GRHTA
Glob Reg Health Technol Assess 2024; 11 (Suppl. 2): 1-4
ISSN 2283-5733 | DOI: 10.33393/grhta.2024.3108
EDITORIAL

Place in therapy of dalbavancin to treat Gram-positive infections in antimicrobial resistance era: an overview

Rosario Cultrera[1,2,3]

[1]Infectious Diseases, Azienda Ospedaliero-Universitaria e Azienda Unità Sanitaria Locale di Ferrara, Ferrara - Italy
[2]Antimicrobial Stewardship Program Team, Azienda Ospedaliero-Universitaria e Azienda Unità Sanitaria Locale di Ferrara, Ferrara - Italy
[3]Department of Traslational Medicine, University of Ferrara, Ferrara - Italy

Antimicrobial resistance (AMR) is widespread and represents a current global public health problem, with the forecast of 10 million deaths per year globally by 2050 (1). AMR occurs when bacteria, virus, fungi and parasites no longer respond to the antimicrobial agents. A microorganism is defined as multidrug-resistant when it does not show susceptibility to at least one agent in three or more antimicrobial categories when tested in vitro (2,3). Multidrug-resistant organisms (MDROs) threaten the security of healthcare systems and communities both on economic and health safety levels (4,5). When antimicrobials become ineffective, infections become difficult to threat, increasing the risk of disease spread, severe illness and death. According to the latest report on the global burden of bacterial AMR, deaths in the world related to AMR amount to approximately 4.95 million, and those actually attributed to the onset of resistant bacterial strains is approximately 1.27 million (6). Added to this is the lack of commitment to research and development of new antimicrobials, which has led the World Health Organization (WHO) to highlight that AMR is one of the top 10 global public health threats facing humanity.

In 2020, there were approx. 800,000 infections with 35,000 deaths in the European Economic Area (EEA), while the economic burden of AMR was estimated to range at least €1.5 billion in the year 2007 alone (7-9).

Antimicrobial resistance surveillance is essential to evaluate the resistance of specific pathogens to different classes of therapeutically relevant antibiotics, to study the spread of antibiotic resistance in the country and to follow its trend over time. The Italian Antibiotic-Resistance Surveillance System (AR-ISS), coordinated by the Istituto Superiore di Sanità (the National Institute of Health in Italy), is based on a network of hospital laboratories present throughout the country, which send routine antibiotic susceptibility data for selected pathogens from invasive infections (blood or cerebrospinal fluid). The results of the surveillance for the year 2022 and the trend evaluation for 2015-2022 showed the reports obtained from 173 laboratories of 21 Italian regions. The main microorganisms isolated from 77,121 isolates obtained from blood (99%) and liquor (1%) were *Escherichia coli* (n = 25,879; 33.6%), *Staphylococcus aureus* (n = 14,909; 19.3%), *Klebsiella pneumoniae* (n = 11,790; 15.3%), *Enterococcus faecalis* (n = 8,284; 10.7%), *Enterococcus faecium* (n = 6,084; 7.9%), *Pseudomonas aeruginosa* (n = 6,042; 7.8%), *Acinetobacter* spp. (n = 2,898; 3.8%) and *Streptococcus pneumoniae* (n = 1,235; 1.6%). This report was conducted when the SARS-CoV-2 pandemic was still ongoing.

The data obtained from the AR-ISS show that in 2022 the percentages of resistance to the main classes of antibiotics, for the eight pathogens under surveillance, generally remain high. After a clear decrease in the percentage value of methicillin-resistant *Staphylococcus aureus* (MRSA) in 2021 (30.5% compared to an average of around 34% in the period 2015-2020), the percentage of MRSA remained stable in 2022 at 29.9% compared to 2021. Regarding *E. faecium*, the percentage of resistance to high-dose aminoglycosides (gentamicin, streptomycin) decreased in recent years (from 79.7% in 2015 to 67.9% in 2022) and was stable in the last three years at an average value of approximately 68%, while resistance to ampicillin remained high (89.3%) in 2022. A progressive and worrying increase in the percentage of resistance to vancomycin was found, which increased from 11.1% in 2015 to 30.7% in 2022. The resistance of *E. faecalis* to high-dose aminoglycosides (gentamicin, streptomycin), after 2 years of trend increase in 2020 and 2021, decreased in 2022, settling at 38.1% while the resistance to vancomycin remained low, no more than 2% of the isolated strains (10).

Hospitalization exposes patients to a greater infectious risk and healthcare-associated infections (HAIs) are an important aspect of AMR (HAI). HAIs and AMR are closely related as shown by the European EARS-Net network: in 2015, 63.5% of infections caused by resistant bacteria were associated

Received: May 2, 2024
Accepted: May 2, 2024
Published online: July 29, 2024

Corresponding author:
Rosario Cultrera
email: ctr@unife.it

with healthcare (11). Moreover, 75% of infections caused by antibiotic-resistant bacteria are HAIs (12,13).

Excessive use of antibiotics, long-term treatments and incorrect source control measures are among the main factors influencing the onset of HAIs. For example, overuse of antibiotics in hospital stays during the COVID-19 pandemic led to an accelerated emergence and spread of antibiotic resistance (14-16).

According to data from the Italian Medicines Agency (AIFA-Agenzia Italiana del Farmaco) in 2021, the overall public and private consumption of antibiotics in Italy was equal to 17.1 DDD (Defined Daily Dose) per 1,000 inhabitants per day, a reduction of 3.3% compared to 2020, but still higher than the European average (16.4 DDD/1,000 inhabitants per day) for the same year. Almost 90% of the consumption of antibiotics by the Italian National Health Service (NHS; 11.5 DDD/1,000 inhabitants per day) is provided under an agreement with the NHS, by primary care clinicians, with three out of ten citizens who receive at least one antibiotic compared to the North. The greatest consumption of antibiotics is found in children in the first 6 years of life (one in two children has received at least one antibiotic prescription), choosing second-line drugs rather than first-line antibiotics four times out of 10, and in adults after 75 years of age with higher for women in the intermediate age groups and for men in the extreme ones (17).

Interventions aimed at monitoring and guiding the use of antimicrobials in the hospital tend to improve the clinical outcome, reduce the spread of resistant germs and reduce the adverse effects of antibiotics. Acute bacterial skin and skin structure infection (ABSSSI) represent one of the infections, with a great impact on hospitalization and related costs. To optimize economic resources in the healthcare field, the therapeutic approach to the patient with ABSSSI and complicated infections increasingly often involves the early transition from intravenous to oral therapy (early switch) or early discharge with an important impact on hospitalization and consistent savings for the NHS. Dalbavancin is a lipoglycopeptide antibiotic approved for treating ABSSSI caused by Gram-positive aerobe and anaerobe bacteria, including MRSA, *Enterococcus* spp., *Streptococcus* spp., *Clostridium* spp., *Peptostreptococcus* spp., *Bacillus* spp. and *Corynebacterium* spp. (18-20).

Dalbavancin has an extended half-life of over 1 week. Due to its pharmacokinetic feature, dalbavancin may be administered intravenously in two doses, 1,000 mg followed by 500 mg 1 week apart, or 1,500 mg as a single dose (21).

Real-life experience reports several dalbavancin off-label use in treating Gram-positive infections that usually require long-term intravenous antibiotics including bone and joint infections (22,23), bloodstream infections (24) and infective endocarditis (25-27). The promising efficacy in these challenging, off-label scenarios makes dalbavancin a viable alternative to daily intravenous or outpatient antimicrobial regimens. The simplified single or weekly administration regimen allows an early discharge, especially when adherence to oral therapy cannot be guaranteed or no oral choices are available (28,29).

Furthermore, de-hospitalization aimed to evaluate how the use of dalbavancin had an impact on the length of hospitalization and therefore on the treatment-related costs in ABSSSI or in other Gram-positive bacterial infections, as reported in Italy by several authors (30-32).

A budget impact model from several European countries also suggests significant savings when dalbavancin is used for ABSSSI among hospitalized patients, predicated on the possibility of earlier discharge from the hospital (4). One primary difference among these studies is often the setting in which dalbavancin is being used. When comparing dalbavancin use in hospitalized patients to standard of care (SoC) or to those receiving outpatient parenteral antibiotic therapy (OPAT) for ABSSSI, there certainly may be observed cost advantages by reducing hospital length of stay, infusion centre– or home health–related costs, or avoiding other line-associated complications. These differences in settings represent one of the challenges for infectious diseases clinicians and stewards when comparing cost-effectiveness analyses, even for the same agent and condition.

One condition to take into consideration is patients with ABSSSI, especially mild to moderate cases, who do not necessarily require intravenous therapy and may receive oral antibiotics. Oral antibiotics provide a path to avoid infusion-related costs altogether, especially considering the low average wholesale price of many of these agents (e.g. trimethoprim/sulfamethoxazole, doxycycline, cephalexin). Adherence may be a problem (20) in patients receiving oral antibiotic treatment after hospital discharge for skin and soft tissue *S. aureus* infections. They found that patient adherence to oral antibiotic therapy for these infections after hospital discharge was low (57%), compared to the 96% rate of self-reported adherence ($p < 0.0001$) and associated with poor clinical outcome (33). Therefore, the advantage of a single dose of dalbavancin, starting and, at the same time, completing the therapy, is the certainty of the patient's adherence to the therapy which is not given by oral antibiotics. In this issue, the experience reported by Crapis and colleagues confirms the advantage that dalbavancin has over SoC in reducing hospitalization while maintaining good safety and efficacy (34). The authors highlight in their experience that the true potential of the use of dalbavancin in ABSSSI and in infections that require a long period of antibiotic treatment lies precisely in completely avoiding hospitalization. The review by Carbonara is a careful review of the literature that confirms the effectiveness of dalbavancin in the treatment of ABSSSI (35). The author highlights the strong impact that dalbavancin has in reducing the length of hospital stay and related costs and the positive impact of dalbavancin in reducing organizational and economic stress on ABSSSI patients and their families, which also translates into greater comfort and better quality of life for these individuals. The effectiveness of dalbavancin is particularly highlighted in the review in terms of organization of patient care and costs, in patients at risk of poor adherence to oral antibiotic therapy and in patients in whom OPAT is challenging to implement.

Dalbavancin may have its place in non-adherent patients, in the setting of people who inject drugs or have difficult access to healthcare and in patients with reduced gastrointestinal absorption. The long half-life, wide distribution volume, good tissue and intracellular penetration and

anti-biofilm activity place them among the therapeutic tools for chronic infections, especially for bone and joint infections and endocarditis.

Disclosures

Conflict of interest: Outside the submitted work, R.C. has received funding for scientific advisory boards, travel and speaker honoraria from Angelini, Menarini, MSD, Pfizer, Shionogi and TRX Italy.

Financial support: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Payment of medical writing and publication fees was supported by an unconditional grant by Angelini Pharma S.p.A.

References

1. Tang KWK, Millar BC, Moore JE. Antimicrobial resistance (AMR). Br J Biomed Sci. 2023;80:11387. CrossRef PubMed
2. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-281. CrossRef PubMed
3. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control. 2007;35(10)(suppl 2):S165-S193. CrossRef PubMed
4. Ancillotti M, Nihlén Fahlquist J, Eriksson S. Individual moral responsibility for antibiotic resistance. Bioethics. 2022;36(1):3-9. CrossRef PubMed
5. Glasner C, Berends MS, Becker K, et al. A prospective multicentre screening study on multidrug-resistant organisms in intensive care units in the Dutch-German cross-border region, 2017 to 2018: the importance of healthcare structures. Euro Surveill. 2022;27(5):1. CrossRef PubMed
6. Murray CJL, Ikuta KS, Sharara F, et al; Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-655. CrossRef PubMed
7. ECDC and EMEA Joint Working Group. ECDC/EMEA Joint Technical Report. The bacterial challenge: time to react. 2009. Online.
8. European Centre for Disease Prevention and Control, Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2018, Publications Office of the European Union, 2019, Online. Accessed April 2024.
9. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? Clin Microbiol Infect. 2014;20(10):973-980. CrossRef PubMed
10. 10. Iacchini S, Boros S, Pezzotti P e il gruppo di lavoro AR-ISS. AR-ISS: sorveglianza nazionale dell'Antibiotico-Resistenza. Dati 2022. Roma: Istituto Superiore di Sanità; 2023. (Rapporti ISS Sorveglianza RIS-4/2023). Online. Accessed April 2024.
11. Cassini A, Högberg LD, Plachouras D, et al; Burden of AMR Collaborative Group. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019;19(1):56-66. CrossRef PubMed
12. Italian Health Ministry. Antibiotico-resistenza nel settore umano. Aggiornamento 24/11/23. Online. Accessed April 2024.
13. Suetens C, Latour K, Kärki T, et al; Healthcare-Associated Infections Prevalence Study Group. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017. Euro Surveill. 2018;23(46):1800516. CrossRef PubMed
14. Moretto F, Sixt T, Devilliers H, et al. Is there a need to widely prescribe antibiotics in patients hospitalized with COVID-19? Int J Infect Dis. 2021;105:256-260. CrossRef PubMed
15. Langford BJ, So M, Raybardhan S, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect. 2021;27(4):520-531. CrossRef PubMed
16. Bardi T, Pintado V, Gomez-Rojo M, et al. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis. 2021;40(3):495-502. CrossRef PubMed
17. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia. Rapporto Rappporto OsMed 2022. Published August 7, 2023. Online. Accessed April 2024.
18. Pfaller MA, Mendes RE, Duncan LR, Flamm RK, Sader HS. Activity of dalbavancin and comparator agents against Gram-positive cocci from clinical infections in the USA and Europe 2015-16. J Antimicrob Chemother. 2018;73(10):2748-2756. CrossRef PubMed
19. Goldstein EJC, Citron DM, Merriam CV, Warren Y, Tyrrell K, Fernandez HT. In vitro activities of dalbavancin and nine comparator agents against anaerobic Gram-positive species and corynebacteria. Antimicrob Agents Chemother. 2003;47(6):1968-1971. CrossRef PubMed
20. Soriano A, Rossolini GM, Pea F. The role of dalbavancin in the treatment of acute bacterial skin and skin structure infections (ABSSSIs). Expert Rev Anti Infect Ther. 2020;18(5):415-422. CrossRef PubMed
21. Molina KC, Miller MA, Mueller SW, Van Matre ET, Krsak M, Kiser TH. Clinical pharmacokinetics and pharmacodynamics of dalbavancin. Clin Pharmacokinet. 2022;61(3):363-374. CrossRef PubMed
22. Cojutti PG, Rinaldi M, Zamparini E, et al. Population pharmacokinetics of dalbavancin and dosing consideration for optimal treatment of adult patients with staphylococcal osteoarticular infections. Antimicrob Agents Chemother. 2023;65(5):e02260-20. CrossRef PubMed
23. Morata L, Cobo J, Fernández-Sampedro M, et al. Safety and efficacy of prolonged use of dalbavancin in bone and joint infections. Antimicrob Agents Chemother. 2019;63(5):e02280-18. CrossRef PubMed
24. Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by Gram-positive pathogens. Clin Infect Dis. 2005;40(3):374-380. CrossRef PubMed
25. Hidalgo-Tenorio C, Vinuesa D, Plata A, et al. DALBACEN cohort: dalbavancin as consolidation therapy in patients with endocarditis and/or bloodstream infection produced by Gram-positive cocci. Ann Clin Microbiol Antimicrob. 2019;18(1):30. CrossRef PubMed
26. Krsak M, Morrisette T, Miller M, et al. Advantages of outpatient treatment with long-acting lipoglycopeptides for serious Gram-positive infections: a review. Pharmacotherapy. 2020;40(5):469-478. CrossRef PubMed
27. Tobudic S, Forstner C, Burgmann H, et al. Dalbavancin as primary and sequential treatment for Gram-positive infective endocarditis: 2-year experience at the general hospital of Vienna. Clin Infect Dis. 2018;67(5):795-798. CrossRef PubMed

28. Keyloun KR, Lofgren E, Hebert S. Modeling operational quality metrics and costs of long-acting antibiotics for acute bacterial skin and skin structure infection treatment in the emergency department. J Med Econ. 2019;22(7):652-661. CrossRef PubMed
29. Marcellusi A, Bini C, Rotundo MA, Cultrera R, Mennini FS. Costo-utilità di dalbavancina versus standard of care (SoC) in pazienti con ABSSSI non severa in Italia. Glob Reg Health Technol Assess. 2020;7(1):92-100. CrossRef PubMed
30. Oliva A, Carbonara S, Cianci V, et al. Direct or early discharge of acute bacterial skin and skin structure infection patients from the emergency department/unit: place in therapy of dalbavancin. Expert Rev Anti Infect Ther. 2023;21(7):703-721. CrossRef PubMed
31. Poliseno M, Bavaro DF, Brindicci G, et al. Dalbavancin efficacy and impact on hospital length-of-stay and treatment costs in different Gram-positive bacterial infections. Clin Drug Investig. 2021;41(5):437-448. CrossRef PubMed
32. Pascale R, Maccaro A, Mikus E, et al. A retrospective multicentre study on dalbavancin effectiveness and cost-evaluation in sternotomic wound infection treatment: DALBA SWIT Study. J Glob Antimicrob Resist. 2022;30:390-394. CrossRef PubMed
33. Eells SJ, Nguyen M, Jung J, Macias-Gil R, May L, Miller LG. Relationship between adherence to oral antibiotics and post-discharge clinical outcomes among patients hospitalized with Staphylococcus aureus skin infections. Antimicrob Agents Chemother. 2016;60(5):2941-2948. CrossRef PubMed
34. Crapis, M., Venturini, S., Callegari et al. Usefulness of dalbavacin in early discharge and non-hospitalisation and ER experience. It's time to throw your heart over the obstacle?. Glob Reg Health Technol Assess 2024; 11. CrossRef
35. Carbonara S. The efficacy of Dalbavancin and impact on hospitalization and treatment costs in patients with ABSSSI. Glob Reg Health Technol Assess 2024; 11. CrossRef