Christopher Vought, PharmD Candidate 2020
April Yarbrough, PharmD, BCPS; Peds ID and Stewardship Pharmacist

# ALTERNATIVES TO VANCOMYCIN FOR MRSA INFECTIONS

## THE HISTORY OF VANCOMYCIN: [1]

In the 1950's, a campaign to discover compounds with activity against drug resistant organisms was launched by Eli Lilly. Soon, a compound was discovered with impressive activity against these organisms, and researchers quickly began investigating the compound's antibiotic capabilities. In vitro studies and animal testing proved positive, and reports of its efficacy were sent to the FDA. Due to high demand for a broad-spectrum antibiotic and a lack of an effective approved alternative, the compound was approved and named Vancomycin in 1958. Shortly after approval, practitioners nationwide began using vancomycin in everyday practice.

During the clinical trials, few serious adverse reactions were noted. The most common reaction was redness, chills, and irritation shortly after infusion, and were not considered more harmful than a typical infusion reaction. With an increase in vancomycin use, other reactions began occurring that were not documented in clinical trials. The most significant of these was ototoxicity. This was originally thought to occur only in patients with renal impairment, because of the increased vancomycin concentrations in these patients compared to those with normal renal function. It was also noted that as vancomycin dose was decreased, an improvement in hearing ability was noted, suggesting a correlation with vancomycin dose and level of toxicity. While the dose-related phenomenon is a cause of ototoxicity, the high occurrence of ototoxicity during this period was later attributed to impurities in the powder for reconstitution form that was administered at that time. Once a more purified commercial product was formed, ototoxicity and skin reactions occurred less frequently. Less commonly, nephrotoxicity was noted in approximately 5% of patients, and this occurrence was noted to be higher with concomitant aminoglycoside use. Like ototoxicity, nephrotoxicity was noted to be reversible upon dose reduction. In response to the rise in adverse events associated with the drug, vancomycin was considered a less-safe alternative to conventional treatments at the time. Its use was then reserved for those patients who had beta-lactam allergies, or for use against organisms that were known to be resistant to other agents.

However, the vancomycin hiatus did not last long. Beginning in the 1980s and continuing over the next 20 years, the use of vancomycin increased 100-fold. This spike is attributed to a rise in cases of pseudomembranous enterocolitis, which is commonly caused by vancomycin susceptible organisms like *Clostridium dificile* and *Staphylococcus aureus*. Oral vancomycin was frequently used in these cases, and by 1987 had attributed the evolution of vancomycin resistant enterococcus (VRE) species. Another cause was the ever-increasing amount of drug resistant organisms that developed as a result of frequent antibiotic use, including PRSP and MRSA.

## VANCOMYCIN TODAY: [2]

After 50 years, intravenous vancomycin is still considered the first line treatment for many MRSA infections, and as empiric treatment in suspected MRSA infections. The most common of these are skin and soft tissue infections, bacteremia, endocarditis, and bone/joint infections. In its oral form, it is also still treatment of choice for *C. difficile* infections. In many cases, vancomycin use is contraindicated or questionable due to comorbid conditions, drug-drug interactions or reactions, and acute events during treatment such as acute kidney injury, Red Man Syndrome, and anaphylaxis. Luckily, there are more recently developed drugs considered equal or are proven noninferior in clinical trials[5] to vancomycin as treatment in certain instances, as indicated below.

Christopher Vought, PharmD Candidate 2020
April Yarbrough, PharmD, BCPS; Peds ID and Stewardship Pharmacist

## Antibiotics with Activity Against MRSA

| Drug | Dosing and Duration* | Indications |
|---|---|---|
| **Bactrim (Oral and IV)** | 8 to 12 mg TMP/kg/day in divided doses BID | SSTI, bone/joint Infections, CNS infections (abscess), diabetic foot infections, septic arthritis, meningitis |
| **Doxycycline (Oral)** | Children ≥8 years old and adolescents:<br>≤45 kg: 2 mg/kg/dose BID for 5 to 10 days.<br>>45 kg: 100 mg BID for 5 to 10 days. | SSTI, bone/joint infections |
| **Minocycline (Oral and IV)** | Children >8 years old and adolescents:<br>4mg/kg initially then 2mg/kg/dose BID for 5-10 days;<br>3-6 months for joint infections | SSTI, prosthetic joint infections |
| **Clindamycin** (Oral and IV)** | IV: 25 to 40 mg/kg/day in divided doses TID<br>Oral: 30 to 40 mg/kg/day in divided doses TID<br>Complicated SSTI: 7-14 days;<br>Uncomplicated SSTI: 5-10 days; | SSTI, bacteremia, bone/joint infections, pneumonia, diabetic foot infection |
| **Linezolid*** (Oral and IV)** | <5 years old: 8mg/kg/dose Q8H (uncomplicated SSTI);<br><12 years old: 10mg/kg/dose Q8H;<br>≥12 years old: 600mg Q12H | SSTI, bacteremia, pneumonia, bone/joint infections, diabetic foot infection, CNS infections (abscess), meningitis, prosthetic joint infections, catheter infections, |
| **Ceftaroline (IV only)** | <2months: 6mg/kg/dose Q8H<br>≥2months to <2 years: 8mg/kg/dose Q8H<br>≥2 years to <18 years and ≤33kg: 12mg/kg/dose Q8H;<br>>33kg: 400mg Q8H or 600mg Q12H | SSTI, pneumonia, Cystic Fibrosis exacerbation by MRSA |
| **Daptomycin[+] (IV only)** | ≤6 years: 12 mg/kg/dose Q24H<br>7 to 11 years: 9 mg/kg/dose Q24H.<br>≥12 years and <17 years: 7 mg/kg/dose Q24H<br>≥18 years: 6 mg/kg/dose Q24H | SSTI, bone/joint infections, bacteremia, CSF infection, diabetic foot infections, endocarditis, CNS infection (abscesses), meningitis |
| **Dalbavancin[++] (IV only)** | Single-dose regimen:<br>≥3 months to <6 years: 22.5 mg/kg as a single dose<br>≥6 years to <18 years: 18 mg/kg as a single dose<br>Two-dose regimen:<br>≥3 months to <6 years: IV: 15 mg/kg as a single dose on day 1 then 7.5 mg/kg as a single dose on day 8.<br>≥6 years to <18 years: 12 mg/kg as a single dose on day 1 then 6 mg/kg as a single dose on day 8 | Acute SSTI |
| **Telavancin (IV only)** | 10mg/kg/dose once daily for 7-21 days | SSTI, bacteremia, HAP/VAP |
| **Tigecycline (IV only)** | 8 to 11 years: 1.2 to 2 mg/kg/dose Q12H<br>≥12 years: IV: 50 mg Q12H | Should only be used as a "last resort" when Vancomycin and other options are exhausted. |

*Unless otherwise noted, duration depends on severity of infection. Bone/joint infections, CNS infections, severe pneumonia, etc. commonly require 3-6 weeks of treatment and the higher end of the dosing range. Less severe infections such as bacteremia, mild/moderate SSTI's, mild/moderate pneumonia, etc. require shorter durations (1-2 weeks).

**Empiric Clindamycin should only be used in the setting of low regional Clindamycin resistance and low probability of inducible resistance by MRSA.[2]

*** Linezolid is bacteriostatic against staphylococci and enterococci and is therefore not considered first line for MRSA Bacteremia/Endocarditis.

[+] Daptomycin has proven beneficial as an alternative to first line therapy for high inoculum MRSA infections.[5] It is also a guideline[6] recommended therapy in bacteremia with previous vancomycin failure.

[++] Dalbavancin: a newer generation glycopeptide recently approved. Its mechanism is similar to vancomycin in that it is a bactericidal agent that prevents peptidoglycan cross-linking and therefore inhibits cell wall synthesis.
Of note: Dalbavancin's half-life is 346 hours, allowing for once weekly dosing. Due to the high cost of this new medication, it is considered non-formulary, and is only prescribed in the outpatient setting and administered by home health, infusion clinics, etc.

Christopher Vought, PharmD Candidate 2020
April Yarbrough, PharmD, BCPS; Peds ID and Stewardship Pharmacist

## IN SUMMARY

The purpose of this article is to highlight the less-frequently prescribed drugs that are of use in MRSA infections. Vancomycin remains the treatment of choice for most of these infections, but there are many indications when another option is also appropriate, namely in step down therapy or as an alternative due to adverse reactions. It is important to remember that vancomycin will only continue to work if healthcare providers prescribe it responsibly. Overprescribing leads to resistance, and as with all antibiotics, the more diligently they are prescribed, the longer we will be able to use them to save patient's lives.

### Alternatives to Vancomycin for MRSA

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E | T | T | I | G | E | C | Y | C | L | I | N | E | M |
| D | I | L | O | Z | I | D | E | T | N | C | Y | E | I |
| G | E | N | T | A | M | I | C | I | N | A | D | N | N |
| E | N | I | L | C | Y | C | Y | X | O | D | A | I | O |
| F | T | B | L | C | S | E | B | M | L | I | L | Z | C |
| S | C | I | I | E | T | I | A | I | I | E | B | A | Y |
| V | M | C | N | I | E | C | C | R | A | I | A | I | C |
| I | C | O | F | F | C | Y | I | T | O | N | V | D | L |
| D | D | I | C | Y | T | N | M | C | Y | E | A | A | I |
| C | Y | N | C | E | M | A | N | A | O | I | N | F | N |
| C | O | B | C | Z | F | E | R | B | D | A | C | L | E |
| N | Y | D | B | Z | A | A | N | N | I | L | I | U | N |
| Y | Z | T | E | L | A | V | A | N | C | I | N | S | A |
| I | G | D | I | L | O | Z | E | N | I | L | D | Z | G |

BACTRIM
DOXYCYCLINE
TIGECYCLINE
MINOCYCLINE
DALBAVANCIN
LINEZOLID
TEDIZOLID
SULFADIAZINE
TELAVANCIN
GENTAMICIN

## VANCOMYCIN FUN FACTS: [1]

- Vancomycin was discovered in a sample of dirt isolated by a missionary in Borneo in 1952.
- It was originally given the name "Mississippi Mud" due to its brown color in the early stages of development, before it was purified for animal trials and human use.
- The name Vancomycin was chosen because of its ability to "vanquish" many types of organisms.

## REFERENCES:

1. Levine DP. Vancomycin: A History. Clinical Infectious Diseases: Infectious Diseases Society of America 2006; 42:S5-12. Available from: https://academic.oup.com/cid/article-abstract/42/Supplement_1/S5/275962
2. VanEperen AS, Segreti J: Empirical Therapy in Methicillin-Resistant Staphylococcus Aureus infections: An Up-To-Date Approach. Journal of Infection and Chemotherapy 2016; 22:351-359. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27066882
3. Bactrim (2019 Nov 18); Clindamycin (2019 Dec 4); Doxycycline (2019 Dec 5); Minocycline (2019 Nov 28); Linezolid (2019 Nov 21); Ceftaroline (2019 Dec 2); Daptomycin (2019 Nov 28); Tigecycline (2019 Nov 17); Gentamicin (2019 Nov 6) in: Lexi-Drugs, Lexi-Comp [AUHSOP Intranet]. Hudson (OH): Lexi-Comp/Wolters Kluwer Health [cited 2019 Dec 2]. Available from: http://online.lexi.com/lco/action/home
4. Kaushik A, Kest H. Pediatric Methicillin-Resistant Staphylococcus aureus Osteoarticular Infections. Microorganisms. 2018;6(2):40. Published 2018 May 4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6027280/
5. Choo EJ, Chambers HF. Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia. *Infect Chemother*. 2016;48(4):267–273. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5204005/
6. Liu C, Bayer A, Cosgrove SE, Daum, RS, et. al, Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children, *Clinical Infectious Diseases*, Volume 52, Issue 3, 1 February 2011, Pages e18–e55. Available from: https://academic.oup.com/cid/article/52/3/e18/306145