderate to severe renal disease. Neoplasm: solid malignant tumor, leukemia, lymphoma, or any metastasis. Central nervous system (CNS) disease: cerebrovascular disease, dementia. Chronic pulmonary disease: chronic obstructive pulmonary disease. Charlson's comorbidity index (CCI) (92) was derived from the hospital discharge database using coding algorithms developed by Quan H *et al* (93). CCI was then categorized 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 >100mg/l and leukocyte count <4 or >12x10^9/l as proxies for severe infection, and serum creatinine >130μmol/l as proxy for renal impairment (33). 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 led to the automatically-triggered ARUSC launch. 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 as seniors. Data on physicians' designation and ethnicity were obtained from the institution's 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, their respective prescribing and attending physicians and clinical specialties, their receipt of ARUSC antibiotic recommendations and subsequent clinical outcomes by diagnosed infection. Next, we explored the relationships between the receipt of ARUSC recommendations, various patients' and physicians' characteristics, and each clinical outcome 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 within their clinical specialties, to account for clustering within prescribing physicians and clustering within attending physicians and clinical specialties respectively. Finally, we constructed two multivariable adjusted multilevel logistic regression models to assess the effect of ARUSC recommendations on each outcome, accounting for potential confounding. We included variables decided *a prior* as factors associated with each clinical outcome particularly those based on prior knowledge to be associated with adherence to antibiotic guidelines in general (not specific for antibiotic CDSS due to limited information on antibiotic CDSS). Collinearity among covariates was assessed by means of the Pearson's correlation coefficient. Strongly correlated variables were excluded from the multivariable models. Statistical interactions between age, comorbidities, infectious diagnoses, illness severity, and receipt of ARUSC recommendations, were respectively explored and product terms included in the models where appropriate. We estimated the odds ratios (OR) and corresponding 95% confidence intervals (CI) 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 (94). To further adjust for potential confounding due to differences in baseline characteristics in patients who received and did not receive ARUSC recommendations, we estimated propensity scores from multilevel exposure models on the receipt of ARUSC recommendations (102,103). Doubly robust estimates were obtained by combining propensity scoring with the multivariable adjusted multilevel logistic regressions above. We compared the results with estimates from the outcome models based on multivariable adjusted multilevel logistic regressions. We conducted further sensitivity analyses by excluding patients whose hospital stay was more than 7 days prior to the antibiotic prescription. We used multiple-imputation for measurement error (MIME) correction for adjustment of potential misclassification of CCI based on a validation sub-study of 198 patients that were randomly sampled from the total cohort for whose medical records were manually reviewed by a physician for the presence of comorbidities (104). Finally, we assessed non-participation and used inverse-

probability-of-selection-weighting to adjust for any potential selection bias. All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

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

6.4 RESULTS

Patient characteristics

During the one-year study period, a total of 1886 inpatients at Tan Tock Seng Hospital were automatically triggered to receive antibiotic recommendations by ARUSC for prescriptions of piperacillin-tazobactam or a carbapenem for empiric therapy.

Pneumonia (64.3%) was the most commonly diagnosed infection, among which patients were the oldest (mean 74.9 years, SD 14.5). Patients with hepatobiliary or intra-abdominal infections had the poorest chronic health status and most severe illness, with almost one-fifth having a CCI >5 (22.5 %) and ICU admission (20.4%) respectively. A much higher proportion of patients treated for pneumonia (33.2%) received ARUSC-recommended antibiotics, compared with patients with sepsis (12.1%) and urinary tract infection (7.1%). Patients with a diagnosis of sepsis had the highest 30-day all-cause mortality (28.8%), while patients diagnosed with urinary tract infection had the highest incidence of CDI (8.2%). Among survivors of the hospitalization episode, 11.2% were readmitted for infection-related causes within 30 days.

Data on patient demographics, comorbidities, illness severity, infectious diagnoses, and clinical outcomes, and the prescribing and attending physician characteristics are presented in Table 6.1.

30-Day All-cause Mortality

Univariate and Multivariable analyses

In univariate analysis, patient factors were similarly associated with 30-day all-cause mortality in both models (Table 6.2). Age>65 (Model 1: OR 1.63, 95% CI 1.24-2.14; Model 2: OR 1.61, 95% CI 1.22-2.13), CCI>5 (Model 1: OR 1.96, 95% CI 1.45-2.64; Model 2: OR 2.13, 95% CI 1.56-2.91), pneumonia (Model 1: OR 2.04, 95% CI 1.15-3.61; Model 2: OR 1.92, 95% CI 1.07-3.44), sepsis (Model 1: OR 3.33, 95% CI 1.77-6.24; Model 2: OR 3.17, 95% CI 1.67-6.00) , and ICU admission (Model 1: OR 1.72, 95% CI 1.25-2.38; Model 2: OR 2.05, 95% CI 1.43-2.95) , were positively associated with mortality. The prescribing physician did not contribute to the variation in mortality, while the attending physician (0.4%) and clinical specialty (1.7%) accounted for small variances.

After controlling for potential confounding in the multivariable multilevel models, receipt of ARUSC antibiotic recommendations was marginally associated with mortality reduction (Model 1: OR 0.54, 95% CI 0.27-1.11; Model 2: OR 0.52, 95% CI 0.26-1.06). Age>65 (Model 1: OR 1.46, 95% CI 1.06-2.01; Model 2: OR 1.43, 95% CI 1.03-1.98) , CCI>5 (Model 1: OR 1.97, 95% CI 1.44-2.68; Model 2: OR 2.12, 95% CI 1.54-2.92), sepsis (Model 1: OR 3.00, 95% CI 1.58-5.70; Model 2: OR 2.61, 95% CI 1.30-5.26), and ICU admission (Model 1: OR 1.85, 95% CI 1.31-2.61; Model 2: OR 2.25, 95% CI 1.54-3.29) were all associated with mortality.

In the propensity score (PS) adjusted multivariable models, the effect of the receipt of ARUSC recommendations (Model 1: OR 0.54, 95% CI 0.26-1.10; Model 2: OR 0.52, 95% CI 0.25-1.05) remained, and the effects of CCI>5 (Model 1: OR 2.00, 95% CI 1.47-2.71; Model 2: OR 2.18, 95% CI 1.59-2.99) and ICU admission (Model 1: OR 1.96, 95% CI 1.40-2.75; Model 2: OR 2.47, 95% CI 1.70-3.58) were enhanced (Table 6.3). At the clinical specialty level, patients managed by a

medical service were 1.5 times as likely as those managed by a surgical service to die within 30 days of the receipt of antibiotics (OR 1.53, 95% CI 1.02-2.30).

We selected the PS adjusted two-level model (Model 1: prescribing physician, patient) as the final multivariable model, as the model provided the optimal fit overall. Interactions between the receipt of ARUSC recommendations and age, comorbidities, illness severity, and infectious diagnoses were assessed. Age>65 was found to interact positively with ARUSC recommendations receipt (OR 2.32, 95% CI 1.08-4.98), and the product term was included in the final model.

After adjusting for the prescribing physician's preference and seniority, and potential confounding by the patient's socio-demographic and comorbidity factors, prior hospitalization and antibiotic exposures, current hospital length of stay prior to antibiotic prescription, time and day of prescription, and current infectious diagnosis and ICU admission, the receipt of ARUSC recommendations halved the mortality risks of patients (OR 0.54, 95% CI 0.26-1.10, *P* = 0.09) (Table 6.3). Among patients aged 65 and below, the receipt of ARUSC recommendations reduced mortality by 55% (OR 0.45, 95% CI 0.20-1.00, *P* = 0.05) (Table 6.4). However, it was not clear whether ARUSC recommendations affected mortality in patients >65 years old (OR 1.28, 95% CI 0.91-1.82, *P* = 0.16). Our study suggests that age (<=65 years) modified the effect of ARUSC recommendation in reducing mortality risk; as such, the combined effects of age and receiving ARUSC recommendation was larger than the combination of their component effects (OR 0.37, 95% CI 0.18-0.72, *P* = 0.004) (Figure 6.1). Effect estimates for age, receipt of ARUSC recommendations, and interactions did not change notably when we restricted our population to the 1,305 patients who had been hospitalized for 7 days or less prior to the antibiotic prescription (Table 6.5).

Secondary Outcomes

The multivariable two-level regression including the propensity score showed that ARUSC recommendations had no effect on the subsequent development of CDI (OR 1.02, 95% CI 0.34-3.01, $P = 0.97$) and MDRO infection (OR 1.06, 95% CI 0.42-2.71, $P = 0.90$) among patients (Table 6.6). As for survivors of the admission episode, patients who received ARUSC-recommended antibiotics did not appear to have increased incidence of 30-day infection-related readmission appreciably (OR 1.16, 95% CI 0.48-2.79, $P = 0.74$).

Sensitivity analysis

With the correction of potential misclassification of CCI, the effect of ARUSC recommendations on 30-day all-cause mortality was unchanged (OR 0.53, 95% CI 0.26-1.10, $P = 0.09$). After adjusting for potential selection bias, the beneficial effect of ARUSC recommendations on 30-day all-cause mortality remained (OR 0.32, 95% CI 0.17-0.63, $P < 0.01$). There was also no change in the non-effect of ARSUC recommendations on the subsequent development of CDI (OR 1.13, 95% CI 0.38-3.33, $P = 0.83$) and MDRO infection (OR 1.18, 95% CI 0.43-3.21, $P = 0.75$), and on 30-day infection-related readmission in survivors (OR 1.66, 95% CI 0.71-3.87, $P = 0.24$).

Table 6.1. Characteristics and clinical outcomes of 1886 patients, by diagnosed infection, October 1, 2011 to September 30, 2012

	Diagnosed infection									
Characteristics	**Pneumonia**		**Sepsis**		**Urinary tract infection**		**Hepatobiliary or Intra-abdominal**		**Others**	
Total, N (%)	1213	(64.3)	215	(11.4)	182	(9.7)	147	(7.8)	129	(6.8)
Demographic data										
Age, mean (SD)	74.9	(14.5)	69.0	(15.9)	72.7	(16.7)	66.7	(17.2)	62.5	(16.0)
Males, N (%)	710	(58.5)	119	(55.3)	75	(41.2)	79	(53.7)	71	(55.0)
Ethnicity, N (%)										
Chinese	986	(81.3)	155	(72.1)	127	(69.8)	110	(74.8)	84	(65.1)
Malay	105	(8.7)	25	(11.6)	26	(14.3)	13	(8.8)	24	(18.6)
Indian	82	(6.8)	19	(8.8)	17	(9.3)	8	(5.4)	8	(6.2)
Other	40	(3.3)	16	(7.4)	12	(6.6)	16	(10.9)	13	(10.1)
Singapore residents, N (%)	1170	(96.5)	203	(94.4)	174	(95.6)	135	(91.8)	118	(91.5)
Private ward class, N (%)	104	(8.6)	20	(9.3)	16	(8.8)	20	(13.6)	12	(9.3)
Medical history										
Co-morbidities, N (%)										
Diabetes mellitus	384	(31.7)	69	(32.1)	72	(39.6)	41	(27.9)	44	(34.1)
Cardiovascular disease	237	(19.5)	40	(18.6)	24	(13.2)	16	(10.9)	22	(17.1)
Liver disease	32	(2.6)	10	(4.7)	9	(5.0)	16	(10.9)	1	(0.8)
Renal disease	241	(19.9)	52	(24.2)	48	(26.4)	22	(15.0)	26	(20.2)
Neoplasia	181	(14.9)	40	(18.6)	20	(11.0)	39	(26.5)	15	(11.6)
CNS disease	277	(22.8)	48	(22.3)	44	(24.2)	9	(6.1)	16	(12.4)
Chronic pulmonary disease	143	(11.8)	6	(2.8)	6	(3.3)	3	(2.0)	1	(0.8)
Charlson's comorbidity index >5, N (%)	151	(12.4)	35	(16.3)	25	(13.7)	33	(22.4)	11	(8.5)
Prior hospitalization, N (%)	478	(39.4)	90	(41.9)	90	(49.5)	52	(35.4)	41	(31.8)

Table 6.1. (Continued)

Characteristics	Diagnosed infection									
	Pneumonia		Sepsis		Urinary tract infection		Hepatobiliary or Intra-abdominal		Others	
Prior antibiotics, N (%)	939	(77.4)	166	(77.2)	156	(85.7)	111	(75.5)	104	(80.6)
Prior proton pump inhibitors, N (%)	721	(59.4)	143	(66.5)	138	(75.8)	92	(62.6)	79	(61.2)
Current Admission										
Length of stay prior to antibiotics, mean (SD)	8.9	(26.0)	8.7	(14.7)	11.1	(15.8)	5.5	(8.1)	14.9	(47.9)
Day of antibiotic prescription, N (%)										
Weekend or Public Holiday	357	(29.4)	46	(21.4)	60	(33.0)	40	(27.2)	33	(25.6)
Weekday	856	(70.6)	169	(78.6)	122	(67.0)	107	(72.8)	96	(74.4)
Time of antibiotic prescription, N (%)										
Night[a]	468	(38.6)	75	(34.9)	54	(29.7)	59	(40.1)	43	(33.3)
Day	745	(61.4)	140	(65.1)	128	(70.3)	88	(59.9)	86	(66.7)
Illness severity, N (%)										
C-reactive protein[b] >100mg/l	415	(38.4)	74	(37.9)	58	(34.5)	58	(51.3)	60	(52.6)
Leukocyte count <4 or >12x10^9/l	584	(48.1)	123	(57.2)	89	(48.9)	88	(59.9)	72	(55.8)
Serum creatinine[c] >130µmol/l	293	(24.2)	81	(37.7)	49	(27.5)	40	(27.6)	43	(33.6)
ICU admission, N (%)	122	(10.1)	40	(18.6)	6	(3.3)	30	(20.4)	20	(15.5)
Prescribing physician, N (%)										
Senior	118	(9.7)	28	(13.0)	18	(9.9)	21	(14.3)	6	(4.7)
Junior	1095	(90.3)	187	(87.0)	164	(90.1)	126	(85.7)	123	(95.3)
Attending physician, N (%)										
Ethnic Chinese	887	(73.1)	148	(68.8)	141	(77.5)	109	(74.1)	97	(75.2)
Ethnic Indian	244	(20.1)	42	(19.5)	31	(17.0)	31	(21.1)	28	(21.7)
Other Ethnicity	82	(6.8)	25	(11.6)	10	(5.5)	7	(4.8)	4	(3.1)

Table 6.1. (Continued)

Characteristics	Diagnosed infection									
	Pneumonia		Sepsis		Urinary tract infection		Hepatobiliary or Intra-abdominal		Others	
Clinical specialties, N (%)										
Medical	986	(81.3)	170	(79.1)	142	(78.0)	64	(43.5)	63	(48.8)
Surgical	227	(18.7)	45	(20.9)	40	(22.0)	83	(56.5)	66	(51.2)
Receipt of ARUSC recommendation, N (%)	403	(33.2)	26	(12.1)	13	(7.1)	19	(12.9)	9	(7.0)
Clinical outcomes										
30-day all-cause mortality, N (%)	241	(19.9)	62	(28.8)	18	(9.9)	26	(17.7)	14	(10.9)
180-day *C. difficile* infection, N (%)	58	(4.8)	8	(3.7)	15	(8.2)	1	(0.7)	3	(2.3)
180-day MDRO infection, N (%)	69	(5.7)	12	(5.6)	25	(13.7)	13	(8.8)	21	(16.3)
	Survivors at hospital discharge									
Total Survivors, N (%)	953	(63.9)	144	(9.7)	163	(10.9)	119	(8.0)	113	(7.6)
30-day infection-related readmission	111	(11.6)	15	(10.4)	18	(11.0)	6	(5.0)	17	(15.0)

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

[b] C-reactive protein closest to prescription date (within 7 days), missing in pneumonia (133/1213=11.0%), sepsis (20/215=9.3%), urinary tract infection (14/182=7.7%), hepatobiliary or intra-abdominal infection (34/147=23.1%) , other infections (15/129=11.6%)

[c] Creatinine level closest to prescription date (within 7 days), missing in pneumonia (3/1213=0.2%), sepsis (0/215), urinary tract infection (4/182=2.2%), hepatobiliary or intra-abdominal infection (2/147=1.4%), other infections (1/129=0.8%)

Table 6.2. Results of univariate and multivariable analyses of factors associated with 30-day all-cause mortality (Model 1: 2-level logistic regression analysis of data on 1886 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)

	Survivor (n = 1525)		Non-survivor (n = 361)		Model 1						Model 2					
					Univariate analysis			Multivariable analysis			Univariate analysis			Multivariable analysis		
Factor	**N**	**%**	**N**	**%**	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**
Patient Factors																
Age >65 years	1042	68.3	281	77.8	1.63	(1.24 - 2.14)	0.0004	1.46	(1.06 - 2.01)	0.0218	1.61	(1.22 - 2.13)	0.0008	1.43	(1.03 - 1.98)	0.0304
Male gender	843	55.3	211	58.5	1.14	(0.90 - 1.44)	0.2757	1.16	(0.91 - 1.49)	0.2179	1.16	(0.92 - 1.47)	0.2200	1.18	(0.92 - 1.51)	0.1884
Ethnicity																
Chinese	1171	76.8	291	80.6	1.61	(0.88 - 2.92)	0.1209	1.17	(0.59 - 2.33)	0.6447	1.56	(0.85 - 2.86)	0.1473	1.15	(0.57 - 2.33)	0.6948
Malay	155	10.2	38	10.5	1.58	(0.80 - 3.14)	0.1873	1.39	(0.65 - 2.97)	0.3942	1.55	(0.78 - 3.09)	0.2127	1.35	(0.62 - 2.94)	0.4506
Indian	115	7.5	19	5.3	1.07	(0.50 - 2.28)	0.8660	0.88	(0.39 - 2.02)	0.7695	1.03	(0.48 - 2.21)	0.9427	0.86	(0.37 - 1.99)	0.7174
Other	84	5.5	13	3.6	1.00	.. .. ..	..	1.00	.. .. ..	..	1.00	.. .. ..	..	1.00	.. .. ..	..
Singapore resident	1449	95.0	351	97.2	1.84	(0.94 - 3.60)	0.0742	1.22	(0.53 - 2.79)	0.6425	1.77	(0.90 - 3.49)	0.0958	1.21	(0.45 - 3.26)	0.7118
Private ward class	149	9.8	23	6.4	0.63	(0.40 - 0.99)	0.0455	0.66	(0.39 - 1.12)	0.1243	0.64	(0.40 - 1.01)	0.0542	0.65	(0.38 - 1.13)	0.1288
Comorbidity																
Diabetes	503	33.0	107	29.6	0.86	(0.67 - 1.10)	0.2225	-	- - -	-	0.82	(0.63 - 1.05)	0.1210	-	- - -	-
Cardiovascular disease	238	15.6	101	28.0	2.10	(1.61 - 2.75)	<.0001	-	- - -	-	2.09	(1.58 - 2.76)	<.0001	-	- - -	-
Hepatopathy	52	3.4	16	4.4	1.31	(0.74 - 2.33)	0.3505	-	- - -	-	1.32	(0.73 - 2.36)	0.3562	-	- - -	-
Renal disease	293	19.2	96	26.6	1.23	(1.08 - 1.41)	0.0020	-	- - -	-	1.21	(1.06 - 1.39)	0.0054	-	- - -	-
Neoplasia	219	14.4	76	21.1	1.59	(1.19 - 2.13)	0.0018	-	- - -	-	1.72	(1.26 - 2.35)	0.0006	-	- - -	-
CNS disease	329	21.6	65	18.0	0.80	(0.59 - 1.07)	0.1345	-	- - -	-	0.84	(0.61 - 1.15)	0.2767	-	- - -	-
Chronic pulmonary disease	129	8.5	30	8.3	0.98	(0.65 - 1.49)	0.9271	-	- - -	-	0.95	(0.61 - 1.48)	0.8275	-	- - -	-
Charlson's comorbidity index >5	180	11.8	75	20.8	1.96	(1.45 - 2.64)	<.0001	1.97	(1.44 - 2.68)	<.0001	2.13	(1.56 - 2.91)	<.0001	2.12	(1.54 - 2.92)	<.0001
Prior hospitalization	602	39.5	149	41.3	1.08	(0.85 - 1.36)	0.5303	1.00	(0.77 - 1.30)	0.9730	1.02	(0.81 - 1.30)	0.8412	0.97	(0.75 - 1.27)	0.8458
Prior antibiotics	1190	78.0	286	79.2	1.07	(0.81 - 1.42)	0.6217	1.11	(0.81 - 1.53)	0.5029	1.07	(0.80 - 1.42)	0.6644	1.07	(0.78 - 1.48)	0.6650
Length of stay prior to antibiotics >7 days	468	30.7	113	31.3	1.03	(0.80 - 1.32)	0.8205	0.97	(0.74 - 1.27)	0.8448	1.12	(0.86 - 1.45)	0.4106	1.05	(0.80 - 1.39)	0.7215
Antibiotic prescription on weekend/public holiday	426	27.9	110	30.5	1.13	(0.88 - 1.45)	0.3370	1.16	(0.90 - 1.51)	0.2485	1.13	(0.88 - 1.46)	0.3292	1.17	(0.90 - 1.52)	0.2348
Antibiotic prescription at night[a]	560	36.7	139	38.5	1.08	(0.85 - 1.37)	0.5284	1.05	(0.82 - 1.35)	0.6722	1.06	(0.83 - 1.34)	0.6460	1.04	(0.81 - 1.33)	0.7854
Diagnosed Infection																
Pneumonia	972	63.7	241	66.8	2.04	(1.15 - 3.61)	0.0150	1.72	(0.95 - 3.12)	0.0731	1.92	(1.07 - 3.44)	0.0293	1.53	(0.79 - 2.94)	0.2030

Table 6.2. (Continued)

Factor	Survivor (n = 1525) N	%	Non-survivor (n = 361) N	%	Model 1 Univariate analysis OR	(95% CI)	*P* value	Model 1 Multivariable analysis OR	(95% CI)	*P* value	Model 2 Univariate analysis OR	(95% CI)	*P* value	Model 2 Multivariable analysis OR	(95% CI)	*P* value
Sepsis	153	10.0	62	17.2	3.33	(1.77 - 6.24)	0.0002	3.00	(1.58 - 5.70)	0.0008	3.17	(1.67 - 6.00)	0.0004	2.61	(1.30 - 5.26)	0.0071
Urinary tract infection	164	10.8	18	5.0	0.90	(0.43 - 1.89)	0.7832	0.84	(0.39 - 1.79)	0.6500	0.85	(0.40 - 1.79)	0.6644	0.75	(0.33 - 1.69)	0.4924
Hepatobiliary or Intra-abdominal	121	7.9	26	7.2	1.77	(0.88 - 3.55)	0.1109	1.51	(0.74 - 3.08)	0.2630	1.87	(0.91 - 3.82)	0.0865	1.62	(0.75 - 3.52)	0.2195
Other	115	7.5	14	3.9	1.00	.. ..	..	1.00	.. ..	..	1.00	.. ..	..	1.00	.. ..	..
ICU Admission	158	10.4	60	16.6	1.72	(1.25 - 2.38)	0.0009	1.85	(1.31 - 2.61)	0.0004	2.05	(1.43 - 2.95)	0.0001	2.25	(1.54 - 3.29)	<.0001
Abnormal C-reactive protein[b]	522	38.2	143	46.9	1.43	(1.11 - 1.83)	0.0055	-	- -	-	1.48	(1.15 - 1.91)	0.0026	-	- -	-
Abnormal Leukocyte count	743	48.7	213	59.0	1.51	(1.20 - 1.91)	0.0005	-	- -	-	1.54	(1.22 - 1.95)	0.0003	-	- -	-
Renal impairment[c]	359	23.7	147	40.7	2.21	(1.74 - 2.82)	<.0001	-	- -	-	2.18	(1.70 - 2.78)	<.0001	-	- -	-
Prescribing Physician Factor (ICC=0%)																
Junior physician	1370	89.8	325	90.0	1.02	(0.70 - 1.50)	0.9136	1.05	(0.70 - 1.56)	0.8206	-	- -	-	-	- -	-
Attending Physician Factor (ICC = 0.4%)																
Ethnic Chinese	1121	73.5	261	72.3	-	- -	-	-	- -	-	1.12	(0.68 - 1.82)	0.6586	-	- -	-
Ethnic Indian	300	19.7	76	21.1	-	- -	-	-	- -	-	1.19	(0.70 - 2.01)	0.5271	-	- -	-
Other ethnicity	104	6.8	24	6.6	-	- -	-	-	- -	-	1.00	.. ..	..	-	- -	-
Clinical Specialty Factor (ICC = 1.7%)														-	- -	-
Medical specialty	1137	74.6	288	79.8	-	- -	-	-	- -	-	1.26	(0.86 - 1.86)	0.2363	1.46	(0.95 - 2.25)	0.0833
Receipt of ARUSC Recommendation	373	24.5	97	26.9	1.14	(0.87 - 1.47)	0.3414	0.54	(0.27 - 1.11)	0.0922	1.11	(0.85 - 1.44)	0.4578	0.52	(0.26 - 1.06)	0.0728
Receipt of ARUSC Recommendation*Age>65	-	-	-	-	-	- -	-	2.34	(1.09 - 5.04)	0.0296	-	- -	-	2.39	(1.11 - 5.16)	0.0262

Abbreviations: CNS, central nervous system; ICC, intraclass correlation coefficient; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

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

[b] C-reactive protein closest to prescription date (within 7 days), missing in survivors (160/1525=10.5%) and non-survivors (56/361=15.5%)

[c] Creatinine level >130µmol/l within 7 days of antibiotic prescription, missing in survivors (10/1525=0.7%) and non-survivors (0/361)

Table 6.3. Propensity score (PS)-adjusted and conventional multivariable analyses of factors associated with 30-day all-cause mortality (Model 1: 2-level logistic regression analysis of data on 1886 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							
	PS[a]-adjusted multivariable analysis				Conventional multivariable analysis				PS[a]-adjusted multivariable analysis				Conventional multivariable analysis			
Factor	**OR**	**(95% CI)**		***P* value**	**OR**	**(95% CI)**		***P* value**	**OR**	**(95% CI)**		***P* value**	**OR**	**(95% CI)**		***P* value**
Patient Factors																
Age >65 years	**1.46**	**1.07 - 2.00**		**0.0179**	**1.46**	**1.06 - 2.01**		**0.0218**	**1.41**	**1.02 - 1.95**		**0.0353**	**1.43**	**1.03 - 1.98**		**0.0304**
Male gender	1.19	0.93 - 1.51		0.1616	1.16	0.91 - 1.49		0.2179	1.19	0.94 - 1.52		0.1540	1.18	0.92 - 1.51		0.1884
Ethnicity																
Chinese	1.13	0.58 - 2.22		0.7164	1.17	0.59 - 2.33		0.6447	1.10	0.55 - 2.17		0.7890	1.15	0.57 - 2.33		0.6948
Malay	1.31	0.62 - 2.76		0.4811	1.39	0.65 - 2.97		0.3942	1.27	0.60 - 2.71		0.5376	1.35	0.62 - 2.94		0.4506
Indian	0.86	0.38 - 1.95		0.7187	0.88	0.39 - 2.02		0.7695	0.82	0.36 - 1.87		0.6354	0.86	0.37 - 1.99		0.7174
Other	1.00	.. ..		..	1.00	.. ..		..	1.00	.. ..		..	1.00	.. ..		..
Singapore resident	1.23	0.54 - 2.80		0.6170	1.22	0.53 - 2.79		0.6425	1.23	0.54 - 2.81		0.6252	1.21	0.45 - 3.26		0.7118
Private ward class	0.68	0.40 - 1.13		0.1386	0.66	0.39 - 1.12		0.1243	0.67	0.39 - 1.12		0.1269	0.65	0.38 - 1.13		0.1288
Charlson's comorbidity index >5	**2.00**	**1.47 - 2.71**		**<.0001**	**1.97**	**1.44 - 2.68**		**<.0001**	**2.18**	**1.59 - 2.99**		**<.0001**	**2.12**	**1.54 - 2.92**		**<.0001**
Prior hospitalization	-	- -		-	1.00	0.77 - 1.30		0.9730	-	- -		-	0.97	0.75 - 1.27		0.8458
Prior antibiotics	-	- -		-	1.11	0.81 - 1.53		0.5029	-	- -		-	1.07	0.78 - 1.48		0.6650
Length of stay prior to antibiotics >7 days	-	- -		-	0.97	0.74 - 1.27		0.8448	-	- -		-	1.05	0.80 - 1.39		0.7215
Antibiotic prescription on weekend/public holiday	-	- -		-	1.16	0.90 - 1.51		0.2485	-	- -		-	1.17	0.90 - 1.52		0.2348
Antibiotic prescription at night[b]	-	- -		-	1.05	0.82 - 1.35		0.6722	-	- -		-	1.04	0.81 - 1.33		0.7854
Diagnosed Infection																
Pneumonia	-	- -		-	1.72	0.95 - 3.12		0.0731	-	- -		-	1.53	0.79 - 2.94		0.2030
Sepsis	-	- -		-	**3.00**	**1.58 - 5.70**		**0.0008**	-	- -		-	**2.61**	**1.30 - 5.26**		**0.0071**
Urinary tract infection	-	- -		-	0.84	0.39 - 1.79		0.6500	-	- -		-	0.75	0.33 - 1.69		0.4924
Hepatobiliary or Intra-abdominal	-	- -		-	1.51	0.74 - 3.08		0.2630	-	- -		-	1.62	0.75 - 3.52		0.2195
Other	-	- -		-	1.00	.. ..		..	-	- -		-	1.00	.. ..		..

Table 6.3. (Continued)

Factor	Model 1				Model 2			
	PS[a]-adjusted multivariable analysis		Conventional multivariable analysis		PS[a]-adjusted multivariable analysis		Conventional multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
ICU Admission	**1.96 (1.40 - 2.75)**	**<.0001**	**1.85 (1.31 - 2.61)**	**0.0004**	**2.47 (1.70 - 3.58)**	**<.0001**	**2.25 (1.54 - 3.29)**	**<.0001**
Prescribing Physician Factor (ICC=0% [PS], 0% [Conventional])								
Junior physician	1.02 (0.69 - 1.51)	0.9340	1.05 (0.70 - 1.56)	0.8206	- - -	-	- - -	-
Attending Physician Factor (ICC = 0.1% [PS], 0% [Conventional])	- - -	-	- - -	-				
Clinical Specialty Factor (ICC = 0.8% [PS], 1.0% [Conventional])							- - -	-
Medical specialty	- - -	-	- - -	-	**1.53 (1.02 - 2.30)**	**0.0413**	1.46 (0.95 - 2.25)	0.0833
Receipt of ARUSC Recommendation	0.54 (0.26 - 1.10)	0.0882	0.54 (0.27 - 1.11)	0.0922	0.52 (0.25 - 1.05)	0.0686	0.52 (0.26 - 1.06)	0.0728
Receipt of ARUSC Recommendation*Age>65	**2.32 (1.08 - 4.98)**	**0.0302**	**2.34 (1.09 - 5.04)**	**0.0296**	**2.38 (1.11 - 5.13)**	**0.0267**	**2.39 (1.11 - 5.16)**	**0.0262**

Abbreviations: CNS, central nervous system; ICC, intraclass correlation coefficient; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

[a] Propensity score derived from diagnosed infection, time and day of antibiotic prescription, hospitalization days prior to antibiotics, prior hospitalization, and prior antibiotics.

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

Table 6.4. Association between receipt of ARUSC recommendation and 30-day all-cause mortality risk, according to age group, October 1, 2011 to September 30, 2012

Analysis and receipt of ARUSC recommendation	Age <= 65 years		Age > 65 years		*P*-interaction[a]
	OR	(95% CI)	OR	(95% CI)	
Unadjusted analysis					
Non-receipt	1.00	Referent	1.00	Referent	0.0187
Receipt	0.52	(0.26 - 1.05)	1.29	(0.97 - 1.72)	
Adjusted analysis[b]					
Non-receipt	1.00	Referent	1.00	Referent	0.0302
Receipt	0.45	(0.20 - 1.00)	1.28	(0.91 - 1.82)	

Abbreviations: OR, odds ratio; CI, confidence interval

[a] Multiplicative scale

[b] Adjusted using a propensity score derived from diagnosed infection, time and day of antibiotic prescription, hospitalization days prior to antibiotics, prior hospitalization, and prior antibiotics, and further adjusted for prescribing physician's seniority, and patient's gender, ethnicity, resident status, ward class, Charlson's comorbidity index >5, and ICU admission.

Table 6.5. Propensity score (PS)-adjusted multivariable analysis of factors associated with 30-day all-cause mortality (Model 1: 2-level logistic regression analysis of data on 1886 patients seen by 575 prescribing physicians; Model 2: 2-level logistic regression analysis of data on 1305 patients with ≤7 hospitalization days prior to antibiotic prescription seen by 477 prescribing physicians)

	PS[a]-adjusted multivariable analysis (Model 1)			PS[b]-adjusted multivariable analysis (Model 2)		
Factor	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**
Patient Factors						
Age >65 years	**1.46**	**(1.07 - 2.00)**	**0.0179**	**1.47**	**(1.01 - 2.14)**	**0.0463**
Male gender	1.19	(0.93 - 1.51)	0.1616	1.01	(0.75 - 1.35)	0.9584
Ethnicity						
Chinese	1.13	(0.58 - 2.22)	0.7164	1.42	(0.62 - 3.24)	0.4028
Malay	1.31	(0.62 - 2.76)	0.4811	1.52	(0.61 - 3.79)	0.3675
Indian	0.86	(0.38 - 1.95)	0.7187	0.93	(0.33 - 2.57)	0.8835
Other	1.00	.. ..	..	1.00	.. ..	..
Singapore resident	1.23	(0.54 - 2.80)	0.6170	1.12	(0.45 - 2.77)	0.8081
Private ward class	0.68	(0.40 - 1.13)	0.1386	0.89	(0.50 - 1.58)	0.6803
Charlson's comorbidity index >5	**2.00**	**(1.47 - 2.71)**	**<.0001**	**2.03**	**(1.37 - 3.00)**	**0.0004**
ICU Admission	**1.96**	**(1.40 - 2.75)**	**<.0001**	**2.30**	**(1.55 - 3.43)**	**<.0001**
Prescribing Physician Factor (ICC=0%[Model 1], 0%[Model 2])						
Junior physician	1.02	(0.69 - 1.51)	0.9340	1.05	(0.70 - 1.56)	0.3307
Receipt of ARUSC recommendation	0.54	(0.26 - 1.10)	0.0882	0.46	(0.18 - 1.15)	0.0976
Receipt of ARUSC Recommendation*Age>65	**2.32**	**(1.08 - 4.98)**	**0.0302**	**2.73**	**(1.04 - 7.15)**	**0.0408**

[a] Propensity score derived from diagnosed infection, time and day of antibiotic prescription, hospitalization days prior to antibiotics, prior hospitalization, and prior antibiotics.

[b] Propensity score derived from diagnosed infection, time and day of antibiotic prescription, prior hospitalization, and prior antibiotics.

Table 6.6. Propensity score (PS)-adjusted multivariable analysis of factors associated with *Clostridium difficile* infection, MDRO infection, and 30-day infection-related readmission (2-level logistic regression analysis of data on 1886 patients seen by 575 prescribing physicians)

	***Clostridium difficile* infection[a]**				**MDRO infection[b]**				**30-day infection-related readmission [b,c]**			
Factor	**OR**	**(95% CI)**		***P* value**	**OR**	**(95% CI)**		***P* value**	**OR**	**(95% CI)**		***P* value**
Patient Factors												
Age >65 years	1.38	(0.75 -	2.52)	0.2964	1.22	(0.79 -	1.88)	0.3774	2.21	(1.34 -	3.64)	0.0018
Male gender	1.00	(0.63 -	1.57)	0.9840	1.31	(0.90 -	1.89)	0.1553	1.08	(0.77 -	1.50)	0.6666
Ethnicity												
Chinese	1.53	(0.34 -	6.90)	0.5782	0.99	(0.37 -	2.70)	0.9881	0.44	(0.21 -	0.93)	0.0305
Malay	1.99	(0.40 -	9.86)	0.3979	1.05	(0.35 -	3.20)	0.9278	0.37	(0.15 -	0.92)	0.0329
Indian	0.96	(0.16 -	5.74)	0.9615	1.12	(0.35 -	3.64)	0.8468	0.28	(0.10 -	0.77)	0.0141
Other	1.00	..	..	..	1.00	..	..	..	1.00	..	..	..
Singapore resident	4.17	(0.48 -	36.03)	0.1943	7.85	(0.95 -	64.98)	0.0560	3.35	(0.89 -	12.62)	0.0746
Private ward class	1.44	(0.64 -	3.24)	0.3725	0.52	(0.22 -	1.26)	0.1474	0.87	(0.45 -	1.70)	0.6893
Charlson's comorbidity index >5	1.17	(0.63 -	2.20)	0.6151	1.10	(0.67 -	1.81)	0.7181	0.61	(0.33 -	1.12)	0.1103
ICU Admission	0.88	(0.41 -	1.91)	0.7536	3.21	(2.08 -	4.95)	<.0001	0.73	(0.38 -	1.40)	0.3459
Prescribing Physician Factor (ICC=11.8%[CDI], 3.1%[MDRO], 0%[Readmission])												
Junior physician	0.94	(0.44 -	2.01)	0.8639	1.42	(0.73 -	2.76)	0.2986	1.02	(0.59 -	1.77)	0.9426
Receipt of ARUSC Recommendation	1.02	(0.34 -	3.01)	0.9743	1.06	(0.42 -	2.71)	0.9008	1.16	(0.48 -	2.79)	0.7354
Receipt of ARUSC Recommendation*Age>65	0.60	(0.18 -	2.03)	0.4076	0.74	(0.25 -	2.15)	0.5774	0.89	(0.35 -	2.29)	0.8148

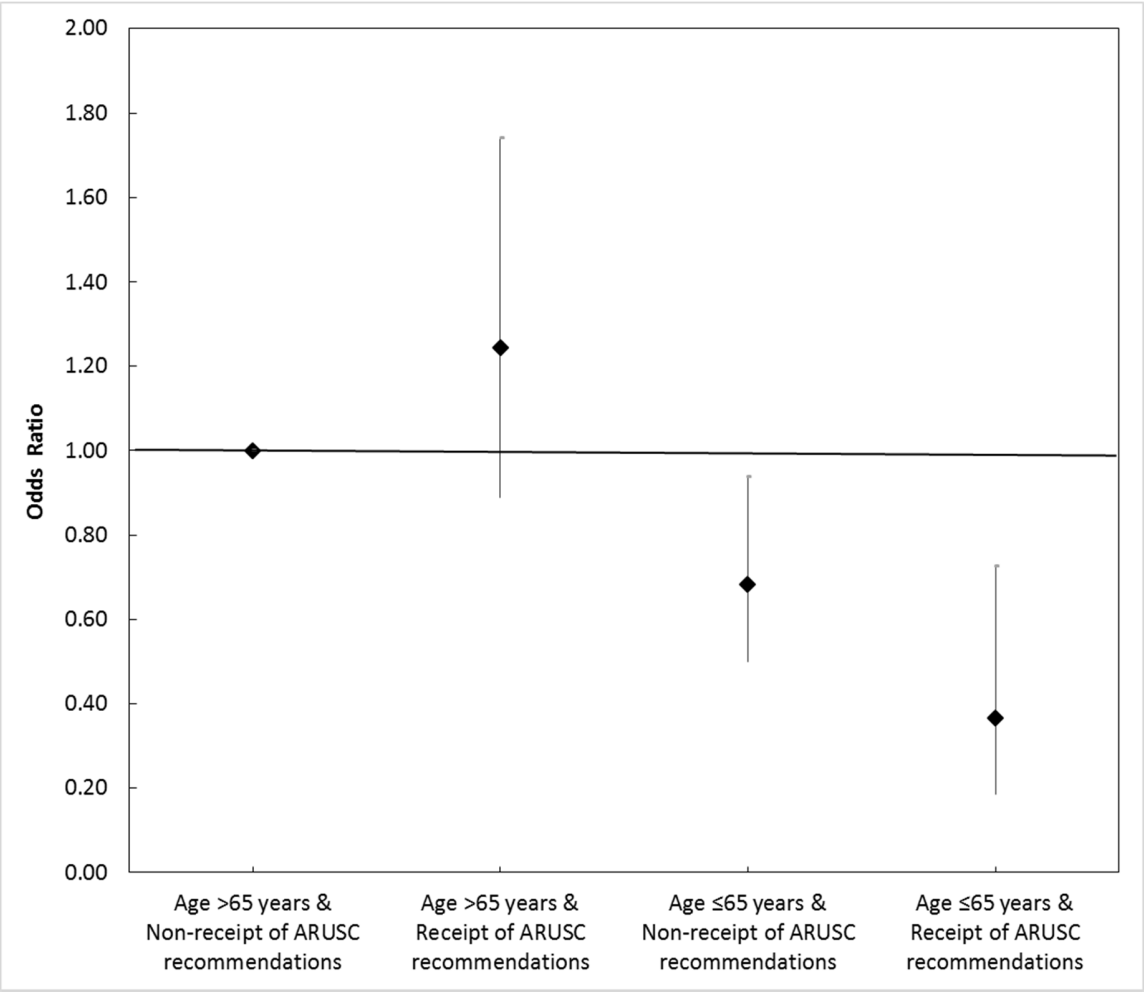
Abbreviations: ICC, intraclass correlation coefficient; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

[a] Propensity score derived from diagnosed infection, time and day of antibiotic prescription, hospitalization days prior to antibiotics, prior hospitalization, prior antibiotics, and prior proton pump inhibitors.

[b] Propensity score derived from diagnosed infection, time and day of antibiotic prescription, hospitalization days prior to antibiotics, prior hospitalization, and prior antibiotics.

[c] Survivors of hospitalization episode only

Figure 6.1. Joint effects of age and receipt of ARUSC recommendations on 30-day all-cause mortality risk



6.5 DISCUSSION

We found that the receipt of ARUSC antibiotic recommendations reduced the risk for 30-day all-cause mortality in patients aged 65 years and below (OR 0.45, 95% CI 0.20-1.00, *P* = 0.05), and did not increase the risk in older patients >65 years old (OR 1.28, 95% CI 0.91-1.82, *P* = 0.16). A recent meta-analysis on the effect of antimicrobial stewardship interventions intended to increase appropriate antimicrobial therapy for all infections reported no increase in mortality (combined risk ratio 0.91, 95% CI 0.81-1.06, *P* = 0.25) (9). In the limited studies on the clinical effects of antibiotic CDSS in hospitals in the US, Europe, and Australia, no difference was observed in 30-day mortality (17,35,63). In a more recent study in Germany on ICU patients with sepsis, low adherence to CDSS recommendations was found to be associated with increased risk of ICU mortality (OR 2.43, 95%CI 1.13-5.24, *P* = 0.02) (39). Our study will add to the body of literature on the effects of antibiotic CDSS. CDSS presents a promising future for optimizing antibiotic selection and improving clinical outcomes (27,64). More studies are needed in different settings, including Asia (64). To our knowledge, this study is the first to report on the effects of an antibiotic CDSS in an Asian hospital. Furthermore, none of the previous studies has explored the modifying effects of patient factors on clinical outcomes. Our study showed that the joint effect of younger age (<=65 years) and ARUSC recommendation on the reduction of mortality risk was larger than the combination of each of the component effects of younger age and ARUSC recommendation (OR 0.37, 95% CI 0.18-0.72, *P* = 0.004). Targeted efforts should be made to promote ARUSC to physicians managing younger patient populations.

We further observed that ARUSC had no effect on the subsequent development of CDI (OR 1.02, 95% CI 0.34-3.01, *P* = 0.97) and MDRO infection (OR 1.06, 95% CI 0.42-2.71, *P* = 0.90) among patients. Although decreases in CDI and MDRO infection have been reported in studies on antibiotic restriction and antimicrobial stewardship policies, the effect of antibiotic CDSS on such

infections have not been studied (9,55,61). Previous studies have employed quasi-experimental before-and-after study designs which are prone to ecologic bias. In contrast, our study followed up individual patients longitudinally for the development of CDI and MDRO infection.

Among survivors, patients who received ARUSC-recommended antibiotics did not have an increased incidence of 30-day infection-related readmission (OR 1.16, 95% CI 0.48-2.79, P = 0.74). Other studies have observed an increase in hospital readmissions associated with antimicrobial stewardship interventions intended to decrease excessive antibiotic prescribing (combined risk ratio 1.26, 95% CI 1.02-1.57, P = 0.03), but did not observe a difference between intervention and control groups for infection-related readmissions (9). However, there has been no published literature on the effect of CDSS on readmissions.

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 or 180 days after antibiotic initiation. 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 was likely to be minimal. Bias analysis revealed that the potential misclassification of CCI had no influence on the outcome. Unlike most studies assessing adherence to antibiotic guidelines and which involved study investigators manually reviewing prescriptions that may be error-prone and biased by low inter-rater reliability, our study electronically matched antibiotics prescribed on the CPOE system with ARUSC recommendations to determine patient receipt of ARUSC recommendations. Hence, exposure

measurement was not subject to differential misclassification. Furthermore, we were able to analyze individual patient-level data on their clinical outcomes; hence, our study was not prone to any ecologic bias.

Second, our study used multilevel modelling techniques to account for the clustering of patients within prescribing physicians, and attending physicians and clinical specialties. Many previous studies were not able to do so, and employed standard modelling techniques. The multilevel models provide an improved ability to model clinical outcomes (8). We were able to study and estimate the relative plausible effects of the prescribing physician, attending physician, and clinical specialty on clinical outcomes.

Third, we derived propensity scores and used doubly robust estimations to compare effects. The corroboration of results from the different methods supported our findings. We further adjusted for potential selection bias in our models and our conclusions remained unchanged.

Our study may have been limited by our inability to capture unmeasured patients' and physicians' factors, due to the non-availability of those data electronically. However, critical patient factors that could influence clinical outcomes were available and included in our models. Prescribing and attending physicians were not found to contribute substantially to the variability in clinical outcomes. Hence, the non-availability of detailed information on physicians is unlikely to bias our results. Our study population did not include children, and our findings cannot be generalized to pediatric populations. Nonetheless, our findings may be relevant to other adult tertiary-care centers with antibiotic CDSS.

This study provided insight into the comparative effectiveness of an antibiotic CDSS in an Asian hospital. The receipt of CDSS antibiotic recommendations reduced the 30-day all-cause mortality risk in patients aged 65 and below, and did not seem to increase the risk in older patients. Physicians should be made aware of the mortality benefits to patients in order to increase their use of CDSS recommendations in their clinical practice.

7. CONCLUSIONS

This dissertation investigated physician and patient factors associated with physicians' acceptance or patients' receipt of computerized antibiotic stewardship intervention, the comparative effectiveness of computerized antibiotic stewardship intervention on individual patients' clinical outcomes, and the modifying effects of patient factors on the clinical outcomes.

Using a mixed methods approach that triangulated data from qualitative FGDs and a quantitative study, we evaluated physicians' perceptions and attitudes toward an antibiotic CDSS and determined psychosocial factors associated with physicians' acceptance of CDSS recommendations for empiric antibiotic therapy. Previous studies on antibiotic prescribing behaviors have been either qualitative or quantitative in nature (70,71).

Five themes emerged from the qualitative phase, including "trust in CDSS's recommendations" and "patient factors". Five latent factors were derived from the quantitative survey, which included the "willingness to consult CDSS for common and complex infections" and "preference for personal or team decision over CDSS". We developed a new instrument that demonstrated high reliability (Cronbach's alpha of 0.64 to 0.88) for the measurement of physicians' attitudes and perceptions toward the acceptance of CDSS recommendations. To date, there is no such validated scale available. The tools developed and validated in this study would facilitate similar studies in other hospital settings.

We observed that both junior and senior physicians expressed confidence in the credibility of the antibiotic CDSS's recommendations. However, senior physicians acknowledged having to override CDSS recommendations for complex patients with multiple infections or allergies.

Willingness to consult CDSS for common and complex infections was positively associated with acceptance of CDSS recommendations (OR 1.68; 95%CI 1.16–2.44), while preference for personal or team decision was negatively associated (OR 0.61; 95%CI 0.43–0.85). Physicians' willingness to consult an antibiotic CDSS determined the acceptance of its recommendations. Physicians would choose to exercise their own or clinical team's decision over the CDSS recommendations in complex patient situations when the antibiotic prescribing needs were not met. Our study is the first to describe the psychosocial determinants of physicians' acceptance of recommendations by an antibiotic CDSS. Previous studies have reported determinants of physicians' adoption of antibiotic CDSS (77), but not of acceptance of recommendations by such systems. Understanding these factors would help in the design of new systems and the enhancement of existing ones.

Using a cohort of 1886 inpatients who were prescribed piperacillin-tazobactam or a carbapenem for empiric therapy and auto-triggered to receive antibiotic recommendations by the hospital's homegrown antibiotic CDSS, we examined patient and physician factors associated with patients' receipt of antibiotic CDSS recommendations.

Our study was able to use multilevel modelling 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 modelling techniques which were prone to type I error. Furthermore, we were able to study and estimate the relative effects of the prescribing physician, attending physician, and clinical specialty on patients' receipt of recommendations by an antibiotic CDSS. Further analyses using log-binomial and Poisson

regression models to estimate risk ratios yielded expectedly smaller effect sizes, but the results corroborated with our findings with the logistic regression models.

We observed that the prescribing physician —but not the attending physician or clinical specialty— accounted for some (13.3%) of the variation in patients' receipt of CDSS recommendations. Prior hospitalization (OR 1.32, 95% CI 1.01-1.71) and presumed pneumonia (OR 6.77, 95% CI 3.28-13.99) were positively associated with receipt of CDSS recommendations, but ICU admission (OR 0.38, 95% CI 0.21-0.66) and renal impairment (OR 0.70, 95% CI 0.52-0.93) were negative predictors. Patients admitted to the ICU and those with renal impairment might have more complex clinical conditions that require a physician's assessment in addition to antibiotic CDSS.

In the longitudinal follow up of the inpatient cohort, we were able to assess the comparative effectiveness of the hospital's antibiotic CDSS on the clinical outcomes of individual patients. 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 was likely to be minimal. Unlike most studies assessing adherence to antibiotic guidelines which involved study investigators manually reviewing prescriptions that may be error-prone and biased by low inter-rater reliability, our study electronically matched antibiotics prescribed on the CPOE system with ARUSC recommendations to determine patient receipt of ARUSC recommendations. Hence, exposure measurement was not subject to differential misclassification. Furthermore, we were able to analyze individual patient-level data on their clinical outcomes; hence, our study was not prone to any ecologic bias.

Our multilevel models provided an improved ability to measure clinical outcomes (8). We were able to study and estimate the relative plausible effects of the prescribing physician, attending physician, and clinical specialty on clinical outcomes. We also derived propensity scores and used doubly robust estimations to compare effects. The corroboration of results from the different methods supported our findings. We further adjusted for potential selection bias using inverse-probability-of-selection-weighting in our models and our conclusions remained unchanged.

We observed that patients' receipt of CDSS recommendations halved the odds of all-cause mortality in patients (OR 0.54, 95% CI 0.26-1.10). Patients aged <= 65 years had a greater mortality benefit (OR 0.45, 95% CI 0.20-1.00) than patients aged >65 (OR 1.28, 95% CI 0.91-1.82). No effect was observed on the incidence of CDI (OR 1.02, 95% CI 0.34-3.01) and MDRO infection (OR 1.06, 95% CI 0.42-2.71). No increase in infection-related readmission (OR 1.16, 95% CI 0.48-2.79) was found in survivors.

Physicians are primarily concerned with individual patients' clinical outcomes rather than the risk of antibiotic resistance in their antibiotic choices. Informing physicians of the mortality benefits to patients can increase their acceptance of CDSS recommendations in their clinical practice, which will result in more appropriate use of antibiotics and the reduction of antibiotic resistance.

This dissertation research has provided new insights into physicians' antibiotic prescribing behaviors and predictors of patients' receipt of computerized antibiotic stewardship intervention, and the much needed evidence on the clinical benefits of computerized antibiotic stewardship interventions, using robust methods to address potential biases and errors that are commonly encountered in clinical epidemiologic studies. Our findings will be particularly useful for American

healthcare institutions, as the US government incentivizes institutions to embrace technology and informatics to improve patient care (Centers for Medicare and Medicaid Services. EHR incentive programs, 2013). Our studies can help healthcare institutions in the planning and design of new antibiotic CDSSs and in the enhancements of existing ones, to promote the optimal use of antibiotics in the global battle against antibiotic resistance.

8. APPENDICES

8.1 APPENDIX I. Antimicrobial Resistance Utilization and Surveillance Control

In 2009, Tan Tock Seng Hospital launched its homegrown antibiotic computerized decision support system, Antimicrobial Resistance Utilization and Surveillance Control (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. 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.

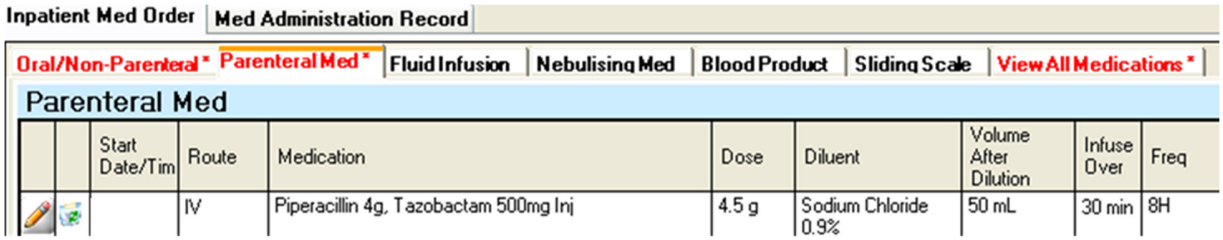


Figure 1. Screenshot of the hospital's computerized physician order entry (CPOE) system. When piperacillin-tazobactam is ordered on the CPOE, it will automatically launch ARUSC.

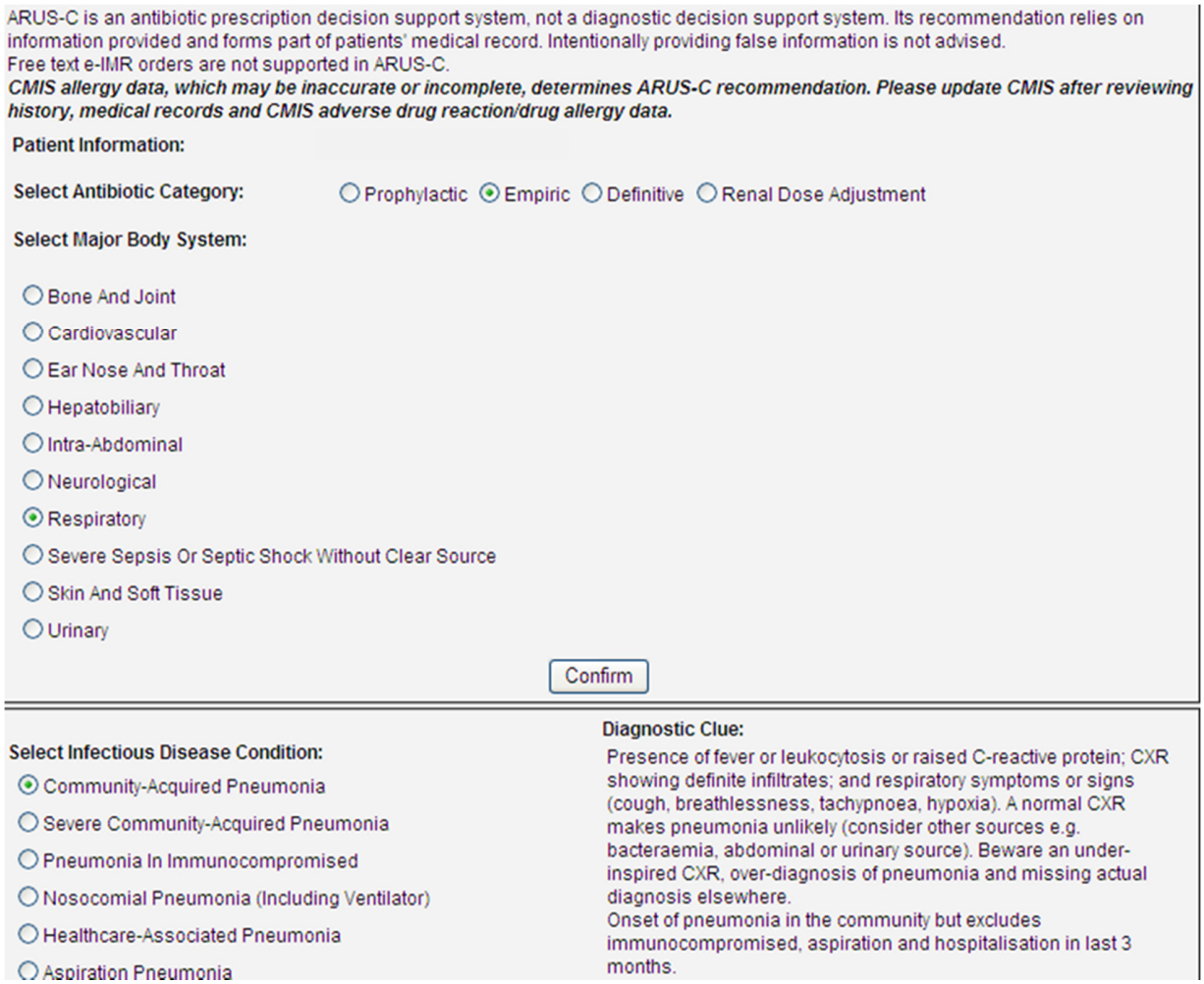


Figure 2. Screenshot of the first page of ARUSC when launched. As the patient's microbiologic results are pending and the patient is being treated empirically for the infection, the prescribing physician selects "empiric" as the antibiotic category and "community-acquired pneumonia" as the infectious disease condition. Educational clues on diagnosis are also provided (bottom right of screenshot).

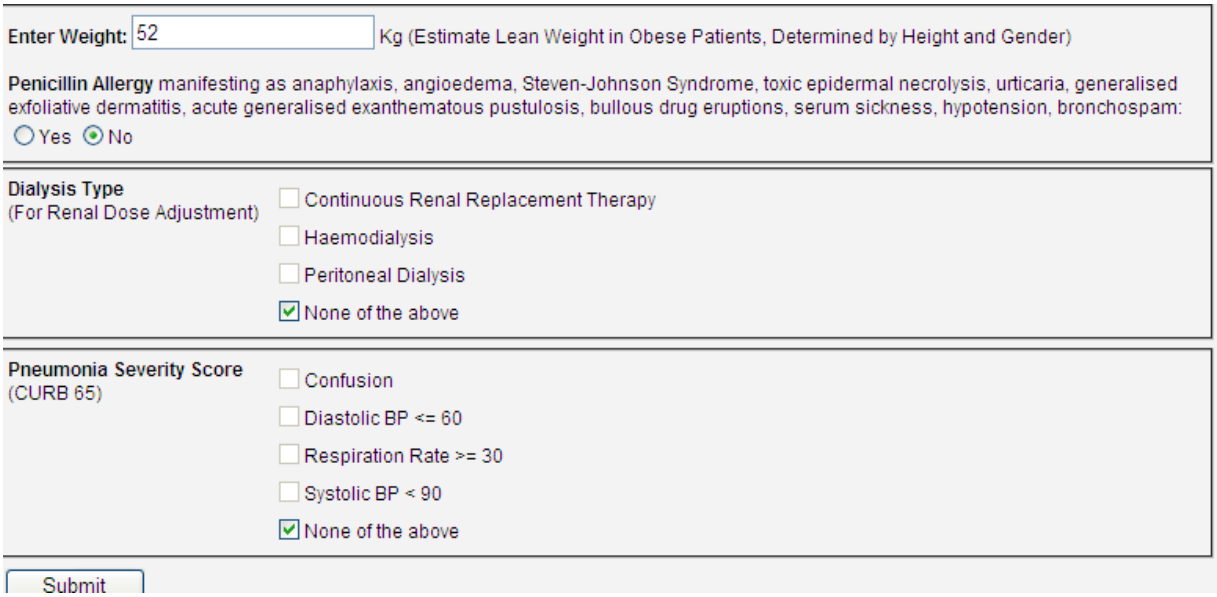


Figure 3. Next, the system prompts the prescribing physician to enter the patient's weight which is used in the auto-calculation of creatinine clearance. As the reported drug allergy information lacks details on severity, the prescriber is requested to confirm the absence or presence of severe penicillin 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 seconds.

Summary of Patient Information

Patient Name: **Patient NRIC:**
Date of Birth: **Gender:** F **Admission Date:**
Major Body System Selected: Respiratory **Antibiotic Category Selected:** Empiric
ID Condition Selected: Community-Acquired Pneumonia

Creatinine: 48 umol/L **Creatinine Clearance:** 79 ml/min
White Blood Cell Count: 11.6 x10 9/L **C-Reactive Protein:** 142.3 mg/L
Urea: 1.5 mmol/L **X-Ray Result:** Abnormal

Severe Penicillin Allergy (Y/N): No **CMIS Reported ADR/DA:** Not Found

Antibiotic Recommendation
Based on data provided, ARUS-C recommends the following antibiotic(s).

+ Monitoring Tests
+ Remarks

Check To Accept	Antibiotic	Route, Dose, Frequency	Start Date	End Date	Estimated cost per standard dose/day
☑	Amoxicillin 1g, Clavulanic Acid 200mg [Co-amoxiclav 1.2g]	IV,1.2 g,8H	11/09/2014	13/09/2014	38.94 SGD
☑	Clarithromycin	PO,500 mg,12H	11/09/2014	13/09/2014	0.68 SGD

Figure 4. Patient's administrative details (Patient Name, Patient NRIC, Admission Date), demographics (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 in 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.

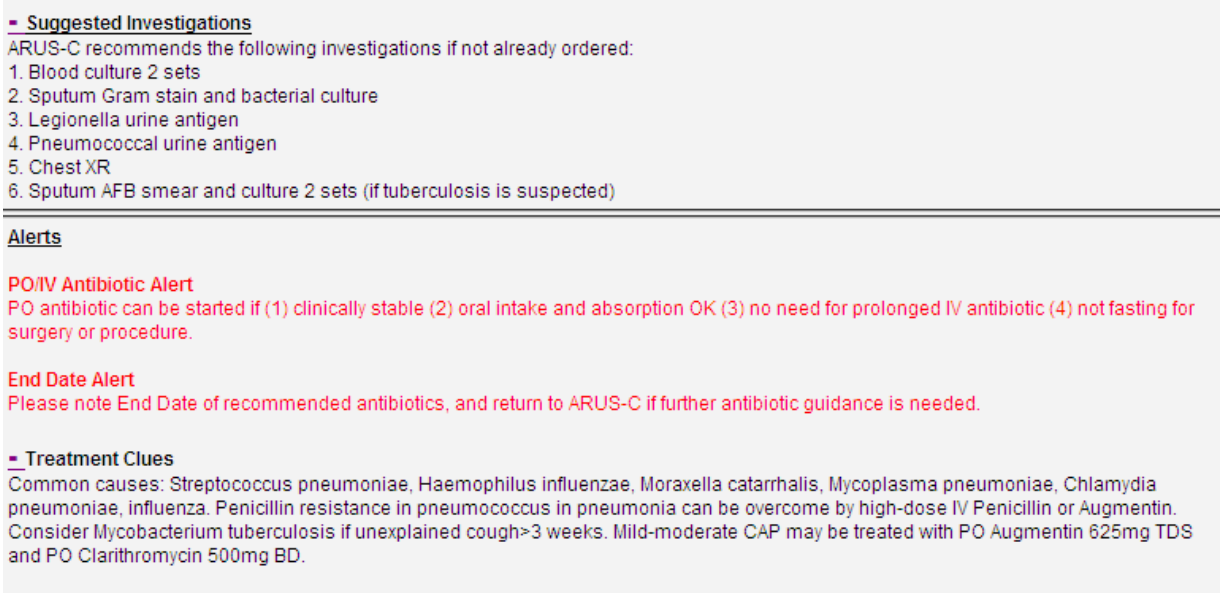


Figure 5. Educational advice on suggested investigations, treatment, and criteria for oral antibiotic step-down is further provided in the next page.

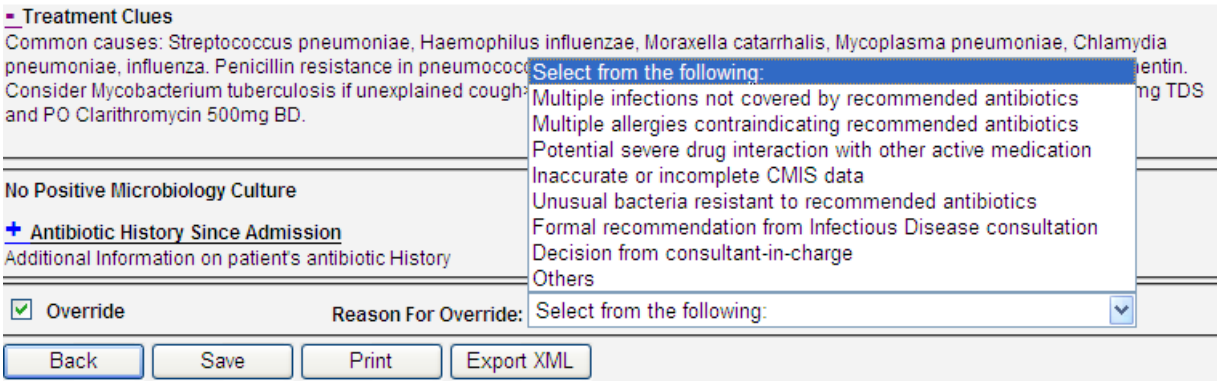


Figure 6. Option is provided for the prescribing physician to override ARUSC's recommendations. If the prescriber accepts the recommendations, clicking on the "Save" button will auto-populate the recommended antibiotics back into the CPOE within 5-10 seconds.

8.2 APPENDIX II. Physician Survey Questionnaire

ANTIMICROBIAL STEWARDSHIP PROGRAMME SURVEY

This is a brief survey of our hospital's Antimicrobial Stewardship Programme.

We are interested in understanding your perceptions of antimicrobial resistance and stewardship in TTSH.

All responses will be anonymous and kept confidential.

Neither your name nor identifying information is required in this survey. Thus, there is no way your supervisor (or colleagues) will know how you've responded to the survey questions.

If you have any questions about this survey, please contact the study PI, Dr Angela Chow, at 6357 7477, or Angela_Chow@ttsh.com.sg .

Thank you for taking the time to complete our survey!

Designation: □ House Officer □ Medical Officer □ Registrar
□ Associate Consultant □ Consultant □ Senior Consultant

Department: _____

Length of practice in Department: □ <3 mths □ 3-6 mths □ 6-12 mths
□ 1-5 years □ >5 years

Length of practice in TTSH: □ <3 mths □ 3-6 mths □ 6-12 mths
□ 1-5 years □ >5 years

For each of the following questions, please indicate your agreement or disagreement for **BOTH** (i) **Empiric** and (ii) **Definitive** therapy:

ASP Guidelines:	**(i) Empiric Therapy** (Prior to availability of laboratory-confirmed culture results)						**(ii) Definitive Therapy** (After laboratory-confirmed culture results are available)					
	Strongly Disagree	Disagree	Neither	Agree	Strongly Agree	N.A.	Strongly Disagree	Disagree	Neither	Agree	Strongly Agree	N.A.
1. I regularly refer to **ASP guidelines** to learn about antimicrobial therapy.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. I regularly refer to **guidebooks** and **apps** (eg. Sanford Guide to Antimicrobial Therapy) to learn about antimicrobial therapy.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. I would refer to ASP guidelines more often during **weekend coverage**, and/or **on-call nights**.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. I use ASP guidelines for **renal dose adjustment**.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. I am confident that the current ASP guidelines are **up-to-date** and **accurate**.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

For each of the following questions, please indicate your agreement or disagreement for **BOTH** (i) **Empiric** and (ii) **Definitive** therapy:

ARUS-C:	**(i) Empiric Therapy** (Prior to availability of laboratory-confirmed culture results)						**(ii) Definitive Therapy** (After laboratory-confirmed culture results are available)					
	Strongly Disagree	Disagree	Neither	Agree	Strongly Agree	N.A.	Strongly Disagree	Disagree	Neither	Agree	Strongly Agree	N.A.
6. For patients presenting with **common** infections (eg. Pneumonia, UTI):												
i) I would **consult ARUS-C** before prescribing antibiotics	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ii) ARUS-C is a useful guide for **de-escalation** (Broad- to Narrow-spectrum)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
iii) ARUS-C is a useful guide for **IV-to-Oral conversion**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
iv) I would exercise **my clinical discretion** when accepting/rejecting an ARUS-C recommendation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
v) I would follow my **team's clinical discretion**, even if it requires me to **override** ARUS-C's recommendation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. For patients presenting with **complicated** conditions (eg. Multiple concurrent infections, Infections in immunocompromised patients):												
i) I would **consult ARUS-C** before prescribing antibiotics	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ii) ARUS-C is a useful guide for **de-escalation** (Broad- to Narrow-spectrum)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
iii) ARUS-C is a useful guide for **IV-to-Oral conversion**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
iv) I would exercise **my clinical discretion** when accepting/rejecting an ARUS-C recommendation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
v) I would follow **my team's clinical discretion**, even if it requires me to **override** ARUS-C's recommendation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. ARUS-C is useful as it allows us to consider the following factors, when making an antibiotic recommendation:												
i) Current microbiology results and antibiogram (antibiotic sensitivity patterns)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ii) Current laboratory parameters (eg. WBC, CRP)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
iii) Drug allergies	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

For each of the following questions, please indicate your agreement or disagreement for **BOTH** (i) **Empiric** and (ii) **Definitive** therapy:

ARUS-C:	**(i) Empiric Therapy** (Prior to availability of laboratory-confirmed culture results)						**(ii) Definitive Therapy** (After laboratory-confirmed culture results are available)					
	Strongly Disagree	**Disagree**	**Neither**	**Agree**	**Strongly Agree**	**N.A.**	**Strongly Disagree**	**Disagree**	**Neither**	**Agree**	**Strongly Agree**	**N.A.**
9. I feel that ARUS-C should also include the following (additional features):												
i) My patient's current clinical status	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ii) Microbiology results and antibiogram from previous admissions	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
iii) Past medical history	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
iv) Rationale for antibiotic recommendations (eg. Amoxicillin-clavulanate is recommended for Community-Acquired Pneumonia as current evidence suggest that the most common cause is *Streptococcus pneumoniae* and local strains tend to be resistant to macrolides)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
v) Others (please specify):												
10. I refer to ARUS-C more often during **weekend coverage**, and/or **on-call nights**.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. ARUS-C provides educational information for team-based discussions on antimicrobial therapy.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. I use ARUS-C for **renal dose adjustment**.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Process evaluation: In general, I would have to go through **many procedural steps** to obtain an ARUS-C recommendation.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
14. In general, ARUS-C's user interface is **organized and easy to navigate**.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

For each of the following questions, please indicate your agreement or disagreement:

	Strongly Disagree	Disagree	Neither	Agree	Strongly Agree	N.A.
15. Antibiotic resistance is a problem in TTSH.	☐	☐	☐	☐	☐	☐
16. In general, TTSH provides adequate staff education on antibiotic prescribing and antimicrobial resistance	☐	☐	☐	☐	☐	☐
17. In general, ASP physicians' recommendations are useful in guiding antibiotic prescribing practices.	☐	☐	☐	☐	☐	☐
18. In general, ASP pharmacists' recommendations are useful in guiding antibiotic prescribing practices.	☐	☐	☐	☐	☐	☐
19. In general, Blood Culture Service is useful in guiding antibiotic prescribing practices.	☐	☐	☐	☐	☐	☐

Please rank the following items (**1: Most preferred** & **6: Least preferred**):

20. In general, I would accept a recommendation from:	**ASP Pharmacist**	**ASP Physician**	**ASP Guideline**	**ARUS-C**	**Blood Culture Service**	**ID Blue Letter**

21. I would like to obtain ARUS-C's recommendations through a mobile app: **Yes** ☐ **No** ☐

SUGGESTIONS TO IMPROVE ASP GUIDELINES/ARUS-C:

_____

_____

THANK YOU

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