ABOD, Leila, ILNICKA, Natalia, MATYJA, Daria, SADLIK, Maria and ZUZIAK, Patrycja. Lefamulin - a recently developed antibiotic for treatment of community-acquired bacterial pneumonia (CABP). Journal of Education, Health and Sport. 2023;15(1):186-196. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.15.01.018
https://apcz.umk.pl/JEHS/article/view/45573
https://zenodo.org/record/8318305

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. L.p. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 07.08.2023. Revised: 24.08.2023. Accepted: 05.09.2023. Published: 07.09.2023.

Lefamulin - a recently developed antibiotic for treatment of community-acquired bacterial pneumonia (CABP)

Leila Abod[1*], Natalia Ilnicka[2], Daria Matyja[3], Maria Sadlik[4], Patrycja Zuziak[5]

[1]Jan Mikulicz-Radecki University Teaching Hospital Borowska 213, 50-556 Wrocław;

[2]Regional Specialist Hospital in Wroclaw, Research and Development Centre, H. Kaminski Street 73a, 51-124 Wroclaw, Poland;

[3]J. Gromkowski Regional Specialist Hospital Koszarowa 5, 51 - 149 Wrocław;

[4]Jan Mikulicz-Radecki University Teaching Hospital Borowska 213, 50-556 Wrocław;

[5]T. Marciniak Lower Silesian Specialist Hospital - Emergency Medicine Centre, Fieldorfa 2, 54-049 Wrocław;

[*]Corresponding Author

ABSTRACT

Introduction and aim. Nowadays, the increasing resistance of bacteria is a concerning and challenging issue in terms of effective treatment of bacterial infections. The amount of available antibiotics has been quite constant for many years. The search for substances alternative to older classes of drugs, among which resistance is growing, has been ongoing for years. One of the newly introduced available alternatives is lefamulin. The aim of this paper is to present the potential benefits of its use in comunity-acquired bacterial pneumonia (CABP).

Material and methods. A review of the available literature was performed by searching the PubMed and GoogleScholar databases using the following key words: lefamulin; BC3781; pleuromutilin; CABP; community acquired pneumonia.

Analysis of literature. Lefamulin is a bacteriostatic antibiotic from the group of pleuromutilins, which has a unique mechanism of action consisting in binding to the bacterial 50S ribosomal subunit in the peptidyl transferase center. Thanks to this, it rarely causes resistance among other groups of antibiotics and is characterized by a safe action profile. Its spectrum of action includes bacteria causing CABP. In phase III studies, the efficacy of lefamulin monotherapy was comparable to that of moxifloxacin with or without linezolid in CABP. Thanks to broad spectrum of action its usefulness may also extend to treatment of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and multidrug-resistant organisms associated with sexually transmitted infections, e.g., *Neisseria gonorrhoeae, Mycoplasma genitalium,* although more additional clinical and pharmacodynamic data is needed.

Conclusion. Lefamulin is a promising addition to the antibiotic armamentarium for treating CABP. Its unique mechanism of action, activity against typical and atypical bacteria, flexible dosing options, and favorable safety profile make it a beneficial choice for clinicians.

Keywords. lefamulin; BC3781; pleuromutilin; CABP; pneumonia; community acquired pneumonia

Introduction

Pleuromutilins are natural compounds that inhibit growth of *S. aureus* and were first identified in the 1950s from the edible fungus *Clitopilus scyphoides*.[1]

The first pleuromutilin approved for human use was retapamulin, a topically applied lipophilic ointment, registered in 2007 for the treatment of impetigo caused by methicillin-sensitive strains of *S. aureus* (MSSA) or *Streptococcus pyogenes.*[1-3] The first systemically administered antibiotic from the pleuromutilin group is called lefamulin.[4] Its mechanism of action involves inhibiting the synthesis of bacterial proteins by binding to the A and P sites of the bacterial 50S ribosomal subunit, creating interference with peptidyl transferase. This inhibition leads to the prevention of peptide bond formation and elongation of the chain.[5,6] This mechanism results in a low occurrence of cross-resistance to other commonly used antibiotic groups,[5] including β-lactams, macrolides, tetracyclines, oxazolidinones, and fluoroquinolones.[7] In vitro studies have shown the development of resistance due to various point mutations in the ribosomal proteins within the domain V of 23S rRNA, which can affect the structure of the peptidyl transferase center (PTC).[8] The most common mechanism of resistance involves mutations in 23S rRNA and includes the genes rplC and rplD, which encode the ribosomal proteins L3 and L4, respectively. Mutations in these genes can cause

conformational changes in the PTC, making it difficult for pleuromutilins to properly position themselves in the matched binding pocket of the A and P sites.[7,8]

Aim

The aim of this paper is to present lefamulin as novel antibiotic and to find data upon its effectiveness in bacterial infections.

Material and methods

A review of the available literature was performed by searching the PubMed and GoogleScholar databases using the following key words: lefamulin; BC3781; pleuromutilin; CABP; community acquired pneumonia.

Analysis of literature

Spectrum of action

Lefamulin has a broad spectrum of antibacterial activity, especially against Gram-positive, some Gram-negative and atypical bacteria. The in vitro activity of lefamulin was evaluated based on a global collection of pathogens available through the SENTRY Antimicrobial Surveillance Program.[9] The bacteria for which the antibiotic exhibited minimum inhibitory concentrations required to inhibit the growth by 50% (MIC50) and 90% (MIC90) respectively were as follows: *Streptococcus pneumoniae* (including multidrug-resistant strains) 0.06/0.12 μg/ml, 100% growth inhibition at ≤1 μg/ml; methicillin-resistant *Staphylococcus aureus* (MRSA) 0.06/0.12 μg/ml, 99.8% growth inhibition at ≤1 μg/ml; *Haemophilus influenzae* 0.5/1 μg/ml, 93.8% growth inhibition at ≤1 μg/ml; and *Moraxella catarrhalis* 0.6/0.12 μg/ml, 100% growth inhibition at ≤0.25 μg/ml.[9] These results were consistent with a previous analysis of SENTRY isolates from 2010 concerning community-acquired bacterial pneumonia (CABP) and acute bacterial skin and its structure infections. The analysis also revealed strong activity against other microorganisms, with MIC50/90 for beta-hemolytic streptococci (0.03/0.03 μg/ml), group A/B streptococci (0.03/0.03 μg/ml), viridans group streptococci (0.12/0.5 μg/ml), coagulase-negative staphylococci (0.06/0.12 μg/ml), and *Enterococcus faecium* (including vancomycin-resistant strains) (0.12/4 μg/ml).[10, 11] Additional studies have also confirmed in vitro activity against common atypical pathogens, including *Legionella pneumophila* (0.06/0.5 μg/ml), *Mycoplasma pneumoniae* (0.006/0.006 μg/ml), and *Chlamydophila pneumoniae* (0.02/0.04 μg/ml).[12] In addition to typical pathogens causing CABP, lefamulin also demonstrates activity against bacterial sexually transmitted

infections (STI), including those caused by *Neisseria gonorrhoeae* (MIC50/90 = 0.12/0.5 μg/ml), *Chlamydia trachomatis* (MIC50/90 = 0.02/0.04 μg/ml), and *Mycoplasma genitalium* (MIC50/90 = ≤0.008/0.06 μg/ml).[13] Further analysis has shown activity against multidrug-resistant isolates of gonococci.[14] Lefamulin does not exhibit activity against Enterobacteriaceae, non-lactose fermenting Gram-negative bacteria, *E. faecalis*, *Clostridioides difficile*, and *Bacteroides* sp.[15]

Application in community-acquired bacterial pneumonia

Community-acquired bacterial pneumonia (CABP) is one of the leading causes of morbidity and mortality worldwide as well as a major cause of hospitalizations. Pneumonia is an inflammatory condition of the lung parenchyma characterized by infiltration of inflammatory cells and exudate in the alveolar spaces. The main symptoms include cough, excessive production and expectoration of sputum, chest pain, dyspnea, and signs of infection such as fever and weakness. Respiratory dysfunction can lead to the development of ketoacidosis and septic shock.[16] Pneumonia can be classified into two groups: community-acquired (CAP), when the infection occurs outside of hospital, and hospital-acquired, when the infection occurs during a minimum of a 48 h hospital stay. It has been estimated that approximately 1 million people in Europe require hospitalization due to CABP each year. According to data from the Central Statistical Office in Poland, pneumonia was the fourth leading cause of death among the population aged ≥65 years in 2018 (approximately 5% of all deaths), following cardiovascular diseases and cancer.[17] Risk factors of pneumonia include age, lifestyle, and certain comorbidities. Tobacco smoking, excessive alcohol consumption, frequent contact with children, chronic obstructive pulmonary disease, and immunosuppressive diseases such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) increase the chance of developing CABP.[18] Children up to 2 years of age and individuals over 65 years old are at a higher risk.[19] The most common bacteria causing CABP include *Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis, Chlamydia pneumoniae,* and *Legionella pneumophila*. Among them, *Streptococcus pneumoniae* is the most common pathogen causing the disease.[20,21]

Phase III studies "Lefamulin Evaluation Against Pneumonia 1 (LEAP 1)" and "Lefamulin Evaluation Against Pneumonia 2 (LEAP 2)" were crucial in assessing the efficacy of lefamulin compared to moxifloxacin in patients with community-acquired bacterial pneumonia.

LEAP 1 [22] was conducted as a multicenter, randomized, double-blind, double-dummy, active-controlled trial in parallel groups, in which 551 participants with CABP were randomly assigned (1:1) to receive either lefamulin or moxifloxacin. Participants received lefamulin intravenously at a dose of 150 mg every 12 hours, with the option to switch to oral form of drug after six doses if pre-specified improvement criteria were met (n = 276), or moxifloxacin intravenously at a dose of 400 mg every 24 hours (n = 275). Participants receiving moxifloxacin also received linezolid intravenously at a dose of 600 mg every 12 hours if MRSA was suspected as causative agent. In such cases, placebo linezolid was added to lefamulin. If MRSA was no longer suspected after the baseline culture, linezolid or placebo was discontinued. The duration of therapy for participants ranged from 5 to 10 days. To participate in the study, participants had to meet the following criteria: age above 18 years old, radiographic evidence of pneumonia, pneumonia severity index (PSI/PORT score) class III or higher, illness that occurred within 7 days of enrollment, and three or more CABP symptoms (shortness of breath, new or worsening cough, purulent sputum production, chest pain). Participants were excluded from the study if they fell into one of the following categories: received antibiotic treatment for the current illness within 3 days of randomization, were hospitalized for at least 2 days within 90 days of symptom onset, had confirmed or suspected CABP caused by *Pseudomonas aeruginosa* or any Enterobacteriaceae bacteria, or had a non-infectious cause of pulmonary infiltrates. At the beginning of the study, out of 551 participants, 86.7% were of White race, 7.9% were Yellow race, and 4.1% were of Black race; 43.5% of participants were aged 65 or older, and 59.8% were male. The primary endpoint for the Food and Drug Administration FDA was achieving early clinical response (ECR), defined as a significant improvement in health status occurring 96 ± 24 hours after the first dose of the investigated drug. At the end of the study, the lefamulin group had an ECR of 87.3% (241/276), and the moxifloxacin group showed an ECR of 90.2% (248/275). The difference of -2.9% in ECR was not significant. The primary endpoint for the European Medicines Agency (EMA) was investigator assessment of clinical response (IACR) in the test of cure (TOC) (5-10 days after the last dose of the examined drug). Lefamulin was shown to be non-inferior to moxifloxacin by EMA IACR asseessment. In the lefamulin-treated group, IACR was 80.8% compared to 83.6% in the moxifloxacin-treated group. The difference of -2.8% was not significant. Differences in ECR in the treatment of CABP in PORT risk class III and IV were not significant. Due to the small sample size (<10), differences in ECR could not be assessed in the II and V classes. Lefamulin met the criteria for equivalence in pharmacotherapy compared to moxifloxacin.

LEAP 2 [23] was a randomized, multicenter, double-blind, double-dummy trial involving 738 participants divided into two groups. 370 participants with confirmed CABP received 600 mg of lefamulin orally every 12 hours for 5 days, and 368 participants received 400 mg of moxifloxacin orally every 24 hours for 7 days. The inclusion criteria for the study were nearly identical to those defined in LEAP 1, namely: age above 18 years, radiographic evidence of pneumonia, PORT risk class III or higher, illness that initially occurred within 7 days of enrollment, and three or more CABP symptoms (shortness of breath, new or worsening cough, purulent sputum production, chest pain). Patients were excluded from the study if they fell into any of the following categories: received antibiotic treatment for the current illness within 3 days of randomization, were hospitalized for two or more days within 90 days of symptom onset, were at risk of a serious cardiac event, had serious liver diseases, had confirmed or suspected CABP caused by MRSA, *Pseudomonas aeruginosa*, or any Enterobacteriaceae bacteria, or had a non-infectious cause of pulmonary infiltrates. At the start of the study, out of 738 participants, 73.7% were of White race, 13.5% were Asians, 11.2% were Hispanics, and 5.5% were of Black race. 37.5% of participants were aged 65 or older, 52.4% were male, and 50.1% had renal impairment. The most reported pre-existing conditions were hypertension (36.2%), asthma or chronic obstructive pulmonary disease (16.7%), and diabetes (13.4%). The primary endpoint for the FDA was ECR at 96 hours (±24 hours) after receiving the first dose of either drug. Both treatment groups showed an ECR of 90.8%. The difference of 0.1% in ECR was not significant. Similarly to the LEAP 1 study, the EMA endpoint (secondary in FDA) was IACR in TOC (5-10 days after the last dose). The success rates of IACR were not significant and were 87.0% for lefamulin and 89.1% for moxifloxacin. Lefamulin met the criteria for equivalence with moxifloxacin.

In August 2019, the U.S. FDA approved lefamulin for oral and intravenous administration in adults with CABP for treatment.[24]

The potential clinical application of lefamulin in other bacterial infections.

MRSA

Lefamulin demonstrates high activity against MRSA with a reported MIC90 value of 0.12,[9] however, clinical studies regarding its use in severe MRSA infections are lacking. It has been found that lefamulin is more effective compared to vancomycin or linezolid in a murine model of *S. aureus* peritonitis-induced bacteremia, which included MRSA.[25] Furthermore, lefamulin has shown comparable efficacy to daptomycin and vancomycin in reducing bacterial burden against MSSA and has proven to be superior to linezolid and tigecycline.[26] Other potential areas of clinical application may include prosthetic joint infections,

osteomyelitis, orbital cellulitis, or chronic oral suppressive therapy, yet unfortunately, there is a lack of data in this topic.

Vancomycin-resistant Enterococcus faecium

Infections caused by vancomycin-resistant *E. faecium* pose a continuous threat, considering the limited number of antimicrobial agents effective in treating such infections and the associated morbidity and mortality. Both strains resistant to daptomycin and linezolid, which are considered first-line therapy, are spreading, especially among immunocompromised patients and those previously treated with antibiotics.[27, 28] The most common infections caused by this pathogen include pneumonia, bacteremia, endocarditis, and urinary tract infection. Lefamulin has shown strong activity against *E. faecium*, including vancomycin-resistant strains (0.12/4 μg/ml).[10, 11] However, before it can be used as targeted therapy for enterococcal infections, additional clinical and pharmacodynamic data are needed to assess its in vivo efficacy.

Neisseria gonorrhoeae and Mycoplasma genitalium

Antimicrobial-resistant *N. gonorrhoeae* is considered an urgent threat by the CDC due to its ease of transmission, ability to develop resistance, and complications associated with untreated infections.[29] Lefamulin has exhibited minimal cross-resistance with gonococci when tested against isolates resistant to macrolides, quinolones, and tetracyclines, which certainly could be beneficial for global and public health in the future. The MIC50/90 for 251 *N. gonorrhoeae* strains ranged from 0.25/1 mg/l and was within the range of 0.004–2 mg/l.[14] Further studies on the pharmacokinetics, pharmacodynamics, resistance, and clinical efficacy of lefamulin may prove valuable in the treatment of multidrug-resistant *N. gonorrhoeae*. Currently, there is a lack of clinical studies confirming the effectiveness of lefamulin in the treatment of sexually transmitted infections.

Conclusion

Lefamulin is a promising addition to the antibiotic armamentarium for treating CABP. Its unique mechanism of action, activity against typical and atypical bacteria, flexible dosing options, and favorable safety profile make it a beneficial choice for clinicians.

Declarations

Funding

This research has received no external funding.

Author contributions

Conceptualisation, N.I.; Methodology, P.Z.; Software, M.S.; Validation, D.M.; Formal Analysis L.A.; Investigation, P.Z.; Resources, M.S.; Data Curation, D.M.; Writing – Original Draft Preparation, N.I.; Writing – Review & Editing, N.I., M.S.; Visualisation, P.Z.; Supervision, D.M.; Project Administration: N.I., L.A.

Conflicts of interest

Authors have no conflicts of interest to declare.

References

1. Adhikary S, Duggal MK, Nagendran S et al. Lefamulin: a New Hope in the Field of Community-Acquired Bacterial Pneumonia. *Curr Pharmacol,* 2022;8:418–426. doi: 10.1007/s40495-022-00297-6

2. Label (PDF)-FDA. XENLETA (Lefamulin). Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211672s000,211673s000lbl.pdf. Accessed March 1, 2023.

3. Watkins RR, File TM. Lefamulin: A Novel Semisynthetic Pleuromutilin Antibiotic for Community-acquired Bacterial Pneumonia. *Clin Infect Dis.* 2020;71(10):2757-2762. doi: 10.1093/cid/ciaa336

4. Veve MP, Wagner JL. Lefamulin: Review of a Promising Novel Pleuromutilin Antibiotic. Pharmacotherapy. 2018;38(9):935-946. doi: 10.1002/phar.2166

5. Novak R, Shlaes DM. The pleuromutilin antibiotics: a new class for human use. *Curr Opin Investig Drugs.* 2010;11(2):182–191.

6. Eyal Z, Matzov D, Krupkin M, et al. Structural insights into species-specific features of the ribosome from the pathogen Staphylococcus aureus. *Proc Natl Acad Sci U S A.* 2015;112(43):5805–5814.

7. Paukner S, Riedl R. Pleuromutilins: potent drugs for resistant bugs-mode of action and resistance. *Cold Spring Harb Perspect Med* 2017; 7 pii: a027110. doi:10.1101/cshperspect.a027110

8. Mendes RE, Paukner S, Doyle TB, Gelone SP, Flamm RK, Sader HS. Low Prevalence of Gram-Positive Isolates Showing Elevated Lefamulin MIC Results during the SENTRY Surveillance Program for 2015-2016 and Characterization of Resistance Mechanisms. *Antimicrob Agents Chemother*. 2019;63(4):02158–18.

9. Paukner S, Gelone SP, Arends SJR, Flamm RK, Sader HS. Antibacterial Activity of Lefamulin against Pathogens Most Commonly Causing Community-Acquired Bacterial Pneumonia: SENTRY Antimicrobial Surveillance Program (2015-2016). *Antimicrob Agents Chemother.* 2019 Mar 27;63(4):02161-18. doi: 10.1128/AAC.02161-18

10. Paukner S, Sader HS, Ivezic-Schoenfeld Z, et al. Antimicrobial activity of the pleuromutilin antibiotic BC-3781 against bacterial pathogens isolated in the SENTRY antimicrobial surveillance program in 2010. *Antimicrob Agents Chemother* 2013; 57: 4489–95.

11. Sader HS, Biedenbach DJ, Paukner S, et al. Antimicrobial activity of the investigational pleuromutilin compound BC-3781 tested against gram-positive organisms commonly associated with acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother* 2012; 56: 1619–23.

12. Sader HS, Paukner S, Ivezic-Schoenfeld Z, Biedenbach DJ, Schmitz FJ, Jones RN. Antimicrobial activity of the novel pleuromutilin antibiotic BC-3781 against organisms responsible for community-acquired respiratory tract infections (CARTIs). *J Antimicrob Chemother.* 2012;67(5):1170-5. doi: 10.1093/jac/dks001

13. Paukner S, Gruss A, Jensen JS. *In Vitro* Activity of Lefamulin against Sexually Transmitted Bacterial Pathogens. *Antimicrob Agents Chemother.* 2018;62(5):e02380-17. doi: 10.1128/AAC.02380-17

14. Jacobsson S, Paukner S, Golparian D, Jensen JS, Unemo M. *In Vitro* Activity of the Novel Pleuromutilin Lefamulin (BC-3781) and Effect of Efflux Pump Inactivation on Multidrug-Resistant and Extensively Drug-Resistant Neisseria gonorrhoeae. *Antimicrob Agents Chemother.* 2017;61(11):e01497-17. doi: 10.1128/AAC.01497-17

15. Paukner S, Gelone SP, Arends SJR, Flamm RK, Sader HS. Antibacterial Activity of Lefamulin against Pathogens Most Commonly Causing Community-Acquired Bacterial Pneumonia: SENTRY Antimicrobial Surveillance Program (2015-2016). *Antimicrob Agents Chemother.* 2019;63(4):e02161-18. doi: 10.1128/AAC.02161-18

16. Hryniewicz W, Albrecht P, Radzikowski A (red.). *Rekomendacje postępowania w pozaszpitalnych zakażeniach układu oddechowego.* Warszawa: Narodowy Instytut Leków, 2017

17. Główny Urząd Statystyczny. Rocznik Demograficzny 2020. Warszawa 2020

18. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: A literature review. *Thorax.* 2013;68(11):1057-1065. doi:10.1136/thoraxjnl-2013-204282

19. Pneumococcal disease - transmission and those at high risk. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/pneumococcal/about/risk-transmission.html Accessed March 17, 2023.

20. Regunath H, Oba Y. Community-Acquired Pneumonia. https://www.ncbi.nlm.nih.gov/books/NBK430749/. Updated Feb 11, 2019. Accessed March 3, 2023.

21. Brown JS. Community-acquired pneumonia. *Clin Med (Lond)*. 2012;12(6):538-543. doi:10.7861/clinmedicine.12-6-538

22. File Jr TM, Goldberg L, Das A, et al. Efficacy and safety of intravenous-to-oral lefamulin, a pleuromutilin antibiotic, for the treatment of community-acquired bacterial pneumonia: the phase III Lefamulin Evaluation Against Pneumonia (LEAP 1) trial. *Clin Infect Dis.* 2019;69(11):1856–1867.

23. Alexander E, Goldberg L, Das AF, et al. Oral lefamulin vs moxifloxacin for early clinical response among adults with community-acquired bacterial pneumonia: the LEAP 2 randomized clinical trial. *JAMA*. 2019 Nov 5;322(17):1661-1671. doi: 10.1001/jama.2019.15468

24. Nabriva Therapeutics Receives U.S. FDA Approval of Xenleta™ (lefamulin) to Treat Community-Acquired Bacterial Pneumonia (CABP).

http://https://investors.nabriva.com/news-releases/news-releasedetails/nabriva-therapeutics-receives-us-fda-approval-xenleta. Published: 2019. Accessed March 1, 2023.

25. Wicha WW, Ivezic-Schoenfeld Z, Novak R. Pre-clinical efficacy of BC-3781 in thigh and bacteremia infections caused by staphylococci. https://www.nabriva.com/Portals/_default/Skins/ProfessionalUs/pdfs/2010-%20efficacy-bc-3781-thigh-bacteremia-and-staph.pdf. Accessed June 18, 2023.

26. Fischer E, Kappes BC, Wicha WW. Efficacy of Lefamulin Against Staphylococcus aureus-Induced Bacteremia in a Neutropenic and Immunocompetent Murine Model. *Open Forum Infect Dis.* 2017;4(Suppl 1):S471. doi: 10.1093/ofid/ofx163.1205

27. Mercuro NJ, Davis SL, Zervos MJ, Herc ES. Combatting resistant enterococcal infections: a pharmacotherapy review. *Expert Opin Pharmacother.* 2018;19(9):979–992.

28. DiPippo A, Tverdek FP, Tarrand JJ, et al. Daptomycin non-susceptible Enterococcus faecium in leukemia patients: role of prior daptomycin exposure. *J Inf Secur.* 2017;74(3):243–247.

29. Antibiotic Resistance Threats in the United States. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Published 2019. Accessed March 17, 2023.