The INSPIRE-ASP Trial (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients) for Abdominal (ABD) Infections Statistical Analysis Plan

NCT:05423743

3/29/2024

(**IN**telligent **S**tewardship **P**rompts to **I**mprove **R**eal-time **E**mpiric Antibiotic Selection for Patients)

Statistical Analytic Plan, 3/29/2024

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Background

The **INSPIRE Abdominal Infections Trial** (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients with Abdominal Infections) is a cluster-randomized trial of HCA Healthcare (HCA) affiliated hospitals to determine whether antibiotic prescribing practice for adult hospitalized patients admitted to non-critical care units with abdominal (ABD) infections can be affected by providing physicians with individualized risk estimates for whether a patient with an abdominal infection is likely to have an antibiotic-resistant infection. It compares routine care to a real-time smart prompt to use a standard-spectrum antibiotics when a physician orders an extended-spectrum antibiotic (ES) for a patient whose risk of antibiotic resistant infection is low (<10%). The main goal is to see if there is a difference in the empiric antibiotic prescribing practices for ES. The term "antibiotics" refers to antibacterial antibiotics in this trial. 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.

Extended-spectrum antibiotics are defined in Table 1 below.

Table 1: Extended-Spectrum Antibiotics in the INSPIRE-ASP Abdominal Infections Trial

Category	Extended-Spectrum Antibiotics for INSPIRE CPOE Alerts
Anti-MRSA	Ceftaroline, Daptomycin, Linezolid[1], Vancomycin[2]
Anti-VRE	Daptomycin, Linezolid[1], Tigecycline
Anti-Pseudomonals	Aztreonam, Cefepime, Ceftazidime, Piperacillin/tazobactam
Anti-ESBL	Ertapenem, Imipenem, Meropenem, Ceftolozane/tazobactam
Anti-CRE	Ceftazidime/avibactam, Imipenem/relebactam, Meropenem/vaborbactam, Polymixin B, Colistin, Tigecycline

[1]Both oral and intravenous (IV) formulations
[2]IV formulation only
Note: Does not include aminoglycosides or fluoroquinolones.
Abbreviations: **MRSA -** Methicillin Resistant *Staphylococcus aureus*; **VRE –** Vancomycin Resistant *Enterococci*; **ESBL –** Extended Spectrum Beta Lactamase producer; CRE – Carbapenem Resistant Enterobacteriaceae

Participating hospitals are randomized to:

- **Arm 1 – Routine Care**
- **Arm 2 – Real-Time Risk Estimation Smart Prompt**

  Computerized physician order entry (CPOE) prompt that recommends standard-spectrum

antibiotics in patients admitted for ABD infections who are prescribed extended-spectrum antibiotics and calculated to have low risk (<10%) for an antibiotic resistant infection.

Trial Outcomes

Table 2: Primary and Secondary INSPIRE-ASP Abdominal Infections Trial Outcomes

Outcome	Metric
Primary Trial Outcome	
Total Empiric Extended-Spectrum Antibiotic Days of Therapy (ES-DOT)	The number of different extended-spectrum antibiotics received by the patient each empiric day, summed across the first 3 days of hospitalization.[1]
Secondary Trial Outcomes	
Vancomycin Days of Therapy per Empiric Day	The number of days Vancomycin was received by the patient on the first 3 days of hospitalization.[1]
Total Empiric Antipseudomonal Antibiotic Days of Therapy	The number of different antipseudomonal antibiotics received by the patient each empiric day, summed across the first 3 days of hospitalization.[1]

[1]E.g., if a patient is admitted for 2 days, ES-DOT will be calculated across those 2 days; however if a patient is admitted for 4 days, only the first 3 days will be evaluated.

Safety outcomes planned for the primary manuscript are shown in Table 3. Length of stay and days to ICU transfer are evaluated within 14 days of admission since empiric antibiotic selection within the first 3 hospital days is not expected to be the main driver of either outcome beyond this time; evaluation of baseline data also shows that 93% of abdominal patients have length-of-stay equal to or less than 14 days.

Table 3: Other Pre-Specified Outcomes – Trial Safety Outcomes

Safety Trial Outcomes (other pre-specified outcomes)	
ICU Transfer [Safety Outcome]	Days to ICU transfer, between hospital days ≥ 3 and ≤ 14.
Length-of-stay [Safety Outcome]	Days from hospital admission until discharge or hospital day 14, whichever comes first, where admission day is hospital day 1.

Data Collection Details

The trial will be assessed among the cohort of adult admissions who: 1) have administrative claims codes indicating an abdominal infection is present on admission; 2) received any antibiotic within 3 days of admission; and 3) were admitted to a non-ICU location.

The rationale for including only the first three days of the admission is that this is when the actual status of the patient with respect to the need for an ES antibiotic is unknown. Bearing this in mind, 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 trial baseline period includes January 1, 2019 – December 31, 2019 (12 months). The intervention period includes January 1, 2023 – December 31, 2023 (12 months). The baseline was selected to include time prior to the arrival of the COVID-19 pandemic since hospital operations and case mix were dramatically affected between Winter 2020-Spring, 2022.[1-4] Although COVID-19 surges have continued to occur, clinical operations and patient case mix at most hospitals have largely returned to near pre-pandemic activity. We considered that a state of pre-pandemic normalcy returned by summer of 2022, and introduced our intervention on August 2, 2022. The period between then and December 31, 2022 is considered a phase-in period and is not used in trial evaluation.

Primary Statistical Analysis

The primary trial outcome is defined as the summed number of different ES antibiotics received during each empiric day, on the patient-admission level. An empiric day is a day within the first three days of an admission. We define this outcome as the Total Empiric Extended-Spectrum Days of Therapy (ES-DOT). 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 within each empiric day for each patient admission to determine DOT in that at-risk day.

The main trial results will be based upon as-randomized, unadjusted analyses of admission-level ES-DOT. We note that the national DOT measure defined by CDC is measured at the hospital level. We define ES-DOT at the individual admission level so that we can perform analyses on individuals.

The main evaluation of all outcomes will be based on the difference in differences between the intervention and baseline periods and between study arms.

The unit of analysis will be individual admissions. Individual patients can contribute more than one admission. The analytic model will be a generalized linear mixed effects model for differences in differences, with random effects to account for correlation within hospital between period, within hospital within period between patient, and within patient between admission. We plan to use a Poisson model for analysis of outcomes as follows:

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

where y_{ijph} is the ES-DOT 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 for each hospital and each hospital in the intervention period, respectively. Equivalently, they allow for correlation within hospital at different levels at baseline and at follow-up. The random effect g_j allows each patient to have a different mean ES-DOT. Finally, ed_j is the number of empiric days in the admission. We note that it may not be possible to fit models with the g_j parameter, for various numerical and computational reasons—the most prominent being a relative sparsity of patients with readmissions. If that proves to be the case, we will randomly select one admission per patient and use the model above without that parameter and omitting the j subscript.

The assessment of trial success will be determined by assessing the significance of the arm by period interaction term β_3, which estimates the log relative rate of the outcome due to being in the intervention arm in the intervention period. 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 provide 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 will be assessed using an as-randomized unadjusted model and will include 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 seasonality. All adjusters will be determined a priori. These analyses will be reported as point estimates with confidence intervals and without p-values. 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

Safety outcomes are required because a reduction in ES-DOT might be achieved only by incorrectly withholding ES antibiotics when they were necessary. Each safety outcome will be evaluated for non-inferiority using an as-randomized unadjusted analysis with a one-tailed significance set at alpha = 0.05. For length of stay, the non-inferiority margin is a hazard ratio of 0.98. For days to ICU transfer, the non-inferiority margin is a hazard ratio of 1.1 (fewer days to ICU results in a hazard ratio above 1). Analyses planned for these assessments are proportional hazards models with random effects for each time period, hospital, and admission. 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. As above, it may not be possible to include multiple admissions.

All analyses will be performed using current versions of SAS/STAT and/or R packages lme4 and coxme, unless better packages become available in the meantime.

Further Planned Analyses

We note that there are other pre-specified outcomes intended for exploratory analysis in secondary papers for the INSPIRE ABD trial in Table 5 below.

Table 5: Secondary Manuscripts - Other Pre-Specified Outcomes

Secondary Manuscripts (other pre-specified secondary exploratory analyses for later manuscripts)	
Inpatient Extended-Spectrum Days of Therapy after the Empiric Period	The number of different ES antibiotics received each day, on hospital days ≥4 and ≤14.
Empiric and Total Antibiotic Costs	Empiric and total antibiotic costs during hospitalization
Incidence of Hospital-Onset *C. difficile*	Hospital-onset *C. difficile* positive tests (specimen obtained) on hospital days ≥4 and ≤14.
Incidence of Hospital-Onset MDRO-positive Cultures	Newly-detected hospital-onset MDRO-positive cultures on hospital days ≥4 and ≤14. Includes total MDRO and specific MDRO subsets.

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