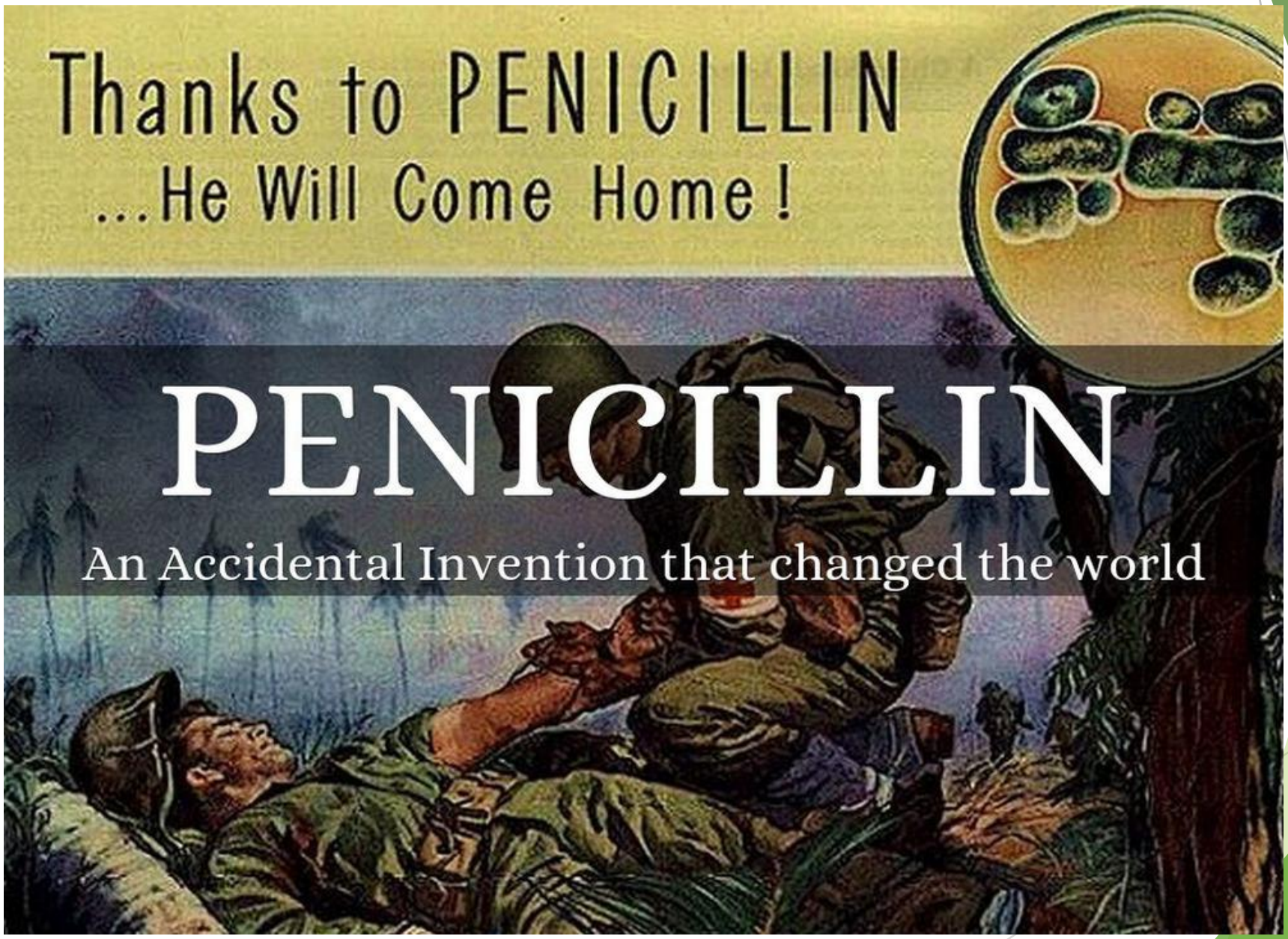
Vai Trò Của Linezolid Trong Điều Trị MRSA

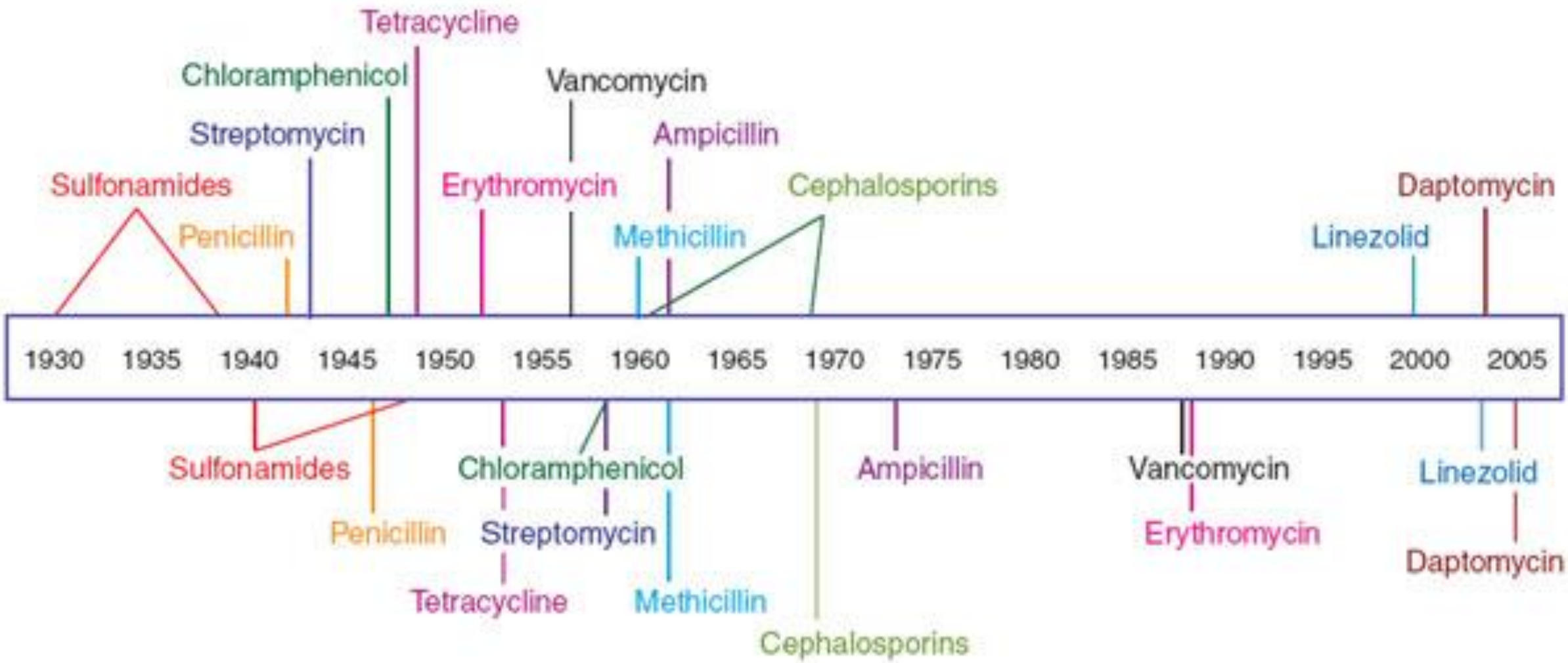
BS Nguyễn Phương Thùy

TỔNG QUAN

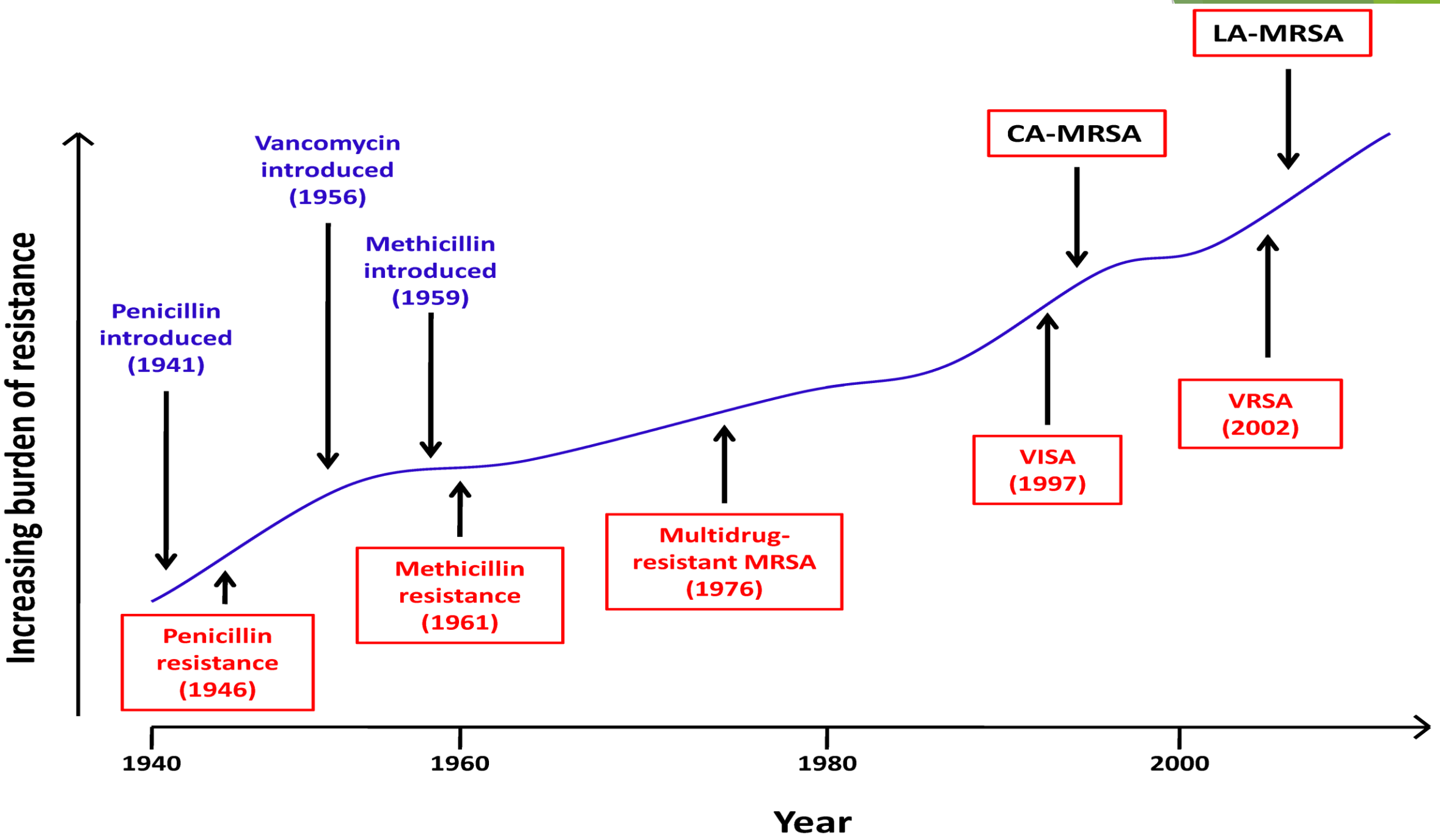
- 1.MRSA
- 2. Cấu trúc và cơ chế tác đông của linezolid
- 3.Vai trò linezolid trong điều trị MRSA
- 4. Kết luận


Thanks to PENICILLIN
...He Will Come Home!
PENICILLIN
An Accidental Invention that changed the world

Antibiotic deployment



Antibiotic resistance observed


Increasing burden of resistance
Penicillin introduced (1941)
Vancomycin introduced (1956)
Methicillin introduced (1959)
Penicillin resistance (1946)
Methicillin resistance (1961)
Multidrug-resistant MRSA (1976)
VISA (1997)
CA-MRSA
VRSA (2002)
LA-MRSA
1940
1960
1980
2000
Year

MRSA

- Methicillin-resistant *Staphylococcus aureus* (MRSA) was first identified in the United Kingdom in 1961, only 2 years after the introduction of methicillin
- Over the next few decades MRSA became established in hospitals throughout North America and Europe, and subsequently Northeast, then Southeast, Asia
- Extensive use of vancomycin to treat infections caused by MRSA led to the emergence of vancomycin- and methicillin-resistant *S. aureus* (VRSA).
- To date, 11 VRSA strains, which have acquired the ***vanA*** operon from glycopeptide-resistant enterococci, have been isolated in the United States (***Staphylococcus aureus* VRSA-11B Is a Constitutive Vancomycin-Resistant Mutant of Vancomycin-Dependent VRSA-11A -** Antimicrob Agents Chemother. 2012 Sep)

Antimicrobial	Susceptibilities rate (%)			*P*-value
	Overall (*n* = 107)	MSSA (*n* = 58)	MRSA (*n* = 49)	
Penicillin	–	7 (12.1)	–	–
Gentamicin	104 (97.2)	56 (96.6)	48 (98.0)	1.000
Kanamycin	80 (74.8)	46 (79.3)	34 (69.4)	0.239
Tobramycin	91 (85.0)	45 (77.6)	46 (93.9)	0.019
Fosfomycin-trometamol	42 (39.3)	24 (41.4)	18 (36.7)	0.624
Erythromycin	52 (48.6)	43 (74.1)	9 (18.4)	0.000
Tetracycline	92 (86.0)	50 (86.2)	42 (85.7)	0.942
Teicoplanin	107 (100)	58 (100)	49 (100)	–
Minocycline	106 (99.1)	58 (100)	48 (98.0)	0.458
Ciprofloxacin	90 (84.1)	55 (94.8)	35 (71.4)	0.001
Clindamycin[a]	74 (69.2)	54 (93.1)	20 (40.8)	0.000
Sulfamethoxazole-trimethoprim	107 (100)	58 (100)	49 (100)	–
Chloramphenicol	103 (96.3)	57 (98.3)	46 (93.9)	0.494
Rifampicin	107 (100)	58 (100)	49 (100)	–
Quinupristin-dalfopristin	107 (100)	58 (100)	49 (100)	–
Linezolid	107 (100)	58 (100)	49 (100)	–
Vancomycin[b]	107 (100)	58 (100)	49 (100)	–

Linezolid

- Linezolid was discovered in the mid 1990s and was approved for commercial use in 2000
- Linezolid is a member of the oxazolidinone class of medications. The oxazolidinones are protein synthesis inhibitors: they stop the growth and reproduction of bacteria by disrupting translation of messenger RNA (mRNA) into proteins in the ribosome.
- As a protein synthesis inhibitor, it affects the ability of bacteria to produce protein. Linezolid binds to the 23S portion of the 50S subunit (the center of peptidyl transferase activity),close to the binding sites of chloramphenicol, lincomycin, and other antibiotics. Due to this unique mechanism of action, cross-resistance between linezolid and other protein synthesis inhibitors is highly infrequent or nonexistent.
- Linezolid is metabolized in the liver, by oxidation of the morpholine ring, without involvement of the cytochrome P450 system. Clearance of linezolid varies with age and gender; it is fastest in children (which accounts for the shorter half-life), and appears to be 20% lower in women than in men

Spectrum of activity

- Linezolid is effective against all clinically important Gram-positive bacteria—those whose cell wall contains a thick layer of peptidoglycan and no outer membrane
- *Enterococcus faecium* and *Enterococcus faecalis* (including VRE)
- *Staphylococcus aureus* (MRSA)
- *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, the *viridans* group streptococci,
- *Listeria monocytogenes*
- *Corynebacterium* species

Clinical Infectious Diseases

IDSA Infectious Diseases Society of America

hivma hiv medicine association

No cover image available

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1 March 2012

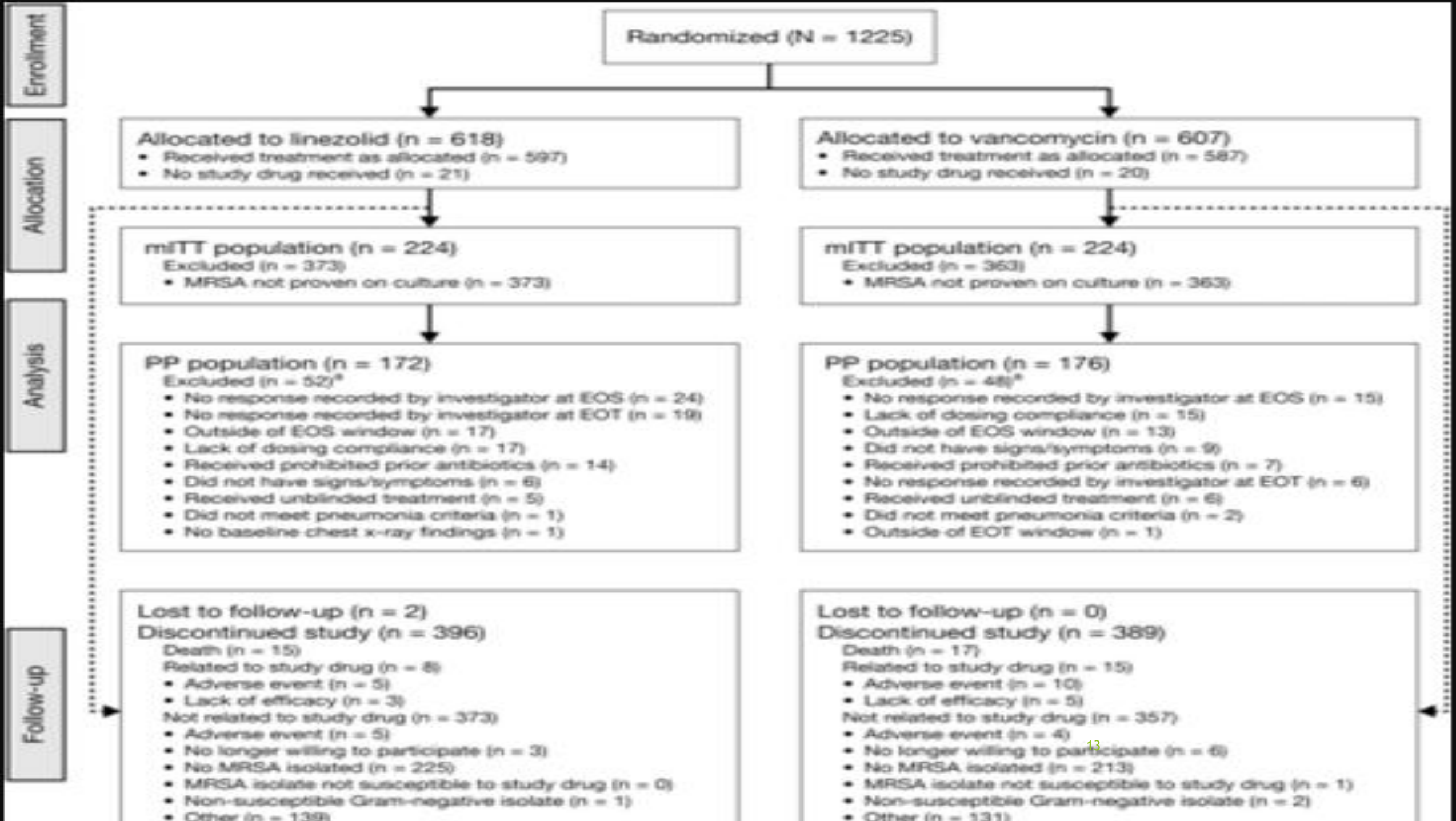
Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study FREE

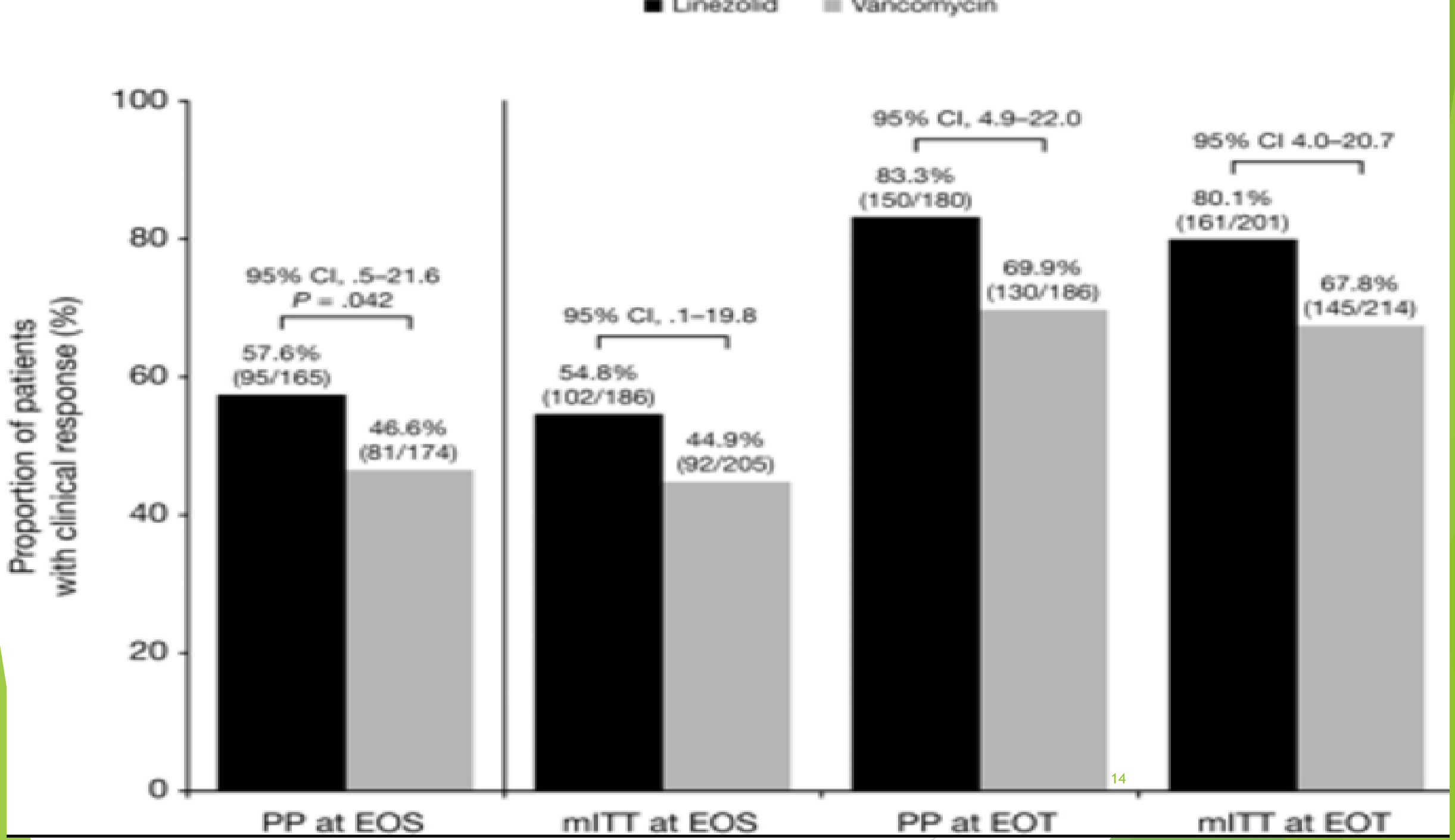
Richard G. Wunderink; Michael S. Niederman; Marin H. Kollef; Andrew F. Shorr; Mark J. Kunkel; Alice Baruch; William T. McGee; Arlene Reisman; Jean Chastre

Clin Infect Dis (2012) 54 (5): 621-629. **DOI:** https://doi.org/10.1093/cid/cir895

Published: 12 January 2012 **Article history** ▾

- ***Background.*** Post hoc analyses of clinical trial data suggested that linezolid may be more effective than vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia. This study prospectively assessed efficacy and safety of linezolid, compared with a dose-optimized vancomycin regimen, for treatment of MRSA nosocomial pneumonia.
- ***Methods.*** This was a prospective, double-blind, controlled, multicenter trial involving hospitalized adult patients with hospital-acquired or healthcare–associated MRSA pneumonia. Patients were randomized to receive intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7–14 days. Vancomycin dose was adjusted on the basis of trough levels. The primary end point was clinical outcome at end of study (EOS) in evaluable per-protocol (PP) patients. Prespecified secondary end points included response in the modified intent-to-treat (mITT) population at end of treatment (EOT) and EOS and microbiologic response in the PP and mITT populations at EOT and EOS. Survival and safety were also evaluated.

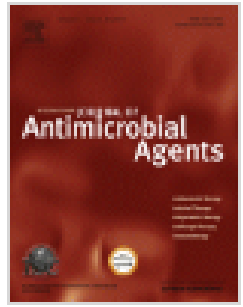

Enrollment
Allocation
Analysis
Follow-up
Randomized (N = 1225)
Allocated to linezolid (n = 618)
• Received treatment as allocated (n = 597)
• No study drug received (n = 21)
Allocated to vancomycin (n = 607)
• Received treatment as allocated (n = 587)
• No study drug received (n = 20)
mITT population (n = 224)
Excluded (n = 373)
• MRSA not proven on culture (n = 373)
mITT population (n = 224)
Excluded (n = 363)
• MRSA not proven on culture (n = 363)
PP population (n = 172)
Excluded (n = 52)*
• No response recorded by investigator at EOS (n = 24)
• No response recorded by investigator at EOT (n = 19)
• Outside of EOS window (n = 17)
• Lack of dosing compliance (n = 17)
• Received prohibited prior antibiotics (n = 14)
• Did not have signs/symptoms (n = 6)
• Received unblinded treatment (n = 5)
• Did not meet pneumonia criteria (n = 1)
• No baseline chest x-ray findings (n = 1)
PP population (n = 176)
Excluded (n = 48)*
• No response recorded by investigator at EOS (n = 15)
• Lack of dosing compliance (n = 15)
• Outside of EOS window (n = 13)
• Did not have signs/symptoms (n = 9)
• Received prohibited prior antibiotics (n = 7)
• No response recorded by investigator at EOT (n = 6)
• Received unblinded treatment (n = 6)
• Did not meet pneumonia criteria (n = 2)
• Outside of EOT window (n = 1)
Lost to follow-up (n = 2)
Discontinued study (n = 396)
Death (n = 15)
Related to study drug (n = 8)
• Adverse event (n = 5)
• Lack of efficacy (n = 3)
Not related to study drug (n = 373)
• Adverse event (n = 5)
• No longer willing to participate (n = 3)
• No MRSA isolated (n = 225)
• MRSA isolate not susceptible to study drug (n = 0)
• Non-susceptible Gram-negative isolate (n = 1)
• Other (n = 139)
Lost to follow-up (n = 0)
Discontinued study (n = 389)
Death (n = 17)
Related to study drug (n = 15)
• Adverse event (n = 10)
• Lack of efficacy (n = 5)
Not related to study drug (n = 357)
• Adverse event (n = 4)
• No longer willing to participate (n = 6)
• No MRSA isolated (n = 213)
• MRSA isolate not susceptible to study drug (n = 1)
• Non-susceptible Gram-negative isolate (n = 2)
• Other (n = 131)


Linezolid
Vancomycin
Proportion of patients with clinical response (%)
100
80
60
40
20
0
95% CI, .5–21.6
P = .042
57.6% (95/165)
46.6% (81/174)
95% CI, .1–19.8
54.8% (102/186)
44.9% (92/205)
95% CI, 4.9–22.0
83.3% (150/180)
69.9% (130/186)
95% CI 4.0–20.7
80.1% (161/201)
67.8% (145/214)
PP at EOS
mITT at EOS
PP at EOT
mITT at EOT

- ***Results***. Of 1184 patients treated, 448 (linezolid, n = 224; vancomycin, n = 224) were included in the mITT and 348 (linezolid, n = 172; vancomycin, *n* = 176) in the PP population. In the PP population, 95 (57.6%) of 165 linezolid-treated patients and 81 (46.6%) of 174 vancomycin-treated patients achieved clinical success at EOS (95% confidence interval for difference, 0.5%–21.6%; *P* = .042). All-cause 60-day mortality was similar (linezolid, 15.7%; vancomycin, 17.0%), as was incidence of adverse events. Nephrotoxicity occurred more frequently with vancomycin (18.2%; linezolid, 8.4%).
- ***Conclusions***. For the treatment of MRSA nosocomial pneumonia, clinical response at EOS in the PP population was significantly higher with linezolid than with vancomycin, although 60-day mortality was similar.

International Journal of Antimicrobial Agents

Volume 41, Issue 5, May 2013, Pages 426–433



Linezolid versus vancomycin for meticillin-resistant *Staphylococcus aureus* infection: a meta-analysis of randomised controlled trials

Mao Mao An[a], Hui Shen[a], Jun Dong Zhang[a], Guo Tong Xu[a,], , , Yuan Ying Jiang[a, b,] ,

- A meta-analysis of randomised controlled trials (RCTs) identified in PubMed, the Cochrane Library and Embase was performed. Nine RCTs, involving 5249 patients, were included in the meta-analysis. The results indicated that linezolid was associated with superior efficacy compared with vancomycin for MRSA-related infection in term
- Clinical treatment success [8 RCTs, 2174 patients, odds ratio (OR) = 1.77, 95% confidence interval (CI) 1.22–2.56]
- Microbiological treatment success (9 RCTs, 1555 patients, OR = 1.78, 95% CI 1.22–2.58)
- Although no difference was found regarding the overall incidence of drug-related adverse events (AEs) and serious AEs (SAEs) between the linezolid and vancomycin therapy groups (drug-related AEs, 8 RCTs, 5034 patients, OR = 1.20, 95% CI 0.98–1.48; SAEs, 5 RCTs, 2072 patients, OR = 1.00, 95% CI 0.74–1.36), the linezolid therapy group was associated with significantly fewer patients experiencing abnormal renal function
- This meta-analysis provides evidence that linezolid possesses significant advantages compared with vancomycin and may be a superior alternative for MRSA-related infection.

Linezolid versus vancomycin for treatment of resistant Gram-positive infections in children

KAPLAN, SHELDON L. MD; DEVILLE, JAIME G. MD; YOGEV, RAM MD; MORFIN, MA RAYO MD; WU, ELBA MD; ADLER, STUART MD; EDGE-PADBURY, BARBARA RPH; NABERHUIS-STEHOUWER, SHARON PhD; BRUSS, JON B. MD; THE LINEZOLID PEDIATRIC STUDY GROUP

Pediatric Infectious Disease Journal: August 2003 - Volume 22 - Issue 8 - pp 677-686
Original Studies

- Background. Pediatric infections caused by resistant Gram-positive infections are an increasing concern with limited treatment options. Linezolid, a new oxazolidinone, is active against staphylococci, streptococci and enterococci.
- Objective. To assess clinical efficacy and safety of linezolid vs vancomycin in antibiotic-resistant Gram-positive infections in children
- Design. Hospitalized children (birth to 12 years of age) with nosocomial pneumonia, complicated skin/skin structure infections, catheter-related bacteremia, bacteremia of unknown source or other infections caused by Gram-positive bacteria were randomized 2:1 to receive linezolid intravenously followed by oral linezolid or vancomycin and then by an appropriate oral agent. Treatment duration was 10 to 28 days.

N= 321	LINEZOLID (n=219)	VANCOMYCIN (n=102)	P
Clinical cure rates	79%	74%	0.36
Pathogen eradication rates			
MSSA	95%	94%	0.82
MRSA	88%	90%	0.89
Days of IV therapy	8.0 ± 4.8	10.9 ± 5.8	< 0.001
Drug-related adverse events	19%	34%	0.003

Conclusions. Linezolid was well-tolerated and as effective as vancomycin in treating serious Gram-positive infections in children

European Journal of Pediatrics

September 2014, Volume 173, Issue 9, pp 1179–1186

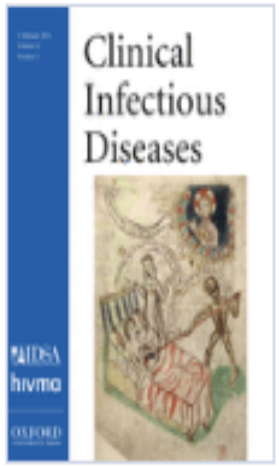
Efficacy and safety of linezolid for the treatment of infections in children: a meta-analysis

Authors Authors and affiliations

Maria Ioannidou, Fani Apostolidou-Kiouti, Anna-Bettina Haidich, Ioannis Niopas, Emmanuel Roilides

- This study aimed to evaluate the efficacy and safety of linezolid in children with infections caused by Gram-positive pathogens. A systematic search was conducted by two independent reviewers to identify published studies up to September 2013. The accumulated relevant literature was subsequently systematically reviewed, and a meta-analysis was conducted.
- Meta-analysis was conducted with random effects models because of heterogeneity across the trials. Two randomized controlled trials (RCTs), involving 815 patients, were included. Linezolid was slightly more effective than control antibiotic agents, but the difference was not statistically significant [odds ratio (OR) = 1.39, 95 % confidence interval (CI) 0.98–1.98]. Treatment with linezolid was not associated with more adverse effects in general (OR = 0.61, 95 % CI 0.25–1.48). Eradication efficiency did not differ between linezolid and control regimens, but the sample size for these comparisons was small

- *Conclusion*: The use of linezolid cannot be steadily supported from the results of the current meta-analysis. It appears to be slightly more effective than control antibiotic agents, but the difference was not significant, and the serious limitations present in this study restrict its use. Further studies providing evidence for clinical and microbiological efficacy of linezolid will support its use.



Volume 52, Issue 3
1 February 2011

Article Contents

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children FREE

Catherine Liu; Arnold Bayer; Sara E. Cosgrove; Robert S. Daum; Scott K. Fridkin; Rachel J. Gorwitz; Sheldon L. Kaplan; Adolf W. Karchmer; Donald P. Levine; Barbara E. Murray; ... Show more

Clin Infect Dis (2011) 52 (3): e18-e55. **DOI:** https://doi.org/10.1093/cid/ciq146

Published: 01 February 2011 **Article history ▾**

What is the management of skin and soft-tissue infections (SSTIs) in the era of community-associated MRSA (CA-MRSA)?

- In hospitalized children with cSSTI, vancomycin is recommended **(A-II).** If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) is an option if the clindamycin resistance rate is low (eg, <10%) with transition to oral therapy if the strain is susceptible **(A-II)**. Linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose PO/IV every 8 h for children <12 years of age is an alternative **(A-II)**.

What is the management of MRSA bacteremia and infective endocarditis?

- In children, vancomycin 15 mg/kg/dose IV every 6 h is recommended for the treatment of bacteremia and infective endocarditis **(A-II).** Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin 6–10 mg/kg/dose IV once daily may be an option **(C-III).** Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus **(B-III).**

What is the management of MRSA pneumonia?

- In children, IV vancomycin is recommended **(A-II).** If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) can be used as empirical therapy if the clindamycin resistance rate is low (eg, <10%) with transition to oral therapy if the strain is susceptible **(A-II)**. Linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose every 8 h for children <12 years of age is an alternative **(A-II)**

CONCLUSION

- In the United States, the indications for linezolid use approved by the U.S. Food and Drug Administration (FDA) are the treatment of vancomycin-resistant *Enterococcus faecium* infections, with or without bacterial invasion of the bloodstream; nosocomial pneumonia (hospital-acquired) and community-acquired pneumonia caused by *S. aureus* or *S. pneumoniae*; complicated skin and skin structure infections (cSSSI) caused by susceptible bacteria, including diabetic foot infection, unless complicated by osteomyelitis (infection of the bone and bone marrow); and *uncomplicated* skin and soft tissue infections caused by *S. pyogenes* or *S. aureus*. The manufacturer advises against the use of linezolid for community-acquired pneumonia or *uncomplicated* skin and soft tissue infections caused by MRSA. In the United Kingdom, pneumonia and cSSSIs are the only indications noted in the product labeling.
- Linezolid appears to be as safe and effective for use in children and newborns as it is in adults

- **Brand names** Linezolid is marketed by Pfizer under the trade names Zyvox (in the United States, United Kingdom, Australia, and several other countries), Zyvoxid (in Europe), and Zyvoxam (in Canada and Mexico)
- Generics are also available, such as Lenzomore (in India, by Morepen), Linospan (in India, by Cipla), Nezocin (in Pakistan, by Brookes), voxazoldin (in Egypt, by Rotabiogen), Lizomed (in India, as a dry syrup by Aglowmed), and Linzolid (in Bangladesh, by Incepta).
-

Tài Liệu Tham Khảo

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3421854/
- https://academic.oup.com/cid/article/54/5/621/325602/Linezolid-in-Methicillin-Resistant-Staphylococcus?searchresult=1
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- http://journals.lww.com/pidj/Abstract/2003/08000/Linezolid_versus_vancomycin_for_treatment_of.2.aspx
- http://journals.lww.com/pidj/Abstract/2001/05000/Linezolid_for_the_treatment_of_community__acquired.4.aspx
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- https://academic.oup.com/cid/article/56/9/1310/293355/The-Global-Spread-of-Healthcare-Associated

THANK YOU!