CSiM | CENTER FOR STEWARDSHIP IN MEDICINE

April 23, 2024

Oral Antibiotics for Cellulitis

- Hayato Mitaka, MD

Agenda

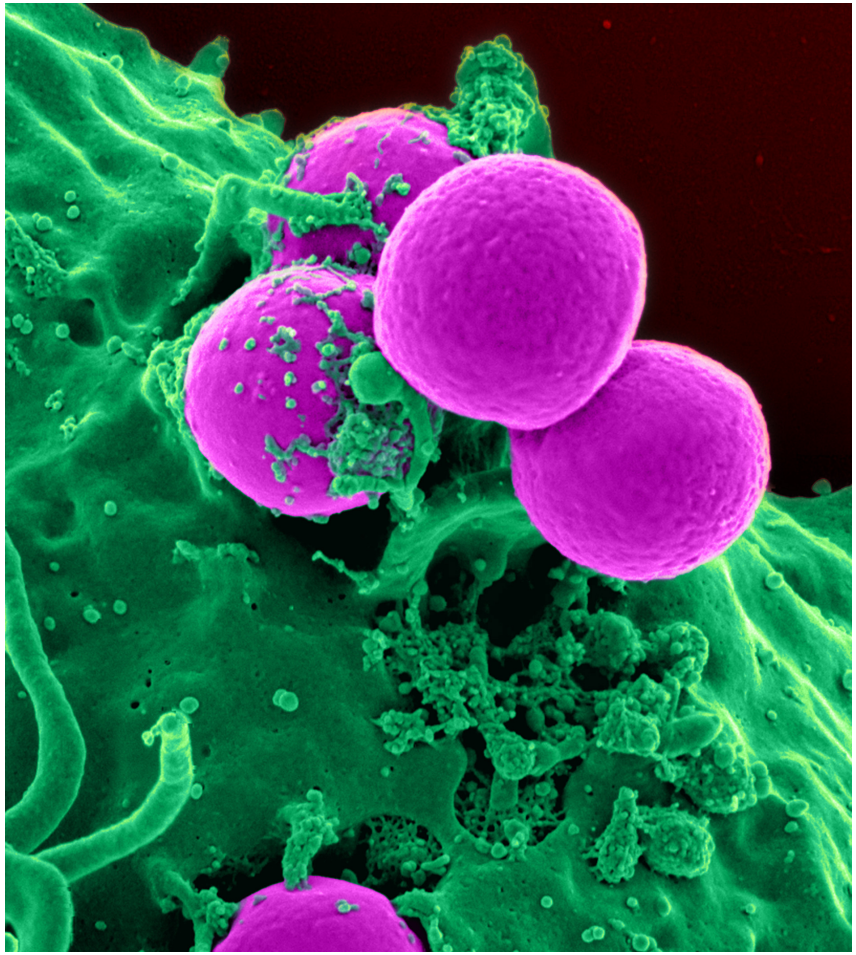
- Overtreatment of cellulitis – Why?
  - MRSA coverage?
  - Combination regimen?
- “Oral antibiotic treatment failure”
  - What does it mean?
- Strategies to mitigate outpatient failure

Why do we overtreat cellulitis?

1. Fear of CA-MRSA

- Cephalexin - active against MSSA and S. pyogenes
- The rise of community-acquired MRSA in 2000s

  → Use of alternative regimens

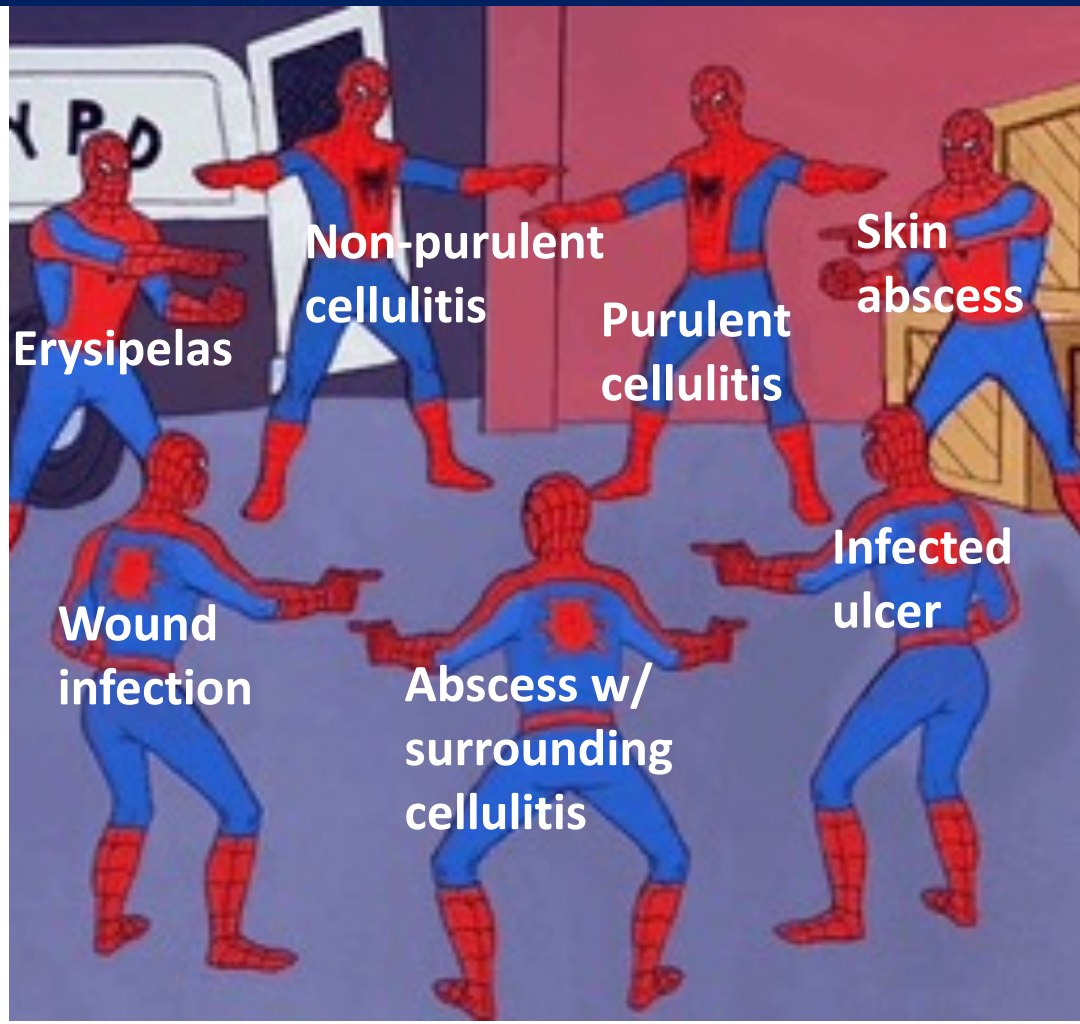


Gunderson CG. J Hosp Med. 2016;11(8):587-90.

Why do we overtreat cellulitis?

2. Confusion due to heterogeneity of SSTI

- "SSTI" is a broad umbrella term
- Different anatomy, different microbiology



Gunderson CG. J Hosp Med. 2016;11(8):587-90.

Why do we overtreat cellulitis?

3. Uncertainty about the microbiology of Non-purulent cellulitis

- Non-purulent cellulitis

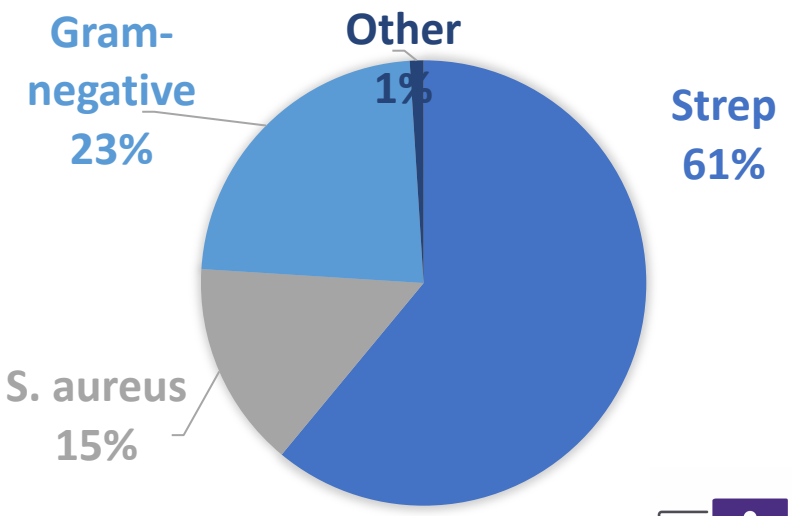
  = Non-culturable

- Microbiology of "SSTI":

  Strep - underrepresented

  MRSA - overrepresented

Systematic review of bacteremia in erysipelas & cellulitis



J Infect. 2012 Feb;64(2):148-55.

Overstatement by a landmark study?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Methicillin-Resistant *S. aureus* Infections among Patients in the Emergency Department

Gregory J. Moran, M.D., Anusha Krishnadasan, Ph.D., Rachel J. Gorwitz, M.D., M.P.H., Gregory E. Fosheim, M.P.H., Linda K. McDougal, M.S., Roberta B. Carey, Ph.D., and David A. Talan, M.D., for the *EMERGE*ncy ID Net Study Group*

METHODS

We enrolled adult patients with acute, purulent skin and soft-tissue infections presenting to 11 university-affiliated emergency departments during the month of

CONCLUSIONS

MRSA is the most common identifiable cause of skin and soft-tissue infections among patients presenting to emergency departments in 11 U.S. cities. When antimicrobial therapy is indicated for the treatment of skin and soft-tissue infections, clinicians should consider obtaining cultures and modifying empirical therapy to provide MRSA coverage.

- Despite eligibility for "purulent" SSTI and 81% of patients having abscess, the authors concluded that empiric MRSA coverage should be considered for (all?) SSTIs.

Moran et al. N Engl J Med 2006;355:666-74.

Most non-purulent cellulitis do not need MRSA coverage

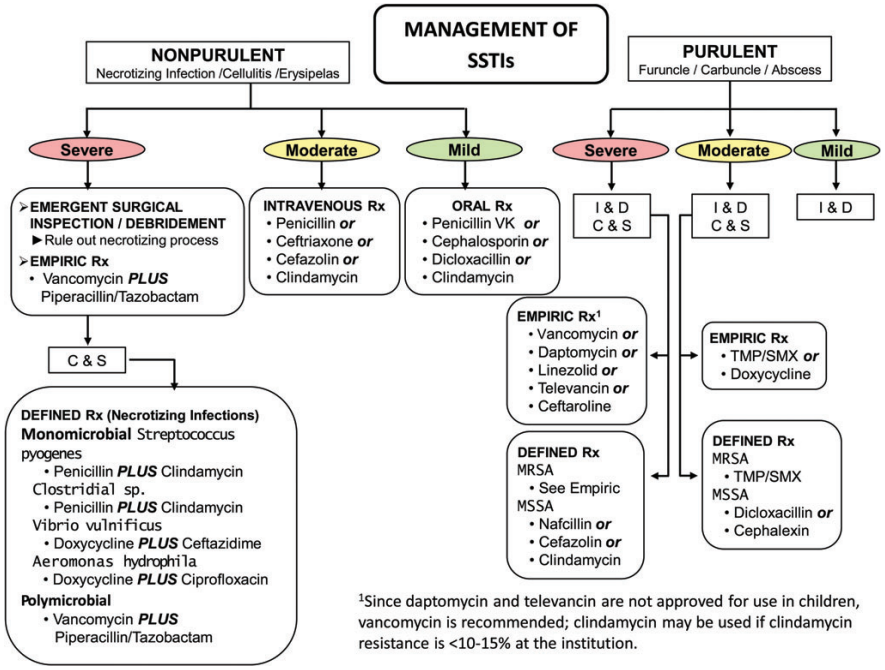
Two RCTs

1. 153 patients w/ **cellulitis without abscess**
   - Comparable cure rates among those treated with
     Cephalexin + TMP-SMX (85%) vs
     Cephalexin + placebo (82%) x 7-14 days.
2. 500 adults w/ **non-purulent** cellulitis in 5 EDs in US
   - Cephalexin + TMP/SMX 2DS tab BID x 7 days
   - Cephalexin + placebo x 7 days
     - In the per-protocol analysis, clinical cure achieved
       182 (84%) of 218 in the cephalexin + TMP-SMX group vs
       165 (86%) of 193 in the cephalexin + placebo group

Moran et al. JAMA. 2017;317(20):2088-2096.
Pallin et al. Clin Infect Dis. 2013;56(12):1754-62.

Why do we overtreat cellulitis?

4. Because guidelines say so



- Definition of severe SSTI includes:
  - Presence of SIRS (e.g., fever + tachy)
  - "Failed PO abx"

    → Justify vanc/zosyn🤯
- UpToDate® recommends:
  - Vancomycin if febrile 🤯

Stevens DL, et al. Clin Infect Dis 2014;59(2):e10–52.

“Outpatient ABX failure”

- What’s the definition? Used loosely in clinical practice
  - Hospitalization
  - Switch from PO to IV
  - Switch to a different class of PO abx
- Recent understanding of the natural course of cellulitis?
  - Visible improvement of skin findings can take >72 hrs
  - Local signs of inflammation improve with abx but still present by day 10
- Do they fail due to ABX choice?

Clin Infect Dis. 2016;63(8):1034.
Williams OM et al. Open Forum Infect Dis 2023 Oct.
(https://doi.org/10.1093/ofid/ofad488. opens in new tab)

Treatment fails because…

Outpatient treatment fails because of…

- Chronic, unresolved issues (chronic ulcer, chronic edema)
- Severity of the infection (fever, sepsis)
- or we made the wrong diagnosis!*

Predictors of empiric outpatient ABX failure in ED patients with cellulitis**

Predictor Variable	Adjusted OR	95% CI
Fever (T > 38°C) at triage	4.3	1.6–11.7
Chronic leg ulcers	2.5	1.1–5.2
Chronic edema or lymphedema	2.5	1.5–4.2
Prior cellulitis in the same area	2.1	1.3–3.5
Cellulitis at wound site	1.9	1.2–3.0

*Cutler TS, et al. J Hosp Med 2023 Mar (https://doi.org/10.1002/jhm.12977. opens in new tab)
**Peterson D, et al. Acad Emerg Med. 2014;21(5):526-31.

Obesity and inadequate dosing as risk for treatment failure

Table 3 Risk factors for clinical failure of complicated skin soft tissue infections.[a]

Risk factor	Univariate[b] OR (95% CI)	*P*-value	Multivariate[b] OR (95% CI)	*P*-value
Age ≥65 years old	0.54 (0.15–1.88)	0.33	–	–
Male	0.72 (0.37–1.49)	0.42	–	–
Weight ≥100 kg	2.09 (1.04–1.71)	0.03	5.20 (1.49–18.21)	0.01
Body mass index (BMI) ≥40	1.79 (0.82–3.89)	0.14	4.10 (1.21–13.84)	0.02
Diabetes	1.28 (0.62–2.66)	0.51	–	–
Immunosuppression	1.42 (0.49–4.16)	0.52	–	–
Renal disease	0.76 (0.29–1.96)	0.57	–	–
Intravenous drug use	1.21 (0.54–2.70)	0.64	–	–
Length of hospital stay ≥7 days	1.25 (0.43–3.60)	0.69	–	–
Antibiotics in last 90 days	3.99 (1.83–8.70)	< 0.01	2.98 (1.10–8.10)	0.03
Hospital admission in last 90 days	2.26 (1.11–4.62)	0.03	0.93 (0.36–2.39)	0.88
Incision & drainage or debridement	0.78 (0.39–1.58)	0.49	–	–
MRSA on culture	1.34 (0.53–3.38)	0.53	–	–
Inadequate empiric therapy	4.88 (1.34–17.80)	0.02	9.25 (1.87–45.73)	<0.01
Low empiric dose	1.85 (0.87–3.96)	0.11	2.01 (0.84–4.77)	0.11
Low discharge dose	2.75 (1.19–6.34)	0.02	3.64 (1.41–9.41)	<0.01
Duration of therapy ≥7 days	2.50 (0.84–7.48)	0.10	3.27 (0.93–11.55)	0.07

MRSA = Methicillin-resistant *Staphylococcus aureus*.

[a] Risk factors were only assessed in patients with evaluable outcomes ($n = 106$).

[b] Univariate and multivariate logistic regression analyses. Variables with a *P*-value <0.2 upon univariate logistic regression analysis were included in the multivariate analysis.

*Insufficient empiric therapy also identified as a predictor, but prob a small contribution overall

Halilovic J, et al. J Infect. 2012;65(2):128-34.

Strategies to improve management of cellulitis

- ✓Correct diagnosis
  - Purulent vs Non-purulent
- ✓Focus on adequate dosing
- ✓Recognize patient's comorbidities that put them at high risk for treatment failure
- ✓Rephrase "PO abx failure"

Dosing - High-dose cephalexin?

- An RCT that showed similar cure rates among those treated with cephalexin + TMP-SMX (85%) vs those treated with cephalexin alone (82%)
  - Higher, weight-based Cephalexin dosing
    <60 kg: 500 mg 4 times daily
    60–80 kg: 1000 mg 3 times daily
    >80 kg: 1000 mg 4 times daily
  - Diarrhea 34%, nausea 18%, vomiting 11%

- A pilot RCT comparing high vs standard dose
  - 1000mg BID vs. 500mg QID (for *7 days*)
  - 134 pts recruited
  - Treatment failure in 3% high, 14% standard dose
  - More AEs in high-dose (GI)

Yadav K, et al. CJEM. 2023 Jan;25(1):22-30.
Clin Infect Dis. 2013;56(12):1754-62.

Oral abx choices

	MSSA	MRSA	Group A Strep	Dosing
Amoxicillin			++++	500 mg TID
Cephalexin	++++		++++	500mg QID 1000mg BID
Trim/sulfa	++++	++++	???	1-2 DS BID
Clindamycin (Inducible resistance)	++++	++	↑↑ Resistance	300mg TID
Doxycycline	++++	++++	Reported resistance	100mg BID
Linezolid	++++	++++	++++	600 mg BID

Slide adapted from Jeannie Chan

TMP/SMX & Strep – Myth debunked

- The common misunderstanding and traditional teaching "**TMP/SMX is inactive against S. pyogenes**"

  --> using TMP/SMX + β-lactams in combination for SSTI

  - TMP/SMX prevents folic acid synthesis and, thus, the biosynthesis of the nucleic acid thymidine.
  - Agar used for in vitro cultures of streptococci previously contained thymidine, serving as an exogenous source to *S. pyogenes*
  - When tested appropriately using currently recommended thymidine-depleted media, all US isolates 2020-2021 S to TMP/SMX

Clin Infect Dis 2023;77(8):1120–5 (https://doi.org/10.1093/cid/ciad357)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 19, 2015 VOL. 372 NO. 12

Clindamycin versus Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Infections

Loren G. Miller, M.D., M.P.H., Robert S. Daum, M.D., C.M., C. Buddy Creech, M.D., M.P.H., David Young, M.D., Michele D. Downing, R.N., M.S.N., Samantha J. Eells, M.P.H., Stephanie Pettibone, B.S., Rebecca J. Hoagland, M.S., and Henry F. Chambers, M.D., for the DMID 07-0051 Team*

Patients:

- 524 outpatients (30% children) with uncomplicated skin infections who had cellulitis, abscesses >5cm in diameter or both randomized to clindamycin or TMP-SMX
- Cellulitis (53%); Abscess (31%), Mixed (16%)

Microbiology:

- No cultures (44%)
- MRSA (32%); MSSA (10%)
- GAS (2%)

Slide adapted from Jeannie Chan

Clinical Cure

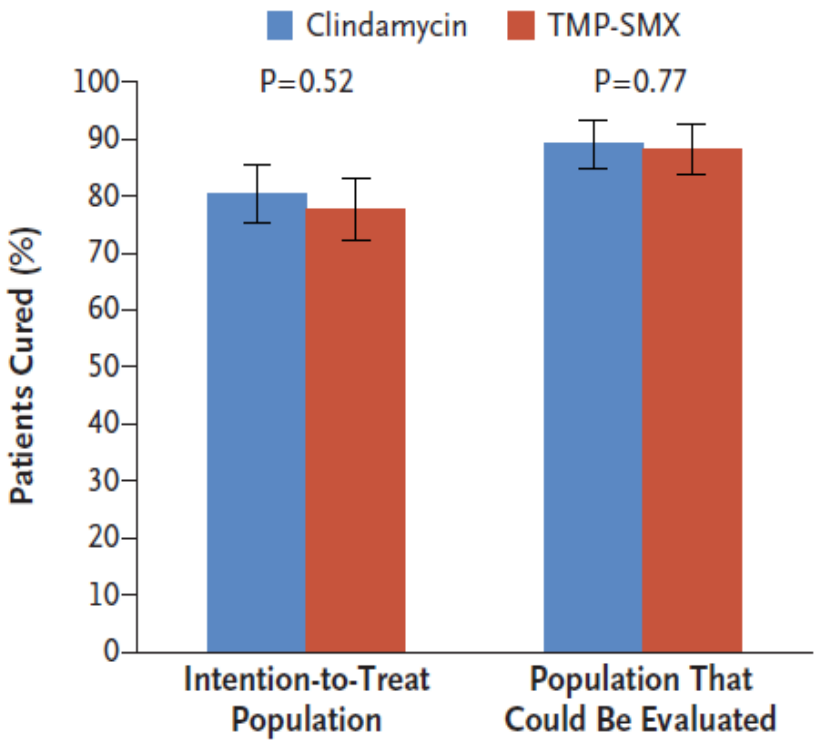


Figure 2. Comparison of the Efficacy of Clindamycin and TMP-SMX in Patients with Uncomplicated Skin Infection.

- No significant difference in subgroups of abscess vs. cellulitis
- TMP-SMX alone is sufficient for uncomplicated skin infection

Slide adapted from Jeannie Chan

Moving away from Clindamycin

1. Not a good empiric choice for cellulitis any more (↑↑ GAS resistance)

Clinda Susceptibility (HMC)	
GAS	49% (in 2021)
MSSA	82% (in 2023)
MRSA	74% (in 2023)

2. Highest risk of CDI among oral ABX
3. β-lactam allergy?
   -> Can cefazolin be used?

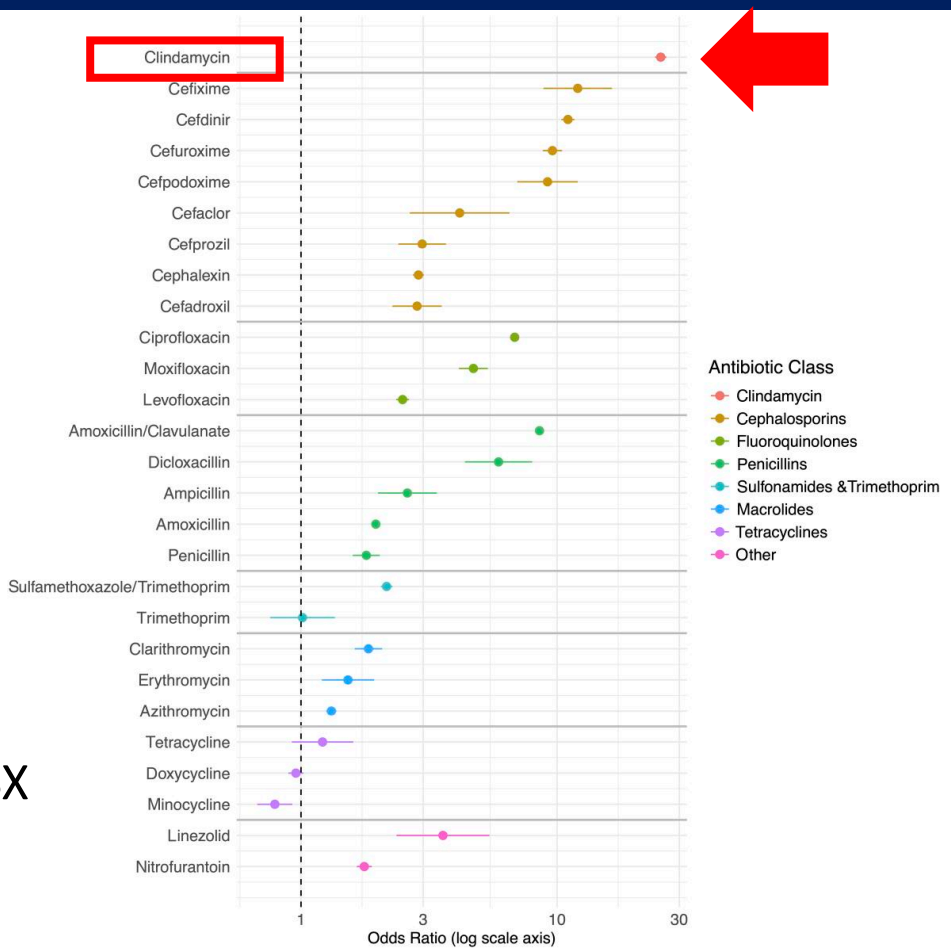


Figure 1. Visual comparison of effect estimates across antibiotic types, grouped by antibiotic class. Point estimates are depicted by the circle and 95% credible intervals by the line segments. Exact values can be found in Table 2.

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

Takeaways

Non-purulent cellulitis	Purulent cellulitis Skin abscess MRSA risk factors
1. Cephalexin	**1. TMP/SMX**
2. TMP/SMX	2. Doxy + Amoxicillin
3. Linezolid	3. Linezolid