Title: Comparative effectiveness of adjunctive clindamycin versus linezolid for β-lactam treated patients with invasive Group A Streptococcal infections: A target trial emulation

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Significance and Background

Despite advances in supportive care, source control, and antibiotics, mortality from invasive Group A *streptococcus* (GAS), remains high [1-3]. Clindamycin, a protein synthesis inhibitor with activity during the stationary phase of bacterial growth has been shown to decrease the expression and production of GAS virulence factors and exotoxins [4,5]. The addition of adjunctive clindamycin therapy to β-lactams is recommended for the management of severe invasive GAS and associated necrotizing soft tissue infection (NSTI)[6,7]. These recommendations were initially made based on clindamycin's anti-toxin effect and animal models, which demonstrated reduced efficacy of penicillin compared to clindamycin due to an inoculum effect [8]. Recently, the preponderance of observational studies has shown a benefit or trend towards benefit with the use of adjunctive clindamycin in invasive GAS infections [3,9-11] .

Linezolid is an oxazolidinone antibiotic with a broad spectrum of activity against Gram-positive organisms. Similar to clindamycin, linezolid inhibits toxin and virulence factor production by inhibiting protein synthesis[12]. Concerns about rising rates of clindamycin resistance among BHS [13] have called into question whether linezolid should remain the adjunctive protein synthesis inhibitor of choice in BHS infections in lieu of clindamycin [14]. However, clinical experience to date is limited.

The severe life-threatening nature of invasive GAS has made recruitment to invasive GAS specific clinical trials difficult due to low numbers and a lack of clinician willingness to randomize to perceived inferior treatments[15]. The global increase in invasive GAS cases [16,17] coupled with the ongoing poor outcomes of these infections has led to many within the ID community to call for a re-assessment the feasibility of conducting appropriately powered interventional clinical trials [18]. Hence, this study aims to emulate a hypothetical target pragmatic multi-center, non-blinded trial of adult inpatients in the PINC AI™ dataset with B-lactam treated culture confirmed monomicrobial invasive Group A streptococcus (GAS) between the years 2015-2021.

Table 1. Summary of Key Elements of Target Trial and Emulation Trial Components

Protocol Component	Description under target trial	Description under Emulation
Eligibility Criteria	Adult inpatients receiving B-lactam therapy for culture confirmed monomicrobial invasive GAS between who can be randomized within 72h of index culture	Adult inpatients receiving B-lactam therapy for culture confirmed monomicrobial invasive GAS between the years 2015-2021 in the PINC AI™ dataset who receive anti-toxin within 3 days of index culture.
Treatment strategies	B-lactam therapy as primary therapy for GAS started within (+/-) 3 days of index GAS culture and continued for a minimum of 3 consecutive days. Adjunctive anti-toxin (clindamycin vs. linezolid) therapy started within (+) 3 days of culture.	Same as target trial.
Assignment procedures	Patients will be randomly assigned within 3 days of culture (grace period) to clindamycin vs. linezolid. Investigators and patients and will be aware of the strategy to which they have been assigned (pragmatic, unblinded, open-label non-inferiority). Switching between linezolid and clindamycin will not be permitted under the protocol.	Patients will be assigned to the anti-toxin therapy compatible with their observed treatment. Difference in baseline characteristics and confounding by indication will be addressed through the creation of a propensity weighted cohort. Those who received both agents within the eligibility period will be excluded.
Follow up period	Starts at time of randomization (anti-toxin initiation) and ends at death, discharge to hospice, loss to follow up or 90 days, whichever occurs earliest.	Starts at time of anti-toxin initiation and ends at death, discharge to hospice or discharge from the hospital to home or facility or administrative censorship on Jan 31st 2022.
Outcome	Primary outcome: Time to all-cause mortality (or discharge to hospice) censored at 90 days. Secondary outcome: infection attributable 90-day mortality, all-cause in-hospital mortality, 90-day disease reoccurrence, length of stay following anti-toxin administration among survivors, occurrence of CDI	Primary outcome: All-cause in-hospital mortality (or discharge to hospice)/ time to death (days). Secondary outcome: Length of stay following anti-toxin administration among survivors, occurrence of CDI requiring treatment following anti-toxin administration.

	requiring treatment following anti-toxin administration up to 90 days, occurrence of serotonin surge syndrome while on therapy.	
Causal contrast of interest	Intention-to-treat effect; per-protocol effect.	Observational analog to Intention-to-treat effect and per-protocol effect.
Analysis plan	Intention-to-treat and per protocol effects estimated via comparison of adjusted 90 day in-hospital mortality risk assigned to each treatment strategy.	Intention-to-treat and per protocol effects estimated via comparison of adjusted in-hospital mortality risk assigned to each treatment strategy. To account for confounding by indication a propensity score (PS) will be generated based on the probability of receiving linezolid using the patient and center level variables selected a priori based on clinical judgment, . Overlap weighting on a propensity-score between the two groups will be performed with downstream adjustment for ICU stay , shock and debridement/source control.

Abbreviations: CDI: Clostridioides difficile infection; GAS: Group A streptococcus.

The study was designed in accordance with the trial emulation approach described by Hernán and Robins [19]. The study aims to emulate a hypothetical target pragmatic multi-center, non-blinded trial.

Eligibility
Adult inpatients patients (=> 18 y of age) with culture confirmed proven or probable (see below) invasive monomicrobial GAS in the PINC AI™ database between 2015-2021 who receive a β-lactam for a minimum of 3 days within 3 days of culture will be eligible for inclusion in the emulated trial. Patient will be included if they then receive anti-toxin therapy within 3 days of culture being drawn, as long as B-lactam therapy has been initiated prior or on the same day as antitoxin therapy.

Proven and probable invasive GAS definitions will be adapted from the CDC ABCs case definition (https://www.cdc.gov/abcs/methodology/case-def-ascertain.html) using a previously used algorithm compatible with EHR data which incorporates ICD-codes[3] . Proven invasive GAS infection will be defined as GAS isolated from a normally sterile site, such as blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, bone, joint/synovial fluid, or internal body site (e.g., lymph node, brain) *OR* GAS isolated from a wound culture and accompanied by necrotizing fasciitis or streptococcal toxic shock syndrome. Probable invasive GAS infection is defined as the isolation of GAS from a non-sterile site in patients with either an ICD-10 code that matches the clinical infection syndrome (eg ICD-10 for lower respiratory infection and BAL culture with GAS) or a non-specific streptococcal infection code. These include lower respiratory, musculoskeletal, genitourinary and/or skin and soft tissue samples as well other miscellaneous deep-seated infections (eg retropharyngeal abscess). Previously identified ICD-9 codes[3] will be cross walked to ICD-10 codes manually with additional manual de-novo search for compatible ICD-10 codes. Final codes and culture site classification will be adjudicated by two infectious diseases clinicians.

Inclusion Criteria
- Adult inpatients patients (=> 18 y of age)
- Monomicrobial Group A streptococcus invasive infection
- Primary therapy with a B-lactam agent (initiated before or on same day as adjunctive anti-toxin therapy)

Exclusion Criteria
Patient will be excluded if they have any of the following :
- Patients with a polymicrobial GAS culture
- Patients who allocated to the linezolid arm but have a documented linezolid resistant isolate
- Patient with concomitant MSSA/MRSA invasive infection (+/- seven days of index GAS eligibility culture)
- Patients who receive both anti-toxin agents (violation of protocol)
- Patient who don't complete at least 3 days of B-lactam (violation of protocol)

Primary Outcome measure:
in-hospital mortality defined as death during hospitalization or discharge to hospice.

Secondary outcome measures:
- Length of stay among survivors

- *Clostridioides difficile* infection
    - Description: C. difficile positive (PCR or antigen) result within same encounter downstream of the antitoxin therapy within 30 days and/or presence of a non present on admission (POA) C. difficile diagnosis code in conjugation with receipt of C. difficile therapy (PO/rectal vancomycin or PO fidaxomicin or IV metronidazole)

Statistical Analysis Plan

To account for confounding by indication a propensity score (PS) will be generated based on the probability of receiving linezolid using the patient and center level variables. Variables thought to be associated with a clinician's decision to initiate adjunctive treatment with linezolid (vs. clindamycin) and with mortality will be selected for inclusion. Overlap weighting on a propensity-score between the two groups will be performed with downstream adjustment for ICU stay, shock and debridement/source control. To take the clustered data structure into account, matching on center will be attempted if feasible, if not , propensity scores will be calculated using a mixed effects model with hospital as a random effect. Covariate balance between the two groups before and after generation of the weighted cohorts will be assessed by examining the standard mean difference for variables across the exposure categories.

Power calculation

Because no randomized clinical trials have previously compared adjunctive treatment options for GAS , the sample size estimation was derived from the largest retrospective study available [3]. In that study the overall in hospital mortality in adjunctive clindamycin group 6.5% in the propensity matched cohort. A published abstract, the only other published clinical data on the topic, found mortality between linezolid (n=26) and clindamycin (n=26) groups to be similar (clindamycin 11.5% and linezolid 7.7%)[21] . This was confirmed by preliminary exploration of GAS blood stream infection cases in our dataset (clindamycin 10%, linezolid 12%).

Based on a mortality rate of 6.5% in the both groups as the most conservative estimate and a noninferiority margin of 5% with 1:4 allocation ratio, 1035 patients (828 clinda + 207 Linezolid) will be needed in total to achieve 80% power with a 2-sided α level of 0.05, allowing for 10% dropout. A 5% noninferiority margin was chosen as the maximal difference in mortality between treatments that would be clinically acceptable, by consultation with infectious disease, critical care specialists within the study team.

Statistical analysis will be performed with R using Rstudio V2022.12.0.353 (R Foundation for Statistical Computing, Vienna, Austria). The reporting of the study will be in line with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines[20]

Sensitivity analysis

The following sensitivity analysis will be performed:

- Analysis of patients with proven GAS only (excluding those with probable GAS)
- Analysis where hospital as a random effect is not included
- An analysis which includes those who receive anti-toxin +/-3 days of index therapy to capture those treated empirically prior to culture results.
- An analysis without PS weighting and only downstream logistical regression (as would be done in a classical observational study).
- An analysis utilizing cloning methodology to account for potential immortal time bias [21]

Subgroup Analysis
We will used similar methods as for the primary analysis to assess the impact of allocation to either treatment group on the following prespecified subgroups

- Patients with NSTI or TSST
- Patients with pressor dependent shock
- Patients admitted to the ICU within one day (+/-) of index GA eligibility culture
- Excluding patients with who received clindamycin that had a clindamycin non-susceptible isolates (defined as resistant or intermediate or a positive D-test)
- Excluding patients with who received clindamycin that had a clindamycin non-susceptible isolates or had clindamycin antimicrobial susceptibility testing missing
- Stratified by days of anti-toxin therapy (>1, >2, >3 days)

Missing Data Plan
Less than 5% missingness across key variables is expected

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