Which trial do we need? Empiric Glycopeptides plus clindamycin versus Oxazolidinones for suspected toxic shock and necrotizing soft tissue infections (Toxic EGO).

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The spectre of severe invasive infections caused by *Streptococcus pyogenes* and *Staphylococcus aureus* haunt clinicians and patients alike. They are the quintessential causes of devastating high profile 'front page sepsis' cases affecting children and adults, often without recognised risk factors, and typically associated with toxic shock syndromes (TSS) and necrotizing soft tissue infections (NSTI), as seen in the global surge of invasive *S. pyogenes* disease from late 2022.(1) These fulminant clinical syndromes demand rapid empiric antibiotic treatment and urgent surgical intervention for source control. Empiric adjunctive therapies are often recommended by guidelines and are widely used despite a lack of evidence. Classical examples include antibiotics to inhibit toxin production (e.g., clindamycin, linezolid) and intravenous immunoglobulin (IVIG).(2, 3) Empiric broad-spectrum antibiotic therapy usually includes anti-methicillin resistant *S. aureus* therapy (e.g., vancomycin, linezolid, clindamycin) and, for NSTI, drugs targeting gram-negative and/or anaerobic pathogens may also be initiated.

Recently there has been a welcome proliferation of pragmatic trials in infectious diseases testing the safety and efficacy of therapeutics for microbiologically confirmed serious infections.(4-6) However, most deaths from sepsis occur early, so that many of the sickest patients are excluded from these trials. Critical care researchers have long studied interventions to improve outcomes in septic shock, and have found that patients who receive early pathogen-directed antibiotics have better outcomes compared to those who do not. We wish to improve outcomes even further and test the safety and efficacy of adjunctive therapies. While patients with suspected NSTI and TSS are objectively and unequivocally very sick, we need to evaluate the impact of different empiric antibiotics and adjunctive therapies as soon as possible, often before the syndrome is fully defined both clinically and microbiologically. A high proportion of patients with suspected NSTI will ultimately have a severe *non-necrotizing* soft-tissue infection, potentially decreasing the observed benefit from the therapeutic being studied. Likewise, many patients with suspected staphylococcal or streptococcal TSS may never satisfy

their stringent research case definitions. Considering this at the design stage, one can account for the interaction between suspected and proven NSTI and TSS and outcomes from adjunctive therapy. Working along these lines, we present a pragmatic initial research question: for children and adults with suspected NSTI and/or TSS, what are the comparative benefits and harms of empiric treatment with linezolid versus vancomycin plus clindamycin?

Despite some well-founded doubts regarding the comparative effectiveness of vancomycin versus linezolid, daptomycin, ceftobiprole, or ceftaroline, a dearth of high-quality prospective comparative trials has left vancomycin as the legacy standard of care for empiric treatment of suspected serious gram-positive bacterial infections.(7) Practically, daptomycin, ceftobiprole, and ceftaroline are unsuitable for high-volume empiric use as they remain prohibitively expensive in most countries. By contrast, linezolid is now off-patent and relatively inexpensive in most countries, has favorable pharmacokinetic and pharmacodynamic (PK/PD) properties compared to vancomycin, an acceptable safety profile for short-duration therapy, and a preponderance of published clinical data suggests it is non-inferior to vancomycin for relevant infections, and possibly superior for skin and soft tissue infection and pneumonia.(8, 9) For suspected NSTI and TSS, empiric linezolid appeals as a 'tantalizing' potential replacement for both vancomycin and clindamycin, as discussed in a 2022 point-counterpoint paper stoking the fires of equipoise, as the authors highlighted the limitations of historical *in vitro* and *in vivo* data, mixed findings from retrospective clinical studies, the unclear influence of rising clindamycin resistance, and the comparative incidence of *Clostridioides difficile* infection (CDI) and acute kidney injury (AKI).(10) The debate ended in a stalemate: 'We agree that adjunctive antitoxin antibiotics should be used…based on *in vitro* and *in vivo* evidence demonstrating biological plausibility and largely concordant observational evidence of benefit

for a rare, rapidly progressive, and frequently fatal disease that may never be studied in a randomized fashion.'(10)

Two retrospective studies have recently examined this question. A retrospective single-center study by Dorazio et al. of 62 matched pairs of adult patients with NSTI who received surgical management within 24 hours of diagnosis during separate time periods before (pre-intervention) and after linezolid replaced vancomycin plus clindamycin in institutional empiric antibiotic treatment protocols for NSTI.(11) Most cases were polymicrobial (only 8 cases of *S. pyogenes*). There was no difference between groups for the primary endpoint of 30-day mortality (8.06% vs 6.45%, p=0.65) or the secondary outcome of CDI (6.45% vs 1.61%, p=0.07). More AKI was observed in the pre-intervention group (9.68% vs 1.61%, p=0.05), which was the major contributing factor to determining the composite outcome of death, AKI, or CDI within 30 days, which was more common for patients in the pre-intervention group (14 [22.58%] vs 6 [9.68%]; HR, 4.67 [95% CI, 1.30–25.33]; P = .02). These outcomes all occurred earlier in the clindamycin and vancomycin group; in the linezolid group, there were no AKI events in the first week, no deaths in the first 2 weeks, and no CDI cases in the first 3 weeks. Another retrospective single-center study by Heil et al. compared outcomes for adult patients with severe necrotizing and non-necrotizing soft tissue infections due to *S. pyogenes* who received either linezolid (n=29) or clindamycin (n=26) for at least 48 hours.(12) There were no between group differences in unadjusted and adjusted (for timing of first surgery) analyses for reduction in Sequential Organ Failure Assessment (SOFA) score over the first 72 hours, inpatient mortality, or any secondary outcomes.

Following these observational studies, and inspired by the pragmatic ACORN randomized trial of cefepime versus piperacillin-tazobactam in adults hospitalized with acute infection(13), we

propose an investigator-initiated, multicountry, pragmatic, open-label, randomized trial in children and adults with suspected NSTI and TSS, evaluating empiric linezolid (600 mg every 12 hours, or pediatric weight-based equivalent) versus vancomycin (dosing per institutional protocol) plus clindamycin (900 mg intravenous every 8 hours, or pediatric equivalent), each with any other empiric recommended antibiotic therapy and/or IVIG. Patients (≥ 6 months of age) with suspected NSTI or TSS (Figure 1) in the emergency department or inpatient unit will be eligible if a clinician initiates an order for clindamycin or linezolid within 12 hours of presentation to hospital. Patients must receive the allocated study antibiotic/s for at least 24 hours. Randomization would be stratified by clinical syndrome: suspected NSTI-with-or-without-TSS or TSS-without-NSTI. Patients with allergies to study drugs will be excluded. There are few other true contraindications to the use of vancomycin, linezolid, or clindamycin. Even the risk of serotonin syndrome with linezolid, a weak monoamine oxidase inhibitor, is generally overstated and concomitant treatment with common drugs including selective serotonin reuptake inhibitors and opioids should not preclude short durations of treatment.(14) Processes for recruitment and eligibility screening would be embedded within electronic medical records where feasible. As in ACORN, the trial would aim to proceed with a waiver of informed consent for randomization and treatment allocation. An initial vanguard study at a few trial sites would focus on feasibility of recruitment (timely randomization and allocation) and acceptability of the study interventions for key stakeholders.

The studies by Dorazio et al. and Heil et al. highlight the difficulty in selecting a meaningful primary outcome. The relative rarity of NSTI and TSS are also important considerations for the feasibility of a randomized controlled trial, particularly when recruitment will precede a confirmed diagnosis. A desirability of outcome ranking (DOOR) analysis would allow for meaningful comparisons with smaller sample sizes whilst evaluating superiority of linezolid to

clindamycin plus vancomycin (standard of care).(15) We will finalize a DOOR for the Toxic EGO trial in consultation with international experts and patient partners. It will likely need to integrate freedom from organ support, limb preservation, serious adverse drug events, and mortality (Figure 2). Patients will be assigned a mutually exclusive rank from most desirable (alive and no undesirable events) to least desirable (dead) according to the occurrence of undesirable events, weighted by severity and seriousness ('event points'). For patients with the same rank, functional status (e.g., activities of daily living, Global Motor Function Classification Scale) will be used as a "tiebreaker" in the DOOR analysis (15-17).

We will calculate the probability of a patient from the linezolid arm having a superior DOOR ranking relative to a patient from the clindamycin plus vancomycin arm, with 95% confidence interval. Superiority will be considered to have been achieved if the 95% confidence interval for probability of having a superior DOOR ranking in the linezolid group does not cross 50%. Assuming a 65% probability of a better DOOR in the linezolid group versus the clindamycin plus vancomycin group, with a 90% power and alpha=0.025 (by one-sided Wilcoxon rank sum test), 78 patients would be required in each treatment group (156 total). We would therefore seek to enroll 156 patients with suspected TSS and 156 patients with suspected NSTI, respectively, although the total number may be less than 312 as NSTI can present with TSS.

The timing of the DOOR outcome is important. An earlier endpoint would be more specific to the effects of the intervention whereas as it may lack sensitivity for downstream harms. Our inclination is to assess the primary outcome at 14 days but this would be a key question to address in a vanguard study collecting the outcome at several timepoints. Pre-specified subgroup analyses will include consideration of final clinical diagnosis (surgically- or pathologically-confirmed NSTI, TSS meeting formal case definitions) and microbiological

diagnoses (including clindamycin-resistance), timing of surgery, use of IVIG, other empiric antibiotic therapy, and the site of the infection (e.g. limb vs. non-limb). Other clinical data will be collected, including comorbidities and administration of corticosteroids or other immunomodulatory therapy that might influence the primary outcome. At any time, treating clinicians could adjust or discontinue antibiotic treatment as clinically indicated but will be encouraged to persist with the allocated protein synthesis inhibitor (clindamycin or linezolid) if there is a continuing indication for an adjunctive anti-toxin antibiotic.

Secondary outcomes would include: 7-, 14-, 30-, and 90-day mortality; change in severity of illness from admission to day 3, 7, and 14 (e.g., ΔSOFA); duration of extracorporeal life support and renal replacement therapy; development and timing of AKI, CDI, thrombocytopenia, and serotonin syndrome; Necrotizing Infection Clinical Composite Endpoint (NICCE) developed for the FDA (NSTI group)(18), hospital length of stay; health economic costs; and discharge destination. At sites with relevant capacity, nested sub-studies incorporating deferred or proxy consent could collect samples to explore wide-ranging pharmacology, immunology, and microbiology questions such as time to antibiotic pharmacokinetic/pharmacodynamic target attainment, prognostic biomarkers, and comparative microbiome effects.

The ‘Toxic EGO’ trial addresses a critical area of uncertainty facing clinicians caring for critically ill patients. One day, perhaps rapid point-of-care diagnostics will virtually eliminate the need for empiric interventions, and patients will receive very early targeted treatments. Until then, we should not give up on improving early empiric treatment for life-threatening infections, moving beyond the simple binary of adequate (susceptible) versus inadequate

(resistant) to compare treatment strategies in randomized trials with meaningful endpoints balancing benefits and harms.

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Author contributions

JO conceptualized the manuscript and wrote the first draft. The other authors contributed to critical review and discussions.

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Figure 1. Pragmatic case definitions of suspected necrotizing soft tissue infection and toxic shock syndrome for the Toxic EGO trial

Suspected necrotizing soft tissue infection (NSTI)

- ≥ 2 SIRS criteria

PLUS ≥ 1 sign, symptom, imaging, or intraoperative finding concerning for NSTI

- Pain that extends past margin of apparent infection
- Severe pain out of proportion to physical findings
- Rapid clinical progression (e.g., rapidly spreading erythema)
- Crepitus
- Skin discolouration or necrosis
- Tense edema with foul smelling grayish or brown wound discharge
- CT or MRI findings of gas in soft tissue or other NSTI imaging feature/s
- Skin infection with features of toxic shock syndrome

Suspected toxic shock syndrome (TSS)

- Hypotension (including symptomatic postural hypotension)
  - In infants and children: this criteria may be met by features of shock such as tachycardia, tachypnea, delayed peripheral perfusion, and temperature instability.

PLUS multiorgan involvement characterized by ≥ 2 of the following

- Mucocutaneous features (erythematous skin rash, conjunctiva, mouth, vagina)
- Gastrointestinal – severe vomiting and/or diarrhea
- Altered mental state
- Renal impairment
- Impaired liver function
- Thrombocytopenia
- Coagulopathy
- Acute respiratory distress syndrome
- (Suspected NSTI)

CT: computer tomography; NSTI: necrotizing soft tissue infection; SIRS: systemic inflammatory response; TSS: toxic shock syndrome

Figure 2. An initial proposal for a Desirability Of Outcome Ranking (DOOR) outcome for the Toxic EGO trial, prior to professional, patient, and public involvement and engagement

DOOR rank		Tie breaker		DOOR Events	Event points
1	• Alive • No events	1a. Better/improved function 1b. Worse/declining function	**Most desirable**	Ongoing ECMO	9
2	• Alive • 1-2 event points	2a. Better/improved function 2b. Worse/declining function		Ongoing CRRT or invasive ventilation	6
3	• Alive • 3-5 event points	3a. Better/improved function 3b. Worse/declining function		Limb amputation	3 for one limb, 2 for additional limb/s
4	• Alive • 6-8 event points	4a. Better/improved function 4b. Worse/declining function		Major bleeding event	3
5	• Alive • ≥ 9 event points	6a. Better/improved function 6b. Worse/declining function		*Clostridoides difficile* infection	2
6	• Death		**Least desirable**	Acute kidney injury, serotonin syndrome	2
				Extremity amputation (e.g. fingers, toes)	2
				Thrombocytopenia, antibiotic rash, non-*C. difficile* antibiotic-associated diarrhea	1 for each

CRRT: continuous renal replacement therapy; ECMO: extra-corporeal membrane oxygenation

References

1. Osowicki J, Nizet V. Malice in Chains. J Infect Dis. 2023;227(10):1117-8.
2. Parks T, Wilson C, Curtis N, Norrby-Teglund A, Sriskandan S. Polyspecific Intravenous Immunoglobulin in Clindamycin-treated Patients With Streptococcal Toxic Shock Syndrome: A Systematic Review and Meta-analysis. Clinical Infectious Diseases. 2018;67(9):1434-6.
3. Bartoszko JJ, Elias Z, Rudziak P, Lo CKL, Thabane L, Mertz D, et al. Prognostic factors for streptococcal toxic shock syndrome: systematic review and meta-analysis. BMJ Open. 2022;12(12):e063023.
4. Bejon PA, Li HK, Rombach I, Walker S, Scarborough M. The OVIVA trial. Lancet Infect Dis. 2019;19(10):1058.
5. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. N Engl J Med. 2019;380(5):415-24.
6. Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA. 2018;320(10):984-94.
7. Rose W, Volk C, Dilworth TJ, Sakoulas G. Approaching 65 Years: Is It Time to Consider Retirement of Vancomycin for Treating Methicillin-Resistant Staphylococcus aureus Endovascular Infections? Open Forum Infect Dis. 2022;9(5):ofac137.
8. Kato H, Hagihara M, Asai N, Shibata Y, Koizumi Y, Yamagishi Y, et al. Meta-analysis of vancomycin versus linezolid in pneumonia with proven methicillin-resistant Staphylococcus aureus. J Glob Antimicrob Resist. 2021;24:98-105.
9. Yue J, Dong BR, Yang M, Chen X, Wu T, Liu GJ. Linezolid versus vancomycin for skin and soft tissue infections. Cochrane Database Syst Rev. 2016(1):Cd008056.
10. Cortés-Penfield N, Ryder JH. Should Linezolid Replace Clindamycin as the Adjunctive Antimicrobial of Choice in Group A Streptococcal Necrotizing Soft Tissue Infection and Toxic Shock Syndrome? A Focused Debate. Clinical Infectious Diseases. 2022;76(2):346-50.
11. Dorazio J, Chiappelli AL, Shields RK, Tsai YV, Skinker P, Nabozny MJ, et al. Clindamycin plus Vancomycin versus Linezolid for Treatment of Necrotizing Soft Tissue Infection. Open Forum Infectious Diseases. 2023.
12. Heil EL, Kaur H, Atalla A, Basappa S, Mathew M, Seung H, et al. Comparison of Adjuvant Clindamycin versus Linezolid for Severe Invasive Group A Streptococcal Skin and Soft Tissue Infections. Open Forum Infectious Diseases. 2023.
13. Qian ET, Casey JD, Wright A, Wang L, Shotwell MS, Siemann JK, et al. Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection: The ACORN Randomized Clinical Trial. JAMA. 2023;330(16):1557-67.
14. Elbarbry F, Moshirian N. Linezolid-associated serotonin toxicity: a systematic review. Eur J Clin Pharmacol. 2023;79(7):875-83.
15. Ong SWX, Petersiel N, Loewenthal MR, Daneman N, Tong SYC, Davis JS. Unlocking the DOOR - how to design, apply, analyse, and interpret desirability of outcome ranking (DOOR) endpoints in infectious diseases clinical trials. Clin Microbiol Infect. 2023.
16. Howard-Anderson J, Dai W, Yahav D, Hamasaki T, Turjeman A, Koppel F, et al. A Desirability of Outcome Ranking Analysis of a Randomized Clinical Trial Comparing Seven Versus Fourteen Days of Antibiotics for Uncomplicated Gram-Negative Bloodstream Infection. Open Forum Infect Dis. 2022;9(6):ofac140.
17. Doernberg SB, Tran TTT, Tong SYC, Paul M, Yahav D, Davis JS, et al. Good Studies Evaluate the Disease While Great Studies Evaluate the Patient: Development and Application of a Desirability of Outcome Ranking Endpoint for Staphylococcus aureus Bloodstream Infection. Clin Infect Dis. 2019;68(10):1691-8.

18. Bulger EM, May A, Dankner W, Maislin G, Robinson B, Shirvan A. Validation of a clinical trial composite endpoint for patients with necrotizing soft tissue infections. J Trauma Acute Care Surg. 2017;83(4):622-7.