Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial
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INSPIRE-ASP Pneumonia Trial
Statistical Analysis Plan

June 3, 2020

Background

The **INSPIRE-ASP Pneumonia Trial** (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients with Pneumonia) is a cluster-randomized trial of HCA Healthcare (HCA) affiliated hospitals to assess best practice in antibiotic stewardship for adult hospitalized patients admitted to non-critical care units with pneumonia (PNA). It compares routine care to the use of a real-time smart prompt that provides a patient's specific risk of antibiotic-resistant pneumonia and alerts the clinician during the antibiotic ordering process to optimize prescribing and ideally improve patient outcomes. The main goal is to see if there is a difference in the empiric antibiotic prescribing practices for extended-spectrum antibiotics (ES). We define antibiotics administered during the first three days of hospitalization as empiric treatment because infecting pathogens and their antimicrobial susceptibilities are typically not known during this period. We refer to these first three days as the empiric period.

Participating hospitals are randomized to:

- **Arm 1 – Routine Care**
- **Arm 2 – Real-Time Risk Estimation Smart Prompt**
  Precision medicine smart prompt using a computerized physician order entry (CPOE) alert that gives a patient-specific risk estimate of antibiotic resistant infection and recommends standard-spectrum antibiotics in patients admitted for PNA who are found to have low risk (<10%) for recovery of a drug resistant pathogen.

Trial Outcomes

Trial outcomes evaluating intervention effectiveness are found in Table 1 below and trial safety outcomes are found in Table 2 below.

Table 1: 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 2. Safety outcomes will be analyzed separately from the main effectiveness outcomes of the trial (see Primary Statistical Analysis section below).

Table 2: 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

Primary Statistical 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 above 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).

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 4 below shows the calculated power and confidence intervals for the primary and secondary outcomes to be evaluated in our primary manuscript.

Table 4. 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 per Empiric Day	84 (77-91)

Extended-spectrum antibiotics are defined in the study protocol and provided below for convenience.

Table 5: INSPIRE-ASP Pneumonia Extended-Spectrum Antibiotics

Pathogen-Directed Antibiotic Category	**Extended-Spectrum Antibiotics Targeted in INSPIRE Pneumonia CPOE Prompts**
Anti-MRSA	Ceftaroline, Daptomycin[1], Linezolid[2], Vancomycin[3]
Anti-VRE	Daptomycin, Linezolid[2]
Anti-*Pseudomonas*	Aztreonam, Cefepime, Ceftazidime, Piperacillin/Tazobactam
Anti-ESBL	Ertapenem, Ceftolozane/Tazobactam, Meropenem, Imipenem
Anti-CRE	Ceftazidime/Avibactam, Colistin, Imipenem/Relebactam, Meropenem/Vaborbactam, Polymixin B, Tigecycline

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

Abbreviations: **CPOE** – Computerized Physician Order Entry, **MRSA -** Methicillin Resistant *Staphylococcus aureus,* **ESBL –** Extended Spectrum Beta Lactamase Producing *Enterobacterales,* including multi-drug *Acinetobacter* and *Pseudomonas* species susceptible to Carbapenem. **VRE –** Vancomycin Resistant *Enterococci***, CRE –** Carbapenem Resistant *Enterobacterales*

[1]Daptomycin not an accepted pneumonia treatment but included in trial analysis in case ordered.

[2]Both oral and intravenous (IV) formulations.

[3]IV formulation only.

Abbreviations:

MRSA - Methicillin Resistant *Staphylococcus aureus*
VRE – Vancomycin Resistant *Enterococci*
MDR- Multi-Drug Resistant
ESBL – Extended Spectrum Beta Lactamase producer
CRE – Carbapenem Resistant *Enterobacteriaceae*
GNR – Gram Negative Rod