Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial
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INSPIRE (INtelligent **S**tewardship **P**rompts to **I**mprove **R**eal-time **E**mpiric **A**ntibiotic **S**election for **P**atients with Pneumonia): The **INSPIRE-ASP Pneumonia Trial Protocol**

A. Background and Goals

A.1.1 Overuse of Antibiotics in the United States

Close to forty percent of patients admitted to U.S. hospitals receive an antibiotic to treat an active infection, with over half of these antibiotics used to treat just two conditions, pneumonia and urinary tract infection (UTI).[1] In treating these infections, the Centers for Disease Control and Prevention (CDC) has found that antibiotic prescribing could be improved in 35-40% of patients.[2] This is critical, as there is a growing threat of antibiotic-resistant bacteria which now infect ~2 million people per year in U.S. hospitals and communities as well as at the global level.[3-5] Concerns about resistance are an important driver of extended-spectrum antibiotic prescribing, which in turn promotes further resistance.[6,7]

Rising antibiotic resistance and the slow development of novel antibiotics have fueled national calls to improve antibiotic choices by frontline physicians.[8-13] There is a 2020 target to reduce "inappropriate" antibiotic prescribing in hospitals by 20%, as discussed in the 2014 "National Strategy for Combating Antibiotic-Resistant Bacteria" released by the White House.[12] While physicians agree that antibiotics are overprescribed, most fail to recognize areas for self-improvement.[14,15] Therefore, hospitals have been charged with developing antimicrobial stewardship programs which provide ongoing education and feedback to physicians and ensure accountability in prescribing.[10,16] To improve the success of these efforts, it is critical to develop evidence about best practices for improving judicious antibiotic prescribing. Evidence, engagement, and education are required to build a culture where it is accepted that rationale antibiotic prescribing is every physician's responsibility.[21]

A.1.2 Multidrug-Resistant Organisms as Drivers of Empiric Extended-Spectrum Inpatient Antibiotic Use

There are many facets of inappropriate antibiotic prescribing, including prescribing antibiotics when they are not indicated, starting unnecessarily broad empiric antibiotics for a patient's condition, selecting the wrong dose or duration, and failing to re-evaluate the choices that have been made. Empiric therapy refers to the selection of an antibiotic prior to knowledge regarding the specific pathogen. We focus here on improving the empiric selection of antibiotics for hospitalized patients that have an appropriate indication.

When selecting initial antibiotics for common community-acquired conditions that cause admission, such as pneumonia and urinary tract infection (UTI), physicians vary widely in their adherence to national guidelines.[18-20] This is often due to misperceptions that multidrug-resistant organisms (MDROs) are more common than they actually are, or beliefs that extended-spectrum antibiotics are more effective in curing infections than standard-spectrum choices, even for pathogens sensitive to standard-spectrum agents.[21] Often, such perceptions are based on studies on critically ill patients and those with infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase producing (ESBL) Enterobacteriaceae.[22-28]

In 2005, the American Thoracic Society and the Infectious Diseases Society of America classified patients with recent healthcare exposure as having a higher risk of MDROs as the infecting pathogen in pneumonia. National guidelines recommended giving empiric extended-spectrum antibiotics to address this potential risk.[29-32] Not surprisingly, the use of extended-spectrum antibiotics has increased.[34] Despite guideline recommendations to consider the local prevalence of MDROs, there has been little guidance on how best to assess local MDRO prevalence.

A.1.3 Knowledge Gaps for Judicious Empiric Antibiotic Prescribing

In understanding the appropriateness of empiric antibiotic selection, it is important to note that the criterion of recent healthcare exposure is a poor predictor of having an infection due to an MDRO.[35,36] In fact, use of empiric extended-spectrum antibiotics has not been associated with differences in mortality in several single or small multicenter studies.[35-38] Furthermore, even when empiric antibiotics are found to be discordant with pathogen antibiotic susceptibilities, transient use of discordant therapy followed by correction to appropriate therapy has not been found to have negative outcomes in single-center studies of non-critically ill patients.[39,40] Thus, several antibiotic stewardship experts have advocated reserving extended-spectrum antibiotic therapy for patients with culture-proven resistance, except in critically ill patients or in hospitals with a high local incidence of MDRO infections.[41] This position may be further justified by the fact that extended-spectrum therapy, often involving more than one drug, has been associated with a higher risk of *Clostridium difficile* infections and increased risk of colonization or subsequent infection with MDROs.[42-44] An additional reason to initiate standard-spectrum therapy is that prescribers rarely modify antibiotic regimens, even after cultures reveal susceptible strains.[45]

To reduce the overuse of extended-spectrum antibiotics as empiric therapy for pneumonia, hospitals have utilized both labor-intensive auditing with feedback and education, as well as point-of-care interventions aimed at changing prescribing practices.[43, 46-49] Nevertheless, successful interventions to improve antibiotic prescribing in hospitals have been called “the missing care bundle,”[50] highlighting the fact that we lack certainty and generalizability in understanding which strategies best effect change in prescribing behavior.

A.1.4 Incorporating Local Evidence into Decision-Making

Knowledge of local and hospital prevalence of MDROs can be an important consideration when determining whether to empirically use extended-spectrum agents. This information is commonly obtained through antibiograms from the clinical microbiology laboratory which note the proportion of each pathogen that tested resistant to common antibiotics in the recent past. The intent of these local antibiograms are to assist physicians in their choice of empiric antibiotics,[51] and to influence hospital guidelines for appropriate antibiotic prescribing.[52-55] Nevertheless, antibiograms are difficult to use when the pathogen is unknown since physicians have to extrapolate the probability that the infection is due to a particular pathogen. As mentioned above, physicians are expected to use local antibiogram data from their microbiology laboratory to determine the risk of an MDRO infection in a given patient.[51-54,92] Yet, these data are not presented in a manner helpful to clinical decision-making.[93] For example, national data shows that over 50% of *S. aureus* are resistant to methicillin (MRSA), and 22% of *E. coli* and 30% of *P. aeruginosa* are resistant to fluoroquinolones.[94]

These data may be misinterpreted as the probability that a patient has an MDRO infection. However, when accounting for the likelihood that a patient is infected with these pathogens, the risk of MDRO infection drops substantially. In two recent studies of patients presenting from the community with pneumonia, there was a 2.5-4.6% risk of MRSA, a 1.0-1.9% risk of Gram-negative *Enterobacteriaceae*, and a 0.7-1.2% risk of *P. aeruginosa* resistant to standard-spectrum antibiotics.[26,94-95]

Instead of providing the MDRO risk by pathogen, physicians would be better served by alerts providing the local probabilities of resistance for specific types of infections. Though precision medicine tools in antibiotic stewardship are lacking, there is evidence that precision medicine approaches can substantially improve patient care.[56-59] This involves reformulating a hospitals’ antibiogram data into disease-specific probabilities of MDRO infection to facilitate appropriate prescribing.

A.1.5 Identifying Best Strategies for Ensuring Judicious Antibiotic Choices

Best strategies for ensuring appropriate antibiotic prescribing have not been evaluated in clinical trials. Most evidence is based upon single center publications which are subject to unique hospital prescribing culture and beliefs. Much has been described about inpatient

antimicrobial stewardship programs and the use of various electronic alerts and labor intensive physician feedback to influence and correct inappropriate prescribing.[46-49, 60-65,-52, 68-72] Furthermore, antibiotic use and choice is highly variable among prescribers, particularly in community hospital settings and prescribing behavior is often difficult to change with conventional methods.[73-75]

A.1.6 Definition of Standard-Spectrum and Extended-Spectrum Antibiotics

National guidelines recommend selection of either a fluoroquinolone such as levofloxacin, or a 3rd generation cephalosporin such as ceftriaxone as empiric therapy for patients presenting from home or clinic and meeting criteria for hospitalization due to pneumonia.[18-20] There is growing evidence that fluoroquinolones are associated with serious adverse drug reactions and an increased risk of C. difficile colitis.[99-101] The Food and Drug Administration (FDA) has also issued a warning (May, 2016) against the routine use of fluoroquinolones for acute bacterial exacerbation of chronic bronchitis.[102] There is increased national attention to decrease the overall use of fluoroquinolones.

A1.7 Adverse Effects of Inappropriate Antibiotic Use

Inappropriate use of antibiotics, particularly extended-spectrum antibiotics have been shown to increase a patient's risk for future MDRO, length of stay, risk for *C. difficile* colitis, healthcare costs, and mortality.[99,103] Data are emerging that there is time to await definitive culture data to inform antibiotic treatment and that a delay in antibiotics targeting resistant organisms is not necessarily harmful and may improve outcomes.[103-105]

B. INSPIRE-ASP Pneumonia Trial Study Design & Population

B.1.1 INSPIRE-ASP Pneumonia Trial Study Design & Population

The INSPIRE-ASP Pneumonia Trial is a two-arm cluster-randomized trial in HCA hospitals comparing routine empiric antibiotic prescribing for patients admitted with pneumonia to prescribing informed by point-of-care precision medicine computerized physician order entry (CPOE) smart prompt for adult patients admitted to general medical or surgical floors. The unit of randomization will be the hospital. The trial will begin with a six-month phase-in period from October 1, 2018-March 31, 2019, followed by a 15-month trial intervention period between April 1, 2019-June 30, 2020. For analysis purposes, the cohort will be defined as adult patients with a primary or secondary claims code indicating pneumonia that is present on admission, did not transfer directly from the ED to ICU, and is treated with an antibiotic within the first 3 days of hospitalization. A baseline period between April 1, 2017-September 30, 2018 will be utilized for comparison with the intervention period at each hospital. Per guidance from the Office for Human Research Protections (OHRP), prisoners will not be included in this trial. Prescribers and antibiotic stewardship teams in intervention facilities will be trained (e.g., coaching calls, usual communication channels (email, flyers)) that prisoners should be excluded from the trial (i.e., the CPOE smart prompt should not be acted upon for these individuals). Data for any prisoners that may be inadvertently included in study datasets will be removed prior to analyses using claims data as well as admission/discharge/transfer codes indicating 'Court/Law Enforcement'.

B.1.2 HCA Healthcare Infrastructure for the INSPIRE-ASP Intervention Arm

HCA Healthcare currently requires physicians to provide an indication when an antibiotic is ordered (see **Appendix B** for example CPOE indication screens). For facilities assigned to the intervention arm of the INSPIRE-ASP Pneumonia Trial, an INSPIRE CPOE smart prompt will be triggered when physicians prescribe an extended-spectrum (ES, **Table 1**) for a

pneumonia indication in the first three days of a hospital stay. This CPOE smart prompt will provide clinicians with a patient-specific estimate of the likelihood that the pneumonia is due to the associated target pathogens (e.g. MRSA, Pseudomonas, ESBL, or CRE, **Table 1**). The smart prompt will also provide guidance for appropriate empiric antibiotic options per trial protocol and hospital policy.

For example, if an anti-MRSA antibiotic is being ordered for pneumonia, the clinician will receive a prompt during the ordering process providing the probability that the patient has pneumonia due to MRSA. Recommendations for using standard-spectrum antibiotics (e.g. ceftriaxone) will be made when the probability of a given MDRO is lower than a given threshold (e.g., <10%). This threshold used in the trial will be finalized after evaluation of the prevalence of MDROs, and after discussion with the INSPIRE-ASP Steering Committee. Similarly, if an ES antibiotic is selected that targets a resistant Gram-negative *Enterobacteriaceae* or *Pseudomonas aeruginosa*, the ordering physician will receive information on the probability that the patient is likely to grow such organisms. The smart prompt will account for personal attributes of the patient as well as local resistance patterns. Hospitals randomized to routine care will continue their baseline stewardship activities, principally involving a decision support tool known as Rx VigiLanz Therapeutic Advisor, which has been adopted by all HCA hospitals. This tool alerts stewardship teams of possible opportunities for intervention, based on microbiology results. Intervention hospitals will also continue these activities.

The study population is defined at the hospital level, where the intervention will be adopted as part of a hospital-wide antibiotic stewardship quality improvement initiative targeting non-ICU adult patients admitted with pneumonia. Hospitals eligibility criteria are outlined in **Section B.1.3**.

Table 1: INSPIRE Pneumonia Trial Extended-Spectrum Antibiotics

Pathogen-Directed Antibiotic Category	Extended-Spectrum Antibiotics Targeted in INSPIRE Pneumonia CPOE Prompts
Anti-MRSA	Ceftaroline, Daptomycin[a], Linezolid[b], Vancomycin[c]
Anti-VRE	Daptomycin, Linezolid[b]
Antipseudomonal	Aztreonam, Cefepime, Ceftazidime, Piperacillin/Tazobactam
Anti-ESBL	Ertapenem, Meropenem, Imipenem, Ceftolozane/Tazobactam
Anti-CRE	Ceftazidime/Avibactam, Colistin, Imipenem/Relebactam, Meropenem/Vaborbactam, Polymixin B, Tigecycline

[a]Daptomycin not an accepted pneumonia treatment but included in trial analysis in case ordered.
[b]Both oral and intravenous (IV) formulations.
[c]IV formulation only.

Abbreviations: **CPOE** – Computerized Provider Order Entry, **MRSA** – Methicillin-Resistant *Staphylococcus aureus,* **ESBL** – Extended-Spectrum Beta-Lactamase Producing Enterobacterales including *Acinetobacter* and *Pseudomonas* species with multidrug-resistance to antipseudomonal antibiotics but can be treated with a carbapenem or ceftolozane/tazobactam, **CRE** – Carbapenem-Resistant Enterobacterales, including Carbapenem-Resistant *Acinetobacter* and *Pseudomonas* species

B.1.3 Recruitment and Eligibility Criteria

Hospitals are eligible to participate if they serve adult patients with pneumonia, are affiliated with the HCA Healthcare and have had MEDITECH as their electronic health record system for at least one year. Target recruitment is a minimum of 40 participating facilities.

Recruitment will be similar to our previous HCA Healthcare trials. First, we will provide webinars through HCA Healthcare's webhosting system to introduce the trial and call for participation. Second, a call for participation will be made by corporate leadership through pharmacy and antibiotic stewardship communication channels. Third, our HCA Healthcare co-investigators, who are system-wide leaders of antibiotic stewardship, quality, and infection prevention, will provide direct-to-hospital endorsement for the trial. Recruitment announcements will utilize usual corporate and local hospital HCA Healthcare communication channels and will be directed at hospital leadership as well as pharmacy and antimicrobial stewardship/infectious diseases leaders. Participation will be confirmed by a signed letter of participation from the individual hospitals' CEOs.

For each hospital participant indicating interest, enrollment criteria will be assessed by administering two electronic surveys. First, a contact survey will be distributed. Second, a facility survey will be distributed to confirm eligibility criteria and obtain information on hospital characteristics and antibiotic stewardship program activities. As done in our previous HCA Healthcare trials, surveys will be administered through HCA Healthcare usual survey channels and results will be compiled and returned to investigators in a database format.

B.1.4 Centralized IRB

Centralized IRB coordination will occur through the Harvard Pilgrim Health Care (HPHC) IRB. HCA Healthcare corporate regulatory affairs and risk management liaison will facilitate delegation of IRB governance from each participating hospital and ensure human subjects training through HCA- Healthcare approved programs. We submit that this intervention of a quality improvement strategy for antibiotic stewardship meets national regulatory standards for waiver of informed consent under the Office of Human Research Protections (OHRP) criteria 45 CFR 46.116(d), 117(c) (2) and Food and Drug Administration (FDA) CFR 56.109(c) (1).(38) since 1) trial activities meet minimal risk criteria, 2) the trial randomizes hospitals, not patients, to a quality improvement strategy, 3) the intervention is not designed to supplant physician judgment, but rather provide relevant information to prescribing physicians who will be educated to choose the treatment they deem most clinically appropriate for individual patients, and 4) all assigned activities will be performed according to usual hospital quality improvement procedures. We will also collect attestations from hospital antibiotic stewardship programs stating that they will continue routine antibiotic stewardship efforts.

B.1.5 Randomization

While this study represents a large cluster-randomized trial of hospitals, simple randomization of hospitals will not ensure balance of key variables by chance alone, and without care could even result in very unequal numbers of hospitals in each arm. Achieving balance on key features of the randomization units (in this case, hospitals) is a critical task in cluster-randomized trials, but little literature on it exists. Unlike individually-randomized trials, information about the clusters is often known in advance, but the number of clusters to be randomized can be relatively small. The existence of a priori data can mitigate the small numbers and help to obtain adequate balance through stratification or other methods. One attractive approach is to establish tuplets—matched sets (pairs, for a two-arm trial) – in which one member of each tuplet is assigned to each arm. Schemes for constructing tuplets need not be guided by theory. A formal approach would be to calculate the Mahalanobis distance between hospitals across all key variables and choose the set of tuplets with the minimum average distance. In this approach, we could standardize the variables, and then multiply by values calibrated to reflect any difference in the importance of balancing them. Other approaches are more ad hoc, such as prioritizing broad classes of balance on a key variable and making pairs within these strata based on lower-priority variables. However, there is no "best" method of tuplet construction, only sets that come closer to meeting the varied needs of each trial.

We will establish the pairs under several plausible tuplet-construction schemes, and use graphical methods to compare all possible realizations for balance between the arms under each scheme. For example,

if two variables were to be balanced, we would tentatively divide the sample into two groups under a tuplet construction scheme and then generate a scatterplot showing the between-arm absolute value of the mean difference for one variable on the x-axis and the second on the y-axis for each possible result of the randomization. We would then divide the groups again under the same scheme, and find another point on the scatterplot. Repeating many times would show the typical and distribution of balance under a scheme. Comparing the resulting scatterplots from each tuplet-construction scheme can reveal the relative risks of imbalance and benefits for balance accruing to each randomization scheme, in a practical sense. One tuplet construction method may result in generally close balance on one key characteristic and very variable balance on the other, while a competing scheme has good median balance on both characteristics, but where each has a long tail implying a few bad-luck assignments with poor balance.

We hope to consider balance on more than two factors, and for assessing the impact on balance in this case, we will use a parallel coordinates plot, a multivariate plot method. After determining key variables where balance across the arms would be highly desirable, we will plot the mean difference between the arms for all key variables for each potential realized randomization.

We will focus on balancing the baseline outcome values in participating hospitals and certain key factors that may be associated with pneumonia such as facility pneumonia admission volume, local prevalence of antibiotic resistance in pneumonia patients, length-of-stay, ICU transfers, and facility case mix of patients with pneumonia. Hospitals that share antibiotic stewardship personnel will be treated as a single hospital unit since the intervention will be overseen by local antibiotic stewardship teams.

B.1.6 Baseline Period Activities

The baseline period will be a 18 month period from April 1, 2017 - September 30, 2018, prior to the phase in and will share a similar month distribution as the intervention period. This period will provide baseline outcome data for both arms (see Analysis **Section B.1.10**). In addition to recruitment and randomization, preparatory activities for Phase-In and Intervention Periods will also begin. The corporate HCA Healthcare Information Technology (IT) team will develop the CPOE smart prompt template which will include creation of smart prompt algorithms, automated compliance reports, and centralized beta testing. CPOE smart prompts will use MDRO infection risk estimates developed in a separate retrospective cohort study. Educational materials and training modules will be developed as described below.

B.1.7 Phase-In Period Activities

There will be a six month Phase-In period prior to the intervention period. This Phase-In period will be from October 1, 2018-March 31, 2019 and is necessary for three key reasons. First, since the intervention will occur as a quality improvement initiative to be adopted at the hospital level, hospital study champions will need time to garner relevant committee approvals and support from key hospital stakeholders. For some hospitals, this may require in-person presentation and support from investigators to affirm the protocol for evidence-based empiric antibiotic recommendations based on local probabilities of the various MDROs from evidence developed in Aim 1 above. Second, we anticipate that physician behavior change will require time for feedback and response. Third, the implementation of the CPOE smart prompt requires both corporate and local IT department efforts. This will require time to accurately implement and ensure sufficient validation and refinement for proper function at each participating intervention arm hospital.

During this period, educational materials will be distributed to study champions at each participating intervention hospital (**Table 2**). In addition, study site champions at intervention facilities will participate in coaching calls monthly during the Phase-In period, ultimately transitioning to every other month calls when implementation and feedback stabilizes. Special coaching calls will also occur at least quarterly for both arms and involve best practice stewardship recommendations from national guidelines and experts. All coaching calls will be led by trial investigators with active attendance and support by HCA Healthcare leadership. Coaching calls will involve a shared PowerPoint slide set followed by a question and answer session. All coaching calls will be recorded and placed on arm-specific INSPIRE-ASP Pneumonia Trial sites on the HCA Healthcare intranet for continued access by designated participants in each arm. Participants will be highly encouraged to share concerns and solutions with one another.

Table 2. INSPIRE-ASP Pneumonia Trial Educational Binder and Distributed Material

Topic	Description
1. Trial Summary	Goals and investigative team
2. Frequently Asked Questions	Answers to common questions about the trial or protocol.
3. Roles and Responsibilities	Description of expected roles and responsibilities of pharmacy and physician antibiotic stewardship champions
4. Talking Points	Talking points for common physician and pharmacist questions about the trial or protocol
5. Committee Protocol or Policy Proposal	Description of CPOE smart prompt antibiotic stewardship initiative for committee approval submission to adopt as hospital protocol or policy
6. Kick-Off PowerPoint	PowerPoint slides used in the kick-off webinar
7. Physician Education PowerPoint Presentations	Description of, and basis for, guidance on appropriate antibiotic use for pneumonia, definition of extended-spectrum antibiotic groups, the INSPIRE-ASP MDRO risk estimate and smart prompt, and compliance feedback reports.
8. Feedback	Process for study champions to feedback compliance reports to physicians

B.1.8 Intervention Phase Activities

The automated point-of-care precision medicine CPOE smart prompts will be implemented at each facility randomized to the intervention arm. Automated compliance feedback reports detailing prescriber response to CPOE prompt recommendations will be generated on a rolling 3-month basis (or sooner if available), including reasons for continuing with extended spectrum antibiotic prescribing. Pharmacy/physician study champions will provide feedback to prescribers that show common and consistent deviation from CPOE smart prompt recommendations.

We will have a dedicated study email and toll-free number for study questions. Hospitals that are not represented on coaching calls will receive an email from core staff asking for their responses to polling questions and directing them to the recorded link of the coaching call.

For both study arms, study site champions will be required to confirm that a) no new hospital initiatives have been planned or implemented. If a site reports a new hospital antibiotic stewardship intervention that may represent a direct conflict with the INSPIRE-ASP Pneumonia trial, they will be asked to report the initiative to the trial Steering Committee for determination of trial conflict. Hospitals that implement interventions that conflict with the trial will be given the options of either not pursuing the conflicting intervention or dropping from the trial.

B.1.9 INSPIRE-ASP Pneumonia Trial Outcomes

The goal of this trial is to reduce unnecessary physician prescribing of empiric extended-spectrum antibiotics (Table 8). Trial outcomes evaluating intervention effectiveness are outlined in **Table 3** and will be applied to the study population of adult patients who have an ICD-10 claims code indicating pneumonia is present on admission, who received any antibiotic within 3 days of admission, and who were admitted to a non-ICU location. For admissions initially on a non-ICU floor and transferred to the ICU, analysis will include only admission days on the non-ICU floor within 3 days of admission.

The primary trial outcome is defined as the summed number of different extended spectrum antibiotics received each day, measured repeatedly over the first three days of an admission and divided by the number of days of the admission within the empiric period. An empiric day is a day within the first three days of an admission. We define this outcome as an Extended-Spectrum Days Of Therapy (ES-DOT) per empiric day. Days of therapy (DOT) is specific to each extended-spectrum antibiotic, where any dose is considered one day's worth of therapy. The ES antibiotics are then aggregated to obtain the total ES DOT. For example, if a patient is started on vancomycin and cefepime for 1 day, this will count as 2 ES DOT for that day. Multiple

doses of the same antibiotic received on the same day are only counted as one day of therapy for that extended spectrum antibiotic. This outcome will include antibiotics in **Table 1**.

Table 3: Primary and Secondary INSPIRE-ASP Pneumonia Trial Outcomes

Outcome	Metric
Primary Trial Outcome	
Extended-Spectrum Days Of Antibacterial Therapy (ES-DOT) per Empiric Day	The summed number of different extended-spectrum antibacterials received each empiric day, measured repeatedly over the first three days of an admission and divided by the number of empiric days of the admission. An empiric day is a day within the first three days of an admission.[1]
Secondary Trial Outcomes	
Vancomycin Days of Antibacterial Therapy per Empiric Day	The summed number of days of Vancomycin received each empiric day per at-risk-day (first 3 days of admission)[1]
Antipseudomonal Antibiotic Days Of Therapy (ES-DOT) per Empiric Day	The summed number of different antipseudomonal antibacterials received each empiric day, measured repeatedly over the first three days of an admission and divided by the number of empiric days of the admission. An empiric day is a day within the first three days of an admission.[1,2]

[1]E.g., if a patient is admitted for 2 days, ES-DOT will be calculated for 2 days and divided by 2 empiric days; conversely if a patient is admitted for 4 days, only the first 3 days will be evaluated.

[2]Does not include aminoglycosides or fluoroquinolones.

Safety outcomes planned for the primary manuscript are shown in **Table 4**. Safety outcomes will be analyzed separately from the main effectiveness outcomes of the trial (see Primary Statistical Analysis section below).

Table 4: Other Pre-Specified Outcomes – Safety Trial Outcomes

Safety Trial Outcomes (other pre-specified outcomes)	
Antibacterial Escalations [Safety Outcome]	Days from start of standard-spectrum antibacterial until switch to extended-spectrum antibacterial during hospital stay
ICU Transfers [Safety Outcome]	Days from start of hospitalization until ICU transfer within hospital stay
Length-of-stay [Safety Outcome]	Days from hospital admission to discharge

B.1.10 Analysis

The primary trial outcome is defined as the summed number of different extended spectrum antibiotics received each day, measured repeatedly over the first three days of an admission and divided by the number of days of the admission within the empiric period. An empiric day is a day within the first three days of an admission. We define this outcome as an Extended-Spectrum Days Of Therapy (ES-DOT) per empiric day. For clarity the calculation is as follows: we define a DOT for a particular ES antibiotic as a day in which any number of doses of that antibiotic is given. Different ES antibiotics are summed across the empiric days for each patient admission, then divided by the empiric days for that patient-admission to determine each admission's DOT per at-risk day. If an admission is less than 3 days, only the number of days the patient is admitted will contribute to the numerator and denominator. Antibiotics given during an associated emergency department visit on the date of hospital admission are counted toward the ES-DOT of the first hospital day.

The main trial results will be based upon as-randomized, unadjusted analyses of admission-level ES-DOT per empiric day. We define ES-DOT per empiric day at the individual admission level so that we can perform analyses on individuals.

The trial will be assessed among the cohort of adult admissions who have an ICD-10 claims code indicating pneumonia is present on admission, who received any antibiotic within 3 days of admission, and who were admitted to a non-ICU location. For admissions initially on a non-ICU floor and transferred to the ICU, analysis will include only admission days on the non-ICU floor within 3 days of admission.

The trial periods are defined as follows: (1) Baseline – April 1, 2017 – September 30, 2018 (18 months); (2) Phase-in – October 1, 2018 – March 31, 2019 (6 months); (3) Intervention – April 1, 2019 – June 30, 2020 (15 months).

The unit of analysis will be individual admissions. Individuals can contribute more than one admission. The analytic model will be a generalized linear mixed effects model for differences in differences, with random effects accounting for correlation within cluster, period-varying random effects to allow for differences between hospitals from baseline to follow-up, and admission-level random effects to account for correlation within person and hospital. Analyses of the baseline data, performed before randomization, found no evidence of overdispersion in a Poisson model, and so we plan to use that model for analysis of outcomes. The model can be expressed as follows:

$$log(y_{ijph}) = \beta_0 + \beta_1 A_{ijph} + \beta_2 T_{ijph} + \beta_3 A_{ijph} T_{ijph} + b_{0h} + b_{1h} T_{ijph} + g_j$$

where y_ijph is the ES-DOT per at-risk day for patient i for admission j in period p at hospital h, and A_ijph=1 if hospital h is in the intervention arm and 0 if not, and T_ijph=1 if p is the intervention period and 0 if baseline period. The random effects b_0h and b_1h allow for different baseline mean admission-level ES-DOT per at-risk day for each hospital and each hospital per period, respectively, while g_j allows different admissions to have different mean ES-DOT per at-risk day across multiple admissions. Equivalently, they allow for correlation within hospital at different levels at baseline and at follow-up.

The assessment of trial success will be determined by the significance of the arm by period interaction term β_3, which assesses whether the log relative rate of the outcome due to being in the intervention arm in the intervention period is different from 0. The exponentiated parameter estimate for β_3 is the estimated relative rate of ES-DOT per at-risk day due to the intervention, relative to the baseline period. For example, if β_3 had a negative value and a p-value <0.05, we would conclude that the patient-specific CPOE smart prompts generated a benefit over routine care. Exponentiating the parameter value would provides an estimate of the relative reduction due to the intervention in the expected ES-DOT per at-risk day.

The primary trial analysis will use an as-randomized unadjusted model with two-tailed significance set at alpha = 0.05. Secondary outcomes also will be assessed using an as-randomized unadjusted model with adjustment for multiple comparisons with two-tailed significance set at alpha = 0.025 for the two secondary outcomes. Subsequent analyses of the primary and secondary outcomes will include both as-treated and adjusted models. Adjusted models will account for individual characteristics such as age, gender, comorbidities, and prior history of MDROs as well as hospital characteristics such as hospital antibiotic resistance. We will also account for randomization unit and for seasonality. These analyses will be reported as point estimates with confidence intervals without p-value. The reason for including these analyses is to provide additional information related to the trial outcomes for readers to assess the effects of potential confounders. The reason to not include them in a formal multiple comparisons adjustment is because these analyses are non-independent evaluations relative to the as-randomized unadjusted analyses.

Safety outcomes noted in the below table will be assessed in the most conservative manner to identify potential safety issues. This is required because a reduction in ES-DOT might be achieved only by incorrectly withholding ES antibiotics when they were really needed. Each safety outcome will be evaluated for non-inferiority using an as-randomized unadjusted model with a one-tailed significance set at alpha = 0.05. Analyses planned for these assessments are proportional hazards models with random effects (to account for hospital effects). These models are sometimes called frailty or shared frailty models. Because these are safety outcomes, we do not intend to make adjustments for multiple comparisons in testing them, further increasing conservatism.

All analyses will be performed using current versions of SAS (Version 9.4, as of writing, SAS Institute, Cary NC) and/or R (Version 4.0, as of writing).

B.1.11 Power Size/Sample Size Calculations

Power assessment proceeded as follows, using a Monte Carlo approach. We used available data to define a baseline period of 10/1/2015-12/31/2016 in a bootstrap procedure. Individuals were selected with replacement from within each hospital, once to represent baseline data and separately to represent

intervention period data. In the randomization portion of the Monte Carlo approach, we ordered the hospitals by “size”, meaning the number of admissions with pneumonia. Then, within strata of 6 hospitals, we ordered by ES-DOT per at-risk day. Then we took pairs of hospitals with adjacent ES-DOT per at-risk day and assigned one member of the pair to one arm. To do this, a single pseudo-random number uniformly distributed between 0 and 1 was generated for each pair. If it was less than 0.5, the arbitrary “first” member of the pair was assigned to Routine Care and the other to Intervention. If it was greater than or equal to 0.5, then the assignments were reversed. The remaining unpaired hospital of the 59 units were assigned as the “first” member of a pair with no match. (Three sets of hospitals each shared a stewardship program and these hospitals were treated as a single hospital within the routine.)

If an admission was in the intervention arm in the intervention period, then their ES-DOT per at-risk day was reduced by a proportion, given below. The reduction of ES-DOT per at-risk day was selected with a lower bound determined by the investigators as the hoped-for effect of the intervention with minimal clinical significance, and the impact in the Monte Carlo calculation on a per-admission basis was to reduce the days of therapy proportionately between this number and 1, on a uniform distribution. In other words, if the effect of the intervention was to multiply doses by as little as .9, each person would have their doses multiplied by between .9 and 1. Then an integer value of doses would be chosen as described above.

We are interested in determining whether the patient-specific CPOE intervention reduces ES-DOT per at-risk day by at least 12.5% relative to usual care. Using the method above, we have 97% power (CI 91-99%) to detect this effect. **Table 5** below shows the calculated power and confidence intervals for the primary and secondary outcomes to be evaluated in our primary manuscript.

Table 5. Power Calculation – Primary and Secondary Outcomes

Primary Trial Outcome	**Power (CI), %**
Extended-Spectrum Antibacterial Days Of Therapy (ES-DOT) per Empiric Day	97 (91-99)
Secondary Trial Outcomes	
Vancomycin Days of Therapy per Empiric Day	92 (85-96)
Antipseudomonal Antibiotic Days Of Therapy (ES-DOT) per Empiric Day	84 (77-91)

References Cited

1. Magill SS, Edwards JR, Beldavs ZG, Dumyati G, Janelle SJ, Kainer MA, Lynfield R, Nadle J, Neuhauser MM, Ray SM, Richards K, Rodriguez R, Thompson DL, Fridkin SK; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. *JAMA* 2014;312(14):1438-46.
2. Fridkin S, Baggs S, Fagan R, Magill S, Pollack LA, Malpiedi P, Slayton R, Khader K, Rubin MA, Jones M, Samore MH, Dumyati G, Dodds-Ashley E, Meek J, Yousey-Hindes K, Jernigan J, Shehab N, Herrera R, McDonald CL, Schneider A, Srinivasan A; Centers for Disease Control and Prevention (CDC). Vital signs: improving antibiotic use among hospitalized patients. *MMWR Morb Mortal Wkly Rep* 2014;63:194-200.
3. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed on May 19, 2015.
4. Marston HD, Dixon DM, Knisely JM, Palmore TN, Fauci AS. Antimicrobial Resistance. *JAMA.* Sep 20 2016;316(11):1193-1204.
5. Arcilla MS, van Hattem JM, Haverkate MR, et al. Import and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis.* Oct 14 2016.
6. Harbarth S, Samore MH. Antimicrobial resistance determinants and future control. *Emerg Infect Dis* 2005;11(6):794-801.
7. Abbo L, Sinkowitz-CochranR, Smith L, Ariza-Heredia E, Gomez-Marin O, Srinivasan A, Hooton TM. Faculty and resident attitudes, perceptions, and knowledge about antimicrobial use and resistance. *Infect Control Hosp Epidemiol* 2011;32:714-8.

8. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: No ESKAPE! An updated from the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:1-12.
9. Boucher HW, Talbot GH, Benjamin DK Jr, Bradley J, Guidos RJ, Jones RN, Murray BE, Bonomo RA, Gilbert D. 10 x '20 Progress--development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. *Clin Infect Dis* 2013;56:1685-94.
10. Centers for Disease Control and Prevention. Get Smart for Healthcare. Available at: http://www.cdc.gov/getsmart/healthcare/. Accessed May 8, 2015.
11. Executive Office of the Presidents, President's Council of Advisors on Science and Technology. Report to the President on Combating Antibiotic Resistance. Available at: https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf. Accessed on May 8, 2015.
12. The White House. National Strategy for Combating Antibiotic-Resistant Bacteria. Available at: https://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf. Accessed on May 19, 2015.
13. Baggs J, Fridkin SK, Pollack LA, Srinivasan A, Jernigan JA. Estimating National Trends in Inpatient Antibiotic Use Among US Hospitals From 2006 to 2012. *JAMA Intern Med.* Nov 1 2016;176(11):1639-1648.
14. Giblin TB, Sinkowitz-Cochran RL, Harris PL, Jacobs S, Liberatore K, Palfreyman MA, Harrison EI, Cardo DM; CDC Campaign to Prevent Antimicrobial Resistance Team. Clinicians' perceptions of the problem of antimicrobial resistance in healthcare facilities. *Arch Intern Med* 2004;164:1662-8.
15. Szymczak JE, Feemster KA, Zaoutis TE, Gerber JS. Pediatrician perceptions of an outpatient antimicrobial stewardship intervention. *Infect Control Hosp Epidemiol* 2014;35(Suppl 3):S69-78.
16. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis.* May 15 2016;62(10):e51-77.
17. Provonost P, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. *BMJ* 2008;337:a1714.
18. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clin Infect Dis* 2007;44:S27-72.
19. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;52:e103-20.
20. Mazzulli T. Diagnosis and management of simple and complicated urinary tract infections (UTIs). *Can J Urol* 2012;19 Suppl 1:42-8.
21. Sanchez GV, Roberts RM, Albert AP, Johnson DD, Hicks LA. Effects of knowledge, attitudes, and practices of primary care providers on antibiotic selection, United States. *Emerg Infect Dis* 2014;20:2041-7.
22. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999;115:462-74.
23. Schramm GE, Johnson JA, Doherty JA, Micek ST, Kollef MH. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: the importance of appropriate initial antimicrobial treatment. *Crit Care Med* 2006; 34: 2069-74.
24. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. *Antimicrob Agents Chemother* 2005;49:1306-11.
25. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, Oh MD, Choe KW. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrob Agents Chemother* 2005;49:760-6.
26. Self WH, Wunderink RG, Williams DJ, et al. Staphylococcus aureus Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes. *Clin Infect Dis.* Aug 1 2016;63(3):300-309.

27. Cilloniz C, Gabarrus A, Ferrer M, et al. Community-Acquired Pneumonia Due to Multidrug- and Non-Multidrug-Resistant Pseudomonas aeruginosa. *Chest.* Aug 2016;150(2):415-425.
28. Ishida T, Ito A, Washio Y, et al. Risk factors for drug-resistant pathogens in immunocompetent patients with pneumonia: Evaluation of PES pathogens. *J Infect Chemother.* Oct 8 2016.
29. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416.
30. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005;128:3854-62.
31. Ewig S, Welte T, Chastre J, Torres A. Rethinking the concepts of community-acquired and health-care-associated pneumonia. *Lancet Infect Dis* 2010;10:279-87.
32. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* Sep 1 2016;63(5):e61-e111.
33. Park KH, Oh WS, Kim ES, Park SW, Hur JA, Kim YK, Moon C, Lee JH, Lee CS, Kim BN. Factors associated with ciprofloxacin- and cefotaxime-resistant Escherichia coli in women with acute pyelonephritis in the emergency department. *Int J Infect Dis* 2014;23:8-13.
34. Huttner B, Jones M, Huttner A, Rubin M, Samore MH. Antibiotic prescription practices for pneumonia, skin and soft tissue infections and urinary tract infections throughout the US Veterans Affairs system. *J Antimicrob Chemother* 2013;68:2393-9.
35. Chalmers JD, Rother C, Salih W, Ewig S. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis* 2014;58:330-9.
36. Grenier C, Pepin J, Nault V, Nault V, Howson J, Fournier X, Poirier MS, Cabana J, Craig C, Beaudoin M, Valiquette L. Impact of guideline-consistent therapy on outcome of patients with healthcare-associated and community-acquired pneumonia. *J Antimicrob Chemother* 2011;66:1617-24.
37. Attridge RT, Frei CR, Restrepo MI, Lawson KA, Ryan L, Pugh MJ, Anzueto A, Mortensen EM. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. *Eur Respir J* 2011;38:878-87.
38. Troitino AX, Porhomayon J, and El-Solh AA. Guideline-concordant antimicrobial therapy for healthcare-associated pneumonia: a systematic review and meta-analysis. *Lung* 2013;191:229-37.
39. Lee SS, Kim Y, and Chung DR. Impact of discordant empirical therapy on outcome of community-acquired bacteremic acute pyelonephritis. *J Infect* 2011;62:159-164.
40. Jeon JH, Kim K, Han WD, Song SH, Park KU, Rhee JE, Song KH, Park WB, Kim ES, Park SW, Kim NJ, Oh MD, Kim HB. Empirical use of ciprofloxacin for acute uncomplicated pyelonephritis caused by *Escherichia coli* in communities where the prevalence of fluoroquinolone resistance is high. *Antimicrob Agents Chemother* 2012;56:3043-6.
41. Webb BJ, Dascomb K, Stenehjem E, Dean N. Predicting risk of drug-resistant organisms in pneumonia: Moving beyond the HCAP model. *Respir Med* 2015;109:1-10.
42. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. *Clin Infect Dis* 2011;53:42-8.
43. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013;4:CD003543.
44. Brown K, Valenta K, Fishman D, Simor A, Daneman N. Hospital ward antibiotic prescribing and the risks of *Clostridium difficile* infection. JAMA Intern Med 2015;175:626-33.
45. Braykov NP, Morgan DJ, Schweizer ML, Uslan DZ, Kelesidis T, Weisenberg SA, Johannsson B, Young H, Cantey J, Srinivasan A, Perencevich E, **Septimus E**, Laxminarayan R. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. *Lancet Infect Dis* 2014;14:1220-7.

46. Fowler S, Webber A, Cooper BS, Phimister A, Price K, Carter Y, Kibbler CC, Simpson AJ, Stone SP. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. *J Antimicrob Chemother* 2007;59:990-5.
47. Charani E, Kyratsis Y, Lawson W, Wickens H, Brannigan ET, Moore LS, Holmes AH. An analysis of the development and implementation of a smartphone application for the delivery of antimicrobial prescribing policy: lessons learnt. *Antimicrob Chemother* 2013;68:960-7.
48. Chandy SJ, Naik GS, Charles R, Jeyaseelan V, Naumova EN, Thomas K, Lundborg CS. The impact of policy guidelines on hospital antibiotic use over a decade: a segmented time series analysis. *PLoS ONE* 2014;9:e92206.
49. Hamilton KW, Gerber JS, Moehring R, Anderson DJ, **Calderwood MS**, Han JH, Mehta JM, Pollack LA, ZaoutisT, Srinivasan A, Camins BC, Schwartz DN, Lautenbach E; Centers for Disease Control and Prevention Epicenters Program. Point-of-prescription intervention to improve antibiotic stewardship. *Clin Infect Dis* 2015;60:1252-8.
50. Cooke FJ and Holmes AH. The missing care bundle: antibiotic prescribing in hospitals. *Int J Antimicrob Agents* 2007;30:25-9.
51. Rodriquez-Maresca M, Sorlozano A, Grau M, Rodriquez-Castano R, Ruiz-Valverde A, Gutierrez-Fernandez J. Implementation of a computerized decision support system to improve the appropriateness of antibiotic therapy using local microbiologic data. *Biomed Res Int* 2014;2014:395434.
52. Deuster S, Roten I, Muehlebach S. Implementation of treatment guidelines to support judicious use of antibiotic therapy. *J Clin Pharm Ther* 2010;35:71-8.
53. Pogue JM, Alaniz C, Carver PL, Pleva M, Newton D, DePestel DD. Role of unit-specific combination antibiograms for improving selection of appropriate empiric therapy for gram-negative pneumonia. *Infect Control Hosp Epidemiol* 2011;32:289-92.
54. Rabs N, Wieczorkiewicz SM, Costello M, Zamfirova I. Development of a urinary-specific antibiogram for Gram negative isolates: impact of patient risk factors on susceptibility. *Am J Infect Control* 2014;42:393-400.
55. Karam G, Chastre J, Wilcox MH, Vincent JL. Antibiotic strategies in the era of multidrug resistance. *Crit Care.* Jun 22 2016;20(1):136.
56. Auffray C, Caulfield T, Griffin JL, Khoury MJ, Lupski JR, Schwab M. From genomic medicine to precision medicine: highlights of 2015. *Genome Med.* Jan 29 2016;8(1):12.
57. Chambers DA, Feero WG, Khoury MJ. Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System: A New Model for Biomedical Research. *JAMA.* May 10 2016;315(18):1941-1942.
58. Khoury MJ, Galea S. Will Precision Medicine Improve Population Health? *JAMA.* Oct 4 2016;316(13):1357-1358.
59. Khoury MJ, Iademarco MF, Riley WT. Precision Public Health for the Era of Precision Medicine. *Am J Prev Med.* Mar 2016;50(3):398-401.
60. Buising KL, Thursky KA, Robertson MB, Black JF, Street AC, Richards MJ, Brown GV. Electronic antibiotic stewardship—reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. *J Antimicrob Chemother* 2008;62:608-16.
61. Rimawi RH, Mazer MA, Siraj DS, Gooch M, Cook PP. Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. *Crit Care Med* 2013;41:2099-107.
62. Boyles TH, Whitelaw A, Bamford C. Moodley M, Bonorchis K, Morris V. Rawoot N, Naicker V, Lusakiewicz I, Black J, Stead D, Lesosky M, Raubenheimer P, Dlamini S, Mendelson M. Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. *PLoS One* 2013;8:e79747.
63. Schulz L, Osterby K, Fox B. The use of best practice alerts with the development of an antimicrobial stewardship navigator to promote antibiotic de-escalation in the electronic medical record. *Infect Control Hosp Epidemiol* 2013;34:1259-65.

64. Lee TC, Frenette C, Jayaraman D, Green L, Pilote L. Antibiotic self-stewardship: trainee-led structured antibiotic time-outs to improve antimicrobial use. *Ann Intern Med* 2014;161(10 Suppl):S53-8.
65. Lesprit P, de Pontfarcy A, Esposito-Farese M, Ferrand H, Mainardi JL, Lafauri M, Parize P, Rioux C, Tubach F, Lucet JC. Postprescription review improves in-hospital antibiotic use: a multicenter randomized controlled trial. *Clin Microbiol Infect* 2015;21:180.e1-7
66. **Platt R**. Predictors of response to therapy for infections caused by *Pseudomonas aeruginosa*. *Rev Infect Dis* 1984;6 Suppl 3:S759-68.
67. **Huang SS, Platt R**. Risk of methicillin-resistant *Staphylococcus aureus* infection after previous infection or colonization. *Clin Infect Dis* 2003;36:281-5.
68. Shojania KG, Yokoe D, Platt R, Fiskio J, Ma'luf N, Bates DW. Reducing vancomycin use utilizing a computer guideline: results of a randomized controlled trial. *J Am Med Inform Assoc* 1998;5:554-62.
69. Zanetti G, Flanagan HL Jr, Cohn LH, Giardina R, **Platt R**. Improvement of intraoperative prohylaxis in prolonged cardiac surgery by automated alerts in the operating room. *Infect Control Hosp Epidemiol* 2003;24:13-6.
70. Simon SR, Smith DH, Feldstein AC, Perrin N, Yang X, Zhou Y, **Platt R**, Soumerai SB. Computerized prescribing alerts and group academic detailing to reduce the use of potentially inappropriate medications in older people. *J Am Geriatr Soc* 2006;54:963-8.
71. Smith DH, Perrin N, Feldstein A, Yang X, Kuang D, Simon SR, Sittig DF, **Platt R**, Soumerai SB. The impact of prescribing safety alerts for elderly persons in an electronic medical record: an interrupted time series evaluation. *Arch Intern Med* 2006;166:1098-104.
72. Langford BJ, Seah J, Chan A, Downing M, Johnstone J, Matukas LM. Antimicrobial Stewardship in the Microbiology Laboratory: Impact of Selective Susceptibility Reporting on Ciprofloxacin Utilization and Susceptibility of Gram-Negative Isolates to Ciprofloxacin in a Hospital Setting. *J Clin Microbiol.* Sep 2016;54(9):2343-2347.
73. Stenehjem E, Hersh AL, Sheng X, et al. Antibiotic Use in Small Community Hospitals. *Clin Infect Dis.* Nov 15 2016;63(10):1273-1280.
74. Goldstein EJ, Goff DA, Reeve W, et al. Approaches to Modifying the Behavior of Clinicians Who Are Noncompliant With Antimicrobial Stewardship Program Guidelines. *Clin Infect Dis.* Aug 15 2016;63(4):532-538.
75. Emanuel EJ, Ubel PA, Kessler JB, et al. Using Behavioral Economics to Design Physician Incentives That Deliver High-Value Care. *Ann Intern Med.* Jan 19 2016;164(2):114-119.
76. Madaras-Kelly KJ, Remington RE, Fan VS, Sloan KL. Predicting antibiotic resistance to community-acquired pneumonia antibiotics in culture-positive patients with healthcare-associated pneumonia. *J Hosp Med.* Mar 2012;7(3):195-202.
77. Goodman KE, Lessler J, Cosgrove SE, et al. A Clinical Decision Tree to Predict Whether a Bacteremic Patient Is Infected With an Extended-Spectrum beta-Lactamase-Producing Organism. *Clin Infect Dis.* Oct 1 2016;63(7):896-903.
78. Anesi JA, Lautenbach E, Nachamkin I, et al. Clinical and Molecular Characterization of Community-Onset Urinary Tract Infections Due to Extended-Spectrum Cephalosporin-Resistant Enterobacteriaceae. *Infect Control Hosp Epidemiol.* Sep 28 2016:1-7.
79. Jacobson KL, Cohen SH, Inciardi JF, et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I beta-lactamase-producing organisms. *Clin Infect Dis.* Nov 1995;21(5):1107-1113.
80. Aliberti S, Reyes LF, Faverio P, et al. Global initiative for meticillin-resistant Staphylococcus aureus pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis.* Sep 1 2016.
81. Hudepohl NJ, Cunha CB, Mermel LA. Antibiotic Prescribing for Urinary Tract Infections in the Emergency Department Based on Local Antibiotic Resistance Patterns: Implications for Antimicrobial Stewardship. *Infect Control Hosp Epidemiol.* Mar 2016;37(3):359-360.
82. Jacobs DM, Kuper K, **Septimus E**, Arafat R, Garey KW. Assessment of Antimicrobial Stewardship Activities in a Large Metropolitan Area. *J Pharm Pract* 2014 (Epub ahead of print).

83. **Septimus EJ**, Kuper K. Clinical Challenges in Addressing Antimicrobial Resistance in the 21st Century. *Cl Pharm and Therap* 2009; 86:336-339.
84. **Septimus E**, Owens R. Need and Potential of Antimicrobial Stewardship in Community Hospitals. *Clin Infect Dis* 2011;53:S8-S14.
85. Fishman N, Patterson J, Saiman L, Srinivasan A, Trivedi KK, van Schooneveld T, Lynfield R, Gerding D, Septimus E, Schwartz D, Daum R, Eglund JA, Harrison CJ, Bradley JS, Newland J. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol* 2012;33:322-7.
86. Moody J, Cosgrove SE, Olmsted R, **Septimus E**, Aureden K, Oriola S, Patel GW, Trivedi KK. Antimicrobial stewardship: a collaborative partnership between infection preventionists and healthcare epidemiologists. *Infect Control Hosp Epidemiol* 2012;33:328-30.
87. **Septimus EJ.** Antimicrobial Stewardship—Qualitative and Quantitative Outcomes: The Role of Measurement. *Curr Infect Dis Rep* 2014;16:433-438.
88. **Calderwood MS**. Role of the Hospital Epidemiologist in Supporting Antimicrobial Stewardship. In: Mylonakis E, Rice L, Drusano G, eds. *Antimicrobial Stewardship: Principles and Practices.* 2015 (in press).
89. McKinnell J, Miller LG, Eells S, Cui E, **Huang SS**. A Systematic Literature Review and Meta-analysis of Factors Associated with MRSA Colonization at Time of Hospital or ICU Admission. *Infect Control Hosp Epidemiol* 2013;34:1077-86.
90. Datta R, Shah A, **Huang SS**, Cui E, Nguyen V, Welbourne S, Quan K, Thrupp L. High nasal burden of methicillin-resistant *Staphylococcus aureus* increases risk for invasive disease. *J Clin Microbiol* 2014;52:312-4.
91. Datta R, **Kleinman K**, Rifas-Shiman S, Placzek H, Lankiewicz J, **Platt R**, **Huang SS.** Confounding by indication affects antimicrobial risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) but not vancomycin-resistant enterococci (VRE) acquisition. *Antibio Resist Infect Control* 2014;3:19.
92. Pakyz AL. The utility of hospital antibiograms as tools for guiding empiric therapy and tracking resistance. Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2007;27:1306-12.
93. Perla RJ and Belliveau PP. Antibiogram-derived radial decision trees: An innovative approach to susceptibility data display. *Am J Infect Dis* 2005;1:124-7.
94. The Center for Disease Dynamics, Economics & Policy. Resistance Map. Available at: http://www.cddep.org/projects/resistance_map/resistance_overview_0. Accessed on May 24, 2015.
95. Falcone M, Russo A, Gianella M, Cangemi R, Scarpellini MG, Bertazzoni G, Alarcon JM, Taliani G, Palange P, Farcomeni A, Vestri A, Bouza E, Violi F, Venditti M. Individualizing risk of multidrug-resistant pathogens in community-onset pneumonia. *PLoS One* 2015;10:e0119528.
96. Self WH, Wunderink RG, Williams DJ, Barrett TW, Baughman AH, Grijalva CG. Comparison of clinical prediction models for resistant bacteria in community-onset pneumonia. *Acad Emerg Med* 2015;22(6):730-40.
97. Elixhauser A, Steiner C. Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8-27.
98. Healthcare Cost and Utilization Project. Comorbidity Software, Version 3.7. Available at: https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp#overview. Accessed on May 27, 2015.
99. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis.* Jan 15 2006;42 Suppl 2:S82-89.
100. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis. Nov 01 2005;41(9):1254-1260.
101. Dhalla IA, Mamdani MM, Simor AE, Kopp A, Rochon PA, Juurlink DN. Are broad-spectrum fluoroquinolones more likely to cause Clostridium difficile-associated disease? Antimicrob Agents Chemother. Sep 2006;50(9):3216-3219.

102. FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. May 12, 2016. U.S. Food and Drug Administration. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM500591.pdf.
103. Kang CI, Kim SH, Park WB, et al. Bloodstream infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. *Antimicrob Agents Chemother.* Dec 2004;48(12):4574-4581.
104. Queen MA, Myers AL, Hall M, et al. Comparative effectiveness of empiric antibiotics for community-acquired pneumonia. *Pediatrics.* Jan 2014;133(1):e23-29.
105. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med.* Apr 2 2015;372(14):1312-1323.