Necrotizing Soft Tissue Infection Guidelines

Background: Historically, clindamycin has been added to treatment for NSTI due to evidence that it improves outcomes in Group A Strep infections. This effect is felt to be in part due to its ability to suppress synthesis of toxin proteins and concerns that penicillins may be less effective in extremely high burden strep infections. In recent years, Group A Strep resistance to clindamycin has been increasing, reaching 30-50% at some centers on the west coast (including our own).

What's new: We are changing the empiric NSTI regimen for UCSF health to the combination of linezolid and piperacillin-tazobactam. This achieves similar coverage of the most common and virulent organisms in NSTI, while using linezolid for toxin suppression in streptococcal infections, to which there is little resistance. It also improves ease of administration. Once culture results have been obtained, patients should be de-escalated to targeted therapy per Figure 1 and Table 1. Duration of therapy recommendations are also updated to reflect recent evidence around shorter courses of therapy.

Empiric therapy:

First line: Piperacillin-Tazobactam + Linezolid IV (ok to transition to PO once clinically stable, taking PO)

Penicillin allergy: Linezolid + Ceftriaxone + Metronidazole IV/PO

Cephalosporin allergy or SJS/TEN or DRESS to Penicillins: Linezolid + Aztreonam + Metronidazole

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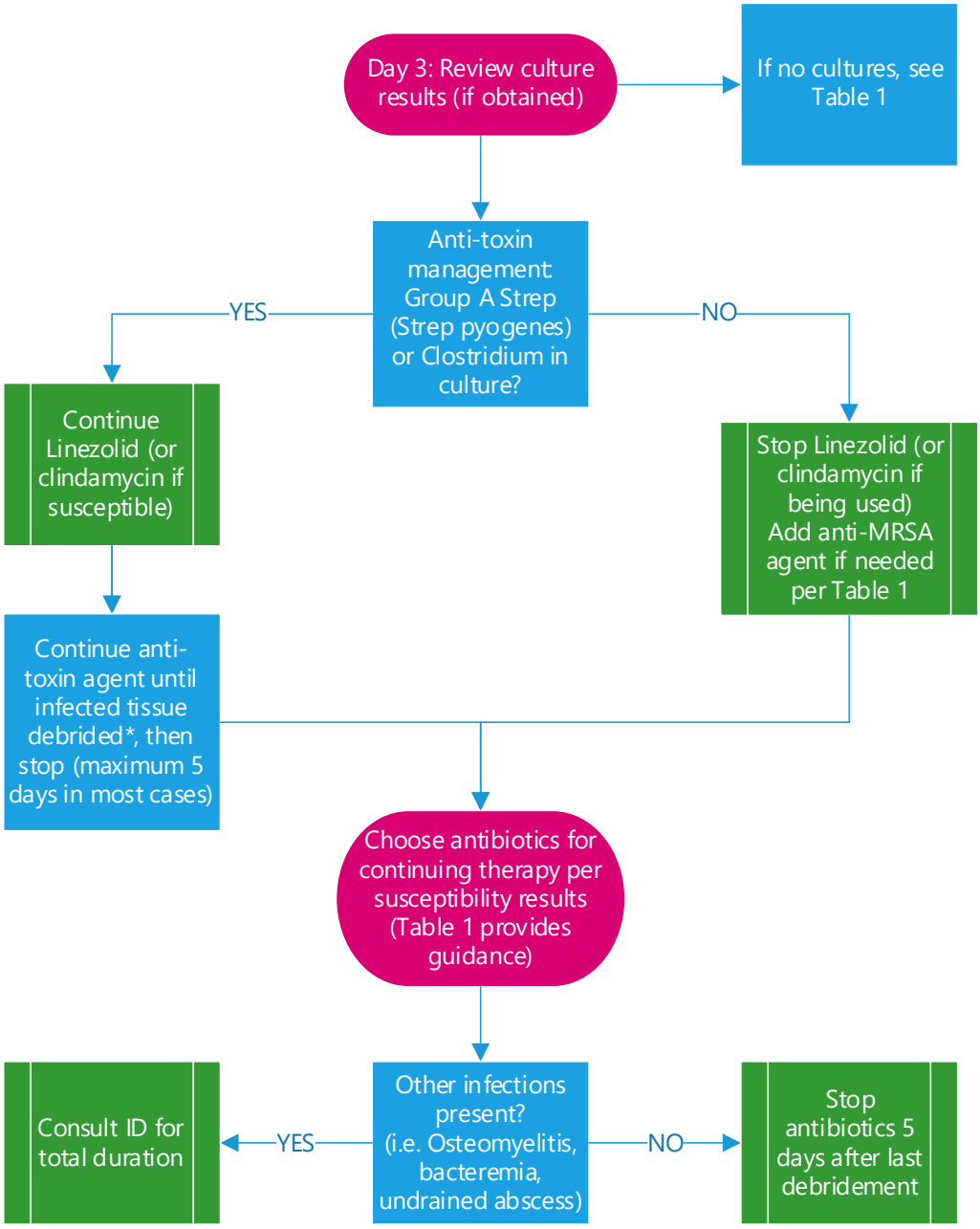
Management after empiric therapy (Figure 1)



*Anti-toxin agents can generally be stopped when all grossly infected tissue has been debrided (gram stain and culture results can help inform this decision), even if further wound debridement/revision is expected, see “Duration of Therapy” below

De-escalation regimens once cultures result (Table 1)

Antimicrobial Stewardship, available on Voalte (UCSF Health) /Epic Secure Chat (ZSFG) during business hours, or Infectious Diseases consultation are available to help in selecting therapy.

SINGLE PATHOGEN GROWING

Pathogen	IV option(s)	PO Agents	Anti-Toxin Notes
Group A Strep**, Group B Strep	Penicillin	Amoxicillin, cephalexin	Per Figure 1
Clostridium Spp.	Penicillin	Amoxicillin, cephalexin	Per Figure 1
MRSA	Vancomycin	TMP/SMX, doxycycline	Not needed
MSSA	Cefazolin	Cephalexin	Not needed
E. Coli, Klebsiella, or Proteus	Ceftriaxone	Varies, refer to susceptibilities	Not needed
Anaerobes other than clostridium	metronidazole	metronidazole	Not needed

MULTIPLE PATHOGENS GROWING (common combinations, for others, discuss with ID or ASP)

Pathogen	IV option(s)	PO Agents	Anti-Toxin Notes
Group A strep** + anaerobes	Ampicillin-sulbactam	Amox-clav	Per Figure 1
Group A strep** + MRSA	Vancomycin (once linezolid stopped)	TMP/SMX + Amoxicillin	Per Figure 1
Group A strep** + MSSA	Cefazolin	Cephalexin	Per Figure 1
MRSA + anaerobes	Vancomycin + metronidazole	TMP/SMX + metronidazole	Not needed
MSSA + anaerobes	Ampicillin-sulbactam OR cefazolin + metronidazole	Amox-clav	Not needed
Culture negative (review outside cultures if available)	Ceftriaxone	Amox-clav	Add linezolid through day 5
No cultures obtained	Vancomycin + ceftriaxone	Amox-clav + TMP/SMX	Use linezolid instead of vancomycin for first 5 days for anti-toxin effects

**** for Patients with Group A Strep and Toxic Shock Syndrome, IVIG should be considered as it may reduce mortality (ID consult also recommended), though benefit in necrotizing fasciitis is unclear.[1,2] Similar benefit has not been demonstrated for staphylococcal toxic shock**

Duration of therapy:

Anti toxin agent duration: If bacteria requiring anti-toxin therapy are isolated (see Table 1), anti-toxin agents should be continued until all grossly infected tissue is debrided (gram stain and culture results can help inform this), or through 5 days of anti-toxin therapy, whichever comes first. In rare cases with ongoing, progressive infection or shock after 5 days, continuation of anti-toxin therapy past 5 days should be considered.

Overall antibiotic duration: **5 days after final debridement, minimum 7 days total.** See figure 1, but there is growing literature that short durations of therapy after completion of debridement are as effective as longer courses, with some centers publishing data suggesting as short as two days after final debridement.[3,4,5,6,7] We currently recommend 5 days of therapy after final debridement, with a minimum total duration of therapy of 7 days. Clinicians should take into account the clinical status of the patient and the status of their infection when using these guidelines. Patients with other sites of infection (bacteremia, bone/joint infection, residual undrained abscess) likely will require longer courses, and should be discussed with the infectious diseases consult service.

Linezolid side-effects:

Linezolid can have drug-drug interactions with serotonergic agents including methadone, fentanyl, anti-psychotics, SSRIs, and SNRIs. Co-administration of these agents is not contraindicated as serotonin syndrome is extremely rare, even in patients on serotonergic agents.[8,9] Monitor patients clinically for fever and confusion.
Prolonged courses of linezolid can be associated with thrombocytopenia, anemia, neutropenia, irreversible neuropathy, and vision changes. Linezolid should be discontinued when no longer needed for toxin suppression.

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[3] Horn DL, Chan JD, Li K, et al. Defining the Optimal Antibiotic Duration in Necrotizing Skin and Soft Tissue Infections: Clinical Experience from a Quaternary Referral Center. *Surg Infect (Larchmt)*. 2023;24(8):741-748. doi:10.1089/sur.2022.294
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[5] Kenneally AM, Warriner Z, VanHoose JD, et al. Evaluation of Antibiotic Duration after Surgical Debridement of Necrotizing Soft Tissue Infection. *Surg Infect (Larchmt)*. 2022;23(4):357-363. doi:10.1089/sur.2021.256
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[8] Traver EC, Heil EL, Schmalzle SA. A Cross-sectional Analysis of Linezolid in Combination with Methadone or Buprenorphine as a Cause of Serotonin Toxicity. *Open Forum Infect Dis*. 2022;9(7):ofac331. Published 2022 Jul 1. doi:10.1093/ofid/ofac331

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[9] Kufel WD, Parsels KA, Blaine BE, Steele JM, Seabury RW, Asiago-Reddy EA. Real-world evaluation of linezolid-associated serotonin toxicity with and without concurrent serotonergic agents. *Int J Antimicrob Agents*. 2023;62(1):106843. doi:10.1016/j.ijantimicag.2023.106843