Clindamycin vs Linezolid – A Toxic Duel. Toxin Production Control in Necrotizing Soft Tissue Infections (NSTIs)

JERRICA LILLEY, PHARMD

PGY1 PHARMACOTHERAPY RESIDENT

UNIVERSITY OF THE INCARNATE WORD

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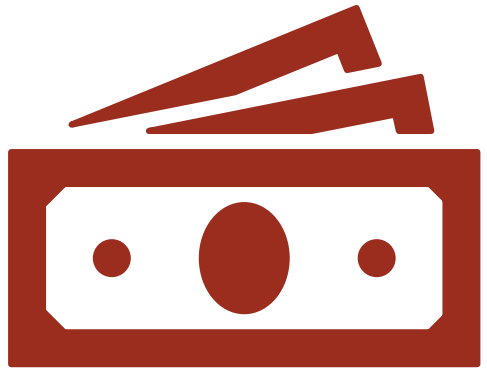


Financial Disclosure

NO FINANCIAL CONFLICTS OF INTEREST TO DISCLOSE

Learning Objectives for Pharmacists

Recognize signs and symptoms of suspected necrotizing soft tissue infections based on patient presentation

List current IDSA treatment guideline recommendations for the management of necrotizing soft tissue infections

Given a patient case, determine when it is safe and appropriate to recommend clindamycin versus linezolid in a confirmed or suspected necrotizing soft tissue infection

Learning Objectives for Pharmacy Technicians

Recall why IDSA guidelines recommend adding clindamycin for treatment of necrotizing soft tissue infections

Recognize the black box warning associated with clindamycin

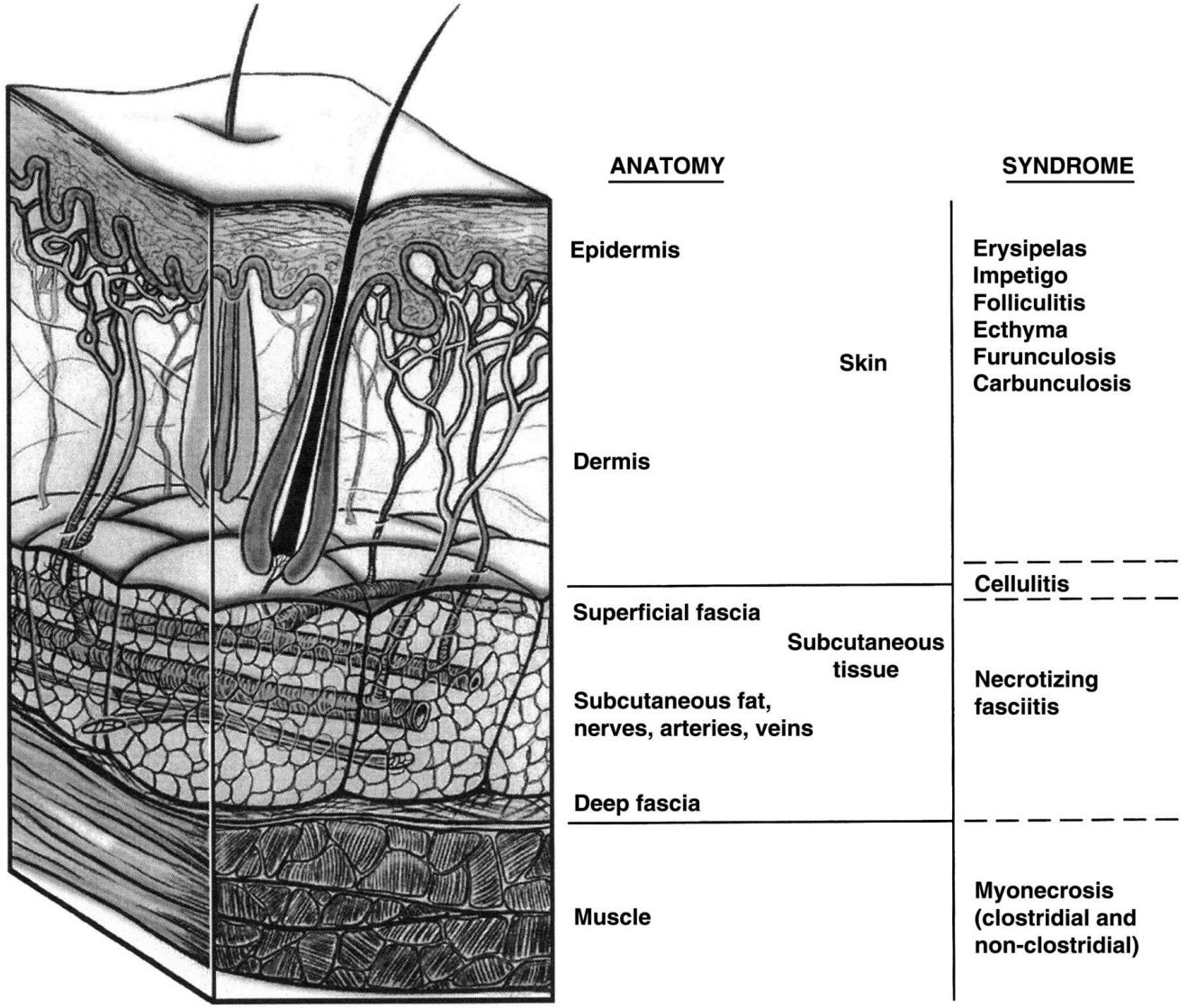
List potential adverse effects associated with use of linezolid

Background

Etiology & Classification of NSTI

Type of NSTI	Cause	Organism	Mortality
Type I (70-80%)	Polymicrobial	Mixed aerobes & anaerobes	Variable, underlying comorbidities contribute
Type II (20-30%)	Monomicrobial, typically skin flora	β-hemolytic Streptococcus or S. aureus	11-22%; > 30% if streptococcal toxic shock syndrome
Type III	Gram-negative, usually water-related organisms	Vibrio spp.	30-40%
Type IV	Fungal, more common in immunocompromised	Candida spp. in immunocompromised, Zygomycetes in immunocompetent	> 50%

Continuing Education in Anaesthesia Critical Care & Pain. 2012;12(5):245-250
Hosp Infect. 2010;75(4):249-57
https://www.cdc.gov/groupastrep/diseases-hcp/necrotizing-fasciitis.html

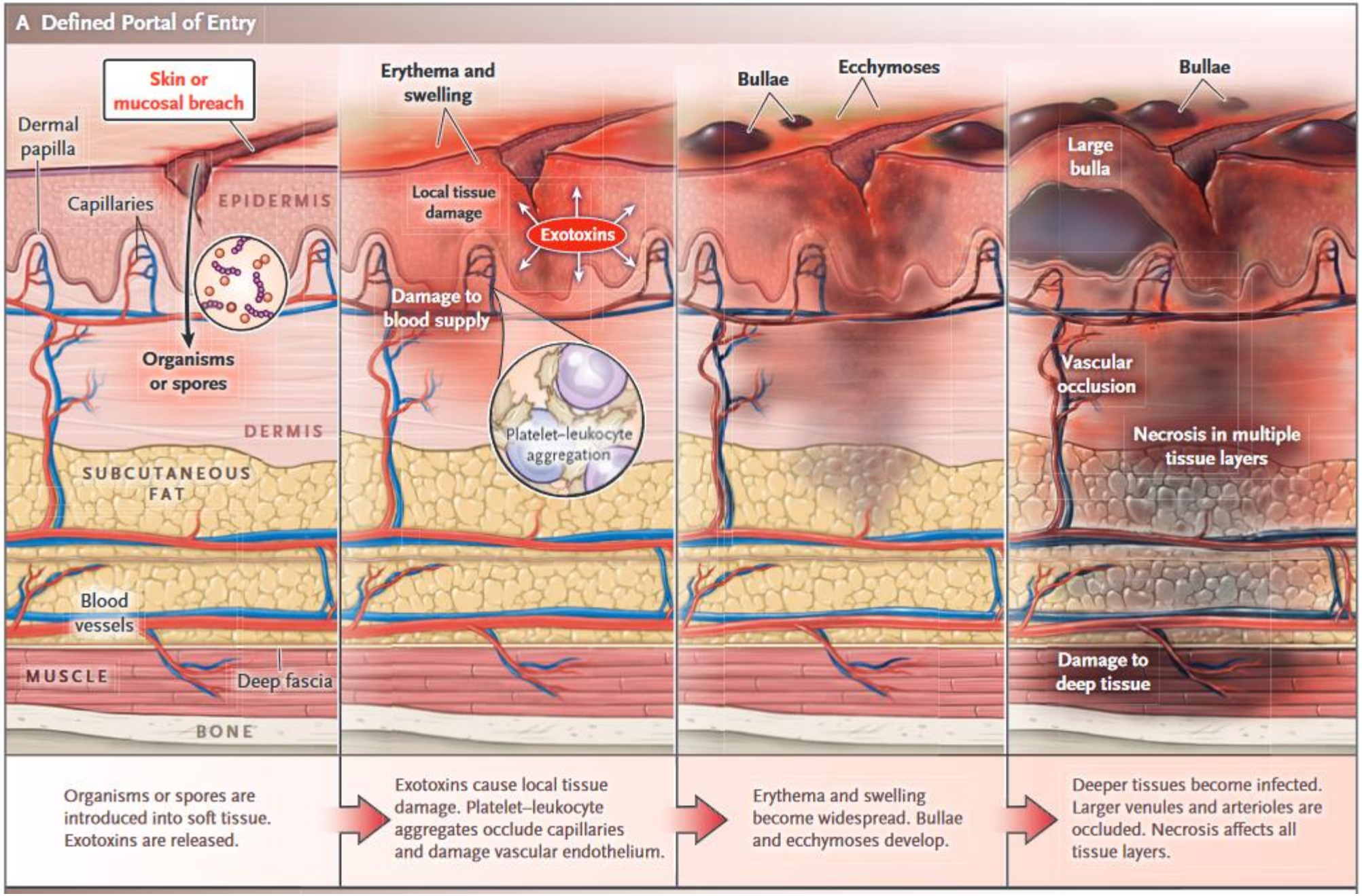


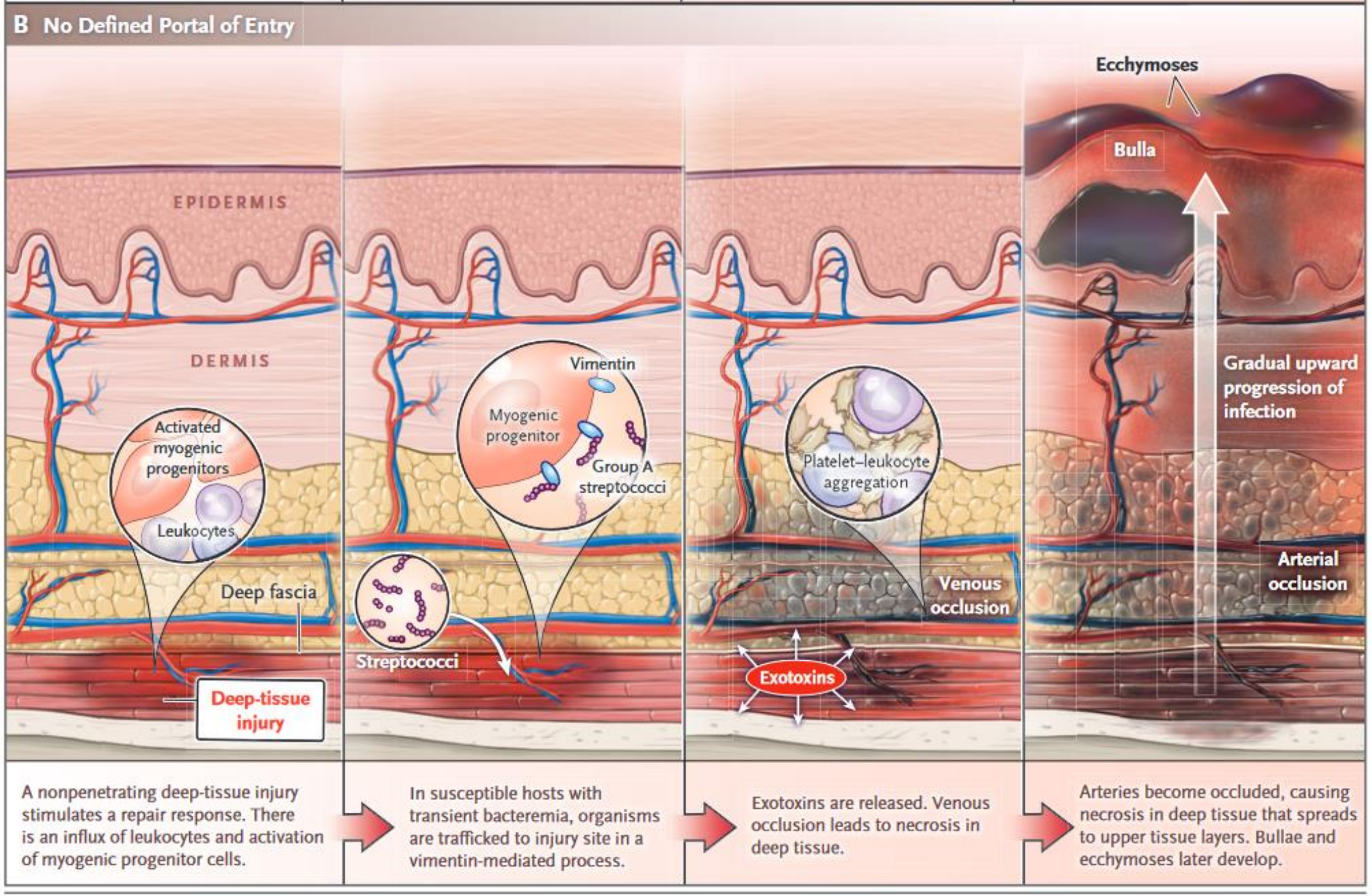
Pathophysiology

Bacteria introduced as a result of:

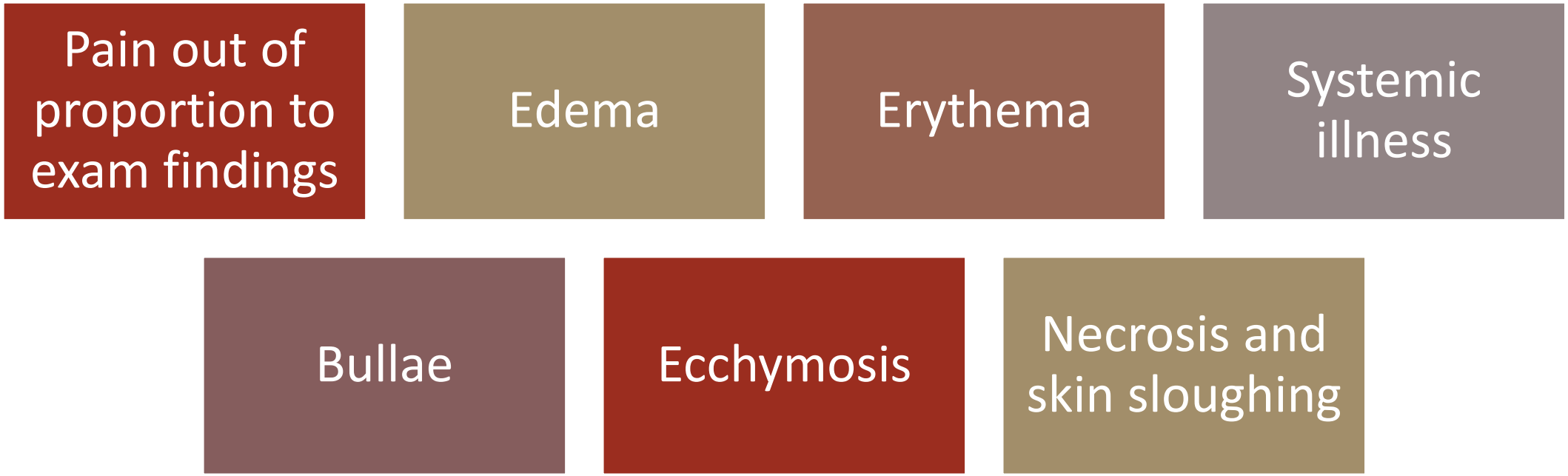
- Breaks in the skin
  - Surgical sites
  - Scrapes or scratches
  - Insect bites
  - Injection sites
  - Boils
- Blunt trauma

Continuing Education in Anaesthesia Critical Care & Pain. 2012;12(5):245-250
Clin Infect Dis. 2014;59(2):e10-e52


A Defined Portal of Entry
Skin or mucosal breach
Dermal papilla
Capillaries
EPIDERMIS
Organisms or spores
DERMIS
SUBCUTANEOUS FAT
Blood vessels
MUSCLE
Deep fascia
BONE
Erythema and swelling
Local tissue damage
Exotoxins
Damage to blood supply
Platelet–leukocyte aggregation
Bullae
Ecchymoses
Bullae
Large bulla
Vascular occlusion
Necrosis in multiple tissue layers
Damage to deep tissue
Organisms or spores are introduced into soft tissue. Exotoxins are released.
Exotoxins cause local tissue damage. Platelet–leukocyte aggregates occlude capillaries and damage vascular endothelium.
Erythema and swelling become widespread. Bullae and ecchymoses develop.
Deeper tissues become infected. Larger venules and arterioles are occluded. Necrosis affects all tissue layers.


B No Defined Portal of Entry
EPIDERMIS
DERMIS
Activated myogenic progenitors
Leukocytes
Deep fascia
Deep-tissue injury
Vimentin
Myogenic progenitor
Group A streptococci
Streptococci
Platelet–leukocyte aggregation
Venous occlusion
Exotoxins
Ecchymoses
Bulla
Gradual upward progression of infection
Arterial occlusion
A nonpenetrating deep-tissue injury stimulates a repair response. There is an influx of leukocytes and activation of myogenic progenitor cells.
In susceptible hosts with transient bacteremia, organisms are trafficked to injury site in a vimentin-mediated process.
Exotoxins are released. Venous occlusion leads to necrosis in deep tissue.
Arteries become occluded, causing necrosis in deep tissue that spreads to upper tissue layers. Bullae and ecchymoses later develop.

Clinical Presentation



LRINEC Scoring Tool

Variable	+ 0	+ 1	+ 2	+ 4
C-Reactive Protein (mg/dL)	≤ 150			> 150
Total WBC Count	< 15	15-25	> 25	
Hemoglobin (g/dL)	> 13.5	11-13.5	< 11	
Sodium (mEq/L)	≥ 135		< 135	
Creatinine (mg/dL)	≤ 1.6		> 1.6	
Glucose (mg/dL)	≤ 180	> 180		

LRINEC – Laboratory Risk Indicator for Necrotizing Fasciitis

Crit Care Med. 2004; 32(7):1535-41

LRINEC Scoring Tool

Risk Category	LRINEC Score	Probability for Presence of Necrotizing Fasciitis
Low	≤ 5	< 50%
Medium	6-7	50-75%
High	≥ 8	> 75%

Controversial scoring tool

- Original study found score ≥ 6 has specificity, sensitivity, positive predictive value, and negative predictive value > 90%
- Systematic review and meta-analysis found score ≥ 6 has sensitivity of 68.2% and specificity of 84.4%

Crit Care Med. 2004; 32(7):1535-41
Ann Surg. 2019;269(1):58-65

IDSA Skin & Soft Tissue Infection Treatment Guidelines

2014 IDSA SSTI Treatment Guidelines

Severe infection defined as:

- Systemic signs and symptoms of infection
  - Temperature > 38 C
  - Heart Rate > 90 bpm
  - Respiratory Rate > 24
  - WBC count < 4,000 or > 12,000
- Failure to respond to oral antibiotics
- Clinical signs of deeper infection
  - Bullae
  - Skin sloughing
  - Hypotension
  - Evidence of organ dysfunction

Clin Infect Dis. 2014;59(2):e10-e52

2014 IDSA SSTI Treatment Guidelines

Empiric management of severe non-purulent necrotizing infection

- Emergent surgical inspection with debridement
  - Rule in or out necrotizing process
  - Perform cultures and sensitivities
- Empiric antibiotics
  - Vancomycin PLUS piperacillin/tazobactam

Clin Infect Dis. 2014;59(2):e10-e52

2014 IDSA SSTI Treatment Guidelines – Necrotizing Fasciitis

Surgical debridement

Primary treatment modality

Repeat debridement every 24-36 hours until source control achieved

Antimicrobial therapy

Clindamycin PLUS penicillin recommended for group A streptococci

Penicillin 2-4 million units IV every 4-6 hours*

Clindamycin 600-900 mg IV every 8 hours

*Assuming normal renal function

Clin Infect Dis. 2014;59(2):e10-e52

Knowledge Check

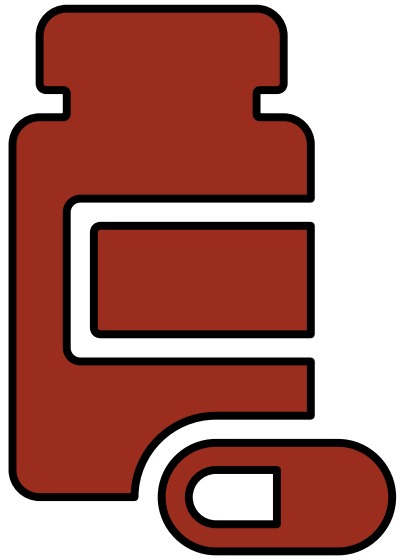
What is the mechanism of action of penicillin?

A. Inhibits bacterial protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit.

B. Binds to penicillin-binding proteins, inhibiting final transpeptidation step of peptidoglycan formation

C. Binds to D-Ala-D-Ala, inhibiting glycopeptide polymerization and cell wall synthesis

D. Inhibits bacterial protein synthesis by binding to the 16S rRNA of the 30S ribosomal subunit



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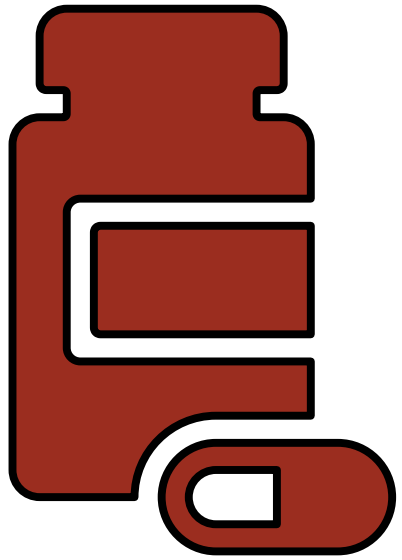


Why Clindamycin?

Knowledge Check

True or False – Clindamycin is often added to empiric treatment of suspected necrotizing soft tissue infections for additional MRSA coverage.

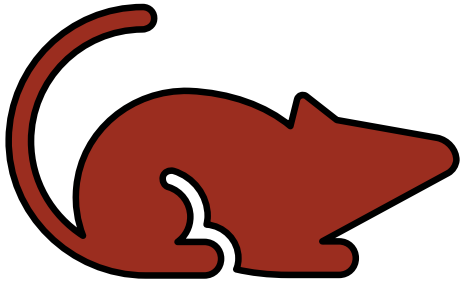
- A. True
- B. False

Knowledge Check

True or False – Clindamycin is often added to empiric treatment of suspected necrotizing soft tissue infections for additional MRSA coverage.

- A. True
- **B. False**

Eagle Effect



Experiment conducted in 1952 by Harry Eagle

S. pyogenes myositis in mice

Delayed treatment (12 hours) with penicillin resulted in slow and irregular bactericidal effect

Larger inoculum size resulted in lower penicillin efficacy

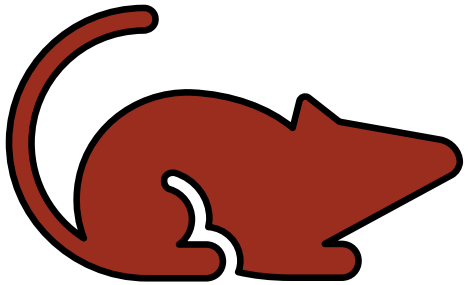
Bacteria in stationary/plateau growth phase

- Inadequate nutrients
- Release of toxic products into environment

Larger doses of penicillin ineffective

Am J Med. 1952;13(4):389-99

Eagle Effect – Stevens et al. 1988



S. pyogenes myositis in mice

Evaluated effects of clindamycin, erythromycin, and penicillin

Clindamycin efficacy not influenced by inoculum size or bacterial growth phase

Proposed mechanisms of efficacy:

- Longer post-antibiotic effects
- Enhanced opsonization and killing of *S. pyogenes* in presence of subinhibitory concentrations of penicillin
- Suppression of extracellular virulence factors (toxins)

Clindamycin Mechanism of Action and Effects on Virulence Factors

Bacterial protein synthesis inhibitor

- Binds to 50S ribosomal subunit

Streptococcal pyrogenic exotoxins

- Clindamycin in combination with penicillin reduced production of SpeA compared to penicillin alone

M Protein

- Resists opsonization and phagocytosis by polymorphonuclear leukocytes
- Clindamycin increased opsonization and phagocytosis

Hyaluronic acid capsule

- Resists phagocytosis
- Clindamycin reduced prevalence of encapsulation

Scand J Infect Dis. 2006;38(11-12):983-7
J Clin Invest. 1981;67(5):1249-56
Antimicrob Agents Chemother. 1995;39(7):1565-8.

SpeA – streptococcal pyrogenic exotoxin A

Why Linezolid?

https://www.idstewardship.com/clindamycin-linezolid-better-toxin-mediation-necrotizing-infections/

Clindamycin Box Warning

WARNING

Clostridium difficile **associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.**

Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate.

Cleocin [package insert]. New York, NY: Pfizer; 2018

Other *C. difficile* Risk Factors

- Age ≥ 65 years
- Recent hospitalization
- Long-term care facility resident
- Use of PPIs
- Immunocompromised (HIV/AIDS, cancer, taking immunosuppressive drugs)
- Previous *C. difficile* infection

PPI – proton pump inhibitor

https://www.cdc.gov/cdiff/risk.html

American Journal of Gastroenterology. 2013;108(4):478-498

2021

Emm type	No. of Isolates	%
Other	406	22.3%
emm 92	134	7.4%
emm 91	56	3.1%
emm 89	81	4.4%
emm 83	66	3.6%
emm 82	189	10.4%
emm 81	86	4.7%
emm 77	137	7.5%
emm 60	27	1.5%
emm 59	50	2.7%
emm 49	277	15.2%
emm 43	76	4.2%
emm 28	59	3.2%
emm 12	22	1.2%
emm 11	135	7.4%
emm 1	22	1.2%
Total	**1823**	**100.0%**

Invasive Group A *Streptococcal* (iGAS) infections

Group A *Streptococcus* commonly colonizes epithelial surfaces of skin and throat

Considered invasive when found in otherwise sterile environments

- Cellulitis
- Pneumonia
- Bacteremia
- Necrotizing fasciitis

Typed based on 5’ variable region of *emm* gene

- > 200 *emm* types

https://www.cdc.gov/abcs/bact-facts-interactive-dashboard.html

Clin Microbiol Rev. 2014;27(2):264-301.

Patterns of Antibiotic Nonsusceptibility Among Invasive Group A *Streptococcus* Infections – United States, 2006-2017

2006-2010: 3.2% iGAS isolates nonsusceptible to clindamycin

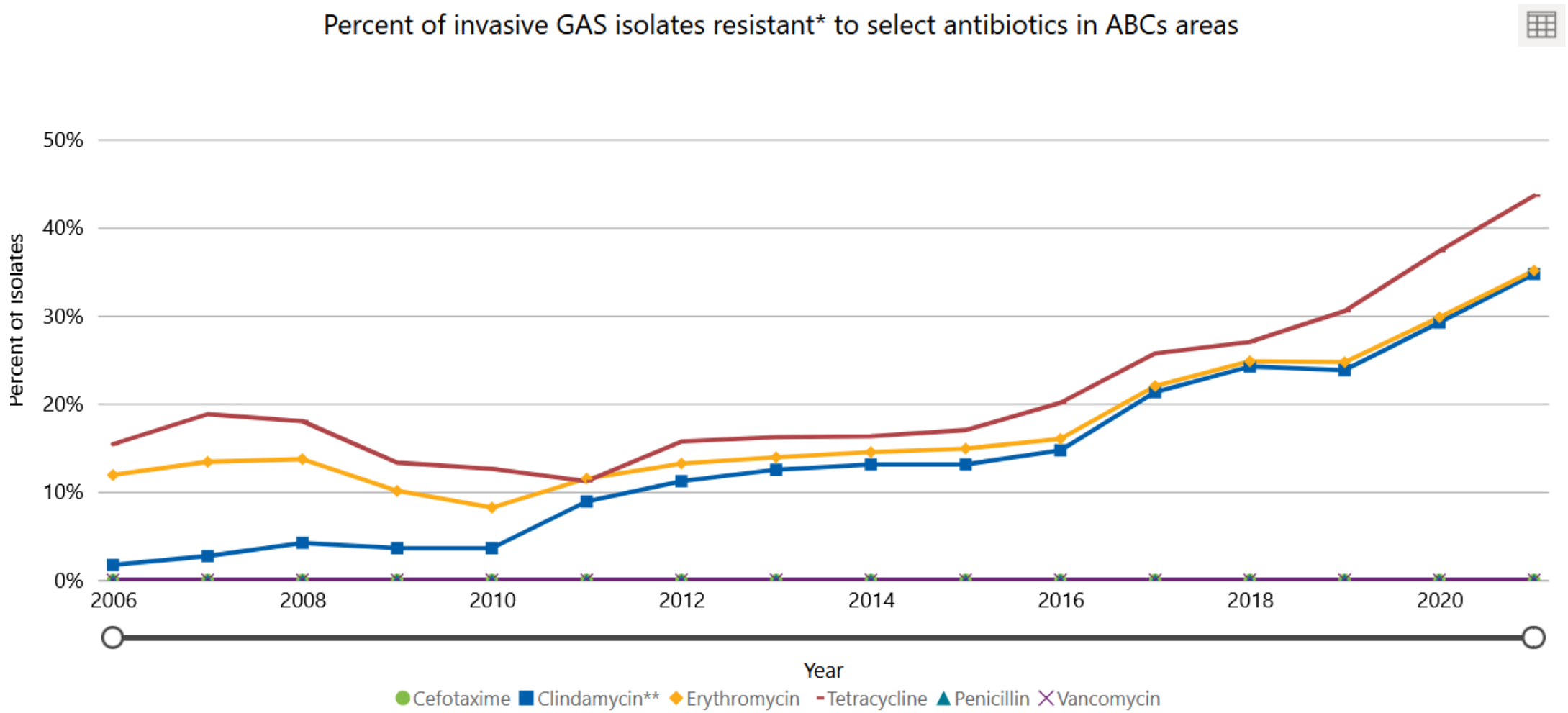
2011-2017: 14.6% iGAS isolates nonsusceptible to clindamycin

Clindamycin resistant GAS more common in:

- LTCF residents (compared to private residence) – OR 1.39 (95% CI 1.16-1.67)
- Homelessness (compared to private residence) – OR 2.08 (95% CI 1.74-2.48)
- Incarcerated patients – OR 2.37 (95% CI 1.1-4.94)
- IV drug use – OR 2.26 (95% CI 1.96–2.6)
- Abuse alcohol – OR 1.5 (95% CI 1.28-1.74)
- Cirrhosis or chronic liver disease – OR 1.7 (95% CI 1.41-2.05)
- HIV/AIDS – OR 3.17 (95% CI 2.56-3.93)

LTCF – Long term care facility

Clin Infect Dis. 2021;73(11):1957-1964



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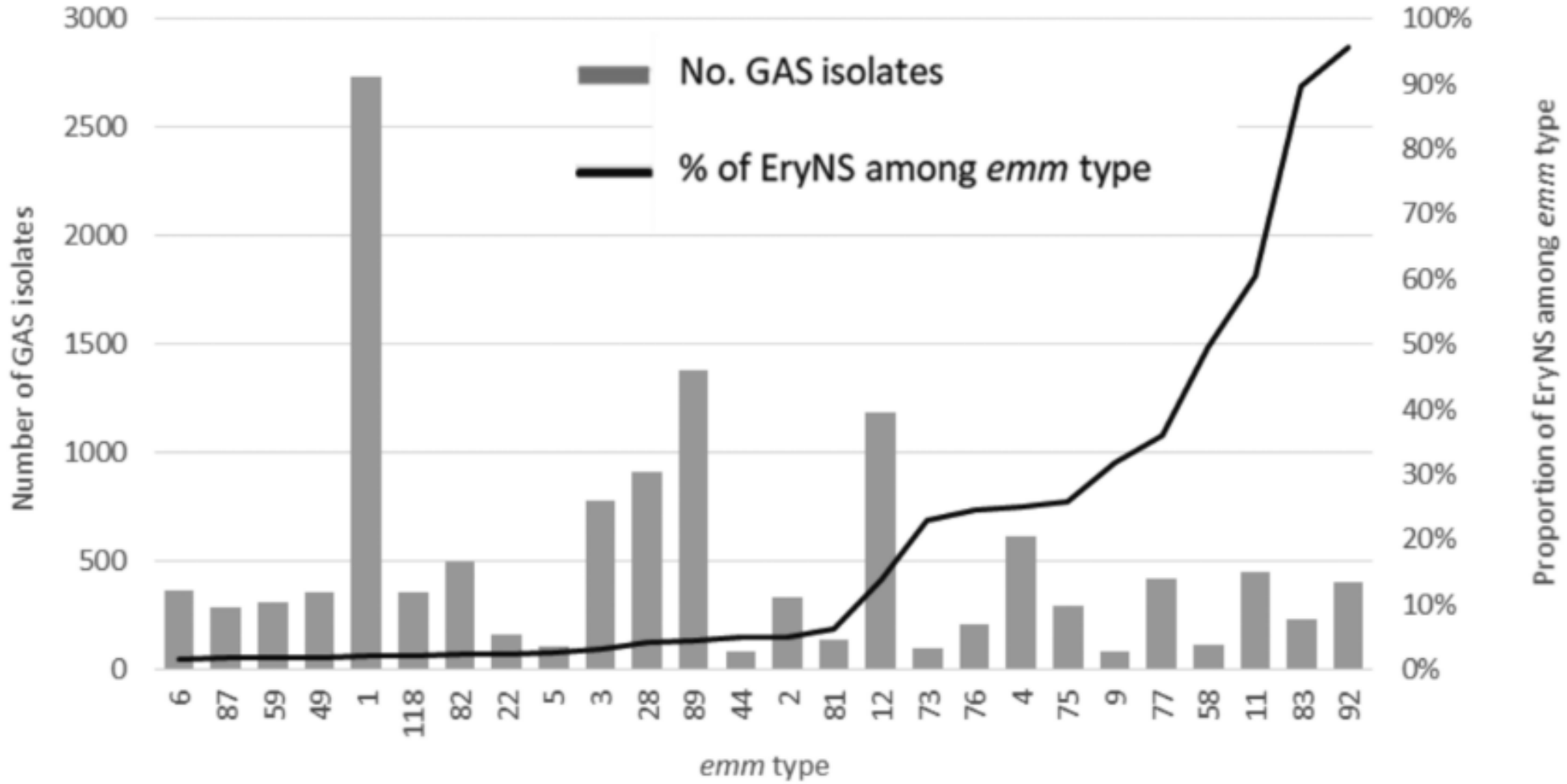
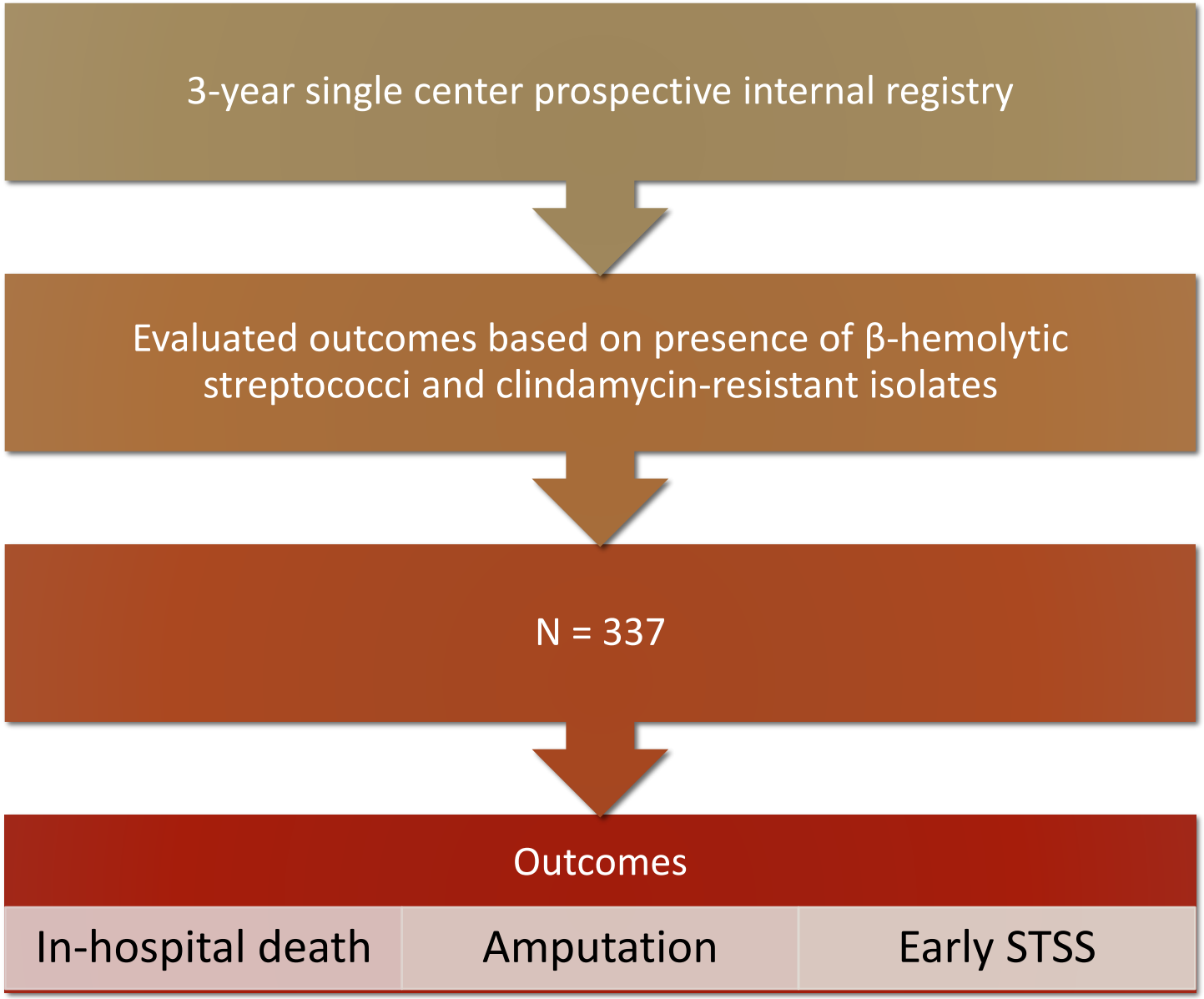


Clin Infect Dis. 2021;73(11):1957-1964

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



SSTS = Streptococcal Toxic Shock Syndrome

Clin Infect Dis. 2021;73(11):e4592-e4598

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

Presence of β-Hemolytic Streptococci

- In-hospital mortality: aRR 0.72 (95% CI 0.40-1.31)
- Amputation: aRR 1.79 (95% CI 1.07-3.01)
- Early streptococcal toxic shock syndrome: occurred in 5% of patients; 33% of those died

Effects of clindamycin-resistant isolates:

- In-hospital mortality: aRR 1.38 (95% CI 0.41-4.63)
- Amputation: aRR 1.86 (95% CI 1.10-3.16)
- Early streptococcal toxic shock syndrome: aRR 1.23 (95% CI 0.25-6.08)

Clin Infect Dis. 2021;73(11):e4592-e4598

Linezolid Mechanism of Action and Effects on Virulence Factors

Bacterial protein synthesis inhibitor

- Binds to 23S rRNA of 50S subunit
- Prevents formation of function 70S initiation complex essential for bacterial translation

In vitro data

- Enhanced opsonization and phagocytosis
- Impaired Streptolysin O production
- Reduced production of SpeA

J Antimicrob Chemother. 2002;50(5):665-72.

Linezolid Adverse Effects

Serotonin syndrome

- Risk low when using ≥ 1 concomitant serotonergic agent

Thrombocytopenia

- Higher risk associated with
  - Use ≥ 7 days
  - Platelet count < 150K
  - CrCl < 60 mL/min

Peripheral or optic neuritis

- Typically associated with use > 28 days

JAMA Network Open. 2022;5(12):e2247426
Basic Clin Pharmacol Toxicol. 2019;124:228–234.
Zyvox [package insert]. New York, NY: Pfizer; 2013.

Knowledge Check

Which patient is more likely to have a clindamycin resistant GAS infection?

A. A 15-year-old male who lives at home with his parents

B. A 54-year-old female with Stage 4 CKD

C. A 23-year-old female living alone who uses cocaine intranasally

D. A 37-year-old male who was recently incarcerated and uses IV heroin

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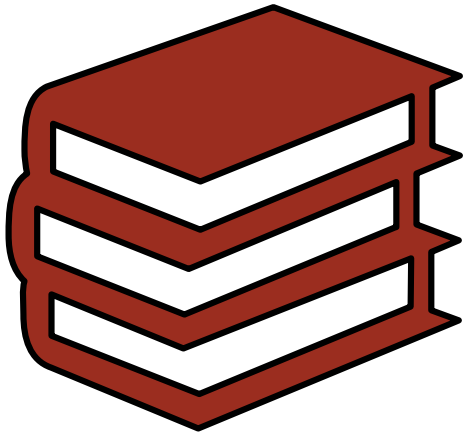
CLINICAL QUESTION

Is linezolid **as effective as** clindamycin in controlling toxin production in necrotizing soft tissue infections?



Literature Review

Effectiveness of adjunctive clindamycin in β-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study

BABIKER ET AL. 2020

Lancet Infect Dis. 2021;21(5):697-710

Babiker et al.

Objective: Examine real-world use patterns of adjunct clindamycin and the association of its use with in-hospital mortality and length of stay in patients with invasive group A β-hemolytic streptococcal (iGAS) infections who already received β-lactam antibiotics

Study Design

Retrospective cohort study

Multicenter – 233 US hospitals

Data from Cerner Health Facts database

Lancet Infect Dis. 2021;21(5):697-710

Babiker et al.

Inclusion Criteria

- Any age
- Any clinical culture positive for β-hemolytic streptococci
- Received β-lactam antibiotics within 3 days of culture sampling

Exclusion Criteria

- Polymicrobial infections
- Isolates not susceptible to clindamycin
- Received linezolid
- Missing variable data needed for analysis

Babiker et al. Interventions

Intervention	• Adjuvant clindamycin within 3 days of culture sampling
Comparator	• No clindamycin

Babiker et al. Outcomes

Primary outcome: Adjusted odds ratio of in-hospital mortality, including discharge to hospice, in the propensity matched iGAS cohort

Subgroup analysis of primary outcome:

- Patients who had proven infection
- Patients with skin, soft tissue, or musculoskeletal infections (adjusted for source control debridement)
- Patients who stayed in the ICU
- Patients without vasopressor-dependent shock or necrotizing fasciitis
- Patients who received early clindamycin (defined as within 1 day on either side of culture sampling)
- Patients who received clindamycin for:
  - > 1 day
  - > 2 days
  - > 3 days

Secondary outcome: Hospital length of stay among survivors

Babiker et al. Statistics

Patients treated with β-lactam antibiotics and had received adjunct clindamycin were propensity-matched 1:2 to those who did not receive clindamycin.

- Utilized nearest-neighbor method and a 20% caliper for standard deviation of the logit of the observed propensity score

Patients were exact-matched on proven invasive β-hemolytic streptococcal infection status, vasopressor use, ICU status, and presence of necrotizing fasciitis.

Babiker et al. Statistics

For baseline characteristics:

- Wilcoxon rank-sum test was used to compare continuous variables
- X^2 test was used to compare categorical variables

For propensity-matched data:

- Friedman's test was used to compare continuous variables
- Cochran-Mantel-Haenszel test was used to compare categorical data

Babiker et al. Baseline Characteristics

Unmatched N = 1079
- Control N = 736
- Clindamycin N = 343

Propensity-Matched N = 777
- Control N = 500
- Clindamycin N = 277

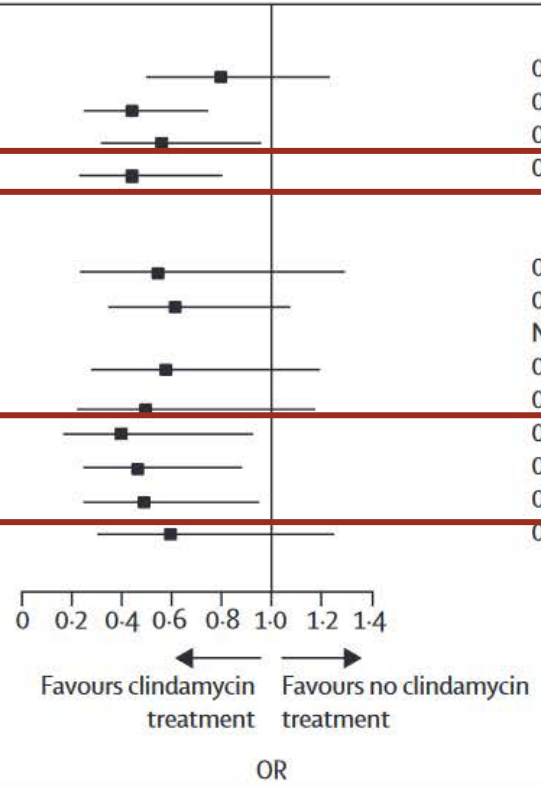
Lancet Infect Dis. 2021;21(5):697-710

Baseline Characteristics

	Unmatched Cohort		Propensity-Matched Cohort	
	Control	Clindamycin	Control	Clindamycin
Age (Median)	51	46	48	47
Male Sex	57.5%	58.3%	58.4%	57.8%
Immunocompromised	7.9%	7.9%	7.8%	7.9%
Proven β-hemolytic streptococcal disease	54.1%	55.7%	56.4%	55.2%
Community-onset	96.1%	95.9%	96.6%	96.4%
Site – SSTI or MSK	37.4%	41.1%	40.4%	41.5%
Necrotizing fasciitis	1.6%	12%	1%	1.8%
Vasopressor use	12.2%	24.2%	11.4%	13.4%
IVIG	1%	8%	1%	1%
Debridement within 3 days of infection	18.6%	28.9%	21.2%	25.3%

Babiker et al. Outcomes

	Clindamycin treatment		No clindamycin treatment		p value	OR (95% CI)
	Patients	Mortality (%)	Patients	Mortality (%)		
Primary analysis						
Unmatched, unadjusted	343	28 (8·2%)	736	74 (10·1%)	0·32	0·80 (0·50–1·24)
Unmatched, adjusted*					0·0031	0·44 (0·25–0·75)
Propensity-matched (1:2), unadjusted	277	18 (6·5%)	500	55 (11·0%)	0·042	0·56 (0·32–0·96)
Propensity-matched (1:2), adjusted*					0·011	0·44 (0·23–0·81)
Subgroup analysis†						
Early clindamycin treatment	97	6 (6·2%)	500	55 (11·0%)	0·16	0·53 (0·22–1·28)
Proven invasive β-haemolytic streptococcal infection	153	18 (11·8%)	282	51 (18·1%)	0·087	0·60 (0·33–1·06)
Probable invasive β-haemolytic streptococcal infection	124	0	218	4 (1·8%)	1·00	NA‡
Intensive care unit patients	55	13 (23·6%)	90	32 (35·6%)	0·13	0·56 (0·26–1·18)
Without vasopressor-dependent shock or necrotising fasciitis	37	12 (32·4%)	57	28 (49·1%)	0·11	0·48 (0·21–1·16)
Without vasopressor-dependent shock	239	6 (2·6%)	442	27 (6·1%)	0·043	0·40 (0·15–0·91)
Clindamycin treatment for >1 days	226	12 (5·3%)	500	55 (11·0%)	0·016	0·45 (0·23–0·87)
Clindamycin treatment for >2 days	183	10 (5·5%)	500	55 (11·0%)	0·032	0·47 (0·23–0·94)
Clindamycin treatment for >3 days	122	9 (6·9%)	500	55 (11·0%)	0·17	0·58 (0·29–1·24)



Secondary outcome: Hospital length of stay among survivors (adjunct clindamycin vs no clindamycin): 7 days vs 6 days; $p < 0.0001$

Babiker et al. Strengths & Limitations

Strengths

- Large US database
- Excluded patients that received linezolid
- Excluded clindamycin-resistant isolates
- Excluded polymicrobial infections

Limitations

- Study design
- Small number of patients with necrotizing fasciitis
- Did not assess rates of *C. difficile* infections

Case Report - Successful Treatment of Necrotizing Fasciitis and Streptococcal Toxic Shock Syndrome with the Addition of Linezolid

BOJIKIAN ET AL. 2017

Case Rep Infect Dis. 2017;2017:5720708

Bojikian et al. Patient Details

67-year-old Caucasian Male

Past Medical History: Coronary artery disease, obstructive sleep apnea

Bitten by insect on right middle finger while traveling in southeastern US 2 days prior to hospital presentation

Bojikian et al. Initial Patient Presentation

Temperature: 102.9˚F

WBC: 2.9 cells/mm^3

SCr 2.3 mg/dL

Blood Pressure: 120/75 mmHg

Bojikian et al. Course of Illness

Developed rapidly progressing right upper extremity swelling, pain, necrotic blisters, and maculopapular rash

Transferred to larger academic medical center for treatment

Blood pressure decreased to 70's/50's mmHg

Aggressive fluid resuscitation

Remained hypotensive – 90's/50's mmHg

Norepinephrine & vasopressin

Intubated and sedated secondary to hypoxia and altered mental status

Case Rep Infect Dis. 2017;2017:5720708

Bojikian et al. Course of Illness

Surgical debridement performed

Empiric antibiotics started

- Vancomycin 15 mg/kg IV every 24 hours
- Clindamycin 600 mg IV every 8 hours
- Ceftazidime 1 gram IV every 8 hours
- Ciprofloxacin 400 mg IV every 12 hours

Day 3 – Extubated

Day 4 – *S. pyogenes* isolated from tissue samples collected, antibiotic selection deescalated

- Penicillin G 4 million units IV every 4 hours
- Clindamycin 900 mg IV every 8 hours

Case Rep Infect Dis. 2017;2017:5720708

Bojikian et al. Course of Illness

Day 5 – Erythema and blisters on right upper extremity worsened, WBC ↑ 15.4 cells/mm^3, platelets ↓ 75 K/mcL

- Linezolid 600 mg IV every 12 hours ADDED to current regimen
- Rationale: Additional antistreptococcal activity and toxin suppression

Day 9 – Final debridement

Day 10 – Clindamycin discontinued

Day 13 – Linezolid and penicillin discontinued

Case Rep Infect Dis. 2017;2017:5720708

Bojikian et al. Conclusion

S. pyogenes isolated from wound cultures – antibiotic selection deescalated appropriately

Condition worsened despite appropriate de-escalation to clindamycin and penicillin

Addition of linezolid resulted in improvement

No susceptibilities reported

Clindamycin vs Linezolid

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

DORAZIO ET AL. 2023

Open Forum Infectious Diseases. 2023;10(6):ofad258

Dorazio et al.

Objective

- Evaluate safety and efficacy of linezolid versus clindamycin plus vancomycin as empiric treatment for necrotizing soft tissue infections when used in combination with standard gram-negative and anaerobic therapy

Study Design

- Retrospective/quasi-experimental
  - Compared preintervention and postintervention data
    - Preintervention: vancomycin + clindamycin
    - Postintervention: linezolid
    - 10-month washout period
- Single-center

Dorazio et al.

Inclusion Criteria

- ICD-10 codes for admission
  - M276 – Necrotizing soft tissue infection
  - N493 – Fournier gangrene
- Surgical management within 24 hours of diagnosis
- At least 1 dose of clindamycin or linezolid

Exclusion Criteria

- Management of infection at outside facility or in emergency department > 24 hours prior to surgical intervention
- Transitioned to comfort care measures only
- Died within 48 hours of admission

Open Forum Infectious Diseases. 2023;10(6):ofad258

Dorazio et al. Intervention

Intervention (Post-intervention)	• Linezolid + appropriate gram-negative and anaerobic bacterial coverage
Comparator (Pre-intervention)	• Clindamycin + vancomycin + appropriate gram-negative and anaerobic bacterial coverage

Dorazio et al. Outcomes

Primary Outcome

- 30-day mortality occurring inpatient or post-discharge

Secondary Outcomes

- Rates of AKI defined as change in SCr of 1.5 to 3 times baseline as defined by RIFLE criteria or initiation of any new renal replacement therapy
- Rates of *C. difficile* infection defined as positive toxin or nucleic acid test and new receipt of oral vancomycin or fidaxomicin within 30 days of antibiotic initiation
- Composite outcome of death, AKI, or *C. difficile* infection at 30 days
- Thrombocytopenia (platelet count < 50 K/mcL)
- Serotonin syndrome (based on any documentation of diagnosis in progress notes)

Open Forum Infectious Diseases. 2023;10(6):ofad258

AKI – Acute kidney injury

Dorazio et al. Statistics

Baseline characteristics were matched for patients from preintervention group with patients from the postintervention group using a combination of propensity score and Mahalanobis distance penalty scoring

- Considered well matched if standardized difference < 0.20 and P value > 0.05
- Tested using Wilcoxon rank-sum test for continuous variables and Fisher exact test for binary variables
- All matched characteristics satisfied requirements

Primary outcome and secondary composite outcome of AKI, CDI, and death were analyzed as time-to-event data with death or end of 30-day follow up as a censoring time

- *P* value < 0.05 indicated statistical significance

CDI – *C. difficile* infection

Dorazio et al. Baseline Characteristics

Matched Cohort N = 124

- Preintervention (Clindamycin + vancomycin) N = 62
- Matched Postintervention (Linezolid) N = 62

All Postintervention (Unmatched, Linezolid) N = 102

Characteristics	Preintervention	Matched Postintervention	All Postintervention
Median age	58.5	57.5	56
Female sex	4.84%	4.84%	6.86%
SCr (mg/dL) day 1 (IQR)	1.1 (0.8-1.8)	1.1 (0.9-1.6)	1.0 (0.8-1.6)
ICU admission	77.4%	77.4%	71.57%
History of immunosuppression	6.45%	8.06%	14.71%
NSTI related to traumatic event	25.81%	12.9%	11.76%
History of chronic wound	20.97%	19.35%	21.57%
Prior diagnosis of diabetes mellitus	50%	48.39%	53.92%
WBC at admission (IQR)	18.3 (12.7-23.7)	16.9 (13.6-20.4)	17.9 (13.8-22.4)
Platelets at admission (IQR)	261.5 (196-365)	277 (184-383)	283.5 (196-390)
Patients on serotonergic agents at time of admission	22.58%	30.65%	29.41%
No. (%) patients who received linezolid	1 (1.61%) Duration: 5 days	62 (100%) Duration: 6 days (IQR 4-9)	97 (95.1%) Duration: 6 days (IQR 4-9)
No. (%) patients who received clindamycin	62 (100%) Duration: 4 days (IQR 3-5)	29 (46.77%) Duration: 1 day	47 (46.07%) Duration: 1 day
Group A Streptococcus positive cultures	5 patients	3 patients (unclear if matched or unmatched population)	

Open Forum Infectious Diseases. 2023;10(6):ofad258

Dorazio et al. Results

Primary outcome

- 30-day mortality – 8.06% vs 6.45%; HR 1.67; 95% CI 0.32-10.73; *p* = 0.65

Secondary outcomes

- Rates of AKI – 9.68% vs 1.61%; HR 6.00; 95% CI 0.73-276; p = 0.05
- Rates of CDI – 6.45% vs 1.61%; *p* = 0.07
- Composite of death, AKI, and CDI at 30 days – 22.58% vs 9.68%; HR 4.67; 95% CI 1.30-25.33); ***p* = 0.02**
- Serotonin syndrome – 0% vs 0%
- Thrombocytopenia – 1.61% vs 1.61%

Dorazio et al. Supplementary Data

Number of Surgical Interventions, median (IQR)	• Preintervention – 4 (2-6) • Postintervention – 3 (2-5)
Time to Source Control (days), median (IQR)	• Preintervention – 8 (5-13) • Postintervention – 5 (2-10)
Patients with positive GAS – 30-day mortality	• Preintervention 0% (0/5 patients) • Postintervention 33% (1/3 patients)
Patients with positive GAS – total duration of all antibiotics median number of days	• Preintervention: 30 days • Postintervention: 18 days

Dorazio et al. Strengths & Limitations

Strengths

- Empiric treatment
- Evaluated safety outcomes

Limitations

- Study design
- Primary outcome of 30-day mortality
- Not adequately powered to conduct multivariable regression analysis to determine factors associated with 30-day mortality
- Number of GAS positive cultures

Comparison of Adjuvant Clindamycin Versus Linezolid for Severe Invasive Group A Streptococcal Skin and Soft Tissue Infections

HEIL ET AL. 2023

Open Forum Infectious Diseases. 2023;10(12):ofad588

Heil et al.

Study Objective

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

Study Design

- Retrospective cohort study
- Single-center

Open Forum Infectious Diseases. 2023;10(12):ofad588

Heil et al.

Inclusion Criteria

- Adults ≥ 18 years of age
- Invasive soft tissue infection or necrotizing fasciitis with group A streptococcus isolated from normally sterile site
- Underwent surgical debridement
- Received either clindamycin or linezolid ≥ 48 hours

Exclusion Criteria

- Received clindamycin and linezolid for > 1 dose

Heil et al. Intervention

Intervention

- Linezolid

Comparator

- Clindamycin

Open Forum Infectious Diseases. 2023;10(12):ofad588

Heil et al. Outcomes

Primary Outcome

- Percent change in Sequential Organ Failure Assessment (SOFA) Score from baseline at hospital admission at through 72 hours

Safety Outcomes

- Hypersensitivity
- *C. difficile* infection based on positive PCR and confirmatory toxin test
- Thrombocytopenia
- Serotonin syndrome

SOFA Score

Score	+0	+1	+2	+3	+4
PaO2/FiO2	> 400	≤ 400	≤ 300	≤ 200	≤ 100
Platelets	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Bilirubin (mg/dL)	< 1.2	1.2-1.9	2-5.9	6-11.9	> 12
Hypotension (doses mcg/kg/min)	No hypotension	MAP < 70	Dopamine ≤ 5 or dobutamine (any use)	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine or norepinephrine > 0.1
GCS	15	13-14	10-12	6-9	<6
SCr (mg/dL) OR urine output	< 1.2	1.2-1.9	2-3.4	3.5-4.9 OR < 500 mL/day	>5 OR < 200 mL/day

MAP – Mean arterial pressure; GCS – Glasgow Coma Scale

SOFA Score

SOFA Score	Mortality – Initial Score	Mortality – Highest Score
0-1	0%	0%
2-3	6.4%	1.5%
4-5	20.2%	6.7%
6-7	21.5%	18.2%
8-9	33.3%	26.3%
10-11	50%	45.8%
12-14	95.2%	80%
> 14	95.2%	89.7%

Mean SOFA Score	Mortality
0-1	1.2%
1.1-2	5.4%
2.1-3	20%
3.1-4	36.1%
4.1-5	73.1%
> 5.1	84.4%

Heil et al. Outcomes

Secondary Outcomes

- Inpatient mortality
- Amputation
- Duration of vasopressor requirement
- ICU length of stay
- Rates of clindamycin resistance

Heil et al. Statistics

Bivariate analysis of baseline characteristics and antibiotic treatment performed using Fisher's exact, X^2, and Mann-Whitney U tests

Associations between outcomes and antibiotic treatment group analyzed using Fisher's exact, X^2, and Mann-Whitney U tests

Frequency distribution in LRINEC scores across clindamycin and linezolid groups done using X^2 test

Linear mixed model used to analyze percentage change in SOFA scores over 12-hour intervals broken down by antibiotic groups, adjusting for time to first surgery determined *a priori*

Heil et al. Baseline Characteristics

Characteristic	Total (n=55)	Clindamycin (n=26)	Linezolid (n=29)	P-value
Age, mean (SD)	50 (18)	49.3 (19)	50.6 (17.4)	0.8
Male Sex, n	38 (69.1%)	16 (61.5%)	22 (75.9%)	0.3
Transferred from outside facility, n	31 (56.4%)	17 (35.4%)	14 (48.3%)	0.2
Baseline SCr ≤ 1.6 mg/dL, n	35 (63.6%)	19 (73.1%)	16 (55.2%)	
Baseline LRINEC Score, median (IQR)	7 (4-9)	7 (4-9)	8 (5-9)	0.7
Baseline SOFA Score, median (IQR)	3 (1-8)	5 (2-8)	2 (1-5)	0.08
Diabetes, n	12 (23.6%)	4 (15.4%)	9 (31%)	0.2
Substance use disorder, n	32 (58.2%)	17 (65.4%)	15 (51.7%)	0.3
Immunocompromised	4 (7.3%)	2 (7.7%)	2 (6.9%)	1.0
Site of Infection				
Perineum or genitals, n	3 (5.5%)	0	3 (10.3%)	0.1
Extremity	46 (83.6%)	20 (76.9%)	26 (89.7%)	0.3

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Heil et al. Baseline Characteristics

Characteristic	Total (n=55)	Clindamycin (n=26)	Linezolid (n=29)	P-value
Organism				
Polymicrobial	27 (49.1%)	12 (46.2%)	15 (51.7%)	0.7
Clostridium	0	0	0	
MSSA	12 (21.8%)	5 (19.2%)	7 (24.1%)	0.7
MRSA	11 (20%)	4 (15.4%)	7 (24.1%)	0.5
Coagulase-negative staphylococcus	8 (14.5%)	2 (7.7%)	6 (20.6%)	0.3
Gram-negative bacilli	7 (12.7%)	3 (11.5%)	4 (13.8%)	> 0.99
Adjunct Therapies				
Time from admission to first surgery, median (IQR)	4.6 (2, 16)	6 (1.7, 18)	4 (2, 14.5)	0.7
IVIG given, n	12 (21.8%)	8 (30.8%)	4 (13.8%)	0.1
Duration of antitoxin therapy (days), median (IQR)	3.3 (2.3, 4.6)	2.7 (2.3, 4.3)	3.5 (2.5, 5.5)	0.4

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Heil et al. Results

Primary outcome

- Percent change in SOFA score from baseline at 72 hour: Clindamycin -61.4% vs Linezolid -48.4%
- Least Squares Mean Difference: -13% (SE 14.1); 95% CI (-41.6 – 15.5); P=0.4

Safety outcomes (clindamycin vs linezolid)

- *C. difficile* during hospital admission: 3.9% vs 3.5% (1 patient per treatment group); P=1
- Thrombocytopenia: 0% vs 3.5% (1 patient in linezolid treatment group); P=1
- No episodes of hypersensitivity or serotonin syndrome reported

Heil et al. Results

Secondary outcomes (clindamycin vs linezolid)

- Inpatient mortality: 7.7% vs 3.4%; P=0.6
- Amputation: 15.4% vs 20.7%; P=0.7
- Duration of vasopressor requirement: 42.1 hrs vs 39.1 hrs; P=0.7 (14 clindamycin and 9 linezolid patients required vasopressors)
- ICU length of stay: 8.2 days vs 9.5 days; P=0.6 (16 clindamycin and 11 linezolid patients required ICU stays)
- Clindamycin resistance: Susceptibility for clindamycin not routinely performed at facility, post-hoc evaluation of susceptibility performed on 17 isolates available in biorepository; 2 isolates resistant to erythromycin, 1 isolate resistant to clindamycin

Heil et al. Strengths & Limitations

Strengths

- Focused on iGAS
- Assessed adverse effects

Limitations

- Study design
- SOFA score as primary outcome
- Missing information related to antibiotic treatment
- Missing information related to treatment prior to transfer
- No rationale provided for treatment group selection

CLINICAL QUESTION

Is linezolid **as effective as** clindamycin in controlling toxin production in necrotizing soft tissue infections?

Conclusion

Limited information

Studies evaluating empiric treatment and confirmed iGAS

No difference found in outcomes assessed

Considerations for Treatment

Patient specific factors to consider

- Risk of *C. difficile* infection
  - Risk factors
  - Previous history of infection
- Risk of clindamycin resistant iGAS
  - Patients experiencing homelessness, incarcerated, or residing in LTCF
  - IV drug use or alcohol abuse
  - Cirrhosis
  - HIV/AIDS
- Renal function
  - Presence of AKI upon admission
  - Development of AKI during treatment

Consider using linezolid

Post-Test Questions

Post-test Question 1

BG, a 55-year-old female with a past medical history of type 2 diabetes mellitus, coronary artery disease, and hyperlipidemia comes to the ER complaining of a wound on her leg. She states she recently had a bug bite that she scratched. The area around the wound appears purple in color, swollen, and has fluid-filled blisters present. She complains of severe pain (9/10) associated with the wound. Her temperature is 101.3 F, HR 93 bpm, RR 22, and her WBC count is 21.

True or False, this wound is highly suspicious of a necrotizing soft tissue infection and would warrant use of adjunct clindamycin or linezolid.

A. True

B. False

Post-test Question 2

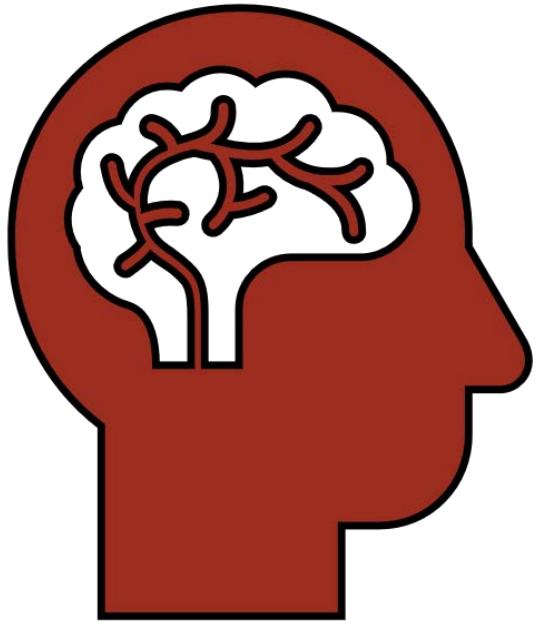
Based on current IDSA treatment guidelines for skin and soft tissue infections, what is the appropriate treatment for a necrotizing soft tissue infection with cultures positive only for *S. pyogenes*?

A. Penicillin G IV + Clindamycin IV

B. Vancomycin IV + Piperacillin/tazobactam IV

C. Penicillin G IV + Clindamycin IV + Surgical debridement

D. Vancomycin IV + Piperacillin/tazobactam IV + Surgical debridement



Post-test Question 3

BG, a 55-year-old female with a past medical history of type 2 diabetes mellitus, coronary artery disease, and hyperlipidemia comes to the ER complaining of a wound on her leg. The team has decided to treat her for a necrotizing soft tissue infection and asks for your recommendation for empiric antibiotics.

BG lives at home with her husband. When asked, she reports no recent use of antibiotics, and has never been diagnosed with *C. difficile.* Her baseline SCr is unknown, but labs show her SCr is currently 0.72 mg/dL (CrCl 98 mL/min).

What is the most appropriate recommendation?

A. Linezolid + piperacillin/tazobactam

B. Linezolid + vancomycin + piperacillin/tazobactam

C. Clindamycin + piperacillin/tazobactam

D. Clindamycin + vancomycin + piperacillin/tazobactam

Post-test Question 4

MJ, a 72-year-old homeless male, is brought to the ER by EMS. He is febrile and hypotensive. Upon examination, a large purplish wound is found on his left forearm. He is experiencing extreme pain when trying to exam in the wound. He states he was given oral antibiotics 5 days ago after an ER visit a different hospital and says he has been taking them as directed. His urine drug screen is positive for amphetamines, and he has noticeable puncture wounds on his hands and arms. The team has decided to treat her for a necrotizing soft tissue infection and asks for your recommendation for empiric antibiotics.

What is the most appropriate recommendation?

A. Linezolid + piperacillin/tazobactam

B. Linezolid + vancomycin + piperacillin/tazobactam

C. Clindamycin + piperacillin/tazobactam

D. Clindamycin + vancomycin + piperacillin/tazobactam

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Clindamycin vs Linezolid – A Toxic Duel. Toxin Production Control in Necrotizing Soft Tissue Infections (NSTIs)

JERRICA LILLEY, PHARMD

PGY1 PHARMACOTHERAPY RESIDENT

UNIVERSITY OF THE INCARNATE WORD

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