CSiM | CENTER FOR STEWARDSHIP IN MEDICINE

March 26, 2024

Bacterial Toxins

- Hayato Mitaka, MD

Necrotizing Soft Tissue Infection: Case

A 30-year-old man presents to the ED for sudden onset of severe left biceps swelling and pain, which has rapidly progressed in the past 6 hours. He also reports fever and chills. Medical history is significant for daily subcutaneous heroin use into the left biceps. On exam, temperature is 38.7 °C, BP is 90/60 mm Hg, HR is 110/min, and RR is 24/min. The left biceps area is exquisitely tender, with associated edema, warmth, and overlying ecchymotic bullous lesions; crepitus and induration are appreciated with palpation.

Surgery was called, given concern for necrotizing soft tissue infection (NSTI).

What empiric ABX would you start (May choose multiple options)?

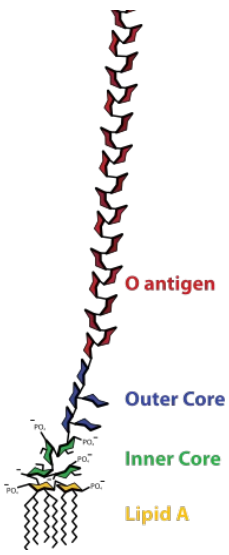
1. Penicillin
2. Pip/tazo
3. Meropenem
4. Vancomycin
5. Linezolid
6. Clindamycin

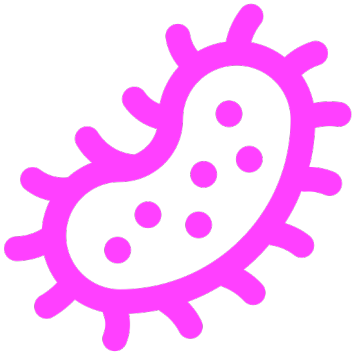
Bacterial Toxins

Bacterial Toxins

Endotoxins

Ex) Lipopolysaccharide (LPS) of Gram-negatives





Exotoxins

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Today's topic

Arsenal of bacterial exotoxins

PVL
(S. aureus)

Damage cell membranes

Diphtheria
Shiga toxin

Inhibit protein synthesis

Superantigens
(S. aureus & S. pyogenes)

Activate
immune response

E.coli
C. diff toxin
Cholera toxin

Activate second messenger pathways

Anthorax
Botulism
Tetanus

Protease

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Arsenal of bacterial exotoxins

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(S. aureus)

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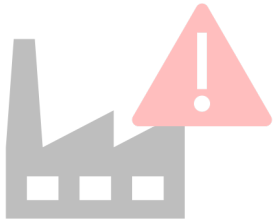

Inhibit protein synthesis

Activate
immune response

Superantigens
(S. aureus & S. pyogenes)

E.coli
C. diff toxin A&B
Cholera toxin

Activate second messenger pathways

Anthorax
Botulism
Tetanus

Protease

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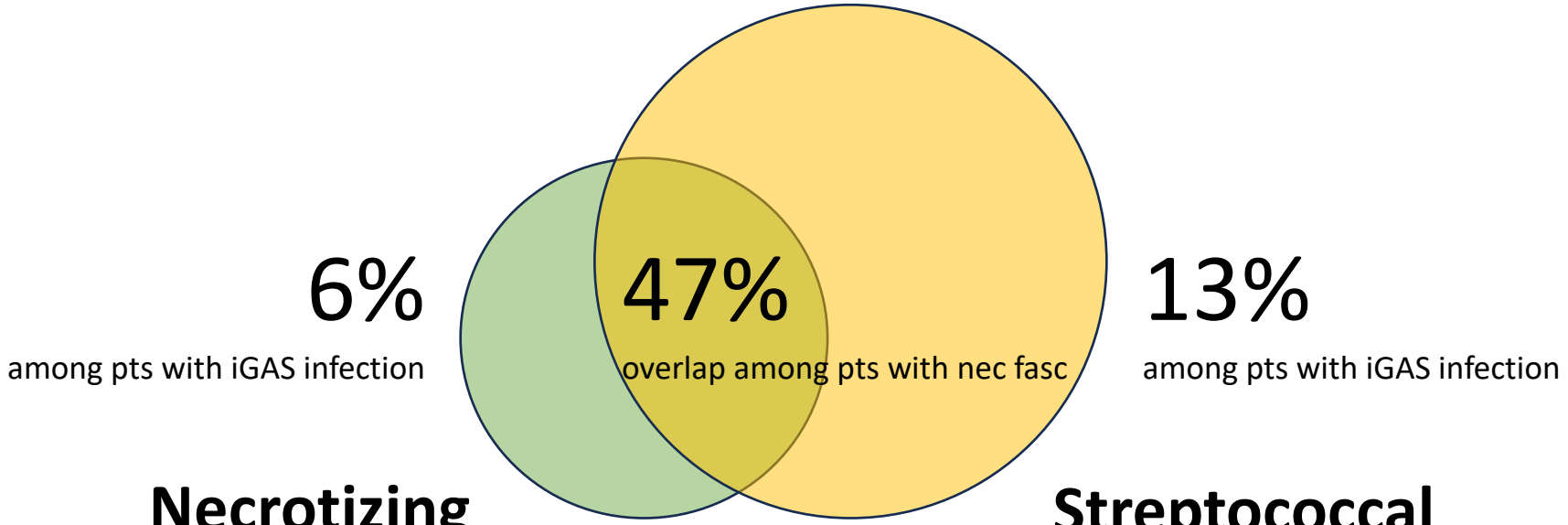
Toxins produced by Group A Strep

Toxin Name	Mechanism	Target	Disease
Streptolysin O	Pore-former	Cholesterol	Strep throat
Streptococcal pyrogenic exotoxins (*Spe*)	**Superantigen** (T-cell activator)	TCR and MHC II	**Toxic shock** Scarlet fever

- *Spe* = one of the most potent T-cell activators → **Cytokine release**
- Not all GAS strains harbor and/or release exotoxins with superantigen activity.

Forbes JD. Clin Microbiol Newsl. 2020;42(20):163-170.

Streptococcal Toxic Shock Syndrome & NSTI: Frequent Overlap and Toxic Combination



- TSS = Invasive GAS infection + hypotension + multiorgan failure
- Mortality: **34%** with GAS nec fasc. **67%** with GAS nec fasc + STSS

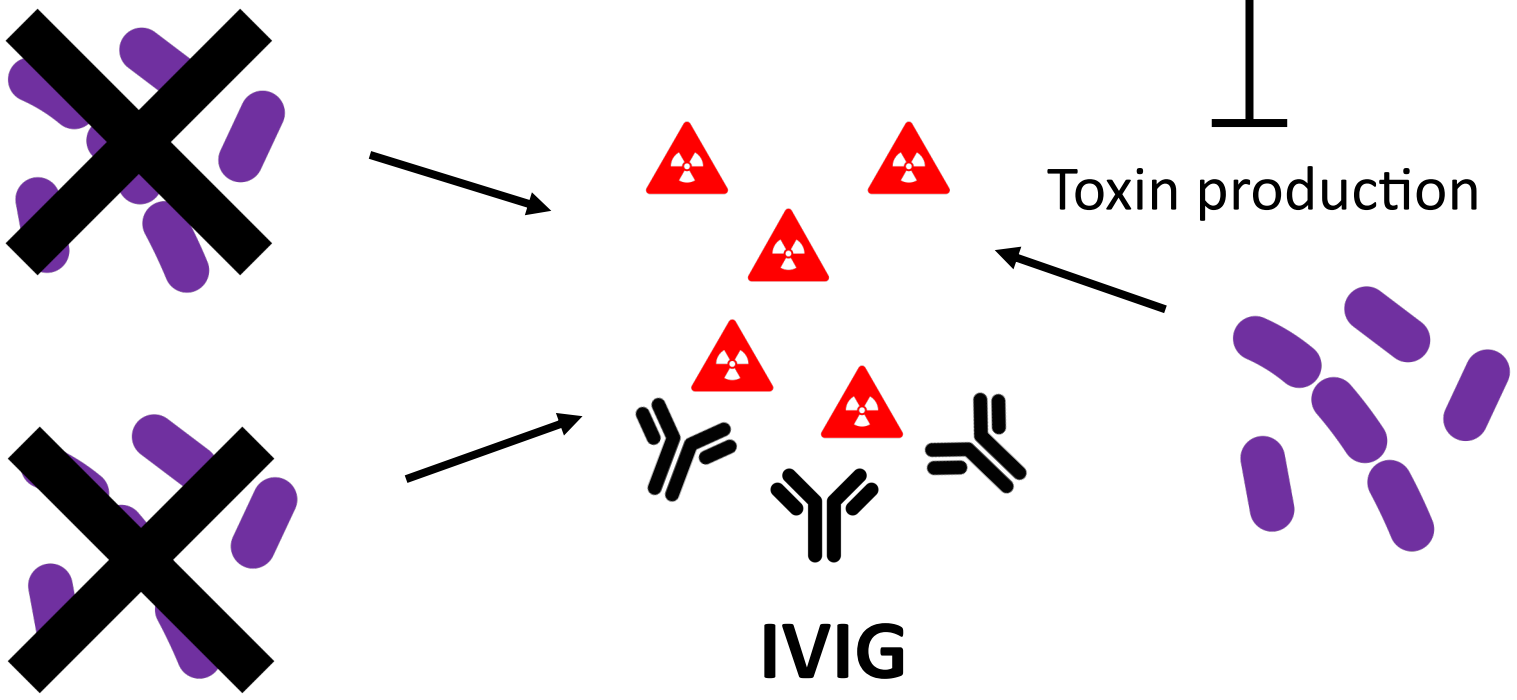
Davies HD, et al. N Engl J Med. 1996;335(8):547-54.
Kaul R, et al. Am J Med. 1997;103(1):18-24.

Treatment of Strep TSS

Source control

Beta-lactam (= Penicillin)

Protein synthesis inhibitor



Inhibition of toxin protein synthesis

Protein synthesis inhibitor ABX	NSTI/TSS
Clindamycin	✅
Aminoglycosides	-
Tetracyclines	-
Rifamycins	-
Macrolides	-
Linezolid	✅

Where did the idea come from?

- In 1950s
- "**Eagle effect**" in GAS **mouse models**
- Concerns that penicillin monotherapy for invasive GAS infections was inadequate

What's the biological basis?

- **In vitro models** showing reduced exotoxin release with clindamycin and linezolid compared to penicillin
- A lot of **retrospective studies**

J Antimicrob Chemother 1997;40:275-7., Antimicrob Agents Chemother 2003;47:1752-5.

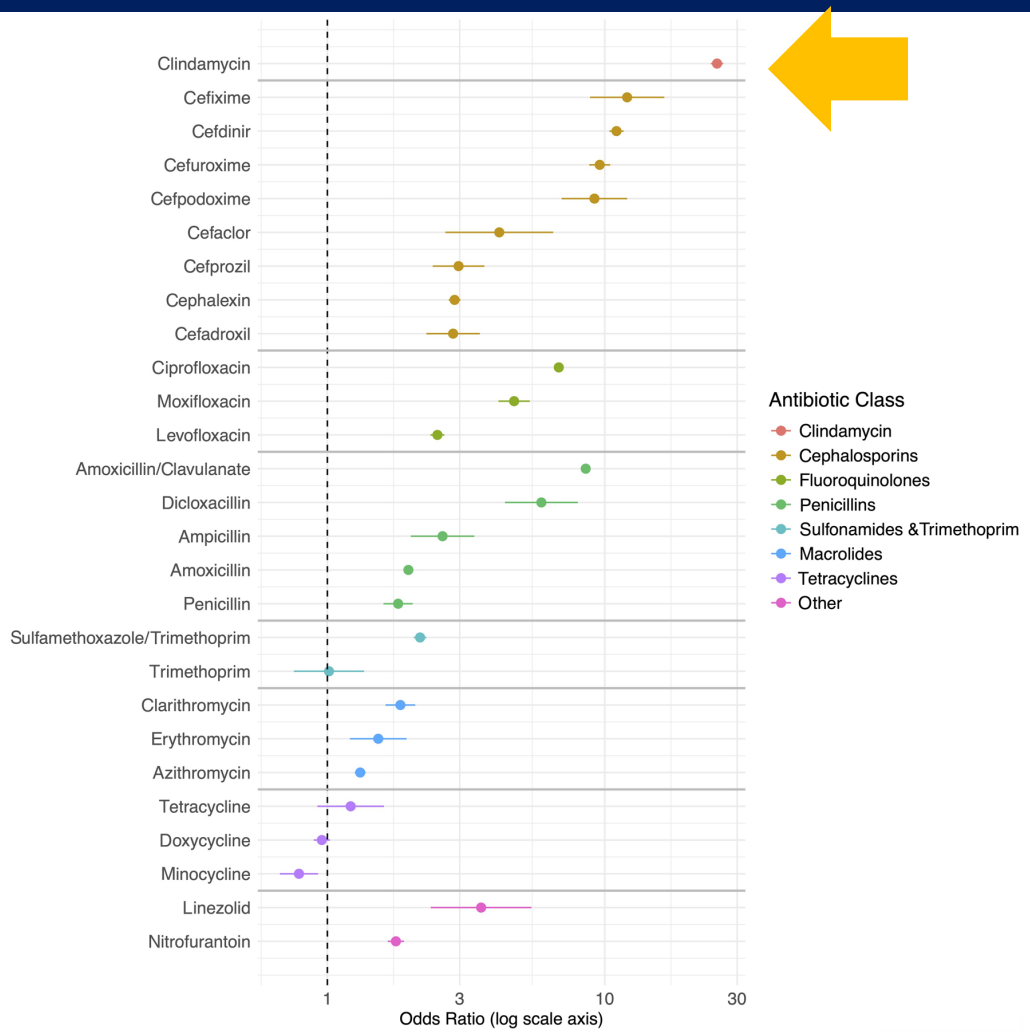
Empiric ABX treatment of NSTI

Historically…

- Carbapenem or pip/tazo (broad-spectrum β-lactam)
- Vancomycin (Anti-MRSA antibiotic)
- Clindamycin (Anti-toxin effect)
  - ⬇️ superantigen production in animal models
  - Retrospective studies showed an association with better mortality

Issues with Clindamycin (1)

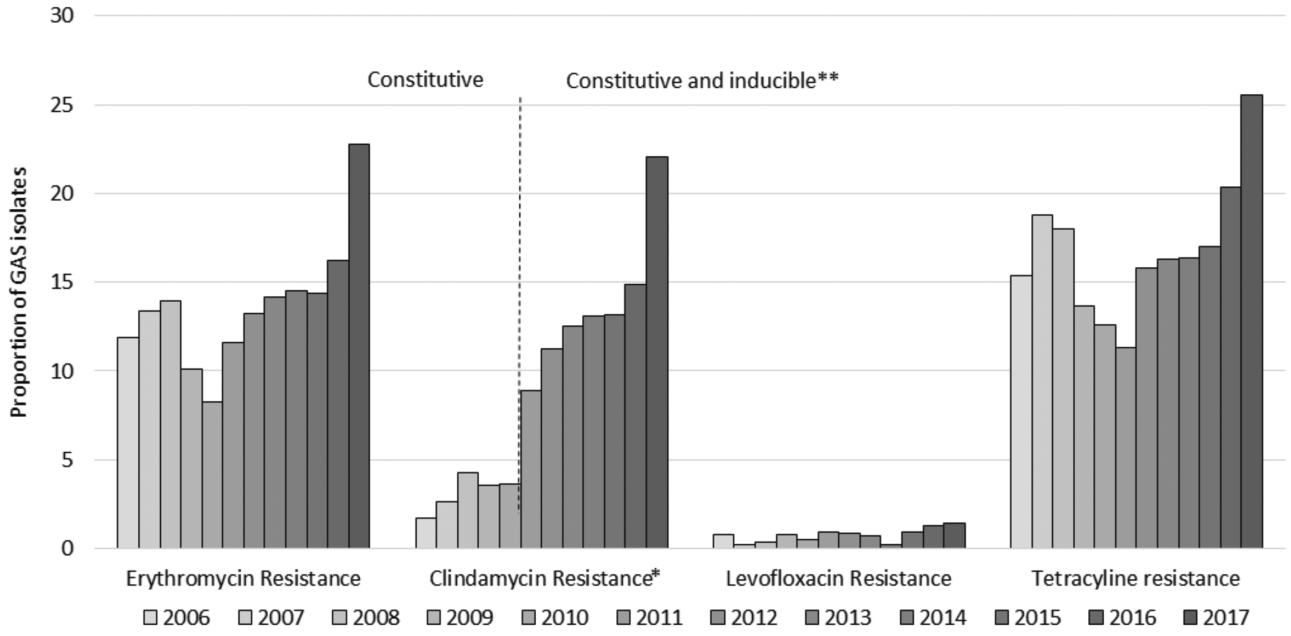
- **C. diff infection**
  - One of ABX with the highest risk of CDI
- GI intolerance
  - including non-C. diff diarrhea



Miller AC, et al. Open Forum Infect Dis. 2023;10(8):ofad413.

Issues with Clindamycin (2)

- **Increasing resistance to Clindamycin**



51%

Clinda resistance GAS Antibiogram 2021 at HMC

Proportion of GAS isolates non-susceptible to multiple ABX, 2006–2017

Fay et al. Clin Infect Dis. 2021;73(11):1957–64.
Horn et al. Clin Infect Dis. 2021;73(11):e4592-e4598.

Clinda + Vanco → Linezolid

Open Forum Infectious Diseases

MAJOR ARTICLE

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

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- A retrospective, single-center, quasi-experimental study at UPMC
- After an update in the local NSTI order set:
  - Pip/tazo + linezolid (in place of clindamycin and vancomycin) as the preferred empiric regimen for NSTI.
- Total 164 patients - No difference in mortality and C.diff, but **less AKI in the post-intervention group**

Dorazio J, et al. Open Forum Infect Dis. 2023 May 11;10(6):ofad258.

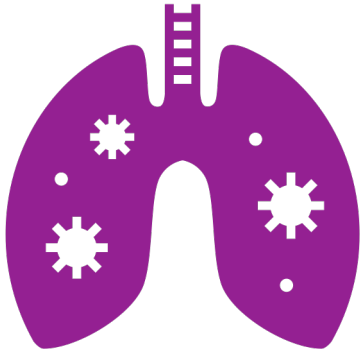
Toxins produced by S. aureus

Toxin Name	Mechanism	Target	Disease
Panton-Valentine leukocidin (PVL)	Pore-former	Cholesterol	• **Necrotizing pneumonia** • **SSTI**
Exfoliative toxin	T-cell activator	TCR and MHC II	Staphylococcal scalded skin syndrome (SSSS)
Enterotoxin	T-cell activator	TCR and MHC II	Food poisoning
Toxic shock syndrome toxin (TSST-1)	T-cell activator	TCR and MHC II	Staphylococcal TSS

Forbes JD. Clin Microbiol Newsl. 2020;42(20):163-170.

Panton-Valentine leukocidin (PVL)

SSTI



Necrotizing Pneumonia

- Strong epidemiological link with CA-MRSA, including USA300 strain
- A predilection for young, immunocompetent patients with high case fatality rates.
- Less frequently, PVL+ hospital-acquired MRSA and MSSA have been reported.

Linezolid vs Vanco for MRSA pneumonia

Is Linezolid better due to the inhibition of toxin production??

→ Not so straightforward…

A controversial RCT in 2012 showed the superiority of linezolid over vancomycin in clinical response

The virulence of CA-MRSA strains is probably not due to PVL based on an animal study.

Linezolid may be better when vancomycin MIC ≥2?

What if complicated by MRSA bacteremia?

Wunderink RG, et al. Clin Infect Dis. 2012;54(5):621-9.

Take Home Points

- Anti-toxin antimicrobial treatment in Strep and Staph infections has been established by in vitro and animal studies, and supported by data from observational studies
- Movement transitioning from clindamycin + vancomycin to linezolid in empiric treatment for NSTI
- Unclear if linezolid vs vancomycin is better in MRSA pneumonia