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MAJOR ARTICLE

# Clindamycin Plus Vancomycin Versus Linezolid for Treatment of Necrotizing Soft Tissue Infection

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***Background.*** Necrotizing soft tissue infections (NSTIs) are life-threatening infections. The aim of this study is to evaluate the safety of clindamycin plus vancomycin versus linezolid as empiric treatment of NSTIs.

***Methods.*** This was a retrospective, single-center, quasi-experimental study of patients admitted from 1 June 2018 to 30 June 2019 (preintervention) and 1 May 2020 to 15 October 2021 (postintervention). Patients who received surgical management within 24 hours of NSTI diagnosis and at least 1 dose of linezolid or clindamycin were included. The primary endpoint was death at 30 days. The secondary outcomes included rates of acute kidney injury (AKI) and *Clostridioides difficile* infection (CDI).

***Results.*** A total of 274 patients were identified by admission diagnosis code for NSTI or Fournier gangrene; 164 patients met the inclusion criteria. Sixty-two matched pairs were evaluated. There was no difference in rates of 30-day mortality (8.06% vs 6.45%; hazard ratio [HR], 1.67 [95% confidence interval {CI}, .32–10.73]; $P = .65$). There was no difference in CDI (6.45% vs 1.61%; HR, Infinite [Inf], [95% CI, .66–Inf]; $P = .07$) but more AKI in the preintervention group (9.68% vs 1.61%; HR, 6 [95% CI, .73–276]; $P = .05$).

***Conclusions.*** In this small, retrospective, single-center, quasi-experimental study, there was no difference in 30-day mortality in patients receiving treatment with clindamycin plus vancomycin versus linezolid in combination with standard gram-negative and anaerobic therapy and surgical debridement for the treatment of NSTIs. A composite outcome of death, AKI, or CDI within 30 days was more common in the clindamycin plus vancomycin group.

**Keywords.** life-threatening infection; NSTI; piperacillin-tazobactam; surgical debridement.

Necrotizing soft tissue infections (NSTIs) are life-threatening infections that require prompt surgical debridement to improve likelihood of survival [1, 2]. Rapid treatment with antibiotics that have in vitro activity against causative pathogens is associated with improved outcomes [1, 3]. Empiric treatment is targeted toward the most common causative pathogens, including *Staphylococcus* spp, *Streptococcus* spp, *Clostridium* spp, and gram-negative and anaerobic bacteria [1, 4]. Treatment with antibiotics that inhibit protein synthesis and suppress toxins produced by group A *Streptococcus* (GAS) lowers patient mortality [5]. Accordingly, the combination of clindamycin, vancomycin, and piperacillin-tazobactam is routinely employed as empiric therapy for NSTI; however, rates of clindamycin resistance in *Streptococcus* spp have steadily increased across the United States [6]. Additionally, treatment with clindamycin is associated with an increased risk of *Clostridioides difficile* infection (CDI) compared to other antibiotic alternatives, and treatment with vancomycin is associated with acute kidney injury (AKI) [7]. Taken together, there is a growing need for new therapeutic options that are both safe and effective in treatment of NSTIs [8].

Linezolid is a protein synthesis inhibitor that decreases toxin production through inhibition of exotoxin expression [7]. It also demonstrates higher in vitro susceptibility rates against common gram-positive pathogens when compared to clindamycin [2, 7, 9]. Linezolid also can be administered orally and has high bioavailability. Given these characteristics, linezolid may be a suitable replacement for both clindamycin and vancomycin for management of NSTIs, resulting in reduced rates of CDI, AKI, and overall antibiotic exposure [10–12].

In May 2020, a multidisciplinary task force comprised of representatives from pharmacy, surgery, critical care medicine, and infectious diseases revised our local NSTI order set (Supplementary Figures 1 and 2). A key change to the

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management guidelines included recommending piperacillin-tazobactam plus linezolid (in place of clindamycin and vancomycin) as the preferred empiric regimen for NSTI. The aim of this study is to evaluate the safety of linezolid versus clindamycin plus vancomycin as empiric treatment of NSTI.

## METHODS

### Study Design

This was a retrospective, single-center, quasi-experimental study evaluating clindamycin plus vancomycin versus linezolid in combination with standard gram-negative and anaerobic therapy for the treatment of NSTI at a large, academic tertiary referral center in western Pennsylvania, United States. Patients admitted from 1 June 2018 to 30 June 2019 (preintervention) and 1 May 2020 to 15 October 2021 (postintervention) were evaluated for inclusion. Patients managed during a washout period from July 2019 through April 2020 were excluded as the new guideline was being developed. This study received approval through the institutional quality review committee as a minimal harm protocol. The study does not include factors necessitating patient consent.

*International Classification of Diseases, Tenth Revision, Clinical Modification* diagnostic codes for admissions related to NSTI (M276) or Fournier gangrene (N493) were used to identify patients for inclusion during the study period. From this group, only patients who received surgical management within 24 hours of NSTI diagnosis and at least 1 dose of linezolid or clindamycin were included. Patients were excluded if they received management at an outside facility or in the emergency department for >24 hours prior to surgical intervention. Patients were also excluded if they were transitioned to comfort measures only or died within 48 hours of admission.

### Patient Consent Statement

This study received approval through the institutional quality review committee as a minimal harm protocol. The study does not include factors necessitating patient consent.

### Outcomes

The primary endpoint was 30-day mortality, occurring at any time inpatient or postdischarge. Secondary outcomes included rates of AKI, CDI, inpatient mortality, 60-day mortality, duration of total antibiotic exposure, admission bacterial culture(s) that grew gram-positive bacteria resistant to clindamycin or linezolid, duration of clindamycin and linezolid, duration of vasopressor use, time to resolution of leukocytosis, intensive care unit (ICU) length of stay (LOS), hospital LOS, discharge to home, thrombocytopenia, and serotonin syndrome.

### Data Collection

Data were extracted from the electronic medical record and verified by at least 2 investigators. Demographic data, culture results, details related to surgical intervention, and medication data were collected in Research Electronic Data Capture (REDCap) software, version 12.2.11. The Charlson Comorbidity Index (CCI) and Sequential Organ Failure Assessment (SOFA) scores were calculated within 24 hours of hospital admission. Empiric antibiotic regimens were recorded and defined as the antibiotics initiated within 24 hours of hospitalization for the treatment of NSTI. Patients who received 1 day or less of clindamycin in the postintervention period were categorized in the linezolid (postintervention) group. Each day the patient received at least 1 dose of an antibiotic was considered 1 day of therapy for that antibiotic, consistent with the National Healthcare Safety Network definition of "day of therapy" [13]. Antibiotic susceptibilities were collected for wound and blood cultures available on the date of the first operating room visit to assess for in vitro appropriateness of empiric antibiotics. Time to source control was defined as time from first operating room trip to last trip for surgical debridement (ie, postoperative note specified debridement of necrotic tissue), in calendar days.

Adverse drug events that occurred during the admission were recorded, including thrombocytopenia (platelet count <50 000/L), serotonin syndrome (any documentation of this diagnosis in any progress note), new onset symptoms of peripheral neuropathy (mentioned in any progress note during admission), and lactic acidosis after initiation of antibiotics (defined as a lactate level >4 mmol/L following initiation of antibiotics). AKI (defined as a change in serum creatinine of 1.5–3 times baseline as defined by the RIFLE [risk, injury, failure, loss, end-stage kidney disease] criteria or any initiation of new renal replacement therapy) was evaluated at any time during the hospitalization [14, 15]. The first recorded serum creatinine measurement on admission was used as the baseline value, since patients with NSTI are critically ill and often present with AKI and the objective was to determine antibiotic-related AKI. Patients on dialysis at baseline were not included in the AKI outcome. CDI was defined as a positive toxin or nucleic acid test and new receipt of oral vancomycin or oral fidaxomicin within 30 days after antibiotic initiation. Recurrent bacterial infections were defined by a positive wound or blood culture for the same causative organism isolated at the onset of NSTI up to 30 days following the admission infection, with time zero starting at 5 days from the last positive culture for NSTI. For patients on vasopressors, time to discontinuation was defined as time from initiation to discontinuation of vasopressors for 12 consecutive hours. Admission cultures were defined as all cultures obtained on the day of the first visit to the operating room.

### Statistical Analysis

Patients in the preintervention period were matched with a patient in the postintervention period. Vasopressor use was

exactly matched between the 2 groups and the remaining matched characteristics (age, age category, serum creatinine baseline score, SOFA score, vasopressor utilization, female sex, body mass index, admit from location, CCI, ICU admission, history of immunosuppression, history of chronic wound, white blood cell count at time of admission, platelet count at admission) were optimally matched using a combination of a propensity score [16] of receipt of clindamycin along with a Mahalanobis distance penalty function [17]. Patients were considered sufficiently matched if they had a standardized difference <0.20 and a $P$ value >.05, which was tested using the Wilcoxon rank-sum test for continuous variables and Fisher exact test for binary variables. All matched characteristics satisfied these criteria. In addition, the matched comparison group was evaluated using a distribution-free test for adjacency called the cross-match test [18]. This compares the overall matching quality to balance obtained by a randomization design. All matching was completed before looking at any of the outcomes, at the suggestion of Rubin [19]. The primary outcome of 30-day mortality and the secondary outcomes of AKI and CDI along with the composite outcome of death, AKI, or CKD were analyzed as time-to-event data with death or end of 30-day follow-up used as a censoring time. These outcomes were tested using the Prentice-Wilcoxon test for paired censored data [18], and hazard ratios (HRs) were calculated using the paired Cox proportional HR [20]. Continuous outcomes were analyzed with the Wilcoxon signed-rank test for medians with a Hodges-Lehmann estimate, and the remaining binary clinical outcomes were evaluated using McNemar test. A resulting $P$ value <.05 indicated statistical significance. The matched comparison group was constructed using the "designmatch" package (version 0.4.1; Zubizarreta, Kilcioglu, Vielma), and Cohn with R Statistical Software (version 4.2.2; R Core Team 2022) [21]. All analysis was done using R software, which included the "sensitivitymv" package for M-statistics (version 1.4.3; Rosenbaum 2018) and "crossmatch" for the cross-match test (version 1.3-1; Heller, Small, and Rosenbaum 2012).

## RESULTS

Two hundred seventy-four patients were identified by admission diagnosis code for NSTI or Fournier gangrene during the study period (Supplementary Figure 3); 164 patients met the inclusion criteria. Overall, 62 patients received treatment during the preintervention period and 102 received treatment during the postintervention period.

Prior to matching, the median age was similar between groups (58.5 years preintervention vs 56 years postintervention). More patients in the preintervention group were male sex assigned at birth, identified as White, required ICU admission, and had higher median SOFA scores (Table 1). Nearly 88% of the entire cohort was admitted from a referring facility. The population was medically complex with a median CCI score of 3. In the total population, compliance with the standardized order set increased from 43.5% in the preintervention group to 75.8% in the postintervention group ($P = .0004$).

After matching, groups were balanced including median SOFA scores, ICU admission, and vasopressor utilization. More patients in the preintervention group identified as White and had a history of a solid tumor cancer; however, overall CCI scores were well matched. Despite matching, fewer patients in the postintervention group were maintained on continuous infusion fentanyl and instead relied on intermittent opioid administration (11.29% postintervention vs 48.39% preintervention, $P < .0001$) due to a separate initiative focused on decreasing opioid use.

### Outcomes

In the matched cohort, there was no difference in rates of 30-day mortality (8.06% vs 6.45%; HR, 1.67 [95% confidence interval {CI}, .32–10.73]; $P = .65$) (Table 2, Supplementary Figure 4). There was no difference in CDI (6.45% vs 1.61%; HR, Infinite [Inf] [95% CI, .66–Inf]; $P = .07$), but AKI occurred more frequently in the preintervention group (9.68% vs 1.61%; HR, 6 [95% CI, .73–276]; $P = .05$) (Table 2, Supplementary Figures 5 and 6). A composite outcome of death, AKI, or CDI within 30 days was more common in the preintervention group (14 [22.58%] preintervention vs 6 [9.68%] postintervention; HR, 4.67 [95% CI, 1.30–25.33]; $P = .02$).

There were no differences in secondary outcomes in the matched cohort, including total duration of antibiotic exposure, time to leukocytosis resolution and discontinuation of vasopressors, and ICU or hospital LOS. Numerically more patients in the preintervention group experienced inpatient mortality within 60 days of surgery (7 [11.29%] vs 3 [4.84%]; HR, 5.00 [95% CI, .56–236]; $P = .22$). Of survivors, there was no difference in patients who discharged home versus a skilled nursing or rehabilitation facility. Adverse events including thrombocytopenia, serotonin syndrome, peripheral neuropathy, and lactic acidosis were extremely rare, with no difference observed between groups (Table 2). The duration of targeted gram-negative therapy was similar between groups (Table 3).

In the overall cohort, all patients received surgery within 24 hours, with similar time from antibiotic initiation to first surgical intervention between groups (median, 3 hours in each group). Source control was similar between groups (91.9% preintervention vs 93.6% postintervention; Supplementary Table 1). In the postintervention group, more patients were discharged on an enteral antibiotic regimen (87% [33/38] vs 67% [14/21]) among patients who continued antibiotics at discharge (Table 3).

Five patients in the preintervention group and 3 patients in the postintervention group had a culture positive for GAS (Supplementary Tables 2 and 3). No one died in the

**Table 1. Baseline Demographics**

| Characteristic | Preintervention (n = 62) | Matched Postintervention (n = 62) | All Postintervention (n = 102) |
|---|---|---|---|
| Age, y, median (IQR) | 58.5 (47–67) | 57.5 (44–68) | 56 (44–67) |
| <50 | 19 (30.65) | 19 (30.65) | 37 (36.27) |
| 50–59 | 17 (27.42) | 17 (27.42) | 20 (19.61) |
| 60–69 | 14 (22.58) | 14 (22.58) | 26 (25.49) |
| 70–79 | 9 (14.52) | 9 (14.52) | 12 (11.76) |
| ≥80 | 3 (4.84) | 3 (4.84) | 7 (6.86) |
| Female sex | 20 (32.26) | 20 (32.26) | 51 (50.00) |
| Patient-reported race | | | |
| White | 49 (79.03) | 41 (66.13) | 66 (64.71) |
| Black | 5 (8.06) | 5 (8.06) | 14 (13.73) |
| American Indian | 1 (1.61) | 1 (1.61) | 2 (1.96) |
| Not reported | 7 (11.29) | 15 (24.19) | 20 (19.61) |
| BMI, kg/m$^2$, median (IQR) | 31.2 (27.00–37.2) | 31.05 (24.80–36.40) | 32.9 (24.9–38.9) |
| Admitted from location | | | |
| Home | 4 (6.45) | 4 (6.45) | 12 (11.76) |
| SNF/LTAC | 3 (4.84) | 1 (1.61) | 1 (0.98) |
| Referring acute care facility | 55 (88.71) | 57 (91.94) | 89 (87.25) |
| Serum creatinine, mg/dL, median (IQR) | | | |
| Day 1 | 1.1 (0.8–1.8) | 1.1 (0.9–1.6) | 1.0 (0.8–1.6) |
| Day 2 | 0.9 (0.7–1.6) | 0.9 (0.7–1.5) | 0.9 (0.7–1.3) |
| Day 3 | 0.9 (0.7–1.3) | 0.8 (0.7–1.2) | 0.8 (0.7–1.2) |
| Day 5 | 0.9 (0.7–1.1) | 0.8 (0.6–1.0) | 0.8 (0.6–1.0) |
| Day 7 | 0.8 (0.6–1.1) | 0.8 (0.6–1.0) | 0.8 (0.6–1.0) |
| Admission requiring ICU stay | 48 (77.42) | 48 (77.42) | 73 (71.57) |
| CCI score, median (IQR) | 3 (2–5) | 3 (2–5) | 3 (2–5) |
| SOFA score, median (IQR) | 3 (1–7) | 4 (1–7) | 3 (1–6) |
| 0–9 | 52 (83.87) | 53 (85.48) | 91 (89.22) |
| 10–14 | 10 (16.13) | 9 (14.52) | 11 (10.78) |
| History of immunosuppression | 4 (6.45) | 5 (8.06) | 15 (14.71) |
| NSTI related to traumatic event | 16 (25.81) | 8 (12.90) | 12 (11.76) |
| History of chronic wound | 13 (20.97) | 12 (19.35) | 22 (21.57) |
| Prior diagnosis of diabetes mellitus | 31 (50.00) | 30 (48.39) | 55 (53.92) |
| WBC count at time of admission, cells/L, median (IQR) | 18.3 (12.7–23.7) | 16.9 (13.6–20.4) | 17.9 (13.8–22.4) |
| Platelet count at time of admission, cells/L, median (IQR) | 261.5 (196.0–365.0) | 277.0 (184.0–383.0) | 283.5 (196.0–390.0) |
| Vasopressor utilization at time of admission | 24 (38.71) | 24 (38.71) | 31 (30.39) |
| Fentanyl continuous infusion at time of admission | 30 (48.39) | 6 (9.68)[a] | 10 (9.80) |
| Patients on serotonergic agents[b] | 14 (22.58) | 19 (30.65) | 30 (29.41) |

Data are presented as No. (%) unless otherwise indicated. Groups were matched by age, age category, serum creatinine baseline score, SOFA score, vasopressor utilization, female sex, BMI, admit from location, CCI, ICU admission, history of immunosuppression, history of chronic wound, WBC count at time of admission, and platelet count at admission. All matched characteristics have standardized difference <0.2 and 2-sample $P > .05$. Some characteristics that were not used in matching have 2-sample $P$ values as noted below.

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ICU, intensive care unit; IQR, interquartile range; NSTI, necrotizing soft tissue infection; SNF/LTAC, skilled nursing facility/long-term acute care; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

[a]Matched $P < .01$. Cross-match test estimate for Upsilon = 0.5484 ($P = .8304$).

[b]Includes patients on 1 or more serotonergic agents (ie, any use) at time of admission. Refer to Supplementary Table 1 for further breakdown of utilization of serotonergic agents.

preintervention group, whereas 1 death occurred in the postintervention group. One case of CDI occurred in the preintervention group, and no cases of CDI occurred in the postintervention group. Infection numbers for this pathogen are too small to draw meaningful conclusions.

## DISCUSSION

In this retrospective, single-center, quasi-experimental study evaluating clindamycin plus vancomycin versus linezolid in combination with standard gram-negative and anaerobic therapy for the treatment of NSTI at a large, academic tertiary referral center, the primary outcome of 30-day mortality occurred with similar frequency in both groups. There was no difference in CDI between groups, but AKI occurred more frequently in the preintervention group.

NSTIs, particularly for cases caused by GAS, are associated with high morbidity and mortality. Early in vitro data demonstrate concern that cell wall synthesis inhibitor antibiotics alone demonstrated less killing of toxin-producing organisms,

**Table 2. Primary and Secondary Outcomes of Antibiotic Selection in Matched Cohort**

| Outcomes | Preintervention (n = 62) | Matched Postintervention (n = 62) | All Postintervention (n = 102) | Paired HR[b] (95% CI) | *P*-W *P* Value[c] |
|---|---|---|---|---|---|
| Primary outcome | | | | | |
| 30-d mortality | 5 (8.06) | 4 (6.45) | 4 (3.92) | 1.67 (.32–10.73) | .65 |
| Secondary outcomes | | | | | |
| CDI | 4 (6.45) | 1 (1.61) | 1 (0.98) | Inf (.66–Inf) | .07 |
| AKI[a] | 6 (9.68) | 1 (1.61) | 1 (1.61) | 6.00 (.73–276.0) | **.05** |
| Death, CDI, or AKI at 30 d | 14 (22.58) | 6 (9.68) | 6 (5.88) | 4.67 (1.30–25.33) | **.02** |
| Additional outcomes[d] | | | | | |
| Total duration of antibiotics, d, median (IQR) | 14 (9–25) | 13 (8–21) | 14 (9–21) | −0.50 (−5.05 to 4.50) | .85 |
| Hospital LOS, d, median (IQR) | 15.85 (9.9–25.5) | 15.75 (9.9–23.6) | 15.45 (10.2–21.0) | 0.75 (−4.15 to 5.55) | .74 |
| ICU LOS, d, median (IQR) | 3 (1–5) | 3 (1–5) | 2.5 (0–5) | 0.27 (−1.00 to 2.00) | .67 |
| Time to resolution of leukocytosis, d, median (IQR) | n = 50<br>3 (2–6) | n = 57<br>3 (1–6) | n = 93<br>3 (1–7) | 0.00 (−1.00 to 1.00) | .66 |
| Time to vasopressor discontinuation, d, median (IQR) | n = 23<br>4 (2–4) | n = 24<br>2.5 (2–4) | n = 31<br>3 (2–4) | 1.00 (−.45 to 2.00) | .14 |
| Admission culture with gram-positive bacteria demonstrating in vitro resistance to linezolid | 0 (0) | 0 (0) | 1 (0.98) | NA | NA |
| Admission culture with gram-positive bacteria demonstrating in vitro resistance to clindamycin | 5 (8.06) | 0 (0) | 0 (0) | Inf (.92–Inf) | .06 |
| Inpatient mortality | 7 (11.29) | 3 (4.84) | 10 (9.80) | 5.00 (.56–236) | .22 |
| 60-d mortality | 9 (14.52) | 4 (6.45) | 11 (10.78) | 3.50 (.67–34.5) | .18 |
| Thrombocytopenia | 1 (1.61) | 1 (1.61) | 2 (1.96) | Inf (.026–Inf) | 1.00 |
| Serotonin syndrome | 0 (0) | 0 (0) | 0 (0) | NA | NA |
| Peripheral neuropathy | 2 (3.23) | 0 (0) | 0 (0) | Inf (.188–Inf) | .50 |
| Lactic acidosis | 0 (0) | 0 (0) | 2 (1.96) | NA | NA |
| Initiation of RRT | 2 (3.23) | 1 (1.61) | 3 (2.94) | 2.00 (.10–118) | 1.00 |
| Discharge location | | | | | |
| Home | 29 (46.77) | 30 (48.39) | 55 (53.92) | 0.92 (.39–2.19) | 1.00 |
| SNF | 24 (38.71) | 23 (37.10) | 30 (29.41) | 1.08 (.47–2.49) | 1.00 |
| Rehabilitation/other | 0 (0) | 5 (8.06) | 6 (5.88) | 0.00 (.00–1.09) | .06 |

Values in bold are significant P values.

Data are presented as No. (%) unless otherwise indicated. HR marked "Inf" if postintervention rate is equal to zero. HR estimate would then have zero as a denominator and not have a defined value.

Abbreviations: AKI, acute kidney injury; CDI, *Clostridioides difficile* infection; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; Inf, infinite; LOS, length of stay; NA, not applicable; P-W, Prentice-Wilcoxon; RRT, renal replacement therapy; SNF, skilled nursing facility.

[a]AKI defined by the RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria by comparing serum creatinine on admission to serum creatinine values on any subsequent day of admission. Patients who initiated RRT at any time during hospitalization were also considered "yes" for AKI.

[b]HR for paired data estimated using the paired Cox proportional hazard model. Resulting CIs and *P* values use this same statistic.

[c]*P* value calculated from the Prentice-Wilcoxon statistic for paired censored data. This test, while similar to the paired proportional hazards model, is influenced by frequency and time to event of the outcomes within each group.

[d]Data in the "Additional outcomes" section are reported as paired difference (95% CI). Difference in continuous outcomes evaluated using paired differences within the matched pairs and tested using the Wilcoxon signed-rank statistic with *P* value reported from result of the test. Reported point estimate and confidence based on the Hodges-Lehmann estimator, which is compatible with the Wilcoxon signed-rank statistic. Binary outcomes analyzed with McNemar test, with its reported point estimate and 95% CI along with its *P* value.

whereas laboratory models evaluating protein synthesis inhibitor antibiotics improved killing in high-inoculum infections [22, 23]. Therefore, adjunctive clindamycin is the guideline-recommended treatment for patients with NSTI and has demonstrated decreased mortality for these infections compared with patients not treated with a protein synthesis inhibitor [24]. More recently, concerns about increasing resistance to clindamycin among streptococcal species, clindamycin-associated toxicities, and replacing clindamycin plus vancomycin with linezolid in order to limit exposure to vancomycin have led to an interest in linezolid as an antitoxin therapy for patients with NSTI. Indeed, some studies have demonstrated resistance >30% to clindamycin among streptococcal isolates cultured from patients with NSTI and suggest that empiric linezolid compared to vancomycin can decrease AKI and shorten total antibiotic exposure [25, 26]. Clindamycin resistance among β-hemolytic streptococcal NSTI has also been associated with increased amputation risk [25]. Accordingly, we updated our NSTI admission order set to prefer linezolid over clindamycin plus vancomycin in May 2020.

To our knowledge, this is the largest published clinical study comparing clindamycin and vancomycin versus linezolid for the treatment of NSTIs. The population was high acuity and received early surgical intervention. It builds upon previous work

**Table 3. Index Antibiotic Selection**

| Antibiotics[a] | Preintervention (n = 62) | Matched Postintervention (n = 62) | All Postintervention (n = 102) |
|---|---|---|---|
| Linezolid | | | |
| No. (%) of patients who received linezolid | **1 (1.61)[b]** | **62 (100)** | **97 (95.10)** |
| Duration of linezolid, d | **5** | **6 (4–9)** | **6 (4–9)** |
| No. of linezolid doses | **8** | **10 (7–18)** | **10 (7–17)** |
| Clindamycin | | | |
| No. (%) of patients who received clindamycin | **62 (100.00)** | **29 (46.77)** | **47 (46.07)** |
| Duration of clindamycin, d | **4 (3–5)** | **1 (1)** | **1** |
| No. of clindamycin doses | **9 (6–12)** | **1 (1–2)** | **1 (1–2)** |
| Duration of piperacillin-tazobactam, d | **7 (5–9) n = 52** | **7 (5–10) n = 52** | **7 (5–10) n = 87** |
| Duration of vancomycin, d | **5 (3–8) n = 57** | **1 (1) n = 24** | **1 (1–2) n = 42** |
| Duration of daptomycin, d | **0 n = 0** | **0 n = 0** | **1 n = 1** |
| Duration of cefepime, d | **3 (1–5) n = 4** | **6 (4–7) n = 9** | **7 (4–9) n = 12** |
| Duration of metronidazole, d | **8 (6–10) n = 8** | **9 (6–12) n = 12** | **10 (7–15) n = 17** |
| Duration of aztreonam, d | **7 (5–8) n = 6** | **5 (3–5) n = 3** | **5 (2–7) n = 6** |
| Duration of meropenem, d | **8 n = 1** | **10 (9–10) n = 2** | **8 (5–10) n = 3** |
| Utilization of NSTI order set, No. (%) | **27 (43.54)** | **48 (77.41)** | **78 (76.47)** |
| Discharged to complete antibiotics via enteral route, No. (%)[c] | **14 (66.67) n = 21** | **16 (25.81) n = 21** | **33 (86.84) n = 38** |

Data are presented as median (interquartile range) unless otherwise indicated.

Abbreviation: NSTI, necrotizing soft tissue infection.

[a]One patient received ceftriaxone and 1 patient received ampicillin-sulbactam; not reflected in table.

[b]Transitioned to linezolid to complete therapy.

[c]Determined by number of patients discharged on oral antibiotics divided by number of patients discharged on any antibiotic. Seven patients in the preintervention cohort and 5 patients in the postintervention cohort were discharged on intravenous antibiotics. Does not include patients who completed antibiotic course while inpatient.

demonstrating that linezolid was a safe and effective alternative to clindamycin plus vancomycin for a surgical population and for patients with documented *Streptococcus pyogenes* infections [26, 27]. Strengths of this study include the robust inclusion criteria, matched statistical analysis, and larger sample size. The postintervention period resulted in less incidence of AKI and increased utilization of a standardized order set on admission. Additionally, an increased percentage of patients were able to discharge and complete antibiotic therapy via an enteral regimen. While not directly evaluated, a collateral benefit of the postintervention order set is decreased vancomycin monitoring including fewer therapeutic drug monitoring laboratory tests ordered for patients and less pharmacist time spent on dosing. Use of continuous infusion fentanyl for sedation also decreased postintervention due to an active decision among critical care attendings to move away from fentanyl infusions that paralleled order set implementation. Infections caused by GAS were rare, and conclusions cannot be drawn from such a small number of patients. The data that toxin inhibitors are useful adjuncts for NSTI are largely drawn from GAS, and so a true difference in efficacy might be obscured by the study's high proportion of polymicrobial infections. No patients experienced serotonin syndrome despite 20% of the linezolid-exposed patients receiving at least 1 serotonergic agent (Supplementary Table 4), consistent with other literature suggesting that linezolid-induced serotonin syndrome is rare [28].

This study is not without limitations. First, it is a retrospective, single-center observational study and is not adequately powered to conduct a multivariable regression to determine factors associated with 30-day mortality. We evaluated many metrics of clinical response but did not evaluate loss of limbs since surgical management is more associated with this outcome rather than antibiotic therapy. Importantly, time to surgery and overall surgical management did not vary in the pre- and postintervention groups. Second, the postintervention group occurred during the coronavirus disease 2019 pandemic where hospital care paradigms shifted, due to limited ICU resources, which could explain the initial disparity of fewer ICU patients in the postintervention group (prior to matching). This evaluation was intentionally conducted on all-comer NSTI admissions since decisions on empiric therapy must be made prior to final culture results; however, patients with GAS

were rare and therefore conclusions of impact of antibiotic choice on outcomes in this subgroup cannot be drawn from these data. More patients in the postintervention group had a genital source of NSTI; anatomical infection origin was not included in matching criteria due to small numbers for some infection origins and the fact that NSTI is a systemic crisis regardless of source of origin. However, the severity and morbidity of a genital-origin infection may be greater than that of limb infections. The health system converted to a 2-step *C difficile* testing algorithm in January 2019; however, all patients had confirmed toxin-producing *C difficile*. Finally, 46% of the postintervention group received 1 day of clindamycin prior to switching to linezolid, likely driven by historic practices in the emergency department or health system transfer services prior to the ability to initiate the updated order set upon ward or ICU admission.

## CONCLUSIONS

In this small, retrospective, single-center, quasi-experimental study, there was no difference in 30-day mortality in patients receiving treatment with clindamycin plus vancomycin versus linezolid in combination with standard gram-negative and anaerobic therapy and surgical debridement for the treatment of NSTIs. A composite outcome of death, AKI, or CDI within 30 days was more common in the clindamycin plus vancomycin group.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

***Potential conflicts of interest.*** All authors: No reported conflicts.

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