Beyond Coverage: Antitoxin Antibiotics in Group A Streptococcal Necrotizing Soft Tissue Infections

Matthew Jones, PharmD

PGY-1 Pharmacy Resident

HCA HealthOne Presbyterian St. Luke's

Preceptor: Corwin Coppinger, PharmD, Adv. Clinical Pharmacist

HCA HealthOne Presbyterian St. Luke's

January 28, 2026

HCA Healthcare®

Disclosures

- The presenter and their preceptor of this CE activity have no relevant relationships to disclose.
- Note: The content presented is for informational purposes only and is based upon the presenter(s) knowledge and opinion. It should not be relied upon without independent consultation with and verification by appropriate professional advisors. Individuals and organizations shall have sole responsibility for any actions taken in connection with the content herein. HealthTrust, the program presenter(s) and their employers expressly disclaim any and all warranties as to the content as well as any liability resulting from actions or omissions of any individual or organization in reliance upon the content.
- This program may contain the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.

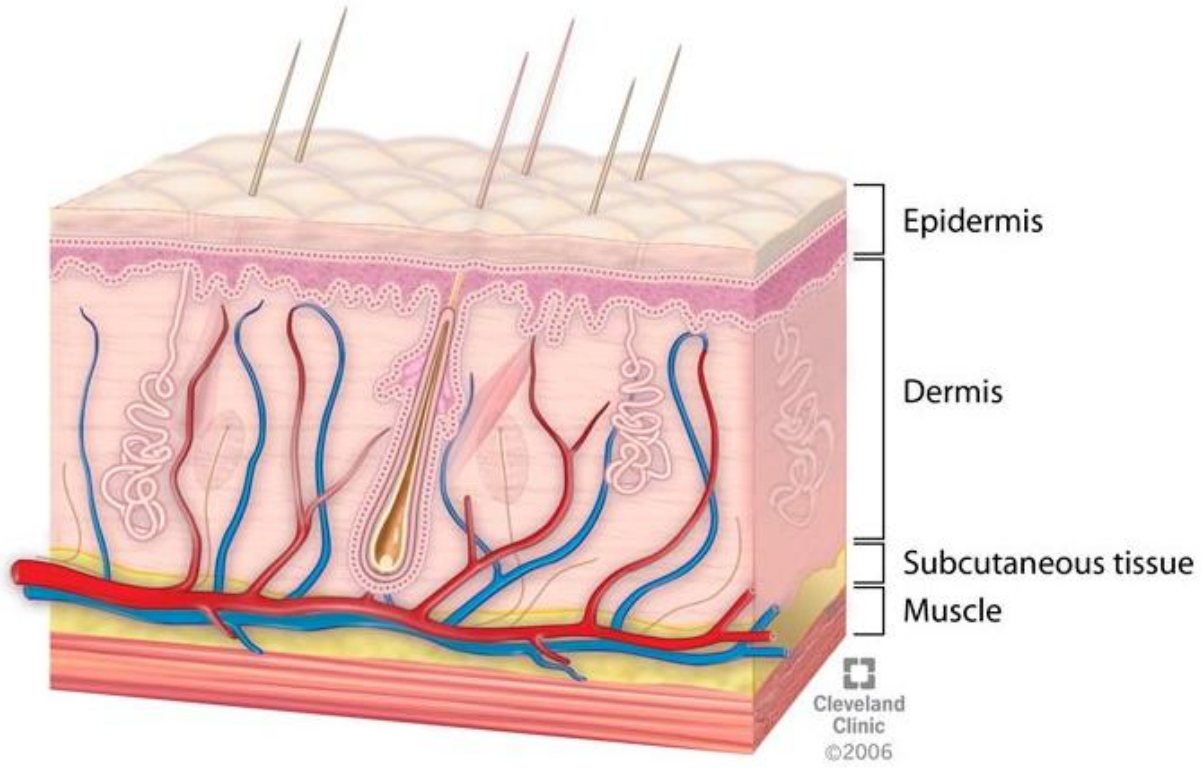
Objectives

- Recall the pharmacodynamic rationale for protein synthesis inhibitors in group A Streptococcus (GAS) necrotizing soft tissue infection
- Identify comparative efficacy, safety and resistance of clindamycin versus linezolid based on current clinical evidence
- Recognize evidence-based recommendations for antibiotic selection and duration in GAS necrotizing soft tissue infection

Background

Necrotizing Soft Tissue Infections (NSTIs)

- Rapidly progressing skin and soft tissue infection
  - Extensive necrosis of the dermis and epidermis
  - Often also involves fascia and muscle
  - Can lead to systemic illness, morbidity, and mortality



Sources: Allaw F, et al. Curr Opin Infect Dis. 2024; 37(2):105-111
Clevland Clinic. https://my.clevelandclinic.org

NSTIs: Clinical Presentation

Clinical Sign	Rate at Presentation	Sensitivity	Specificity
Classic			
Bullae	25.6%	25% – 26%	96%
Skin necrosis	24.1%	24% – 65%	-
Crepitus	20.3%	20%	-
Gas on radiographic evaluation	24.8%	-	-
Nonspecific			
Swelling	80.8%	62% - 92%	-
Pain or tenderness	79%	76% - 83%	-
Erythema	70.7%	71% - 94%	-
Warmth	44%	44%	-
Fever (> 37.5 C)	40%	40% - 67%	77%
Hypotension	21.1%	21%	98%

Sources: McDermott J, et al. JAMA Surg. 2024;159(11):1308-1315
Pelletier J, et al. *J Emerg Med*. 2022;62(4):480-491

Types of NSTIs

	Type I	Type II
Organism	Polymicrobial	Monomicrobial (group A streptococcus)
Gas formation	Often in tissue	No
Anatomic location	Following surgery or injury Head/neck, abdomen, or anogenital area	Often involves the extremities, following minor trauma May or may not involve penetrating trauma
Risk factors	Diabetic or decubitus ulcers, hemorrhoids, rectal fissures, episiotomies, colonic or urologic surgery, gynecologic procedures	May occur in any age group and in persons without any underlying illness

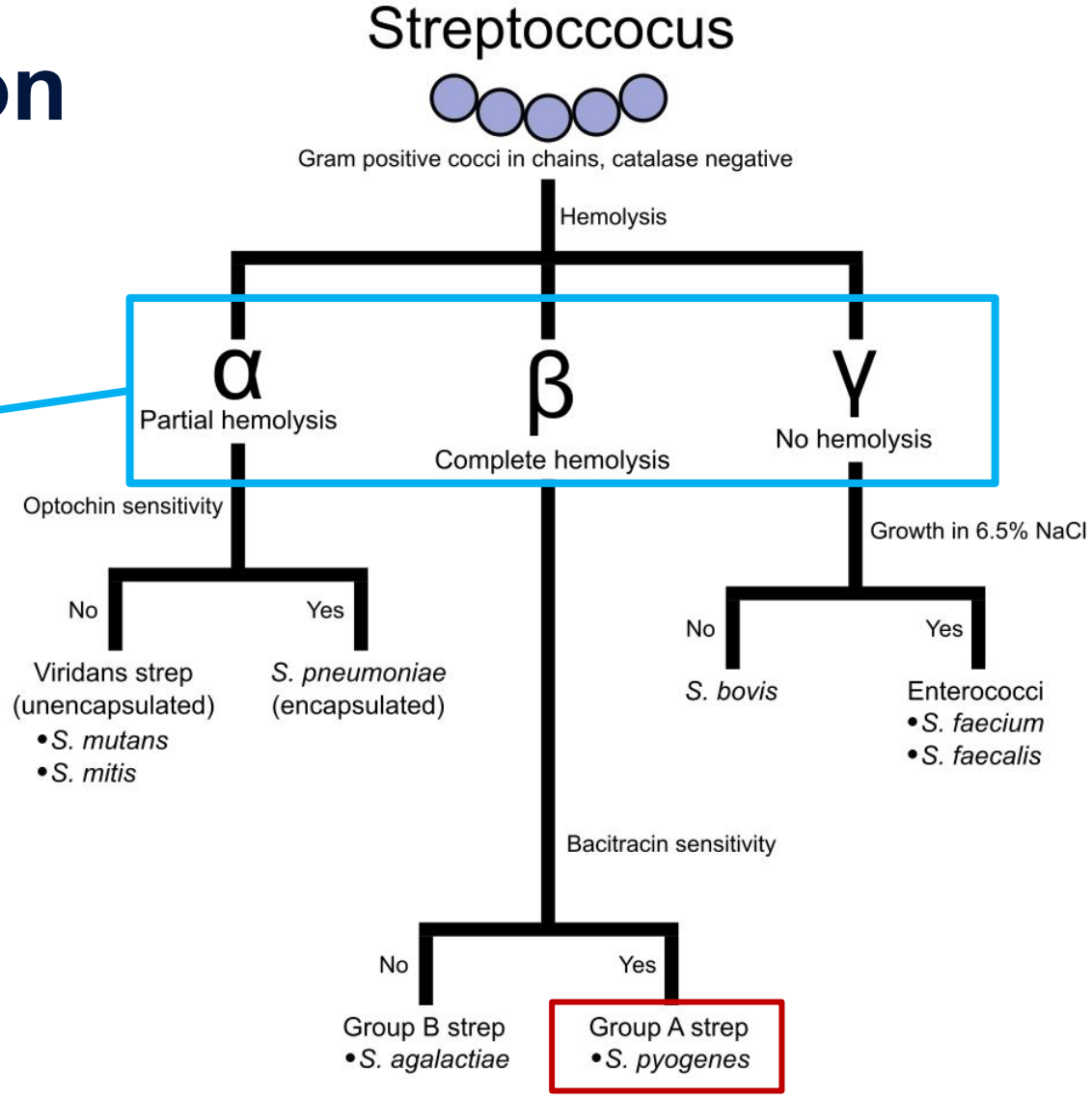
Sources: Pelletier J, et al. *J Emerg Med*. 2022;62(4):480-491
Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

Micro Review

HCA Healthcare®

Streptococci Classification

- Gram-positive cocci in chains, catalase negative
- Hemolytic grouping
  - Based on appearance when grown in culture on blood agar
- Lancefield grouping
  - Subsequent classification based on carbohydrates in the cell wall
  - Groups A through H and K through V



Sources: Bush LM, et al. *Merck Manual*. 2025
Medbullets Step 1. https://step1.medbullets.com.

Group A Streptococcus Virulence Factors

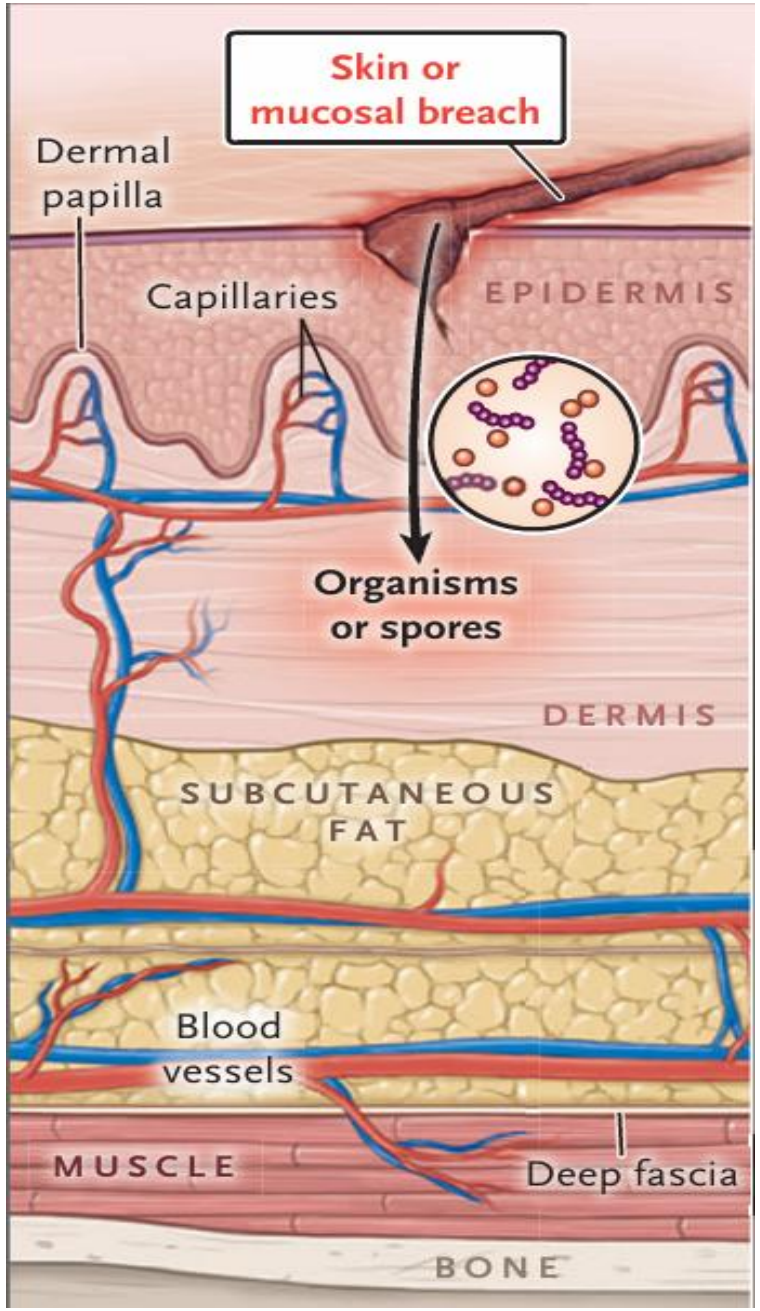
- M Proteins
  - Surface protein that protects the bacteria from phagocytosis
  - Directly responsible for Streptococcal Pyrogenic Exotoxins (SPE) production
    - SPE A
      - Potent antigen that causes T-cell activation and cytokine storm
      - Direct correlation with systemic inflammation with increased IL-6 levels
      - Primary driver of streptococcal toxic shock syndrome
    - SPE B
      - Extracellular cysteine protease
      - Causes direct tissue destruction, inflammation, and shock

 Source: Coyle EA. *Pharmacotherapy*. 2003;23(5):638-42

NSTI Pathophysiology

NSTI Pathophysiology

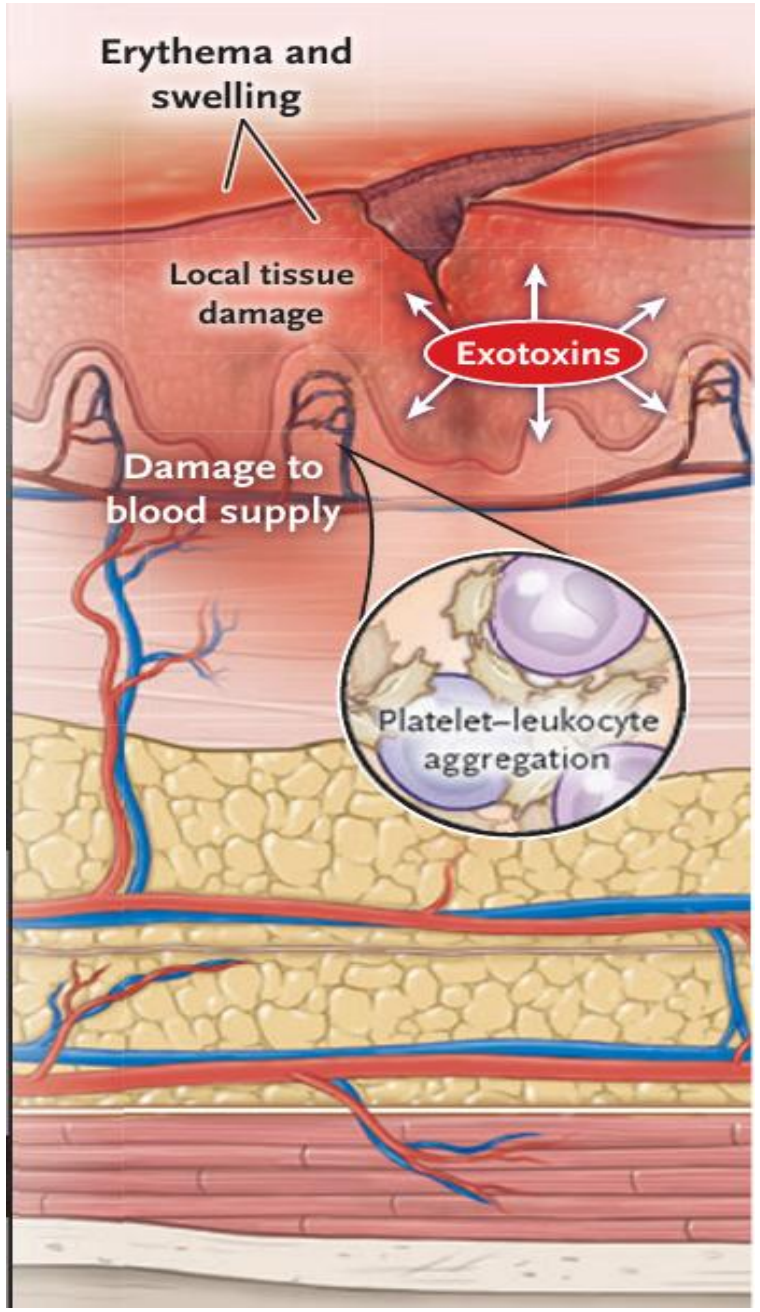
- Defined Portal of Entry
  - Organisms are introduced into soft tissue
  - Exotoxins released



 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Pathophysiology

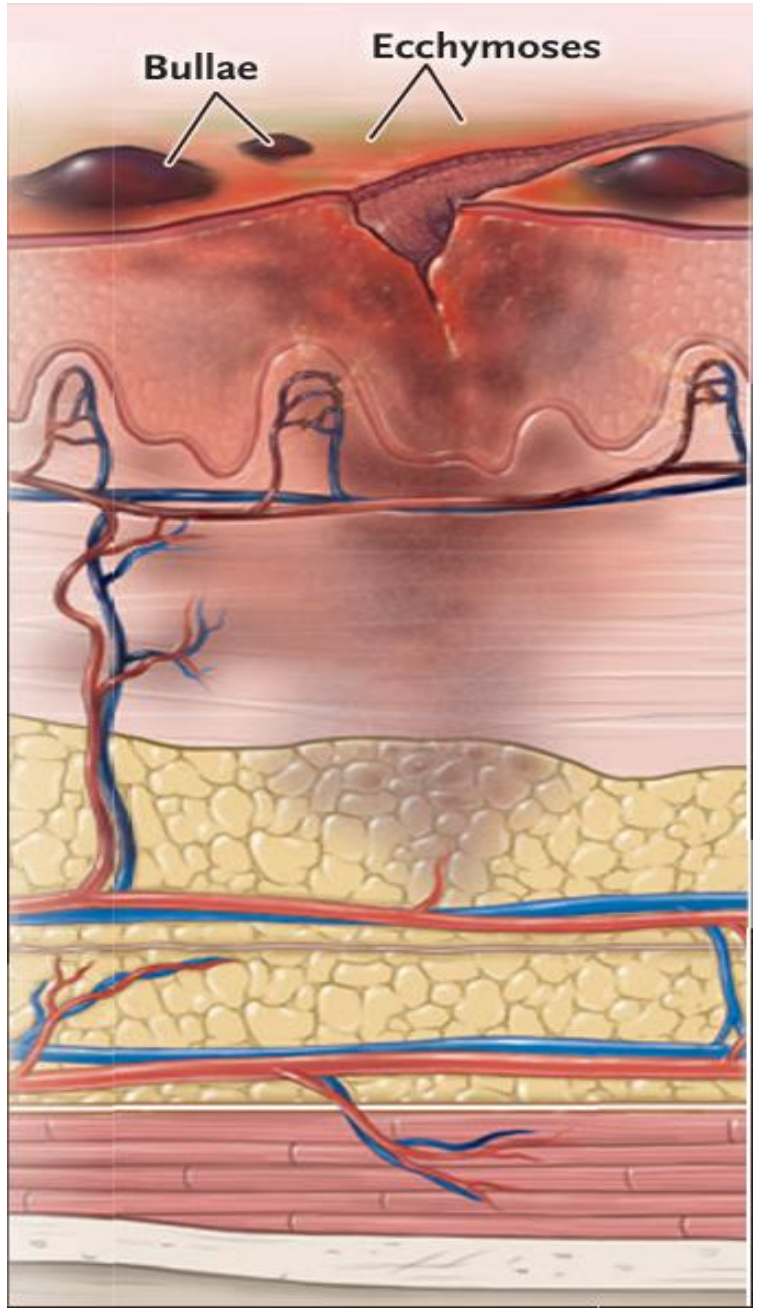
- Defined Portal of Entry
  - Exotoxins cause local tissue damage
  - Platelet-leukocyte aggregates occlude capillaries



 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Pathophysiology

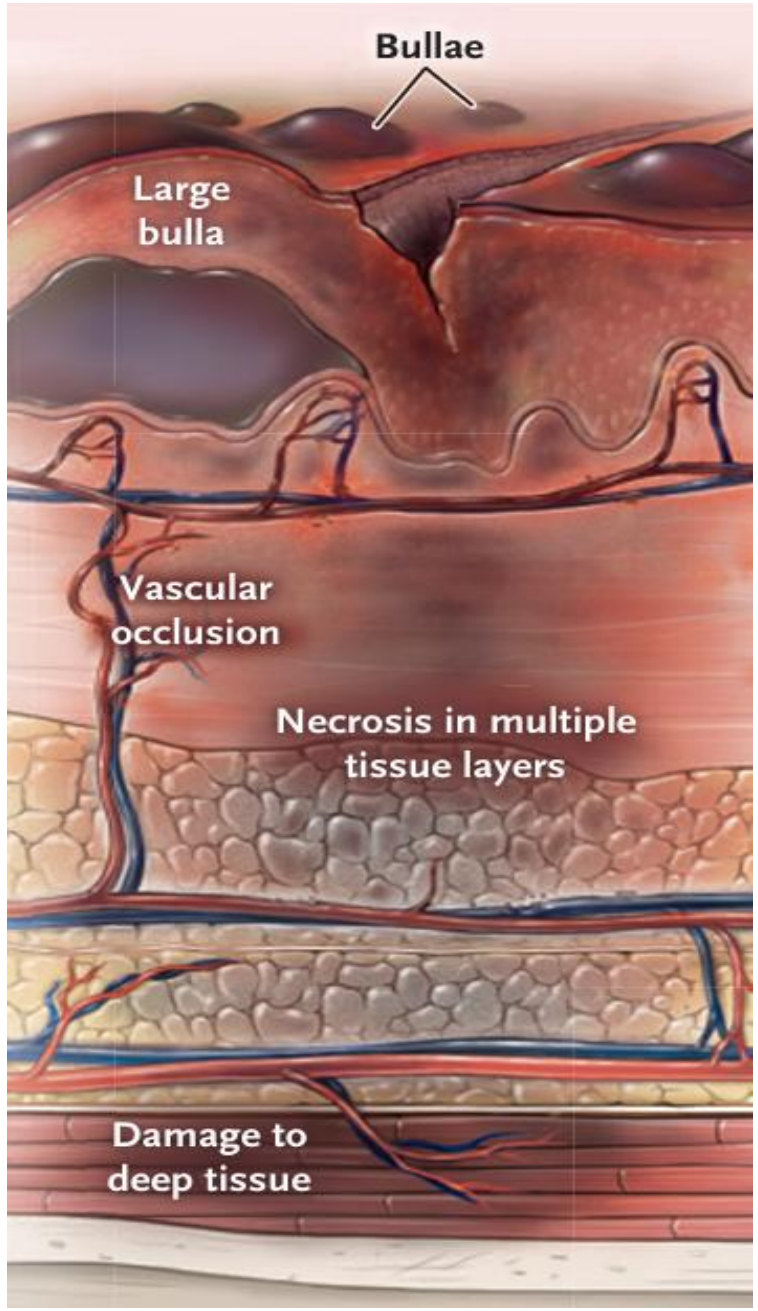
- Defined Portal of Entry
  - Erythema and swelling become widespread
  - Bullae and ecchymoses develop



 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Pathophysiology

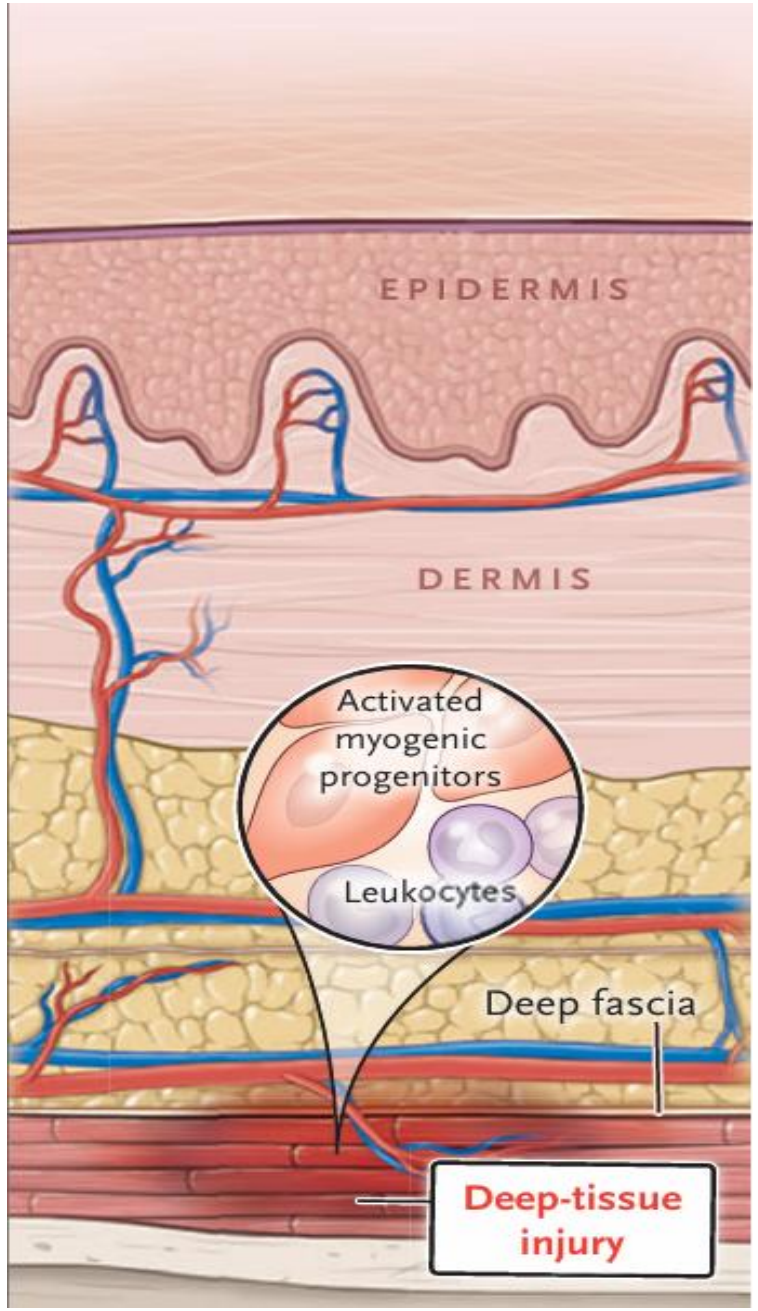
- Defined Portal of Entry
  - Deeper tissues become infected
  - Larger venules and arterioles become occluded
  - Necrosis affects all tissue layers



 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Pathophysiology

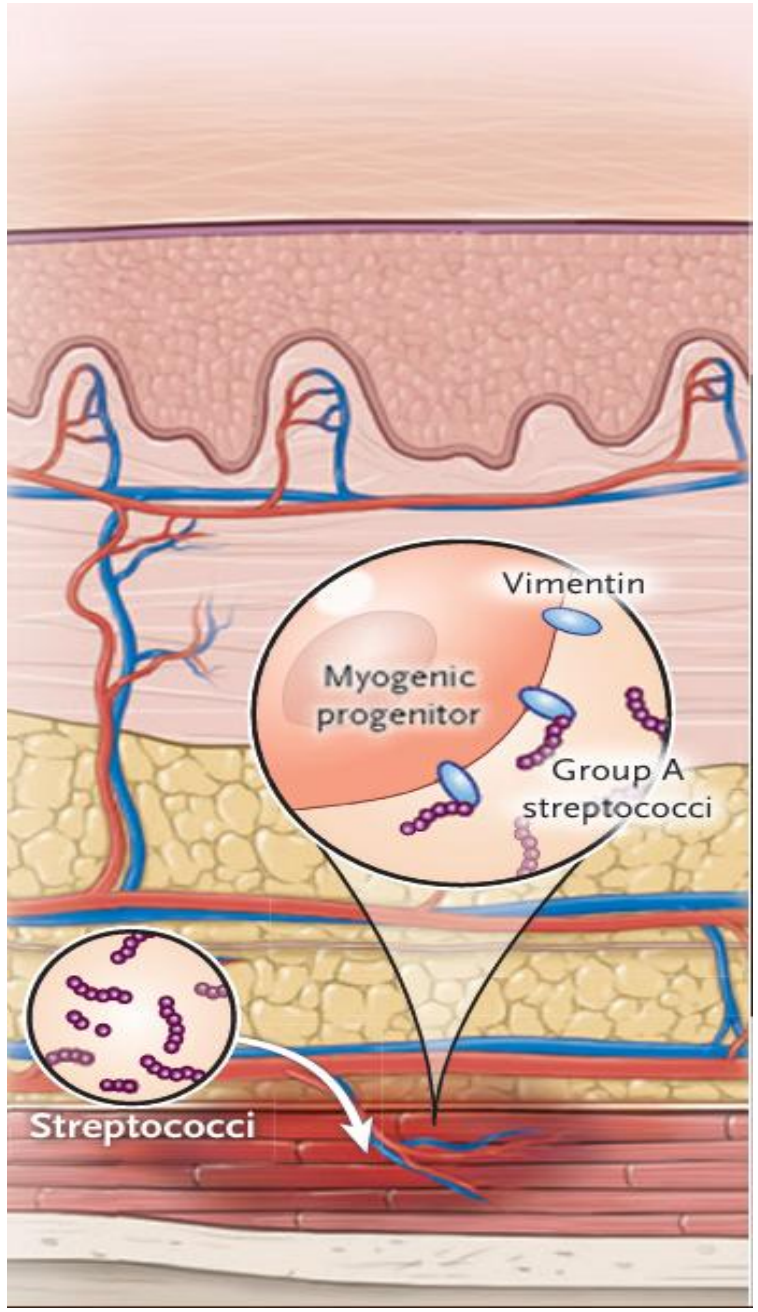
- No Defined Portal of Entry
  - Nonpenetrating deep-tissue injury stimulates repair response
  - Influx of leukocytes
  - Activation of myogenic progenitor cells



 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Pathophysiology

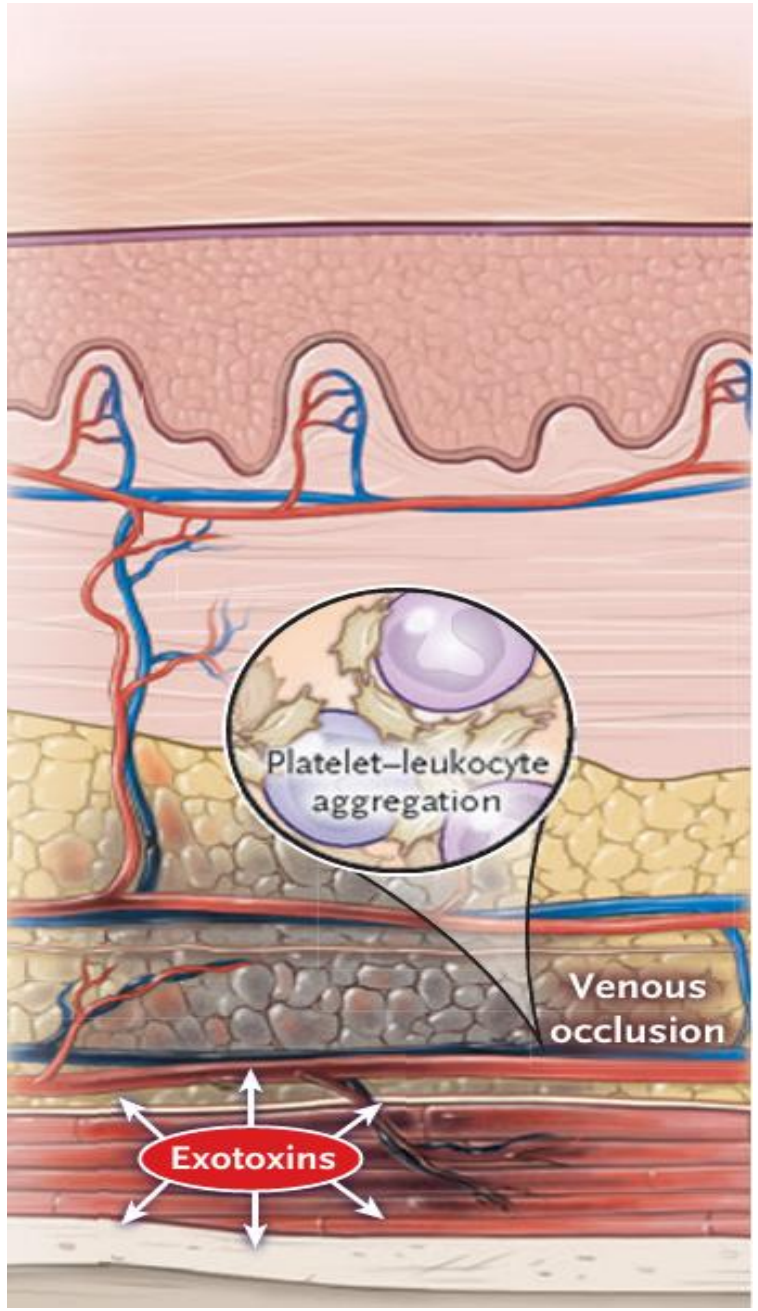
- No Defined Portal of Entry
  - In susceptible hosts, organisms are trafficked to injury site



 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Pathophysiology

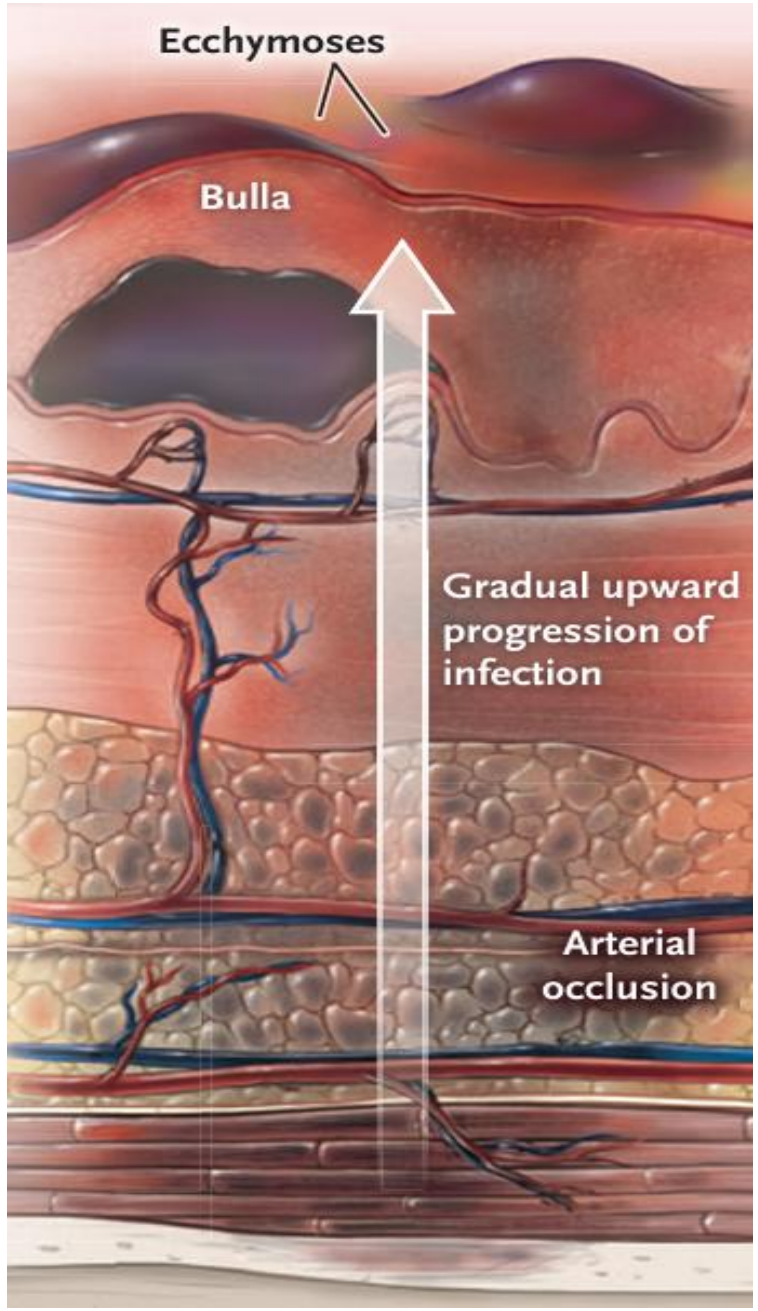
- No Defined Portal of Entry
  - Exotoxins are released
  - Venous occlusion leads to necrosis in deep tissue



 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Pathophysiology

- No Defined Portal of Entry
  - Arteries become occluded
  - Necrosis in deep tissue spreads to upper tissue layers
  - Bullae and ecchymoses later develop

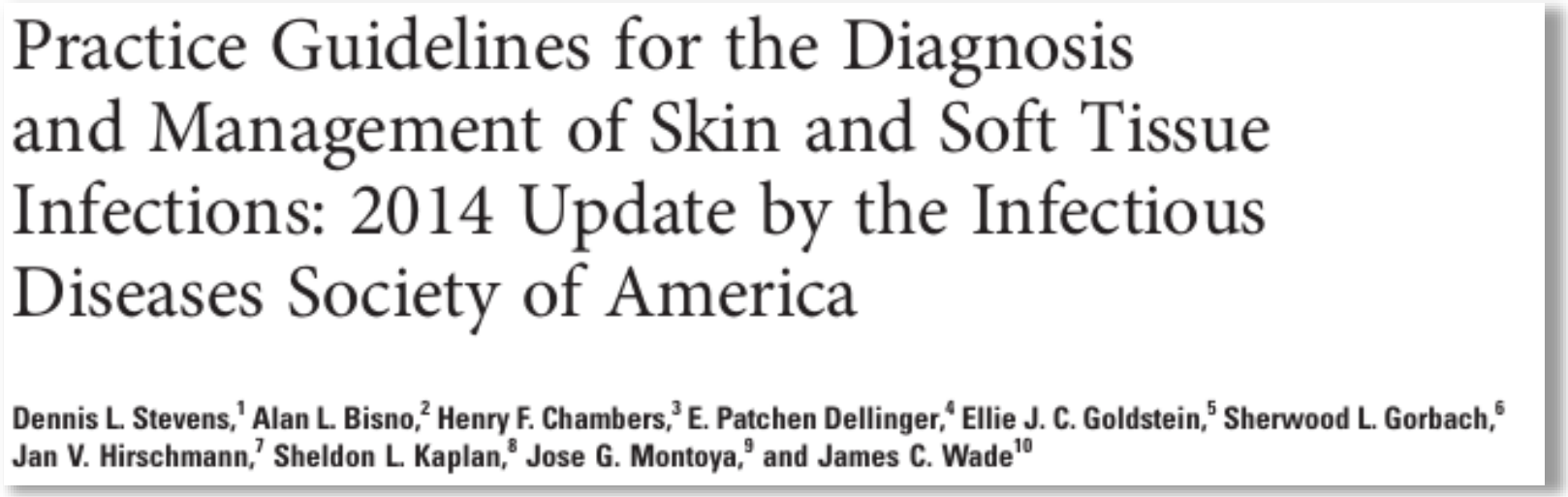


 | Source: Stevens DL, et al. N Engl J Med. 2017;377(23):2253-2265

NSTI Treatment Overview

HCA Healthcare®

Infectious Diseases Society of America (IDSA)



Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

Dennis L. Stevens,[1] Alan L. Bisno,[2] Henry F. Chambers,[3] E. Patchen Dellinger,[4] Ellie J. C. Goldstein,[5] Sherwood L. Gorbach,[6] Jan V. Hirschmann,[7] Sheldon L. Kaplan,[8] Jose G. Montoya,[9] and James C. Wade[10]

IDSA Skin and Soft Tissue Infection Guidelines

Empiric management of severe, non-purulent, necrotizing infection:

Surgical Intervention	• Emergent surgical inspection with debridement • Used to rule in or out necrotizing process and collect cultures
Antibiotics	• Broad coverage • Cover gram-positive, gram-negative, and anaerobic organisms

 Source: Stevens DL, et al. Clin Infect Dis. 2014 Jul 15;59(2):e10-52

IDSA Skin and Soft Tissue Infection Guidelines

Empiric management of severe, non-purulent, necrotizing infection:

Vancomycin
or
Linezolid

+

Piperacillin/tazobactam
or
Carbapenem
or
Ceftriaxone plus metronidazole

Source: Stevens DL, et al. Clin Infect Dis. 2014 Jul 15;59(2):e10-52

IDSA Skin and Soft Tissue Infection Guidelines

Management of necrotizing fasciitis caused by group A streptococci (GAS):

Surgical Debridement	• Primary treatment modality • Repeat debridement daily until source control achieved
Antibiotics	• Penicillin PLUS clindamycin

 Source: Stevens DL, et al. Clin Infect Dis. 2014 Jul 15;59(2):e10-52

IDSA Skin and Soft Tissue Infection Guidelines

Duration of treatment in necrotizing fasciitis:

- Antibiotic therapy should be continued until:
  1. Further debridement is not necessary
  2. Patient improves clinically
  3. Fever has been absent for 48-72 hours

- Guidelines noted lack of definitive clinical trial on duration of therapy

Source: Stevens DL, et al. Clin Infect Dis. 2014 Jul 15;59(2):e10-52

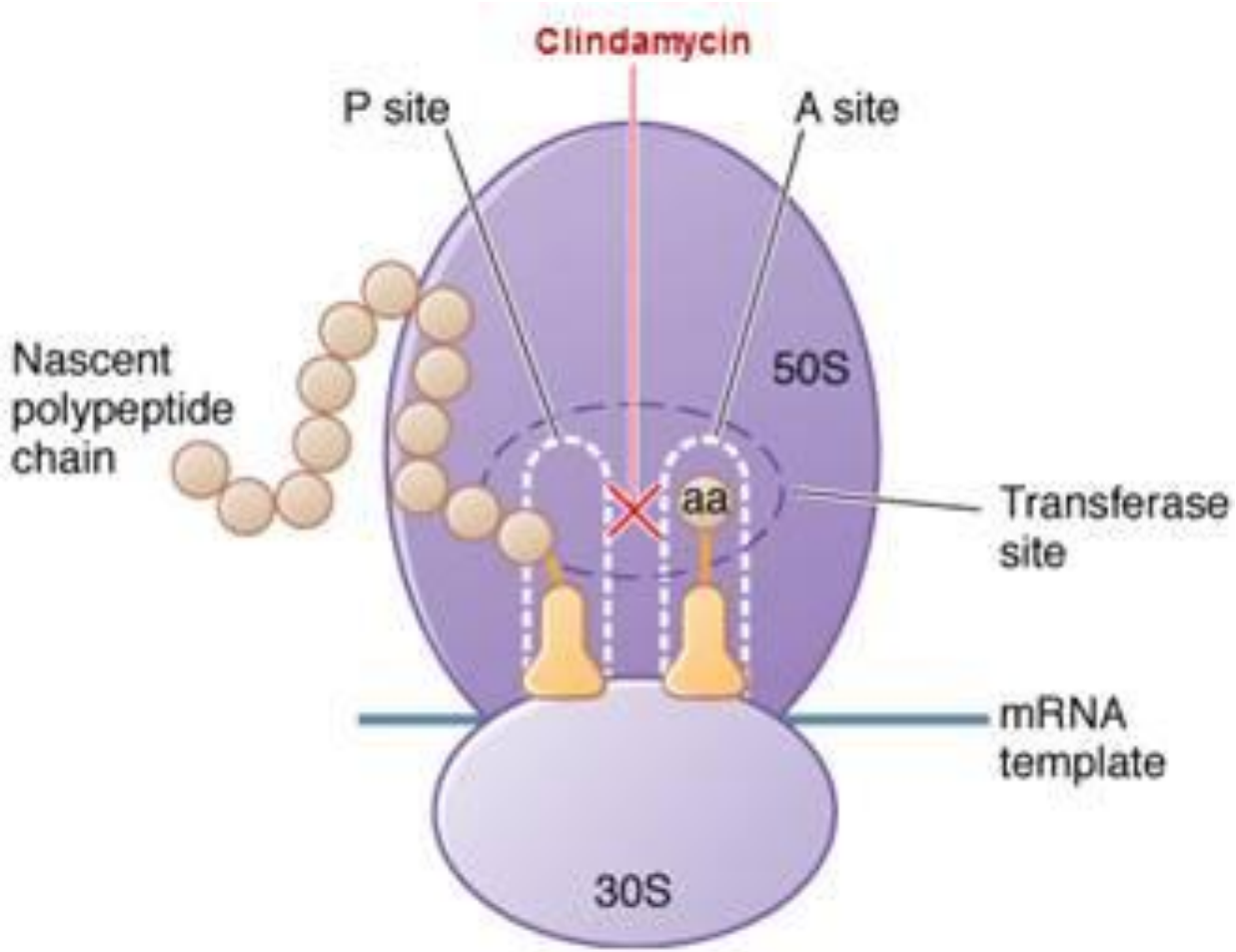
Clindamycin

Clindamycin

Brand Name	Cleocin
MOA	Reversibly binds to 50S ribosomal subunits preventing bond formation thus inhibiting bacterial protein synthesis
Spectrum of Activity	Staphylococci, streptococci, *Clostridium perfringens*, *Fusobacterium*
Dosing	600 to 900mg every 8 hours IV
Warnings	***Clostridioides difficile* infection (CDI)** Hypersensitivity reactions Acute Kidney Injury
Metabolism	Substrate of CYP3A4 (Major)

 Source: Cleocin [Package Insert]. Pharmacia & Upjohn Company LLC; 2025

Clindamycin

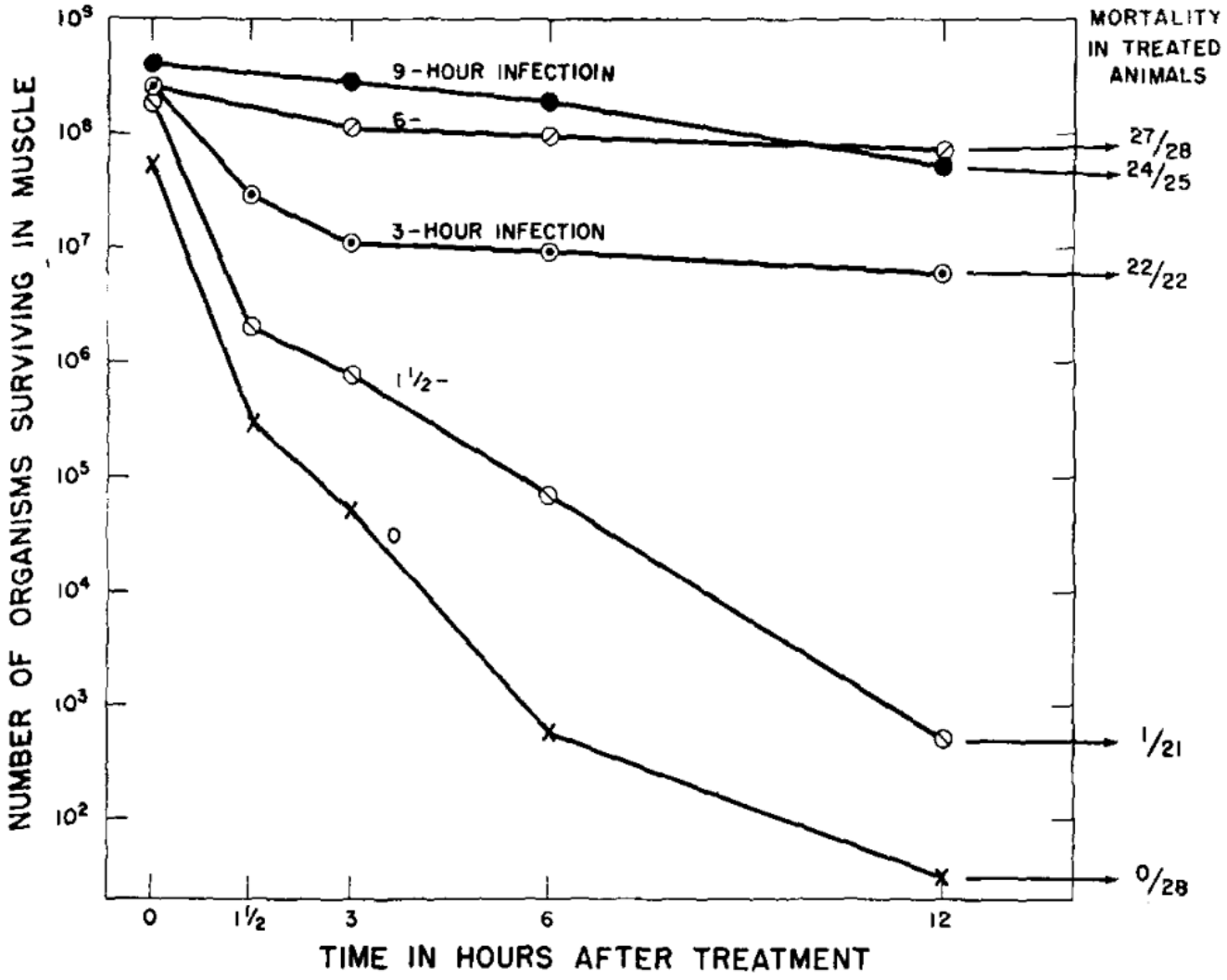


 Source: Antibiotic Drugs, Information, Description on Clindamycin. www.antibiotics-info.org

Why use clindamycin?

Eagle Effect

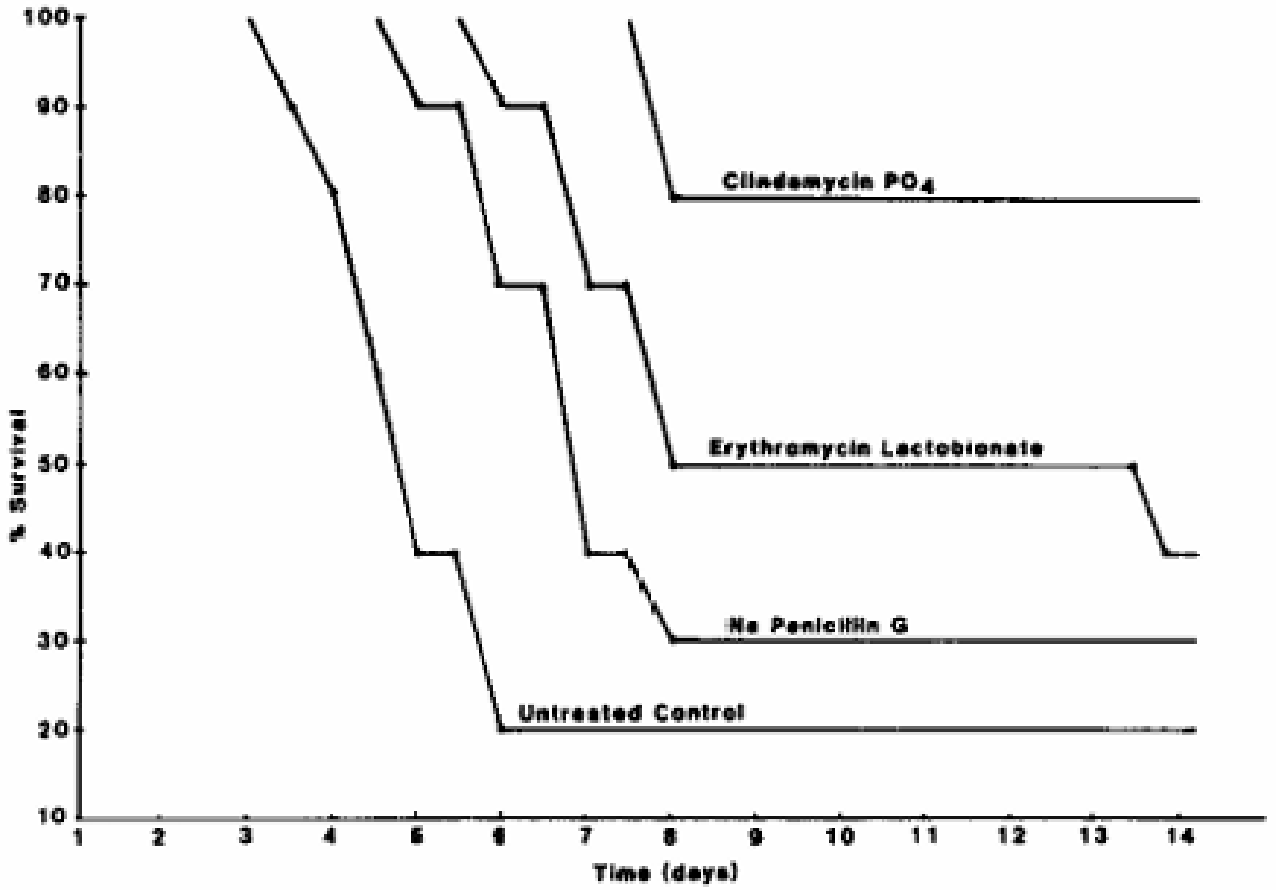
- Paradoxical phenomenon described by Harry Eagle
- 1952 experiment *S. pyogenes* myositis infection in mice
  - Higher bacterial loads decreased efficacy of penicillin
- Penicillin requires actively dividing bacteria
  - In plateau growth phase, fewer penicillin-binding proteins are produced



 Source: Eagle H. *Am J Med*. 1952 Oct;13(4):389-99

The Eagle Effect Revisited

- *S. pyogenes* myositis infection in mice
- Compared clindamycin, erythromycin, and penicillin
- Clindamycin efficacy not diminished with high bacterial loads



 Source: Stevens DL, et al. *J Infect Dis*. 1988 Jul;158(1):23-8.

Clinical Evidence of Adjuvant Clindamycin

Study	Study Design	Intervention	Comparator	Primary Outcome	Results	Significance
Zimbleman et al. 1999	Retrospective single-center cohort	β-lactam + clindamycin	β-lactam alone	Lack of progression of disease after 24 hours	β-lactam + clindamycin 83% (10/12) β-lactam alone 14% (1/7)	p = 0.006
Babiker et al. 2021	Retrospective multi-center cohort	Adjuvant clindamycin within 3 days of culture sampling	No clindamycin	In-hospital mortality	aOR 0.44	95% CI 0.23 to 0.81

Sources: Zimbelman J, et al. *Pediatr Infect Dis J*. 1999 Dec;18(12):1096-100
Babiker A, et al. *Lancet Infect Dis*. 2021;21(5):697-710

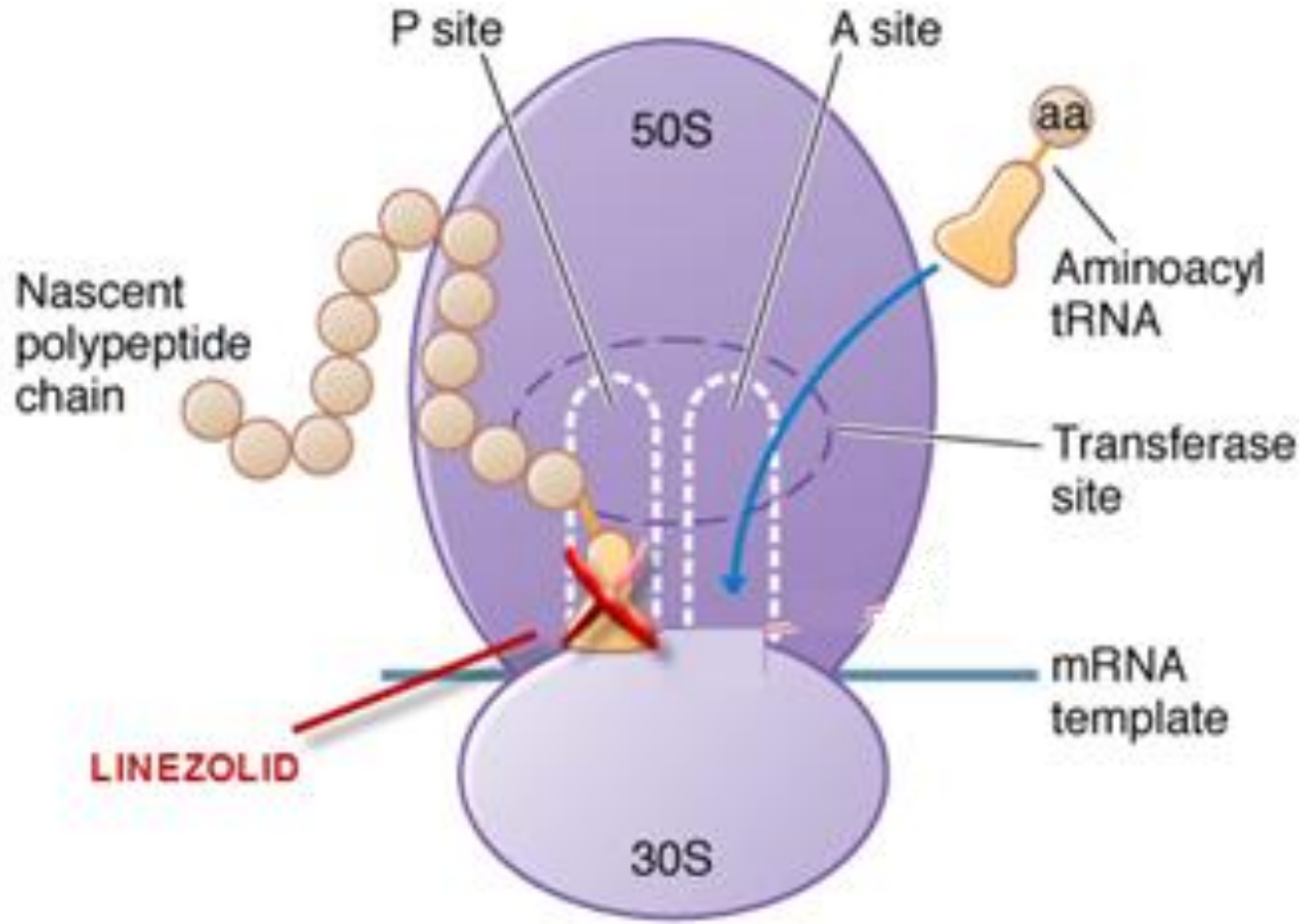
Linezolid

Linezolid

Brand Name	Zyvox
MOA	Inhibits bacterial protein synthesis by binding to bacterial 23S ribosomal RNA of the 50S subunit
Spectrum of Activity	Enterococci, staphylococci (including MRSA), streptococci
Dosing	600mg every 12 hours IV/PO
ADRs (>10%)	Diarrhea
Warnings	Lactic acidosis Myelosuppression Neuropathy Serotonin syndrome
Metabolism	Inhibits Monoamine Oxidase Substrate of CYP2J2 (minor) and CYP4F2 (minor)

 Source: Zyvox [Package Insert]. Hp Halden Pharma AS; 2024

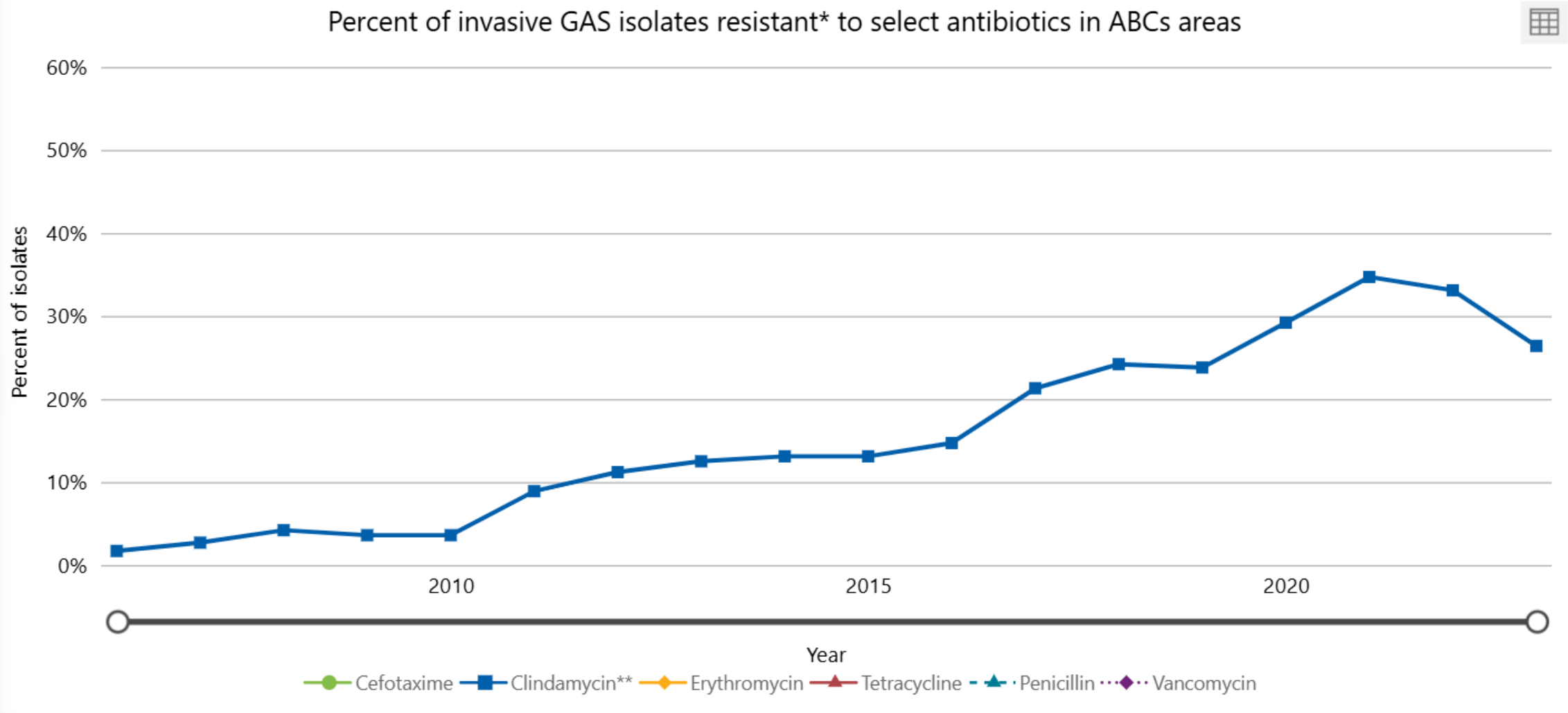
Linezolid



 Source: Antibiotic Drugs, Information, Description on Linezolid. www.antibiotics-info.org

Why use linezolid?

Rising Clindamycin Resistance in GAS



 | Source: CDC. https://www.cdc.gov/abcs/bact-facts/data-dashboard.html

Patterns of Antibiotic Nonsusceptibility Among Invasive GAS Infections in the United States

2006-2010: 3.2% of isolates nonsusceptible to clindamycin

2011-2017: 14.6% of isolates nonsusceptible to clindamycin

Variables associated with nonsusceptible isolates	
Long term care facility residents*	OR 1.39 (95% CI 1.16 to 1.67)
Homelessness*	OR 2.08 (95% CI 1.74 to 2.48)
Incarceration*	OR 2.37 (95% CI 1.1 to 4.94)
IV drug use	OR 2.26 (95% CI 1.96 to 2.6)
Alcohol abuse	OR 1.5 (95% CI 1.28 to 1.74)
Cirrhosis or chronic liver disease	OR 1.7 (95% CI 1.41 to 2.05)
HIV/AIDS	OR 3.17 (95% CI 2.56 to 3.93)

*compared to private residence

 | Source: Fay K, et al. *Clin Infect Dis*. 2021;73(11):1957-1964

Outcomes of β-Hemolytic Streptococcal Necrotizing Skin and Soft-tissue Infections and the Impact of Clindamycin Resistance

Study Objective

- Describe clindamycin resistance patterns and determine whether patient outcomes differed based on the presence of β-hemolytic streptococci and as well as clindamycin-resistant isolates

Study Design

- 3-year, single-center, prospective registry

Results

- 377 patients
- 31% (29/93) had clindamycin-resistant β-hemolytic streptococcal species

 Source: Horn DL, et al. *Clin Infect Dis*. 2021 Dec 6;73(11):e4592-e4598

Outcomes of β-Hemolytic Streptococcal Necrotizing Skin and Soft-tissue Infections and the Impact of Clindamycin Resistance

Outcome	Clindamycin Sensitive	Clindamycin Resistant	Adjusted Risk Ratio*
Amputation†	**Reference**	**86% increased risk**	**1.86 (1.10 – 3.16)**
STSS	Reference	No difference	1.23 (0.25 – 6.08)
Mortality	Reference	No difference	1.38 (0.41 – 4.63)

*Adjusted for injection drug use, transfer status, and age by quintile
†Among patients with extremity involvement (n = 73)

 Source: Horn DL, et al. *Clin Infect Dis*. 2021 Dec 6;73(11):e4592-e4598

In Vitro Evidence of Linezolid in GAS

- In Vitro model comparing linezolid, clindamycin, and penicillin, alone and in combination, on SPE A

Regimen	SPE A Level (pg/mL)	Vs Penicillin
Penicillin	14.23	Reference
Clindamycin	2.00	86% decrease
Linezolid	**1.40**	**90% decrease**
Penicillin + Clindamycin	1.40	90% decrease

Source: Coyle EA, et al. *Antimicrob Agents Chemother*. 2003 May;47(5):1752-5

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

Study Objective

- Evaluate the safety of linezolid versus clindamycin plus vancomycin as empiric treatment of NSTI

Study Design

- Single-center, Quasi-Experimental Protocol Change Study in patients with NSTIs

Intervention

- Institutional policy change of preferred empiric regimen of piperacillin-tazobactam plus linezolid for NSTI

 Source: Dorazio J, et al. *Open Forum Infect Dis*. 2023;10(6):ofad258

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

Inclusion Criteria

- Patients with diagnostic codes for admissions related to NSTI or Fournier gangrene were included
- Patients admitted between June 1, 2018, and June 30, 2019, were included in the preintervention group
- Patients admitted between May 1, 2020, and October 15, 2021, were included in the postintervention group

Primary Outcome

- 30-day mortality, occurring at any time inpatient or post discharge

Secondary Outcomes

- Rates of AKI
- Rates of CDI
- Death, CDI, or AKI at 30 days

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

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)

 Source: Dorazio J, et al. *Open Forum Infect Dis*. 2023;10(6):ofad258

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

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**

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

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)**

Comparison of Adjuvant Clindamycin vs Linezolid for Severe Invasive GAS Skin and Soft Tissue Infections

Study Objective

- Evaluate treatment outcomes in a cohort of patients with severe invasive skin and soft tissue infections caused by GAS who received either linezolid or clindamycin as part of their antibiotic treatment regimen

Study Design

- Retrospective, single-center cohort study

 Source: Heil EL, et al. *Open Forum Infect Dis*. 2023;10(12):ofad588

Comparison of Adjuvant Clindamycin vs Linezolid for Severe Invasive GAS Skin and Soft Tissue Infections

Inclusion Criteria

- Adults aged ≥ 18 years with invasive soft tissue infection or necrotizing fasciitis
- GAS isolated from a normally sterile site
- Underwent surgical debridement of their infection
- Received either clindamycin or linezolid for at least 48 hours

Primary Outcome

- Percent change in SOFA score from baseline at hospital admission through 72 hours

Secondary Outcomes

- Inpatient mortality
- Duration of vasopressor requirement
- ICU and hospital length of stay
- Ventilator days
- Adverse drug events
- Rates of clindamycin resistance

Source: Heil EL, et al. *Open Forum Infect Dis*. 2023;10(12):ofad588

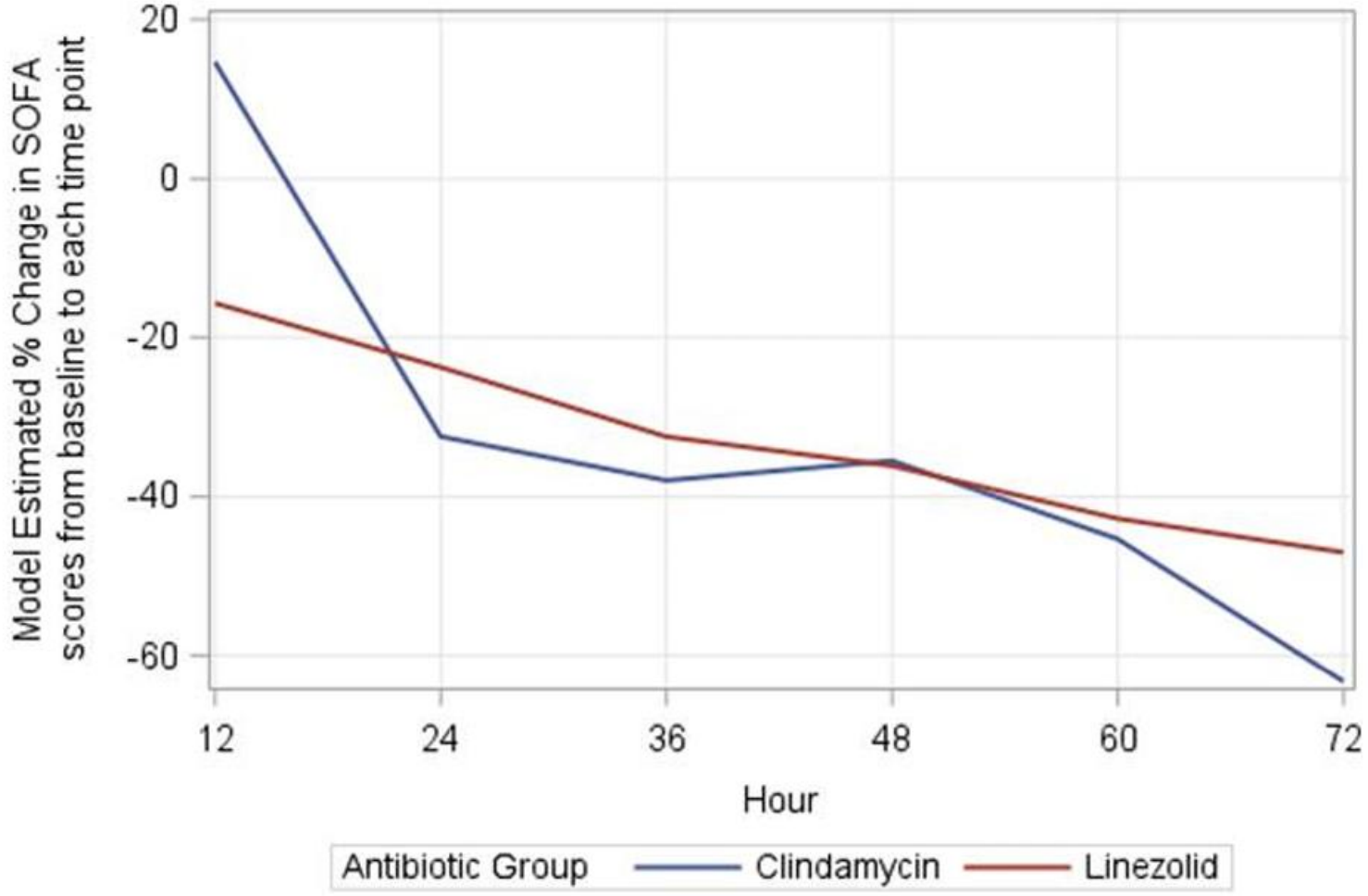
Comparison of Adjuvant Clindamycin vs Linezolid for Severe Invasive GAS Skin and Soft Tissue Infections

Table 1. Patient Characteristics

Characteristic	No. (%) or Median (IQR)			*P* Value
	Total (n = 55)	Clindamycin (n = 26)	Linezolid (n = 29)	
Age, y[a]	50 (18.0)	49.3 (19.0)	50.6 (17.4)	.8
Male sex	38 (69.1)	16 (61.5)	22 (75.9)	.3
Transferred from an outside facility	31 (56.4)	17 (35.4)	14 (48.3)	.2
Body mass index				.2
<35	49 (89.1)	25 (96.2)	24 (82.8)	
≥35	6 (10.9)	1 (3.9)	5 (17.2)	
Baseline serum creatinine, mg/dL				.2
≤1.6	35 (63.6)	19 (73.1)	16 (55.2)	
>1.6	20 (36.4)	7 (26.9)	13 (44.8)	
Baseline score				
LRINEC	7 (4–9)	7 (4–9)	8 (5–9)	.7
SOFA	3 (1–8)	5 (2–8)	2 (1–5)	.08
Comorbidities				
Diabetes	13 (23.6)	4 (15.4)	9 (31.0)	.2
Chronic kidney disease	9 (16.4)	4 (15.4)	5 (17.2)	>.99
Peripheral vascular disease	5 (9.1)	1 (3.9)	4 (13.8)	.4
Substance use disorder	32 (58.2)	17 (65.4)	15 (51.7)	.3
History of tobacco use	26 (47.3)	10 (38.5)	16 (55.2)	.2
Immunocompromised	4 (7.3)	2 (7.7)	2 (6.9)	>.99

 Source: Heil EL, et al. *Open Forum Infect Dis*. 2023;10(12):ofad588

Comparison of Adjuvant Clindamycin vs Linezolid for Severe Invasive GAS Skin and Soft Tissue Infections



 | Source: Heil EL, et al. *Open Forum Infect Dis*. 2023;10(12):ofad588

HCA Healthcare®

Comparison of Adjuvant Clindamycin vs Linezolid for Severe Invasive GAS Skin and Soft Tissue Infections

Table 3. Outcome Distribution of Patients Treated With Clindamycin vs Linezolid

	No. (%) or Median (IQR)			
Outcome	Total (n = 55)	Clindamycin (n = 26)	Linezolid (n = 29)	*P* Value
Inpatient mortality	3 (5.5)	2 (7.7)	1 (3.4)	.6
Amputation	10 (18.2)	4 (15.4)	6 (20.7)	.7
No.	23	14	9	
Time requiring vasopressors, h	41.4 (22.5–83.4)	42.1 (22.5–66.8)	39.1 (30.0–151.2)	.7
No.	26	17	9	
Ventilator days	2 (1–5)	2 (1–4)	4 (2–6)	.2
No.	27	16	11	
Length of stay, d				
Intensive care unit	8.8 (2.6–13.8)	8.2 (3.0–13.0)	9.5 (2.3–16.8)	.6
Hospital	12 (9–24)	14 (9–31)	10 (8–20)	.05
Adverse event				
Clostridioides difficile during hospital admission	2 (3.6)	1 (3.9)	1 (3.5)	>.99
Antibiotic-related thrombocytopenia	1 (1.8)	0	1 (3.5)	>.99

Adjunctive linezolid versus clindamycin for toxin inhibition in β-lactam-treated patients with invasive GAS infections

Study Objective

- Emulate a multi-center, non-blinded, non-inferiority target trial of adult inpatients with β-lactam treated culture-confirmed monomicrobial invasive GAS between the years 2016 and 2021

Study Design

- Trial emulation approach described by Hernan and Robins (2016)

Adjunctive linezolid versus clindamycin for toxin inhibition in β-lactam-treated patients with invasive GAS infections

Inclusion Criteria

- Adult inpatients receiving β-lactam therapy for culture-confirmed monomicrobial invasive GAS between 2016 and 2021 in the PINC AI dataset who receive antitoxin within 3 days of index culture

Primary Outcome

- All-cause in-hospital mortality or discharge to hospice

Secondary Outcomes

- Length of stay following antitoxin administration among survivors
- Occurrence of CDI requiring treatment among survivors

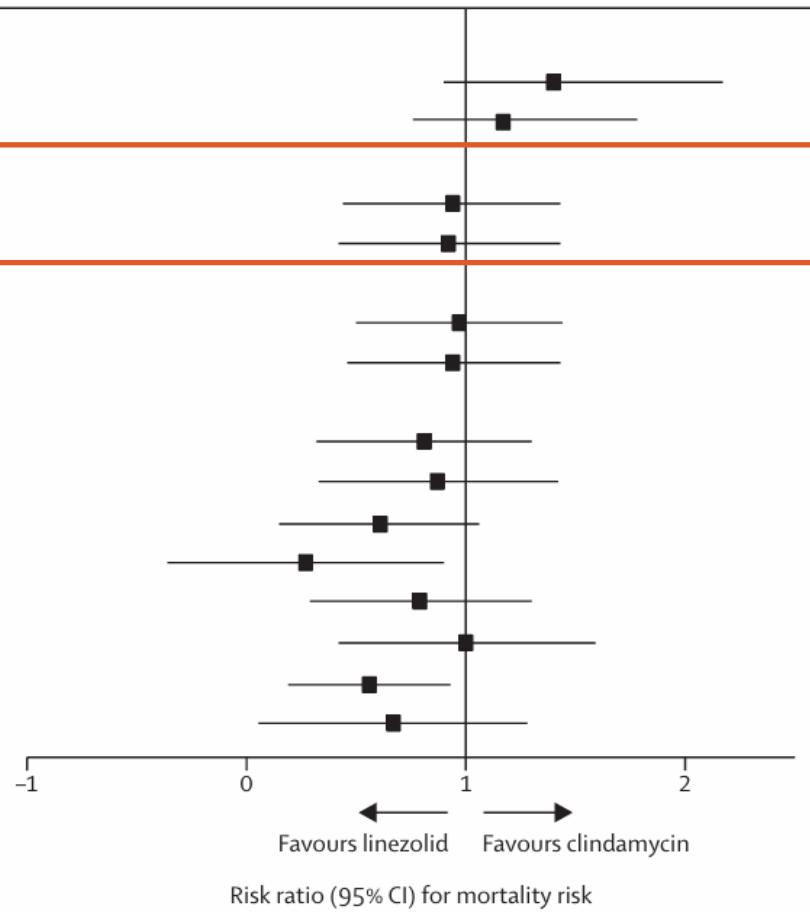
Adjunctive linezolid versus clindamycin for toxin inhibition in β-lactam-treated patients with invasive GAS infections

	Clindamycin (n=829)	Linezolid (n=266)
Age, years	53·0 (16·9)	56·8 (16·4)
Male	497 (60%)	160 (60%)
Female	332 (40%)	106 (40%)
Race		
Non-Hispanic White	568 (69%)	209 (79%)
Non-Hispanic Black	113 (14%)	29 (11%)
Hispanic	57 (7%)	8 (3%)
Other	91 (11%)	20 (8%)
Proven GAS	663 (80%)	166 (62%)
GAS category		
Severe GAS*	97 (12%)	24 (9%)
Bloodstream infection	484 (58%)	124 (47%)
Other	248 (30%)	118 (44%)

	Clindamycin (n=829)	Linezolid (n=266)
(Continued from previous column)		
Duration of antitoxin administration, days	4·9 (4·8)	4·5 (3·8)
Clindamycin susceptibility**		
Not performed or missing	461 (56%)	156 (59%)
Performed—susceptible	269 (32%)	55 (21%)
Performed—non-susceptible	99 (12%)	55 (21%)
Baseline eSOFA Score Category§		
0–2	701 (85%)	202 (76%)
3–4	100 (12%)	44 (17%)
5–6	28 (3%)	20 (8%)
Intravenous immunoglobulin therapy	20 (2%)	<5†
Vasopressor-dependent shock¶	193 (23%)	73 (27%)
Intensive care unit within 1 day of culture	279 (34%)	90 (34%)
Debridement	316 (38%)	76 (29%)
Immunocompromised‖	73 (9%)	31 (12%)

Adjunctive linezolid versus clindamycin for toxin inhibition in β-lactam-treated patients with invasive GAS infections

	Clindamycin		Linezolid		Risk ratio (95% CI)
	Total, n	Mortality, n (%)	Total, n	Mortality, n (%)	
Unweighted analyses					
Unadjusted (n=1095)	829	58 (7·0%)	266	26 (9·8%)	1·40 (0·90 to 2·17)
Adjusted* (n=1095)	829	58 (7·0%)	266	26 (9·8%)	1·17 (0·76 to 1·78)
Clustered overlap weight analyses					
Unadjusted (n=1095)	829	58 (7·0%)	266	26 (9·8%)	0·94 (0·44 to 1·43)
Adjusted* (n=1095)	829	58 (7·0%)	266	26 (9·8%)	0·92 (0·42 to 1·43)
Overlap weight analyses					
Unadjusted (n=1095)	829	58 (7·0%)	266	26 (9·8%)	0·97 (0·50 to 1·44)
Adjusted* (n=1095)	829	58 (7·0%)	266	26 (9·8%)	0·94 (0·46 to 1·43)
Subgroup analyses					
Proven invasive GAS (n=844)	677	55 (8·1%)	167	16 (9·6%)	0·81 (0·32 to 1·30)
Admitted to ICU† (n=369)	279	43 (15·4%)	90	17 (18·9%)	0·87 (0·33 to 1·42)
Vasopressor dependent shock‡ (n=266)	193	37 (19·2%)	73	12 (16·4%)	0·61 (0·15 to 1·06)
Severe invasive GAS (n=121)	97	<5§	24	<5§	0·27 (−0·36 to 0·90)
GAS bacteraemia* (n=608)	484	51 (10·5%)	124	15 (12·1%)	0·79 (0·29 to 1·30)
Clindamycin suseptible and missing AST* (n=996)	730	51 (7·0%)	266	26 (9·8%)	1·00 (0·42 to 1·59)
Clindamycin susceptible* (n=535)	269	27 (10·0%)	266	26 (9·8%)	0·56 (0·19 to 0·93)
Clindamycin non-susceptible* (n=365)	99	7 (7·1%)	266	26 (9·8%)	0·67 (0·055 to 1·28)



 | Source: Babiker A, et al. *Lancet Infect Dis*. 2025;25(3):265-275

Summary of Linezolid Evidence

Study	Study Design	Intervention	Comparator	Primary Outcome	Results	Significance
Dorazio et al. 2023	Single-center, quasi-experimental protocol change study	Pip/tazo + linezolid (n=62)	Vancomycin + clindamycin (n=62)	30-day mortality	Postintervention 6.45% (4/62) Preintervention 8.06% (5/62)	p = 0.65
Heil et al. 2023	Retrospective, single-center cohort study	Adjuvant linezolid (n=23)	Adjuvant clindamycin (n=23)	Percent change in SOFA score from baseline to 72 hours	LS mean difference -13.0	95% CI -41.6 to 15.5
Babiker et al. 2025	Trial emulation approach	Adjuvant linezolid (n=266)	Adjuvant clindamycin (n=829)	In-hospital mortality	aRR 0.92	95% CI 0.42 to 1.43

LS mean difference = least-squares mean difference; aRR = adjusted risk ratio; pip/tazo = piperacillin/tazobactam

Linezolid vs Clindamycin: Is there a clear winner?

Judges Decision: No Contest

Limited number of studies

Studies evaluated more than definitive treatment for GAS NSTI

Very little to no difference in outcomes

Considerations for Treatment

When to consider treatment with linezolid?

- Initiation of empiric NSTI therapy
  - Two for the price of one
- *C. difficile* infection
  - Risk factors
  - Previous history
- Acute Kidney Injury
  - Present at initiation of therapy
  - Development during therapy
- Clindamycin resistance?

Assessment Question 1

- What is the primary advantage of adding a protein synthesis inhibitor to beta-lactam therapy in GAS necrotizing soft tissue infection?
  A. Enhanced bacterial cell wall penetration
  B. Suppression of exotoxin production
  C. Improved biofilm eradication
  D. Synergistic bacterial killing

Assessment Question 1: Correct Response

- What is the primary advantage of adding a protein synthesis inhibitor to beta-lactam therapy in GAS necrotizing soft tissue infection?

A. Enhanced bacterial cell wall penetration

B. Suppression of exotoxin production

C. Improved biofilm eradication

D. Synergistic bacterial killing

Assessment Question 2

- What are the current evidenced-based recommendations for antibiotic selection, dosing, and duration in GAS necrotizing soft tissue?
  A. Penicillin 4 million units IV Q4H + clindamycin 900mg IV Q6H until source control is achieved and guided by clinical response
  B. Doxycycline 100mg BID for 10 days
  C. Vancomycin 15mg/kg/dose IV Q12H + piperacillin/tazobactam 4.5g IV Q6H for 5 days
  D. Ceftriaxone 1g IIV Q24H + metronidazole 500mg IV Q12H for 21 days

Assessment Question 2: Correct Response

- What are the current evidenced-based recommendations for antibiotic selection, dosing, and duration in GAS necrotizing soft tissue?

A. Penicillin 4 million units IV Q4H + clindamycin 900mg IV Q6H until source control is achieved and guided by clinical response

B. Doxycycline 100mg BID for 10 days

C. Vancomycin 15mg/kg/dose IV Q12H + piperacillin/tazobactam 4.5g IV Q6H for 5 days

D. Ceftriaxone 1g IIV Q24H + metronidazole 500mg IV Q12H for 21 days

Assessment Question 3

- Which mechanism explains clindamycin's theoretical advantage in toxin-mediated GAS infection?
  - A. Bactericidal activity at the site of infection
  - B. Inhibition of 50S ribosomal subunit
  - C. Enhanced neutrophil function
  - D. Superior tissue penetration compared to other antibiotics

Assessment Question 3: Correct Response

- Which mechanism explains clindamycin's theoretical advantage in toxin-mediated GAS infection?

A. Bactericidal activity at the site of infection

B. Inhibition of 50S ribosomal subunit

C. Enhanced neutrophil function

D. Superior tissue penetration compared to other antibiotics

Assessment Question 4

- Which potential advantage may favor treatment with linezolid over clindamycin in patients with GAS NSTI?
  - A. Lower risk of AKI
  - B. Fewer drug-drug interactions
  - C. Coverage of MRSA
  - D. Superior efficacy demonstrated in randomized control trials

Assessment Question 4: Correct Response

- Which potential advantage may favor treatment with linezolid over clindamycin in patients with GAS NSTI?

A. Lower risk of AKI

B. Fewer drug-drug interactions

C. Coverage of MRSA

D. Superior efficacy demonstrated in randomized control trials

References

1. Allaw F, Wehbe S, Kanj SS. Necrotizing fasciitis: an update on epidemiology, diagnostic methods, and treatment. *Curr Opin Infect Dis*. 2024;37(2):105-111. doi:10.1097/QCO.0000000000000988
2. Cleveland Clinic. Skin: Layers, Structure and Function. Cleveland Clinic. Published October 13, 2021. https://my.clevelandclinic.org/health/body/10978-skin
3. McDermott J, Kao LS, Keeley JA, Grigorian A, Neville A, de Virgilio C. Necrotizing Soft Tissue Infections: A Review. *JAMA Surg*. 2024;159(11):1308-1315. doi:10.1001/jamasurg.2024.3365
4. Pelletier J, Gottlieb M, Long B, Perkins JC Jr. Necrotizing Soft Tissue Infections (NSTI): Pearls and Pitfalls for the Emergency Clinician. *J Emerg Med*. 2022;62(4):480-491. doi:10.1016/j.jemermed.2021.12.012
5. Stevens DL, Bryant AE. Necrotizing Soft-Tissue Infections. *N Engl J Med*. 2017;377(23):2253-2265. doi:10.1056/NEJMra1600673
6. Bush LM, Vazquez-Pertejo MT. Streptococcal Infections. Merck Manual. Published October 2025. Accessed January 6, 2026. https://www.merckmanuals.com/professional/infectious-diseases/gram-positive-cocci/streptococcal-infections
7. Introduction to Streptococcus - Microbiology - Medbullets Step 1. step1.medbullets.com. https://step1.medbullets.com/microbiology/104175/introduction-to-streptococcus
8. Coyle EA; Society of Infectious Diseases Pharmacists. Targeting bacterial virulence: the role of protein synthesis inhibitors in severe infections. Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2003;23(5):638-642. doi:10.1592/phco.23.5.638.32191

References

9. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10-e52. doi:10.1093/cid/ciu444
10. Cleocin [Package Insert]. Pharmacia & Upjohn Company LLC; 2025
11. Antibiotic Drugs, Information, Description on Clindamycin. www.antibiotics-info.org. http://www.antibiotics-info.org/clindamycin.html
12. EAGLE H. Experimental approach to the problem of treatment failure with penicillin. I. Group A streptococcal infection in mice. *Am J Med*. 1952;13(4):389-399. doi:10.1016/0002-9343(52)90293-3
13. Stevens DL, Gibbons AE, Bergstrom R, Winn V. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *J Infect Dis*. 1988;158(1):23-28. doi:10.1093/infdis/158.1.23
14. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection. *Pediatr Infect Dis J*. 1999;18(12):1096-1100. doi:10.1097/00006454-199912000-00014
15. Babiker A, Li X, Lai YL, et al. Effectiveness of adjunctive clindamycin in β-lactam antibiotic-treated patients with invasive β-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study. *Lancet Infect Dis*. 2021;21(5):697-710. doi:10.1016/S1473-3099(20)30523-5
16. Zyvox [Package Insert]. Hp Halden Pharma AS; 2024
17. Antibiotic Drugs, Information, Description on Linezolid. www.antibiotics-info.org. Published 2016. http://www.antibiotics-info.org/linezolid.html
18. CDC. ABCs Bact Facts Interactive Data Dashboard. Active Bacterial Core surveillance (ABCs). Published May 31, 2024. https://www.cdc.gov/abcs/bact-facts/data-dashboard.html

References

19. Fay K, Onukwube J, Chochua S, et al. Patterns of Antibiotic Nonsusceptibility Among Invasive Group A Streptococcus Infections-United States, 2006-2017. *Clin Infect Dis*. 2021;73(11):1957-1964. doi:10.1093/cid/ciab575

20. Horn DL, Roberts EA, Shen J, et al. Outcomes of β-Hemolytic Streptococcal Necrotizing Skin and Soft-tissue Infections and the Impact of Clindamycin Resistance. *Clin Infect Dis*. 2021;73(11):e4592-e4598. doi:10.1093/cid/ciaa976

21. Coyle EA, Cha R, Rybak MJ. Influences of linezolid, penicillin, and clindamycin, alone and in combination, on streptococcal pyrogenic exotoxin a release. *Antimicrob Agents Chemother*. 2003;47(5):1752-1755. doi:10.1128/AAC.47.5.1752-1755.2003

22. Dorazio J, Chiappelli AL, Shields RK, et al. Clindamycin Plus Vancomycin Versus Linezolid for Treatment of Necrotizing Soft Tissue Infection. *Open Forum Infect Dis*. 2023;10(6):ofad258. Published 2023 May 11. doi:10.1093/ofid/ofad258

23. Heil EL, Kaur H, Atalla A, et al. Comparison of Adjuvant Clindamycin vs Linezolid for Severe Invasive Group A *Streptococcus* Skin and Soft Tissue Infections. *Open Forum Infect Dis*. 2023;10(12):ofad588. Published 2023 Nov 24. doi:10.1093/ofid/ofad588

24. Babiker A, Warner S, Li X, et al. Adjunctive linezolid versus clindamycin for toxin inhibition in β-lactam-treated patients with invasive group A streptococcal infections in 195 US hospitals from 2016 to 2021: a retrospective cohort study with target trial emulation. *Lancet Infect Dis*. 2025;25(3):265-275. doi:10.1016/S1473-3099(24)00507-3

25. 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

Thank you!!

Matthew Jones, PharmD

PGY-1 Pharmacy Resident

Matthew.Jones@HCAHealthone.com

HCA Healthcare®