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Expert Review of Anti-infective Therapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierz20

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To cite this article: Alberto Enrico Maraolo, Milo Gatti, Luigi Principe, Andrea Marino, Giuseppe Pipitone, Gennaro De Pascale & Giancarlo Ceccarelli (10 Apr 2025): Management of methicillin-resistant *Staphylococcus aureus* bloodstream infections: a comprehensive narrative review of available evidence focusing on current controversies and the challenges ahead, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2025.2487163

To link to this article: https://doi.org/10.1080/14787210.2025.2487163

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2025.2487163

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REVIEW

Management of methicillin-resistant *Staphylococcus aureus* bloodstream infections: a comprehensive narrative review of available evidence focusing on current controversies and the challenges ahead

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ABSTRACT

Introduction: Bloodstream infections (BSIs) caused by *Staphylococcus aureus* are common worldwide, representing one of the most relevant issues in clinical infectious diseases practice. In particular, BSIs by methicillin-resistant *S. aureus* (MRSA-BSI) are still today a challenge since mortality burden remains elevated although decades of research.

Areas covered: The following topics regarding MRSA-BSI were reviewed and discussed by resorting to best available evidence retrieved from PubMed/MEDLINE up to October 2024: i) epidemiology; ii) microbiology; iii) classification, with a focus on complicated and not complicated forms; iv) the structured approach to the patient; v) pharmacokinetics and pharmacodynamics of the main antimicrobial options; vi) controversies regarding the best therapeutic approach.

Expert opinion: Despite ongoing efforts to better stratify and manage MRSA-BSI, there is no universally accepted classification system accurately distinguishing between uncomplicated/low risk and complicated/high risk forms. Biomarkers such as interleukin(IL)-10 hold promise in order to enable a more precise stratification, premise for an appropriate treatment plan. There is a theoretical rationale for implementing a combination therapy including a beta-lactam agent upfront, especially for patients considered at higher risk of unfavorable outcomes, but further data are necessary, and the same applies to newer adjuvants. Novel microbiological techniques may help in guiding antimicrobial duration.

ARTICLE HISTORY
Received 17 January 2025
Accepted 21 March 2025

KEYWORDS
Staphylococcus aureus; bacteremia; MRSA; endocarditis; metastatic foci; risk stratification; combination therapy; monotherapy

1. Introduction

Staphylococcus aureus is a significant human pathogen responsible for a diverse spectrum of clinical infections. It is a leading cause of bloodstream infection (BSI) and infective endocarditis (IE), as well as skin and soft tissue, osteoarticular, pleuropulmonary, and device-associated infections [1]. BSI likely represents the paradigmatic form of *S. aureus* infection, carrying a substantial burden of morbidity and mortality worldwide, and is rarely asymptomatic or paucisymptomatic; more commonly, it is associated with a vast array of manifestations, including hematogenous complications, IE, and spread to prosthetic materials [2]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is currently the most significant form of phenotypic resistance [3]. In 2024, the World Health Organization (WHO) revised its 2017 list of drug-resistant bacteria that pose the greatest threat to human health. This update aims to guide the development of new treatments and strategies for combating antimicrobial resistance. MRSA remains classified as a high-priority pathogen due to its significant impact on community health and its increasing levels of resistance [4]. Consequently, it is evident that the management of methicillin-resistant *S. aureus* (MRSA-BSI) represents a critical challenge in contemporary medicine [5]. Along with *Escherichia coli*, *S. aureus* accounts for half of the cases of BSIs worldwide and is the most frequent cause of gram-positive bacteremia [6]. Recent global estimates indicate that infection-related deaths amount to 13.7 million (95% uncertainty interval [UI], 10.9–17.1) annually [7]. Among pathogens, *S. aureus* emerges as the most lethal, accounting for 1,105,000 deaths (95% UI, 816,000–1,470,000) and constituting the primary cause of fatal BSIs with 299,000 deaths (95% UI, 166,000–485,000), with an estimated all-cause age-standardized mortality rate of 14.6% (95% UI, 10.8%–19.4%) [7]. The prevalence of methicillin-resistant strains among *S. aureus* infections exhibits significant global variation; however, the consistent factor is the poorer prognosis of MRSA infections compared to their methicillin-

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Article highlights

- Bloodstream infections by methicillin-resistant *Staphylococcus aureus* (MRSA-BSIs) remain a significant cause of morbidity and mortality globally, accounting for over 1 million deaths annually.
- MRSA develops resistance through mechanisms like the *mecA* and *mecC* genes, which code for low-affinity penicillin-binding proteins. Resistance to beta-lactams, vancomycin, daptomycin, and linezolid involves various genetic mutations and adaptive bacterial strategies.
- There is no universally accepted system to classify MRSA-BSI into uncomplicated or complicated forms. Persistent bacteremia, especially beyond 72 hours, and metastatic infections are key indicators of complicated MRSA-BSI.
- Effective management includes comprehensive risk stratification, timely diagnostics, and appropriate use of follow-up blood cultures and imaging, also including advanced techniques of nuclear medicine to detect metastatic foci.
- Vancomycin remains the first-line treatment, though its limitations include nephrotoxicity and suboptimal efficacy. Daptomycin and fifth-generation cephalosporins like ceftobiprole are viable alternatives.
- Combination therapies have not demonstrated clear superiority over monotherapy in randomized clinical trials.
- Further research is needed to determine the role of combination regimens, especially as salvage therapy for persistent infections.
- Standard therapy duration ranges from 14 to 42 days, depending on whether the infection is classified as uncomplicated or complicated.
- Oral step-down therapy and the use of long-acting antimicrobials may reduce hospitalization time but require further validation. Long-acting lipoglycopeptides such as dalbavancin and oritavancin show potential for outpatient therapy.
- The need for personalized medicine approaches, including biomarker-based risk stratification and antimicrobial duration guidance, is emphasized. Interleukin(IL)-10 seems a promising biomarker for predicting complicated MRSA-BSI.

susceptible counterparts (MSSA), particularly in the context of BSI [8]. Despite decades of medical advancements since MRSA emerged among clinical isolates in the 1960s [9], numerous controversies persist regarding critical aspects such as the definition of complicated or uncomplicated MRSA-BSI, the appropriate structured approach to a patient with MRSA-BSI, the optimal antimicrobial selection, the management of complications, and the follow-up protocol.

This review aims to provide a comprehensive examination of MRSA-BSI, emphasizing the latest developments in antimicrobial options, diagnostic modalities, and management strategies. Particular attention is given to controversies in clinical practice and gaps in evidence, which continue to challenge healthcare providers in tailoring effective patient-centered care. By consolidating the current knowledge, this review seeks to inform and refine approaches to this formidable clinical entity.

2. Methodology

A panel comprising seven experts (four infectious disease physicians, a clinical pharmacist, a clinical microbiologist, and an intensivist) performed a thorough literature search on PubMed/MEDLINE, focusing on English-language publications available up to October 2024. Broad search terms, such as 'MRSA AND bacteremia/bacteraemia,' were used to ensure extensive retrieval of relevant studies, specifically trials, meta-analyses, as well as systematic and narrative reviews. The references of selected articles were also screened and critically assessed. The panel reviewed and discussed the collected literature for each facet of the topic, in order to yield a consistent synthesis of the data.

3. Epidemiology

According to comprehensive estimates, in North America and Europe BSI incidence ranged from 113 to 204 per 100,000 population [10]. In the majority of studies in most setting, *S. aureus* ranks second as cause of BSI, whereas *Escherichia coli* is usually the number one pathogen, often being infections from urinary tract or from abdomen the source [10].

The global epidemiology of MRSA-BSI has demonstrated considerable variation, with some regions experiencing significant declines due to improved infection control practices, while others continue to report high rates of infection. An international population-based surveillance conducted from 2000 to 2008 assessed 83 million person-years of *S. aureus*-BSI (SAB) data [11]. The overall annual incidence rate of SAB was 26.1 per 100,000 population, with specific MSSA- and MRSA-BSI incidence rates of 24.2 and 1.9 per 100,000 population, respectively. The overall incidence of community-onset MSSA-BSI was 15.0 per 100,000, with similar data among regions. However, the authors noted that the rates of hospital-onset MSSA-BSI (9.2 per 100,000), community-onset MRSA BSI (1.0 per 100,000), and hospital-onset MRSA-BSI (0.8 per 100,000) varied worldwide [11]. A European surveillance network collected a total of 573,951 routine clinical antimicrobial susceptibility tests from SAB (including both MRSA and MSSA); data were collected from 2005 to 2018 [12]. During the observation period, the crude percentage of MRSA-BSI decreased from 6,615/27,215 (24%) to 10,130/72,085 (14%); conversely, MSSA-BSI increased from 20,510/27,215 (76%) to 61,955/72,085 (86%) [12]. A recent meta-analysis confirmed a similar resistance percentage for hospital-acquired MRSA-BSI of 18% (95% confidence interval [CI], 5.85–34.75), indicating high heterogeneity among studies (I^2 95%) [13]. A recent population-based Swiss surveillance report collected data of SAB from 2008 to 2021; data showed a + 37% increase in MSSA-BSI, from 17.8 to 24.4 cases per 100,000 inhabitants ($p < 0.01$), and a reduction in MRSA-BSI from 1.9 to 1.2 cases per 100,000 inhabitants ($p < 0.01$) [14]. A specific setting could exhibit a higher percentage: an intensive care unit (ICU) epidemiologic report in the United States revealed an increase in the resistance rate for *S. aureus* isolates from 34% to 64% from 1992 to 2004, with a 3% increase rate per year ($p < 0.01$) [15].

3.1. Risk factors for MRSA-BSI

Although historically contact precautions are considered the cornerstone for infection control and to reduce the risk of infection, a recent meta-analysis demonstrated no significant difference in rates of hospital-associated MRSA infection before and after removing contact precautions (relative risk [RR] 0.84; 95% CI, 0.71–1.01) [16]. As elucidated previously, colonization rates may be elevated in patients with specific comorbidities, and colonization may increase the risk of infection. A recent meta-analysis determined that solid organ

transplant patients colonized by MRSA exhibited a higher risk of infection (odds ratio [OR] 6.81; 95% CI, 3.68–12.61) and, specifically, a higher risk of BSI (OR 2.80; 95% CI, 0.82–9.62) compared to non-colonized patients [17]. The risk of infection in colonized patients could be elucidated by a recent study suggesting that *S. aureus* can cause infections via a 'Trojan Horse' mechanism, wherein neutrophils engulf intestinal MRSA and subsequently travel through the bloodstream [18]. A monocentric observational study identified central venous catheter placement as an independent risk factor for SAB (OR 80.7; 95% CI, 2.2–3,014.1), while prior hospital stays >3 days (OR 4.1; 95% CI, 1.5–5.7) and chronic kidney disease (OR 3.0; 95% CI, 1.01–9.2) were uniquely associated with MSSA [19]. In a single-center observational retrospective study from Italy, evaluating patients admitted to the emergency department for multidrug-resistant organism BSI, the authors identified the following risk factors for MRSA-BSI: dialysis (OR 12.3; 95% CI 1.8–83), antibiotic therapy and/or hospital admission in the past 90-days (OR 3.6; 95% CI 1.2–10.6), and ureteral stent or nephrostomy (OR 7.8; 95% CI 1.5–40.9) [20]. In a Belgian study risk factors associated with MRSA-BSI included not residing at home ($p = 0.001$), prior antibiotic exposure ($p = 0.002$), insulin-requiring diabetes ($p = 0.028$), and nosocomial BSI ($p = 0.031$) [21]. In cancer patients, risk factors were healthcare-associated pneumonia (OR 3.02; 95% CI 1.63–5.59), hospital-acquired infection (OR 5.54; 95% CI 3.27–9.38), and diabetes mellitus if glycemia >140 mg/dL HR 2.58 (95% CI, 1.43–4.67) [22], or nasogastric tube (OR 5.11; 95% CI, 1.36–19.14) and ICU admission (OR 4.70; 95% CI 1.61–13.73) [23].

An observational case–control study conducted at a single center, spanning over a decade, examined 50 patients with MRSA-BSI and 98 with MSSA-BSI [24]. The research team noted a significant quadrupling in MRSA-BSI cases upon hospital admission between 1991 and 2003 ($p < 0.001$) [24]. Bivariable analysis comparing MRSA- and MSSA-BSI patients showed a significant association between methicillin-resistance and being over 60 years old, being female, having a history of MRSA isolation, and healthcare-associated BSI. Multiple-variable analyses identified previous MRSA isolation (OR 41; 95% CI 4–350) and admission from long-term care facilities (OR 37; 95% CI 4.5–316) as standalone risk factors for MRSA-BSI. The study found no disparities in underlying conditions such as diabetes, hemodialysis, immunosuppression, infection source, or mortality rates between the two groups [24].

3.2. Mortality burden of MRSA-BSI

Although MSSA-BSIs are typically more susceptible to a broad range of antibiotics, they are not necessarily less severe. Several data highlight the not negligible mortality in MSSA-BSI, primarily due to the Panton-Valentine leucocidin (PVL) cytotoxin, which is estimated to affect approximately 1.5% of *S. aureus* strains (both MSSA and MRSA), or due to enhanced virulence of some clonal complexes [25]. Among patients with human immunodeficiency virus infection, the hazard ratio (HR) for mortality was 2.61 (95% CI 1.95–3.49, $p < 0.001$), with similar 30-day mortality rates between MSSA- and MRSA-BSI (31.7% each) [26].

Nevertheless, a gradient in mortality between MSSA- and MRSA-BSI exists, which implies a worse prognosis for the latter.

A recent meta-analysis, encompassing 536,791 patients with MSSA- and MRSA-BSI from 341 studies published between 1991 and 2021, demonstrated that SAB mortality decreased over the last three decades [27]. The overall in-hospital mortality (including both MSSA- and MRSA-BSI) decreased from 30.4% (95% CI, 26.6%–34.4%) prior to 2001 to 18.0% (95% CI, 14.9%–21.5%) after 2011. Specifically, in-hospital mortality due to MSSA ranged from 18.8% (95% CI, 16.3%–21.6%) to 14.3% (95% CI, 9.5%–21.1%). Similarly, in-hospital mortality due to MRSA ranged from 40.2% (95% CI, 35.2%–45.5%) prior to 2001 to 28.8% (95% CI, 22.5%–36.1%) after 2011. At any rate, the comparison of in-hospital mortality between MRSA and MSSA-BSI revealed an OR of 1.92 (95% CI, 1.71–2.16), which remained stable throughout the 30-year observational period: in a few words, MRSA-BSI entails a two-fold risk of death compared with MSSA-BSI [27].

4. Microbiology

4.1. Common and less common resistance mechanisms to beta-lactams

As a matter of common knowledge, *S. aureus* can develop resistance to all types of clinically used antibiotics through chromosomal gene mutations or by acquiring resistance determinants via horizontal transfer [9]. Nearly 80% of *S. aureus* strains have developed penicillin resistance by obtaining the beta-lactamase encoded by the *blaZ* gene (Ambler classification class A) [28]. MRSA is characterized by the *mecA* and *mecC* genes, which encode alternative penicillin-binding proteins (PBP2a and 2c, respectively) with reduced affinity for beta-lactams. These proteins confer high-level resistance to oxacillin and other beta-lactam antibiotics, excluding anti-MRSA fifth-generation cephalosporins such as ceftaroline and ceftobiprole. In certain instances, elevated resistance levels have been linked to increased PBP2a expression resulting from *mecA* gene duplication or enhanced transcription [29]. The *mecA* or *mecC* genes are located on a mobile and transposable genetic element known as the staphylococcal chromosomal cassette mec (SCCmec), which can be transferred horizontally between strains [9]. Recent reports have identified MRSA strains with decreased susceptibility to ceftaroline [30].

Alternative phenotypes can confer low-level resistance to oxacillin. Borderline oxacillin-resistant *S. aureus* (BORSA) strains are negative for the production of *mecA* or *mecC* determinants but show low levels of resistance to oxacillin, generally with a minimum inhibitory concentration (MIC) value near 2 mg/L (i.e. 1 to 8 mg/mL). These strains are commonly susceptible to other beta-lactams (except penicillin) [31]. The precise mechanism behind BORSA is unclear; however, these isolates often contain *blaZ*, resulting in hyperproduction of beta-lactamase. No specific diagnostic tests are available for laboratory detection of BORSA. Cefoxitin screening is commonly negative, but in some cases, it can be positive in the absence of *mecA* or *mecC* determinants [31]. BORSA strains are

commonly susceptible to beta-lactam/beta-lactam inhibitor combinations (i.e. piperacillin/tazobactam, amoxicillin/clavulanic acid, ampicillin/sulbactam) due to inhibition of the beta-lactamase encoded by *blaZ* [32]. Another mec-independent oxacillin-resistant phenotype is represented by a modified *S. aureus* (MODSA) phenotype, in which mutations in non-mec-type genes (e.g. *pbp*, *gdpP*, and *yibH*) result in increased oxacillin MICs. This phenotype is very rare and can be selected by means of beta-lactam pressure [33].

4.2. Resistance mechanisms to drugs other than beta-lactams: the case of vancomycin

Vancomycin is a glycopeptide antibiotic that remains a mainstay for the treatment of MRSA-BSI. Vancomycin-resistant *S. aureus* (VRSA), vancomycin-intermediate S. aureus (VISA), and heterogeneous vancomycin-intermediate *S. aureus* (hVISA) phenotypes show resistance to vancomycin: global prevalence of 1.5%, 1.7%, and 4.6%, respectively [34].

VRSA strains commonly show vancomycin MIC values ≥16 mg/L. Actually, *S. aureus* exhibits multiple mechanisms of vancomycin resistance, with the primary one involving reduced permeability and enhanced cell wall thickness, resulting in diminished availability of vancomycin to reach intracellular targets. An additional form of resistance stems from plasmid-mediated vancomycin resistance genes, predominantly *vanA*, which may have been acquired from enterococci [35].

VISA strains typically display vancomycin MIC values ranging from 4 to 8 mg/L. The principal mechanisms underlying reduced vancomycin susceptibility in VISA strains include mutations in genes associated with cell wall formation (leading to thicker cell walls with more peptidoglycan layers) and/or alterations in the ribosomal gene *rpoB* [36]. In contrast, hVISA strains exhibit MICs within the susceptible range (≤2 µg/mL), but contain a subpopulation that expresses a resistant phenotype (MIC values exceeding 8 mg/L) [37].

Vancomycin, a glycopeptide antibiotic, continues to be a crucial treatment for MRSA-BSI. However, certain *S. aureus* phenotypes exhibit resistance to vancomycin: heterogeneous vancomycin-intermediate *S. aureus* (hVISA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA), with global prevalence rates of 4.6%, 1.7%, and 1.5%, respectively [34]. VRSA strains typically display vancomycin MIC values of 16 mg/L or higher. Several mechanisms contribute to vancomycin resistance in *S. aureus*, with the primary one being reduced permeability and cell wall thickening, resulting in decreased vancomycin access to intracellular targets [35]. An alternative form of resistance stems from plasmid-mediated vancomycin resistance genes, predominantly *vanA*, which may have been acquired from enterococcal species [35]. VISA strains generally show vancomycin MIC values ranging from 4 to 8 mg/L. The primary mechanisms for reduced vancomycin susceptibility in VISA strains involve mutations in cell wall-associated genes, leading to thicker cell walls with more peptidoglycan layers, and/or mutations in the ribosomal gene *rpoB* [36]. In contrast, hVISA strains exhibit MICs within the susceptible range (≤2 µg/mL) but contain a subpopulation expressing a resistant phenotype with MIC values exceeding 8 mg/L [37].

4.3. Resistance mechanisms to drugs other than beta-lactams: daptomycin and linezolid

Streptomyces roseosporus produces daptomycin, a cyclic lipopeptide that serves as a crucial non-beta-lactam alternative to vancomycin for treating MRSA infections. In the presence of calcium ions at physiological levels (50 µg/ml), daptomycin attaches to the bacterial cell membrane, causing depolarization through potassium ion efflux from the cytoplasm [38]. This process disrupts cellular membrane function and homeostasis, impeding essential bacterial processes. Daptomycin resistance in *S. aureus* is uncommon [38]. Several factors may contribute to daptomycin non-susceptibility: 1) enhanced positive surface charge of the bacterial membrane due to increased outer layer phospholipids; 2) changes in membrane fluidity resulting from alterations in fatty acid composition; 3) elevated carotenoid pigment levels; and 4) increased teichoic acid production in the cell wall. Previous studies have documented combinations of these factors [39]. Mutations in genes involved in phospholipids metabolism and cell wall permeability are also associated to resistance to daptomycin (*mprF, yycG, cls2, pgsA, vraS*) [38].

Linezolid, a non-beta-lactam anti-MRSA therapeutic option, is a representative oxazolydinone drug. Its mechanism of action is based on the inhibition of bacterial protein synthesis by binding to bacterial ribosomes at the 50S subunit through interaction with the 23S ribosomal RNA, thus obstructing protein synthesis [40]. Resistance of *S. aureus* to linezolid is rare. Linezolid is synthetic in nature, and it was assumed that no resistance gene pool exists in microorganisms [41]. Resistance is based on mutations in 23S rRNA (G2575T, G2576T, G2576U, G2447T, and T2500A), *cfr* (chloramphenicol-florfenicol resistance), mutations in ribosomal proteins (L3 and L4), and other rare mechanisms (hypermutations, homologous recombination). The product of *the cfr* gene is a methyltransferase enzyme that causes methylation of the 23S rRNA gene region known as A2503, mediating resistance to linezolid, chloramphenicol, and clindamycin [42].

4.4. Resistance mechanisms to drugs other than beta-lactams: new lipoglycopeptides

Among the new antibiotics effective against MRSA are dalbavancin and oritavancin, which are classified as long-acting lipoglycopeptides. Dalbavancin functions similarly to vancomycin but offers enhanced potency, greater protein binding, and a significantly longer elimination half-life, up to 60 times that of vancomycin [43]. Nevertheless, VISA and hVISA strains may exhibit reduced susceptibility to dalbavancin [44]. In certain instances, resistance to dalbavancin was accompanied by cross-resistance to vancomycin and daptomycin, attributed to similar mutations in genes involved in cell wall metabolism [45,46]. Oritavancin, on the other hand, works by inhibiting cell wall synthesis and bacterial RNA synthesis, as well as increasing membrane permeability. Unlike dalbavancin, oritavancin has demonstrated antibacterial activity against *vanA*-

positive *S. aureus* isolates [47]. Oritavancin resistance among clinical isolates has not yet been detected; non-susceptible isolates are rare or have not yet been reported.

4.5. When genotypic and phenotypic data are not consistent

Discrepancies between genotypic and phenotypic laboratory methods for MRSA detection could be present when: 1) a resistance gene is detected in an *S. aureus* isolate that is phenotypically susceptible to the predicted agents affected by the resistance gene; and 2) a resistance gene is not detected, but the isolate is found to be resistant to the predicted agents by phenotypic testing. In *S. aureus*, molecular detection of *mecA/SCCmec* in association with oxacillin (and cefoxitin) phenotypic susceptibility could be related to inactive PBP2a, nonfunctional SCCmec remnant, nonfunctional *mecA* gene, and to low or heterogeneous expression of *mecA* gene (the last two are susceptible to oxacillin but resistant to cefoxitin). Moreover, *mecC*-positive strains are commonly resistant to cefoxitin and susceptible to oxacillin *in vitro*. On the other hand, phenotypic detection of resistance to oxacillin, in the absence of the *mecA* gene, could be related to the presence of BORSA or MODSA phenotypes (resistance to oxacillin or borderline resistance to oxacillin, but susceptible to cefoxitin) [48]. Critical evaluation of both molecular and phenotypic results is of utmost importance for optimal treatment assessment.

5. The conundrum of MRSA-BSI classification

Clinicians have consistently endeavored to classify the severity of MRSA-BSI due to various diagnostic objectives (metastatic foci detection), therapeutic management strategies (drug types and treatment duration), and different outcomes. Precise stratification of risk factors could enhance diagnostic efficiency by minimizing unnecessary testing in low-risk patients while ensuring more comprehensive evaluations for those at higher risk of complications. The classical dichotomy between complicated and uncomplicated MRSA-BSI attempts to address this requirement. At present, there is no consensus regarding the precise definitions of 'complicated' and 'uncomplicated' SAB (henceforth uSAB and cSAB, respectively), a controversy that involves also MSSA infections, although here only MRSA is of interest.

Many classifications exist: the most utilized considers bacteremia clearance, metastatic localizations, prosthetic material, and clinical course, as stated by the 2011 version of the Infectious Diseases Society of America (IDSA) guidelines [49].

Typically, uSAB is characterized by an eventful clinical course without evidence of deep-seated or metastatic infection, whereas cSAB involves more severe, potentially life-threatening progression [50,51].

The following factors have historically been seen to be crucial for distinguishing between uSAB and cSAB: i) slow bacteremia clearance; ii) metastatic or deep-seated infections; iii) implanted prosthetic material; iv) fever persistence and not usual clinical symptoms; v) hemodialysis-dependency; vi) acquisition in community rather than in hospital (Figure 1).

With regard to bacteremia clearance: in uSAB, blood cultures typically become negative within 48–72 h after initiating appropriate antibiotic therapy [52]. Persistent bacteremia beyond this period is highly indicative of cSAB. According to Fowler et al., persistent bacteremia is associated with a significantly higher risk of complications such as IE and metastatic infections [53].

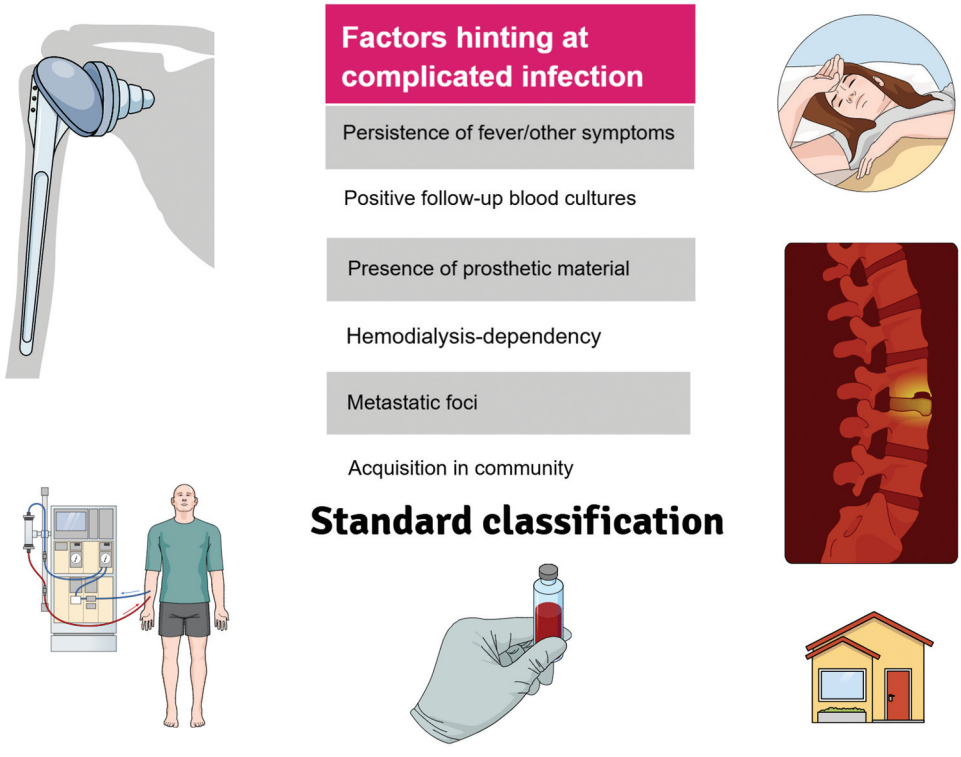

Figure 1. Factors hinting at complicated *Staphylococcus aureus* bacteremia (SAB) according to standard classification.

Similarly, a study by Chang et al. demonstrated that persistent bacteremia lasting beyond 72 h is a strong predictor of adverse outcomes, including metastatic spread and increased mortality [54]. At any rate, a precise definition of persistent SAB remains elusive pertaining to timing: it is likely that, rather than a strict temporal threshold, there exists an incremental risk of worse outcomes associated with each additional day of positive blood cultures. A study encompassing 884 cases of infection (13.4% caused by MRSA) demonstrated that as the duration of bacteremia increased, there was a statistically significant increase of metastatic complications, length of hospital stay, and 30-day mortality rates [55].

About metastatic or deep-seated infections: uSAB lacks evidence of infection dissemination to other anatomical sites, differently from cSAB that is often associated with such complications, that can be clinically silent, and so even more worrisome, in up to 70% of cases [53]. Foci of infection can include bones and joints (osteomyelitis and septic arthritis, respectively), lungs or pleura (pneumonia or empyema), surgical wounds, skin and soft tissues (cellulitis and myositis), the central nervous system, the genitourinary tract, the hepatobiliary system (hepatic infection or splenic abscesses), and the heart (IE) [56]. Multiple sites of infection can occur within a single individual. In a seminal review, Holland et al. emphasized the necessity of resorting to proper imaging techniques to identify these serious complications [57]. Of note, IE, likely the most relevant complication, occurs in around 10–20% of cases, but in almost half of them known predisposing risk factors are lacking, and typical signs (e.g. murmur, embolic events) may be absent [58].

With regard to implanted prosthetic material: the presence of prosthetic devices (e.g. heart valves and joint replacements) significantly increases the risk of *S. aureus* biofilm formation, which can lead to persistent infection. Kaasch et al. demonstrated that SAB in patients with prosthetic devices is associated with a higher likelihood of metastatic infections, particularly IE [59]. Even in the absence of visible signs of infection at the prosthetic site, the difficulty in eradicating *S. aureus* from biofilms renders these cases challenging to manage.

About fever resolution and peculiar symptoms: in uSAB, fever should resolve within 72 h of treatment initiation. However, persistent fever suggests that the infection is either uncontrolled or has disseminated. Fowler et al. showed that persistent fever is a reliable indicator of a more severe infection and higher complication risk [53]. Ongoing fever despite appropriate therapy is frequently associated with complications, such as deep-seated infections [60]. Novel or exacerbating symptoms during an episode of SAB, such as back pain (indicative of vertebral osteomyelitis) or joint pain (suggestive of septic arthritis), constitute common warning signs of a complicated infection. As elucidated by Ringberg et al., metastatic complications of SAB can often present challenges in early detection; however, they are frequently associated with a severe clinical course [61]. Novel heart murmurs, which may indicate IE, were reported as strong predictors of cSAB in studies by Fowler et al. [53] and Tubiana et al. [62].

With regard to hemodialysis-dependency: not only patients on dialysis are at higher risk of SAB [63]], but when suffering from infection they show notable rates of metastatic complications, persistent bacteremia, and BSI-attributable mortality [64].

Eventually, about the epidemiological origin: historically, nosocomial cases of SAB have been considered less likely to lead to complications due to earlier diagnosis and easier identification of a primary site of portal entry with associated source control if necessary (e.g. central line removal) [65]. However, when determining whether a case of SAB is complicated or not, these aspects inherent to nosocomial acquisition must be balanced against the potential elevated morbidity burden of a hospitalized patient [65].

The classic classification tends to skew the clinical determination of cSAB, as patients at higher risk but without cSAB would be treated as complicated forms. Furthermore, this classification may lack precision because it does not focus on the definitive diagnosis (endocarditis, osteomyelitis, catheter-related infection), but rather solely on the SAB characteristics. The uncomplicated/complicated dichotomy (Table 1), while having significant treatment implications (particularly for duration of treatment), inadequately captures the heterogeneity of

Table 1. Characteristics of complicated and uncomplicated *Staphylococcus aureus* bacteremia (SAB).

SAB	Characteristics	References
Uncomplicated	The following criteria must all be met: • Negative blood cultures 2–4 days post-initial set • Resolution of fever within 72 h of initiating effective therapy • Absence of prosthetic material • Absence of endocarditis and metastatic infection	[49]
Complicated	The following are considered indicators of a complicated infection: • Metastatic foci: Presence of infection spread to distant sites. • Infection beyond primary focus: Spread of infection to contiguous tissues or organs. • Positive follow-up blood cultures: Persistent bacteremia, often associated with metastatic infection and increased mortality. • Relapses: Recurrence of infection after initial apparent resolution. Patient-specific factors suggesting a complicated infection include: • Persistent fever: Unresolved fever despite appropriate therapy. • Presence of prosthetic material: Increased risk of persistent infection. • Hemodialysis dependence: Compromised immune status and increased risk of complications.	[50–53]

SAB []. A key flaw in the current definition of cSAB is the conflation of risk factors for metastatic infection (host characteristics, features of the bacteremia, and clinical course) with the actual presence of infectious metastasis that unequivocally represents a sign of complication. This can result in presumptive treatment for cSAB based solely on risk, even in the absence of confirmed metastatic infection. On the other hand, delayed diagnosis of complications can lead to misclassification and subsequent undertreatment. Given these limitations, a more effective SAB classification system or new diagnostic strategies are needed to guide the diagnostic workup. Recently, Kouijzer et al. proposed a novel risk stratification for SAB, categorizing patients as low or high risk for metastatic infection based on factors such as underlying host conditions (e.g. prosthetic devices, use of venous catheters, history of injection drug use, or previous episodes of IE), specific characteristics of the bacteremia (including its duration, time to blood culture positivity, communitarian acquisition, or delay in initiating treatment), and the patient's clinical course (persistent fever, unidentified infection source, or signs of metastatic localization) [66]. For low-risk patients, additional diagnostic workup may not be necessary, allowing them to proceed with antibiotic therapy for uSAB. In contrast, high-risk patients should undergo further diagnostic evaluations to exclude metastatic infections and ensure an accurate diagnosis and tailored antibiotic therapy [59,67]. This in-depth workup would ideally reveal the extent and nature of the *S. aureus* infection (Figure 2).

The new proposed risk stratification system aims to establish a diagnosis of cSAB in a stepwise manner, going beyond the mere equivalence of risk factors with confirmed metastatic infection. This novel tool requires validation, and areas of uncertainty persist, particularly for patients initially categorized as 'undetermined risk.' A recent Korean study demonstrated promising results regarding its application, tested in 380 patients with MRSA-BSI, of which 6.3% were classified as low-risk, 7.6% as indeterminate-risk, and 86.1% as high-risk for metastatic infections [68]. Such outcomes occurred in 0% of low-risk, 6.9% of indeterminate-risk, and 19.6% of high-risk patients. Consequently, efforts are necessary to reduce the high number of cases initially classified as 'high-risk' or 'indeterminate,' emphasizing the need for refinement and improved diagnostic precision [68].

6. A structured approach to evaluate patients with MRSA-BSI

In the light of its relevant prognostic implications [69], the management of SAB in general and of MRSA-BSI in particular necessitates a coordinated set of actions, including not only appropriate antimicrobial therapy but also non-antibiotic measures, especially aimed at identifying complicated courses that require specific further interventions such as source control [70].

A structured approach to patient evaluation is essential for timely diagnosis, appropriate treatment, and improved outcomes. This approach should incorporate a comprehensive history, thorough physical examination, targeted laboratory testing, and appropriate imaging studies (Figure 3).

A key challenge in managing SAB is identifying patients at high risk of metastatic infections. Studies have investigated baseline risk factors for metastatic infection in SAB, grouping

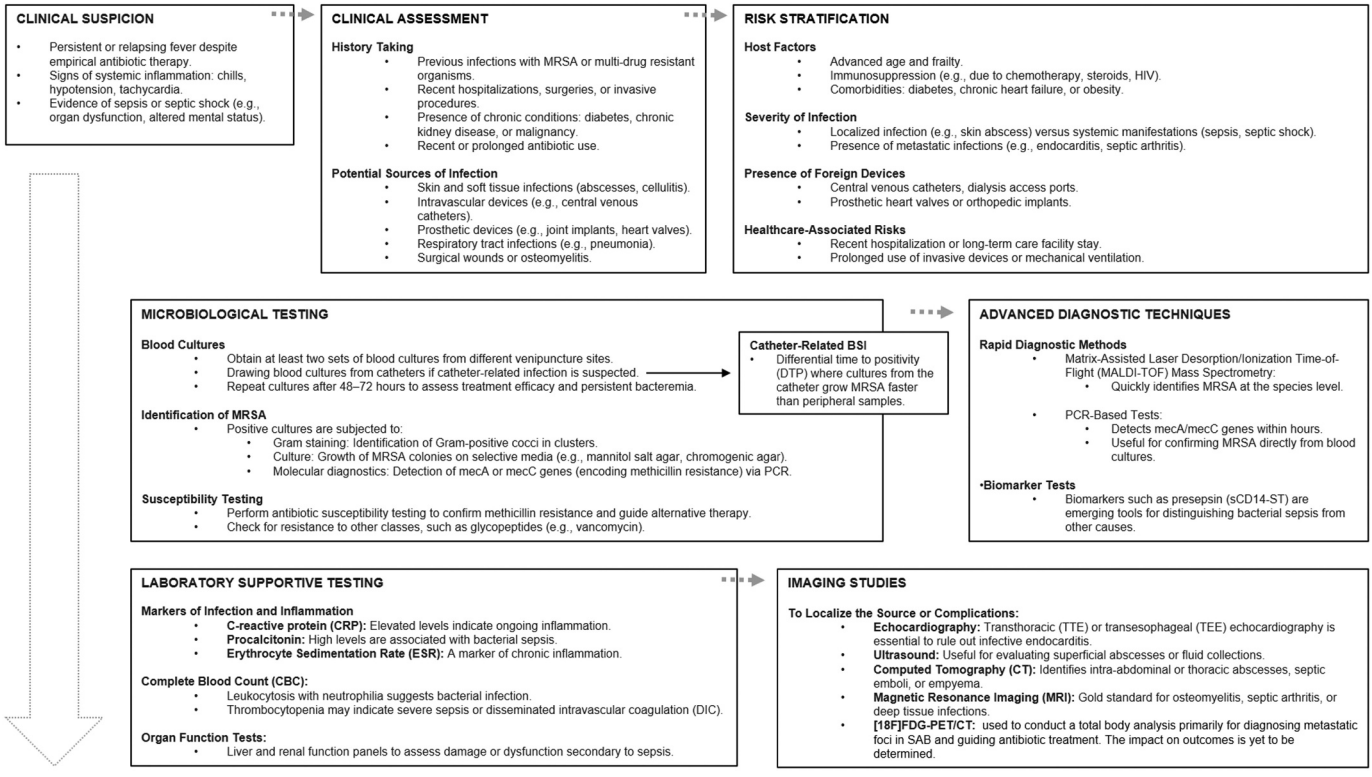

Figure 2. Diagnosis of MRSA bloodstream infections (MRSA-BSI). The diagnosis of MRSA-BSI is critical for timely management and involves a combination of clinical evaluation, microbiological testing, and advanced imaging techniques.

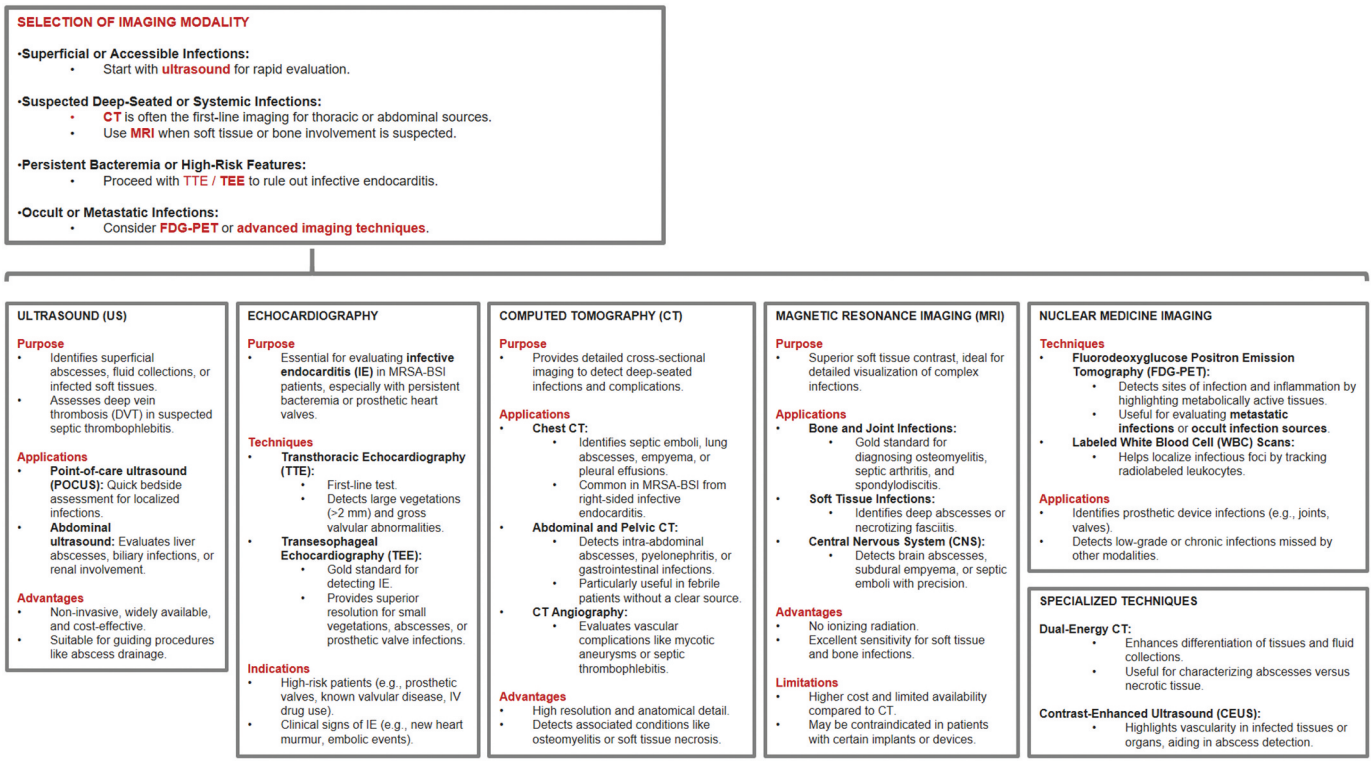

Figure 3. Diagnostic imaging for MRSA bloodstream infections (MRSA-BSI). Imaging plays a critical role in diagnosing MRSA-BSI by identifying infection sources, detecting complications, and guiding interventions.

these factors into several key areas as outlined above: host characteristics, features characteristics of the bacteremia, clinical presentation, and the intensity of the inflammatory response as reflected by inflammatory biomarkers [52,55,71].

While effective in promoting judicious testing by limiting it to low-risk patients, baseline risk factor assessment alone is insufficient to precisely identify all patients at high risk for adverse outcomes. In fact, while the absence of these factors suggests a lower probability of metastatic complications, it does not exclude them. A significant proportion of patients lacking these risk factors can still develop metastatic infections [68]. Effective risk stratification can facilitate more comprehensive evaluation of high-risk patients, but it is not sufficient on its own. A combination of interventions, including repeated physical examinations, follow-up blood cultures (FUBCs) and targeted imaging, is crucial for detecting potential complications, including metastatic disease (Figure 3).

The issue of FUBCs deserves special attention. Because identifying persistent positive blood cultures improves SAB management and outcomes, FUBCs after initiating therapy are essential [72]. Indeed, persistent positive blood cultures after starting effective antimicrobial therapy for SAB strongly predict complications (e.g. metastatic infection, endocarditis) and mortality [55]. Patients with positive FUBCs at or after 2 days of therapy are considered at risk for cSAB, while those with positive blood cultures at or after 4 days are considered to have cSAB [73,74].

However, methodological biases can complicate the interpretation of follow-up blood culture data. Indeed, there is no consensus on the optimal number of blood culture sets for detecting persistent bacteremia [75]. Blood culture sensitivity is highly dependent on volume, and fluctuating positivity (including the 'skip phenomenon') can occur in SAB [76,77]. Furthermore, the blood volume needed for adequate sensitivity during active antibiotic treatment remains not adequately investigated. Regarding timing, most studies empirically examine FUBCs within 2–4 days of starting therapy, taking them every 48 h until negative [49,74]. To ensure acceptable detection of persistent SAB and minimize the risk of the skip phenomenon, a recent study recommends collecting at least two blood culture sets (four bottles) on days 2 and 4 of therapy. Collecting fewer than two sets is strongly discouraged, as this could miss over 25% of persistent cases [78].

Likewise, a comprehensive instrumental assessment for potential complications and metastatic sites is crucial (Figure 4) [56]. Undetected foci of infection are linked to higher mortality rates in SAB. Rapid identification of metastatic *S. aureus* foci is essential for optimal diagnosis. Improving the detection and control of these infection sources could lead to better patient outcomes.

Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) scans are widely used diagnostic tools in clinical practice. Their importance and sensitivity in detecting potential metastatic foci are well-established and exemplified in Figure 4. Of particular interest, however, are several innovative and combined diagnostic techniques not yet widely implemented, but with the potential to significantly enhance diagnostic capabilities in this area [].

2-[^{18}F]fluoro-2-deoxy-d-glucose positron emission tomography with combined computed tomography ([^{18}F]FDG-PET/CT) has emerged as a promising diagnostic tool due to its high sensitivity for extracardiac infections [79,80]. Nonrandomized

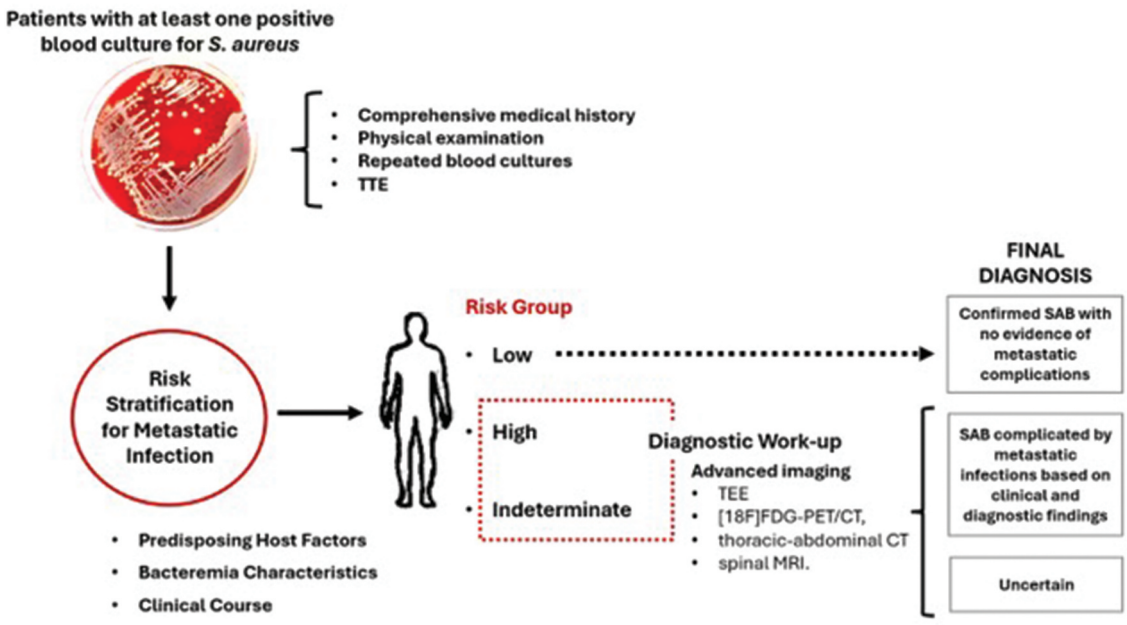

Figure 4. Proposal for a new approach for diagnosis in adults with SAB according to Kouijzer IJE et al. [89].

Note: Risk Group were defined as: 1) *Low* - Lack predisposing factors, negative TTE, blood cultures positive for less than 48 h, hospital-acquired infections, no persistent fever, prompt antibiotic initiation, and no clinical signs of metastatic infection; 2) *High* - predisposing factors or clinical suspicion of IE (based on TTE findings), clinical signs of metastatic infection, implanted prostheses, blood cultures positive for more than 48 h, delayed antibiotic initiation, persistent fever; *Indeterminate* - Do not meet criteria for either low or high risk.

[^{18}F]FDG-PET/CT = 2-[^{18}F]fluoro-2-deoxy-d-glucose positron emission tomography with combined computed tomography; CT = computed tomography; MRI = magnetic resonance imaging; SAB = *Staphylococcus aureus* bacteremia; TEE = transesophageal echocardiography.

studies indicate that [^{18}F]FDG-PET/CT effectively identified metastatic infection foci, including those previously undetected, resulting in increased source control interventions, reduced relapse rates, and decreased mortality in high-risk SAB [79–83]. However, a recent study showed that after adjusting for immortal time bias, [18F]FDG-PET/CT was not associated with 90-day all-cause or infection-related mortality in patients with SAB [84].

The timing of [18F]FDG-PET/CT within the first 14 days after positive blood cultures can vary (early or late) depending on the clinical scenario, potential impact, and expected benefit: In early PET/CT, the suggested clinical scenario is severe clinical presentation and poor response to treatment, with early source control as the potential impact and improved survival as the expected benefit. In late PET/CT, the suggested scenario is a patient with a prosthetic device in situ or SAB with an unknown source. The potential impact of the diagnostic tool is the exclusion of focal infection, and the expected benefits are stopping antibiotic therapy or switching from intravenous to oral treatment [85].

^{18}F-FDG-PET can also be used in combination with MRI [86]. 18F-FDG-PET/MRI, a hybrid imaging technique, combines the sensitivity of PET for detecting metastatic foci with the high-resolution detail of MRI, showing promise for improved staging of SAB [86]. This emerging technology is particularly useful for detecting occult SAB foci, especially in the lower extremities, a common site of infection in patients with diabetes mellitus. Extending the standard imaging field (skull vertex to upper thighs) to include the feet allows for a comprehensive whole-body assessment in a single scan. This approach reduces the need for multiple scans and minimizes ionizing radiation exposure compared to 18F-FDG-PET/CT, a significant advantage for younger patients [86]. Furthermore, 18F-FDG-PET/MRI has demonstrated utility in localized bone and joint infections, offering superior soft tissue information compared to 18F-FDG-PET /CT [87–89].

Further attention is warranted regarding the instrumental contribution to diagnosing infective endocarditis, given the severity of this potential complication. Echocardiography is standard practice for evaluating IE in SAB. Transthoracic echocardiography (TTE) is widely available, safe, inexpensive, and represents the standard of care for patients with SAB. Transesophageal echocardiography (TEE) is recommended with a low threshold when transthoracic echocardiography is negative but clinical suspicion for IE persists, particularly in patients with cardiac implantable electronic devices or prosthetic heart valves [90]. Several multivariable prediction rules and clinical tools, including the PREDICT [91], VIRSTA [62], and POSITIVE [92] scores, have been proposed to risk-stratify patients with SAB for IE and help in determining the need for TEE [93]. Conversely, the combined absence of specific risk factors and adverse prognostic features in SAB may obviate the need for TEE. Overall, TEE demonstrates superior sensitivity compared to TTE for detecting IE in SAB, irrespective of patient risk factors [94]. Whenever feasible, patients with SAB should undergo TEE to assess evidence of IE, particularly when results may influence clinical management.

Finally, an additional aspect worthy of consideration in the structured approach to SAB is the impact of infectious diseases consultation (IDC), which, based on an evidence synthesis of solely observational studies (with varying proportions of MRSA-BSI cases), was found to approximately halve the mortality risk [95]. It is probable that the IDC itself does not

significantly improve the prognosis of SAB patients; rather, the role of IDC serves as a catalyst for fulfilling the bundle of actions (e.g. FUBCs, TEE) necessary for optimal case management [70].

7. Pharmacological features of the main antimicrobial options

The optimization of the available agents for the management of MRSA-BSI should be performed according to the 'antimicrobial puzzle' concepts, considering that wide variations among the different alternatives exist in terms of physicochemical, pharmacokinetic (PK), and pharmacodynamic (PD) features [96]. From a PK/PD point of view, the choice of the most appropriate anti-MRSA agent should be taken into account the bactericidal activity, the penetration into deep-seated sites of infection in case of secondary BSI, and the existence of pathophysiological alterations which may affect the attainment of efficacy threshold concentrations or leading to overexposure and consequent potential toxicity. Considering the high frequency of secondary infections, the knowledge about the features of antimicrobials also in sites different from the bloodstream is of utmost importance. A summary of physicochemical features, optimal pharmacokinetic/pharmacodynamic (PK/PD) target, requirement for dosing adjustment, and implementation of therapeutic drug monitoring (TDM)-guided strategy for each anti-MRSA agent is reported in Table 2.

7.1. PK/PD features of vancomycin, daptomycin, and linezolid

Vancomycin is characterized by high molecular weight, low-to-moderate protein binding (approximatively 10–50%), very low lipophilicity, and limited volume of distribution (0.4–1 L/Kg) [97]. According to its physicochemical and PK properties, vancomycin exhibits low penetration in deep-seated infections, including central nervous system infections (cerebrospinal fluid [CSF]-to-plasma ratio of 0–18%) [98] and pneumonia (lower than 40% in terms of relative penetration, being absolute concentrations in epithelial lining fluid [ELF] inadequate for attaining optimal PK/PD target) [99]. It should be noted that bactericidal activity of vancomycin is strictly dependent on inoculum size in MRSA infections, being affected at higher inoculum [100]. From a PK/PD point of view, the area under time-to-concentration curve-to-minimum inhibitory concentration (AUC/MIC) ratio represents the best predictor for vancomycin efficacy [97]. Although several evidence suggested that attaining an area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio >400 was significantly associated with higher eradication rate and lower mortality in patients affected by MRSA infections [100–104], recent guidelines recommended the attainment of a more aggressive PK/PD target (i.e. AUC/MIC ratio of 400–600) in critically ill patients with MRSA-BSI [105]. Administration by continuous infusion (CI) may be preferred over intermittent infusion for maximizing the attainment of optimal steady-state concentrations (i.e. 20–25 mg/L) and reducing the risk of nephrotoxicity [105].

Daptomycin is characterized by high molecular weight, relevant protein binding (approximatively 90–95%), very low lipophilicity (logP = −5), and limited volume of distribution (approximatively 7 L) [106], resulting in a moderate penetration in deep-seated infections: 70–90% in soft tissue/interstitial fluid [107], 117% in infected bone [108,109], good penetration in cardiac valve and vegetations [110]; on the other hand, penetration is below 1% in CSF [111,112] and there is sequestration by lung surfactant in case of pneumonia [113]. It exhibits a high and rapid bactericidal effect against MRSA [106], thus representing an optimal choice for the management of BSI. The AUC/MIC ratio represents the best predictor of daptomycin efficacy, being an AUC/MIC ratio value >438 or >1,061 required for bacteriostatic or bactericidal effect, respectively [114,115]. With regard to threshold concentrations for daptomycin efficacy and/or toxicity, a previous subgroup analysis including 108 patients receiving daptomycin 6 mg/kg/day for the management of BSI caused by MRSA with and/or without endocarditis found that a trough concentration (Cmin) ≥24.3 mg/L was significantly associated with an increased probability of a creatine phosphokinase (CPK) elevation [116]. Conversely, a peak concentration (Cmax) ≥60 mg/L was suggested as best efficacy threshold for attaining the desired AUC/MIC ratio [117].

Linezolid is characterized by low molecular weight, relatively low protein binding (approximatively 30%), moderate lipophilicity, and a volume of distribution of 36–47 L [118], resulting in optimal penetration in several deep-seated infections. Specifically, linezolid exhibits a penetration rate of approximatively 100% in ELF [119,120], 66–100% in CSF [121–125], 20.2–144% in muscle and subcutaneous/adipose tissue [126–128], and 51–109% in bone [129–131]. Considering its predominantly bacteriostatic activity against Gram-positive strains including MRSA, linezolid may not represent the first-line alternative for the management of BSI. The attainment of an AUC/MIC ratio of 80–120 represents the best PD index of linezolid efficacy against MRSA [132,133]. With regard to threshold concentrations for linezolid efficacy and/or toxicity, several evidence reported that Cmin >2 mg/L are required for efficacy whereas Cmin >8 mg/L are associated with an increased risk of thrombocytopenia [134–136,137]. Although approximately only 30% of linezolid is eliminated by renal route, dosing adjustment is strictly required in case of acute kidney injury of chronic kidney disease in order to minimize the risk of overexposure and consequent potential linezolid toxicity [138].

7.2. PK/PD features of fifth-generation cephalosporins

Fifth-generation cephalosporins (i.e. ceftaroline and ceftobiprole) exhibit common physicochemical and PK features with other beta-lactams, including low molecular weight and lipophilicity, limited volume of distribution (36 and 21.7 L for ceftaroline and ceftobiprole, respectively), low protein binding (15–28% for ceftaroline and 16% for ceftobiprole), and predominant renal clearance [139,140], thus resulting in low-to-moderate penetration in deep-seated infections. Whereas good penetration was found in muscle (approximatively 50% and 70% for ceftaroline and ceftobiprole, respectively) and subcutaneous tissue (47%–58% for

Table 2. Summary of physicochemical features, optimal PK/PD target, and requirement for TDM-guided strategy for the different anti-MRSA agents.

Anti-MRSA agent	Physicochemical features			Static/cidal activity	Optimal PK/PD target	Penetration in deep-sited infections	Threshold concentrations for efficacy	Threshold concentrations for toxicity	Requirement for dosing adjustment in special renal populations	Implementation of TDM-guided strategy
	MW	Protein binding	Solubility							
Vancomycin	High	Moderate	Hydrophilic	Weakly bactericidal	AUC/MIC=400-600	Low-to-moderate	C_{ss} = 20-25 mg/L C_{min} = 15-20 mg/L	C_{ss} >25 mg/L C_{min} >20 mg/L (nephrotoxicity)	Highly recommended	Highly recommended
Daptomycin	High	High	Hydrophilic	Highly bactericidal	AUC/MIC > 1061	Moderate	C_{min} < 24.3 mg/L C_{max} > 60 mg/L	C_{min} >24.3 mg/L (increase in serum CPK levels and muscular toxicity)	Highly recommended	Recommended
Linezolid	Low	Moderate	Lipophilic	Bacteriostatic	AUC/MIC = 80-120	High	C_{min} 2-8 mg/L	C_{min} > 8 mg/L (thrombocytopenia)	Recommended	Highly recommended
Fifth-generation cephalosporins (ceftaroline/ceftobiprole)	Low	Low	Hydrophilic	Highly bactericidal	100%$fT_{>4xMIC}$	Moderate	C_{ss} or C_{min}/MIC > 4	NA	Highly recommended	Highly recommended
Novel lipoglycopeptides (dalbavancin/oritavancin)	High	High	Hydrophilic	Bactericidal	*f*AUC/MIC >111.1 (only for dalbavancin)	Moderate	C_{min} > 8.04 mg/L (only for dalbavancin)	NA	Recommended	Recommended (for dalbavancin only)

AUC: area under time-to-concentration curve; C_{max}: peak concentration; C_{min}: trough concentration; C_{ss}: steady-state concentration; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*; MW: molecular weight; NA: not available; PK/PD: pharmacokinetic/pharmacodynamic; TDM: therapeutic drug monitoring.
Deep green box: optimal activity; light green box: good activity; yellow box: some concerns in efficacy/safety profile; red box: non-optimal activity.

ceftaroline and 49% for ceftobiprole) [141–143], poor penetration rate was reported in ELF (approximatively 25%) [144,145] and in bone (6–22%) [146]. Although data on CSF penetration of fifth-generation cephalosporins are currently limited, a PK behavior similar to those reported for other cephalosporins was reported in preclinical models, being drug penetration strictly associated with the levels of meningeal inflammation [147,148]. From a PK/PD point of view, both ceftaroline and ceftobiprole exhibit time-dependent bactericidal activity against *S. aureus*, being their efficacy associated with the percentage of the dosing interval that the free concentration is maintained above the MIC of the targeted pathogen (%fT>MIC) [149,150]. Preclinical studies found that a 32.1–35%fT>MIC was associated with 2-log-kill activity against MRSA with ceftaroline, although a fT>MIC less than 50% was associated with MRSA regrowth and four-fold MIC increased to ceftaroline [149,151]. Similarly, a hollow-fiber model found that a 29.3%fT>MIC was associated with 2-log-kill activity against MRSA with ceftobiprole [150]. From a clinical point of view, the attainment of a 54.2–55-0%fT>MIC was an independent predictor of microbiological response in patients receiving ceftaroline for the management of acute bacterial skin and skin structure infections [152]. Similarly, attaining a 51.1%fT>MIC was independently associated with clinical cure among patients receiving ceftobiprole for pneumonia [153]. Overall, these findings may suggest the need for attaining aggressive PK/PD targets with fifth-generation cephalosporins as recently reported for Gram-negative infections in order to suppress resistance emergence [154]. In this scenario, the administration by CI may ensure the attainment of aggressive PK/PD target with ceftaroline and ceftobiprole [155,156].

7.3. PK/PD features of new lipoglycopeptides

Novel lipoglycopeptides (dalbavancin and oritavancin) are characterized by high molecular weight, long half-life (approximatively 10 days for dalbavancin and 14–16 days for oritavancin), and high protein binding (93% for dalbavancin and 85% for oritavancin), whereas volume of distribution was limited for dalbavancin (approximatively 7–9 L) and larger for oritavancin (approximatively 1 L/Kg) [157,158]. These physicochemical and PK features result in good penetration of dalbavancin in skin (approximatively 60%) [159], lung (approximatively 36%) [160,161], and bone (approximatively 13.1% coupled with the attainment of absolute bone concentrations able to provide optimal activity against MRSA up to MIC90) [159], whereas low penetration was found in peritoneal fluid (approximatively 5.2%) [162] and CSF [163]. Similarly, oritavancin exhibits a moderate penetration in skin (approximatively 19%) [164] and bone [165], whereas penetration in CSF is less than 5% [166]. Both agents showed high bactericidal activity against MRSA [167]. A preclinical in vivo model found that the attainment of a fAUC/MIC ratio >111.1 ensured 2-log kill activity against MRSA [168]. According to this PK/PD target, a recent proof-of-concept found that a total dalbavancin plasma concentration of 4.02 and 8.04 mg/L ensured the attainment of optimal PK/PD target against S. aureus isolates showing an MIC value equal to MIC90 or clinical breakpoint, respectively [169]. Conversely, no PK/PD target of efficacy currently exists for oritavancin against MRSA.

Therapeutic drug monitoring (TDM) may represent the best tool for ensuring the attainment of optimal PK/PD target with each anti-MRSA agent [170]. A recent international position paper concerning the usefulness and the adoption of a TDM-guided strategy in critically ill patients stated that TDM is highly recommended for vancomycin, beta-lactams, and linezolid [171], thus including most of the current available agents for treating MRSA-BSI. In regard to daptomycin, the expert panel neither recommend nor discourage the adoption of a TDM-guided strategy, whereas no recommendations were provided for novel lipoglycopeptides [171]. However, in regard to dalbavancin, several evidence recently suggested the clinical relevance of adopting a TDM-guided strategy specifically in the scenario of long-term staphylococcal infections requiring at least 6 weeks of treatment [169,172–176]. The expert interpretation of TDM results according to 'antimicrobial puzzle' concepts and the identification of the proper timing in which performing TDM and subsequent reassessments represent crucial issues that should be carefully taken into account in the adoption of a TDM-guided strategy for the management of MRSA-BSI [177].

8. Treatment

The treatment of MRSA-BSI is a multifaceted and dynamic process, involving decisions that span antimicrobial selection, treatment duration, and strategies for addressing complicated and persistent infections. Another aspect is the possibility to transitioning from intravenous to oral treatment allowing completion of therapy after hospital discharge.

8.1. The cornerstone of antimicrobial therapy for MRSA-BSI

Vancomycin has long been regarded as the gold standard for treating significant invasive MRSA infections in general [178], and MRSA-BSI in particular [57]. Vancomycin remains recommended as the first-line treatment for MRSA-BSI in the United States [49] and Europe [179,180]. There have been occasional challenges to its place in therapy; however, the available evidence has disproved the notion that patients with high MIC values within the susceptible range (≥1.5 mg/L) will experience poorer outcomes [181,182] and that the so-called 'MIC creep phenomenon,' namely the progressive increase in vancomycin MIC values for *S. aureus*, has a negative clinical impact [183]. Vancomycin is one of the few drugs originating from the 1950s that remains available in the pharmacological armamentarium, and its long-lasting use is attributed to the consistently high percentage of vancomycin susceptibility demonstrated by *S. aureus* strains over the years [184]. Nevertheless, its limitations are well-documented, encompassing toxicity (particularly renal), narrow therapeutic window, and, most notably, suboptimal efficacy: otherwise, the persistently elevated mortality associated with MRSA-BSI (exceeding one-fourth of cases) would be unexplained [184].

However, no randomized clinical trial (RCT) has demonstrated inferiority of vancomycin compared with other options for MRSA-BSI, so it remains the (imperfect) reference drug.

This appears even more striking considering that for decades vancomycin has been utilized in a manner inconsistent with the most current understanding of its PK/PD

characteristics, as previously elucidated. The current recommendations advocate for an AUC-guided dosing approach utilizing Bayesian software, superseding the through-only monitoring method [105]. Anyway, it is important to note that this paradigm shift is not supported by RCT data and may require substantial resources, an investment that may not be feasible in all healthcare facilities [185]. From a more pragmatic perspective, clinicians should utilize the resources available to them to guide the dosing of vancomycin [186].

Of course, no advanced dosing methods were implemented in the seminal RCT run by Fowler and colleagues around 20 years ago, comparing vancomycin with the bactericidal lipopeptide daptomycin for BSI and right-sided endocarditis related to *S. aureus*, proving non-inferiority of the latter [187]. Actually, MRSA infections represented less than half cases (38%, 89/235), analyzed separately with confirmation of the main results also in the specific subset [188]. No further RCTs have been published on this comparison, thus evidence syntheses have predominantly included observational studies [189,190]. In essence, the findings from Maraolo et al. [189] were more recently replicated by Adamu and colleagues [190]: daptomycin was associated with lower OR of mortality, although not in a statistically significant fashion, but the impact on the composite outcome 'clinical failure' (although variably defined across studies) was relevant for MRSA-BSI when using vancomycin as comparator (OR 0.58; 95% 0.38–0.89 in the first meta-analysis; OR 0.62; 95% 0.41–0.94 in the second one). Of note, daptomycin appeared to be safer, definitely less associated with treatment discontinuation due to safety issues (OR 0.15; 95% CI 0.06–0.36) [189].

Therefore, daptomycin, that has the great advantage of convenient once-daily dosing, has become the main alternative to vancomycin for MRSA-BSI [70], although controversies regarding its optimal utilization persist [191]. In addition to pharmacoeconomic considerations, given the cost-effectiveness of the inexpensive vancomycin, other concerns are the treatment-emergent resistance and the dosage conundrum [178]. In the registrational trial, the standard daily dose of 6 mg/Kg was implemented [187], but subsequent evidence pointed at improved efficacy at higher doses (8–10 mg/Kg) [192].

The latest 'player' sifted through a proper RCT for MRSA-BSI is ceftobiprole, a fifth-generation cephalosporin [193]. Ceftobiprole was tested against daptomycin for cSAB in a population of 390 adult hospitalized patients, of which about 24% had MRSA-BSI, and proved to be non-inferior: overall treatment success was 69.8% versus 68.7% [194]. Of note, in the MRSA subgroup clinical success was lower for ceftobiprole (percentage-point difference −8.3%; 95% CI −25.3-8.6), although not significantly considering the non-inferiority margin equal to −15% [194]. Another important aspect was the dosage regimen: in the majority of patients receiving daptomycin, the administered dose did not exceed 7 mg/kg/day, although the protocol permitted doses up to 10 mg/kg; conversely, for the initial 8 days, ceftobiprole was administered at 500 mg/kg every 6 h [194], an increased frequency compared to the standard regimen of 500 mg/kg every 8 h [195].

8.2. Combination or monotherapy for MRSA-BSI: the dilemma

The interest in combination therapy in this setting arose from the recognition that vancomycin was an imperfect gold standard and that no other monotherapy regimen demonstrated superior efficacy in a high-quality RCT [178]. The underlying rationale for combination therapy is predicated on the potential synergistic effects between diverse drug classes, with the aim of enhancing the likelihood of rapid microbiological eradication, clinical success, and ultimately, improved patient survival [196].

One of the most significant theoretical foundations about combination regimens is the 'seesaw effect:' an inverse relationship between glycopeptides or daptomycin and beta-lactam MICs in MRSA [197]. Essentially, through mechanisms not yet fully elucidated (e.g. altered maturation of PBP2A), the susceptibility to beta-lactams increases at the expense of the susceptibility to the backbone [197]. Furthermore, synergy between daptomycin and beta-lactams has been well-established for a considerable period [198]. Another agent potentially useful in combination regimens is fosfomycin: a bactericidal antibiotic that inhibits an enzyme-catalyzed reaction (the formation of the peptidoglycan precursor UDP *N*-acetylmuramic acid) in the first step of the synthesis of the bacterial cell wall, showing synergism with both beta-lactams and daptomycin [199]. Other experts advocated the role of adjunctive protein synthesis inhibitor antibiotics for toxin suppression in severe *S. aureus* infections [200].

A series of RCTs has tested several combination strategies against different backbones, either specifically for MRSA-BSI or in mixed populations (both MSSA and MRSA), but clear superiority of the combination therapy has not been demonstrated. In Table 3, the main features and the salient findings of these studies are summarized [201–207], although more granular analysis of them is available elsewhere [196,208].

In essence, these results are consistent with pooled available evidence addressing the role of combination therapy for MSSA-BSI [209]. The association between a beta-lactam as backbone with manifold types of companion drugs did not impact positively on mortality, neither in older studies, such as a RCT from Finland featuring levofloxacin with or without rifampicin as third drug for deep-seated infections [210], nor in more recent trials testing daptomycin [211] or fosfomycin [212] as adjunctive therapy. A potential benefit was observed in reducing relapses/recurrences, although countered by a greater burden of adverse events [209].

The latest European guidelines on endocarditis still backed the adjunctive role of gentamicin for prosthetic valve infections from either MSSA or MSSA [213], but already available evidence in favor of this stance was quite low [214]. As shown in the systematic review by Grillo and colleagues on MSSA, for BSI with or without IE the addition of the aminoglycoside to the beta-lactam backbone did not yield a clinical benefit [209]. Regarding MRSA-BSI, the seminal RCT by Fowler et al. actually was a study comparing a combination therapy relying on a backbone agent plus gentamicin (at low dose for 4 days) with daptomycin, even though the aminoglycoside could be added in the latter arm when patients were diagnosed with left-sided IE, but *de facto* the proportion of adjunctive gentamicin was 0.8% in

Table 3. Summary of randomized controlled trials testing combination therapy versus monotherapy for MRSA-BSI.

Source (authors), Publication year	Country, Time period	Population	Percentage of MRSA cases	Regimens		Outcomes	Main findings (ITT population if not otherwise stated)
				Combination	Monotherapy		
CAMERA-1 (Davis et al.) [201]	Australia, from January 2011 to May 2014	60 adult patients randomized within 48 hours of the first positive blood culture obtained (1.7% with endocarditis)	100%	Vancomycin 1.5 g bid plus flucloxacillin 2 g qid for the first 7 days after randomization	Vancomycin 1.5 g bid	Primary: duration of bacteremia (mean days)	1.94 versus 3.00 days ($p = 0.06$)
						Secondary: 28- and 90-day mortality, metastatic infection, nephrotoxicity, or hepatotoxicity	No difference (e.g. 28-day mortality 16% versus 17%, $p = 0.91$)
NCT00871104 (Pericàs et al) [202]	Spain, from October 2009 to December 2014	15 adult patients randomized if they had received less than 72 hours of active antibiotic therapy (53.3% with endocarditis)	100%	Fosfomycin 2 g qid plus imipenem 1 g qid	Vancomycin 30–45 mg/kg daily divided into 2–3 doses to maintain trough levels at least or above 15 mg/L	Primary: persistent bacteremia at seven days Secondary: clearance of blood cultures at 72 h after the initiation of study treatment, safety issues, relapses and mortality during treatment, at four or at 12 weeks of follow up	Overall, cure rates were 50% versus 43%
ARREST (Thwaites et al.) [203]	Australia, from December 2012 to October 2015	758 adult patients randomized if they had received less than 96 hours of active antibiotic therapy (4% with endocarditis)	6%	Backbone antibiotic (active *in vitro*) plus rifampicin 600 mg/die or 900 mg/die	Backbone antibiotic (active *in vitro*)	Primary: time to bacteriologically confirmed treatment failure or disease recurrence, or death (all-cause), from randomization to 12 weeks	17% versus 18% experienced the composite outcome (HR 0.94; 95% CI 0.68–1.35), 34.6% versus 13.3% in the MRSA subgroup (HR 2.74; 95% CI 0.74–10.15)
						Secondary: time to all-cause mortality from randomization to 2 weeks; time to death or clinically defined treatment failure or disease recurrence from randomization to 12 weeks; duration of bacteremia; safety	No differences except that there were higher drug-modifying adverse events in the rifampicin group (17% versus 10%, $p = 0.004$), and more frequent drug interactions (6% versus 2%, $p = 0.005$)
NCT02660346 (Geriak et al.) [204]	United States, from February 2016 to December 2016	40 adult patients randomized within 72 hours of the first positive blood culture obtained (10% with endocarditis)	100%	Daptomycin 6–8 mg/Kg/die plus ceftaroline 600 mg tid	Vancomycin at a dosage to maintain trough levels of 15 to 20 µg/mL or daptomycin 6–8 mg/Kg/die	Primary: duration of bacteremia and in-hospital mortality	No deaths in the intervention group opposed to 26% in the comparator arm leading to early cessation of the study; median days of bacteremia 3 in both arms ($p = 0.56$)
						Secondary: later (60- and 90-day) mortality and length of hospital stay	No deaths at 90 days in in the intervention group opposed 30% of cases in the comparator arm; median days of hospital stay 11 versus 12 ($p = 0.24$)
CAMERA-2 (Tong et al.) [205]	Australia, Singapore, Israel, and New Zealand from August 2015 to July 2018	356 adult patients randomized within 72 hours of the first positive blood culture (4.3% with endocarditis)	100%	Vancomycin at a dosage to maintain trough levels of 15 to 20 µg/mL or daptomycin 6–10 mg/Kg/die plus a beta-lactam for the first 7 days after randomization (flucloxacillin 2 g qid or cloxacillin 2 g qid)	Vancomycin at a dosage to maintain trough levels of 15 to 20 µg/mL or daptomycin 6–10 mg/Kg/die	Primary: composite of mortality at day 90, persistent bacteremia at day 5, microbiological relapse, and microbiological failure	35% versus 39% (RD − 4.2; 95% CI − 14.3 to 6.0)
						Secondary: all-cause mortality at 14, 42, and 90 days; persistent bacteremia; AKI; microbiological failure or relapse, treatment duration	No difference about mortality; RD was −8.9% (95% CI − 16.6 to − 1.2) regarding persistent bacteremia at day 5 but AKI was 23% versus 6% (RD 17.2; 95% CI 9.3 to 25.2) leading to early termination

(*Continued*)

Table 3. (Continued).

Source (authors), Publication year	Country, Time period	Population	Percentage of MRSA cases	Regimens		Outcomes	Main findings (ITT population if not otherwise stated)
				Combination	Monotherapy		
NCT01898338 (Pujol et al.) [206]	Spain, from December 2013 to November 2017	167 adult patients randomized within 72 hours of the first positive blood culture (11.6% with endocarditis among the 155 patients composing the mITT)	100%	Daptomycin 10 mg/Kg/die plus fosfomycin 2 g qid mg/kg of daptomycin intravenously daily	Daptomycin 10 mg/Kg/die	Primary: treatment resolution at TOC (alive and resolution of clinical manifestations of infection and negative blood cultures after completion of therapy)	54.1% versus 42.0% (RR 1.29; 95% CI 0.93–1.8), relatively to the mITT
						Secondary: persistent bacteremia, microbiological failure (persistent or bacteremia or emergence of resistance), safety issues, overall mortality	Relatively to the mITT, no difference about mortality at test of cure (24.3% versus 27.2%, RR 0.9; 95% CI 0.53–1.54), higher treatment discontinuation rate due to safety issues in the combination arm (17.6% versus 4.9%, RR 3.56; 95% CI 1.21–10.44), no cases of microbiological failure at TOC in the combination group (0% versus 11.1%, $p = 0.003$)
CASSETTE (Campbell et al.) [207]	Australia, from July 2018 to October 2020.	34 patients, both pediatric (32.4%) and adult randomized within 72 hours of the first positive blood culture (20.6% with endocarditis)	23.5%	Standard therapy (flucloxacillin or cefazolin for MSSA, vancomycin or daptomycin or ceftarolin for MRSA) plus clindamycin 10 mg/kg/dose in children or 450–600 mg tid/qid in adults for 7 days	Standard therapy (flucloxacillin or cefazolin for MSSA, vancomycin or daptomycin or ceftarolin for MRSA)	Primary: number of days alive and free of SIRS within 14 days post-randomization (mean)	4.76 versus 4.59 (no significant difference)
						Secondary: all-cause mortality, time to first resolution of SIRS, relapse, microbiological failure, safety issues	No significant difference, but no deaths were reported up to 90 days in the combination arm, whereas in the comparator group there were three cases of exitus at 42 days and four at 90 days

AKI: acute kidney injury; BID: bis in die; BSI: bloodstream infection CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; mITT: modified intention-to-treat; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible; QID; quarter in die; RR: relative risk; SIRS: systemic inflammatory response syndrome; TID: ter in die; TOC: test-of-cure.

the daptomycin arm and 93% in anti-staphylococcal penicillin/vancomycin group [187]. Notably, in the MRSA subgroup daptomycin was administered always as stand-alone therapy [188]. As previously stated, daptomycin turned out to be non-inferior, another brick in the wall of evidence against the routinary use of combination therapy [187,188].

At any rate, what stands out from Table 3 is the remarkable statistical, clinical, and methodological heterogeneity of the RCTs published so far: different regimens, diverse dosages and antibiotic duration, highly variable proportion of IE, disparate outcomes. Often sample size was very limited, as it happened for the study showing more favorable results for the association of daptomycin and ceftaroline [204]. Despite their differences, these RCTs shared a common objective: they were conceived to test combination as upfront therapy.

On the other hand, this approach might be reserved as salvage therapy in case of persistent BSI or clinical failure. Unfortunately, no RCT to date has addressed this question [215]. Observational studies have the further limitation of highly varying definitions of bacteremia persistence and treatment failure [216]. Moreover, rescue therapy may simply imply switching from a monotherapy to another stand-alone regimen: a study from the Veterans Affairs cohort in the United States suggested a clinical benefit in early transitioning from vancomycin to daptomycin even in the absence of failure criteria [217]. However, salvage therapy often relies on different combination schemes, featuring vancomycin or daptomycin as backbone [217]. Given the absence of a standardized treatment protocol or universally preferred regimen for this scenario, each patient should be assessed on a case-by-case basis, ensuring effective source control and verifying the clearance of FUBCs [218].

8.3. Duration of treatment and strategies for safe discharge

The current trend in the field of antibiotic therapy is to minimize the duration of treatment courses, with the aims of reducing selective pressure, a significant driver of resistance, mitigating the risk of adverse events, including those associated with prolonged hospital stays, and enhancing quality of life [219]. A very recent RCT showed non-inferiority of a 7-day course compared with a 14-day course for BSI by many pathogens with 90-day mortality as main outcome: nonetheless, this study excluded patients with SAB, owing to the peculiar virulence factors of *S. aureus*, enabling it to adhere to host tissues and cause metastatic infection [220].

The research question at hand is: what is the optimal duration of therapy for MRSA-BSI? The necessity of categorizing this entity into complicated and uncomplicated forms is not merely an academic exercise but rather serves as the foundation for developing a definitive treatment plan [66]. In summary, the established practice is based on a 14-day course for uncomplicated MRSA-BSI [49,179], whereas extended durations (28–42 days) are recommended in cases of cSAB [49,179]; even more prolonged periods of therapy may be required for patients who exhibit delayed clearance of bacteremia [221].

Abbreviating treatment duration in cases of SAB may be associated with increased risk due to reduced efficacy rates [49]. However, on an individual basis, a course shorter than 14 days might be considered, although it is important to note that the supporting evidence in this instance is derived solely from observational studies with undefined or low proportions of MRSA cases, thus limiting immediate generalization to MRSA-BSI [222].

However, upon determining a specific duration of treatment, the subsequent question arises: can patients be safely discharged to complete their courses at home? In this regard, a pivotal RCT was the POET study, which recruited patients with left-sided IE [223]. The study demonstrated that transitioning to oral antibiotic treatment (after fulfilling strict criteria of clinical stability) was noninferior to continued intravenous antibiotic treatment, considering a composite primary outcome of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, and relapse of bacteremia [223]. Following randomization, the median length of hospital stay (not a prespecified outcome) was 3 days in the orally treated group and 19 days in the intravenously treated group ($p < 0.001$) [223]. Of note, *S. aureus* accounted for 21.8% of cases, but all were MSSA, therefore, once again external validity for MRSA-BSI in its most important complicated form was hampered [223].

Oral step-down with cotrimoxazole (the association between trimethoprim and sulfamethoxazole) for MRSA-BSI has been proposed by the United Kingdom guidelines (weak recommendation), in case of known susceptibility, but there is no guidance about the type of patient potentially benefitting from this approach [180].

SABATO was a trial just published in 2024 specifically focused on oral step-down in SAB, precisely in what researchers defined as low-risk infections, a synonym for uSAB [224]. According to the protocol, after 5–7 days of intravenous antimicrobial therapy patients were randomized to oral antimicrobial therapy or to continue intravenous standard therapy with a total duration of antimicrobial therapy of 14 days. For MRSA-BSI, the oral options were cotrimoxazole and linezolid; the primary outcome was a composite of relapsing BSI, development of deep-seated infection, and mortality attributable to infection [224]. The trial met its non-inferiority criterion (with a predetermined margin of 10%), as the primary endpoint occurred in 13% of the intervention group compared to 12% in the control group, yielding a treatment difference of 0.7% (95% CI; −7.8–9.1) [224]. However, two significant limitations were identified: an exceptionally low enrollment rate, potentially due to stringent inclusion criteria that resulted in only 213 patients being randomized from a pool of 5,063 screened subjects; and the limited size of the MRSA subgroup (7.5%, 16/213), with no complications observed in the oral therapy group (and a single event in the control arm), thereby constraining the broader applicability of the findings [224].

In real-world studies, the main oral options, only in the setting of step-down therapy, for MRSA-BSI are cotrimoxazole, linezolid, clindamycin, and doxycycline [225]. Supporting data, even for BSI with IE, are predominantly observational in nature, especially concerning cotrimoxazole and linezolid [226]. In spite of their high bioavailability, safety, and tolerability concerns are not negligible, and there are also issues about ideal dosages: for instance, the recommended daily dose of cotrimoxazole can range from 960 mg to 4,800 mg [226]. Of note, cotrimoxazole at high dose (3,840 mg/die in

total, administered first intravenously and then orally at physicians' discretion) was inferior to vancomycin as upfront therapy (pre-specified margin was 15%) for MRSA infections in an RCT studying 252 patients of which 91 (36%) had BSI with treatment failure as primary composite outcome including 7-day death: the worst prognosis of patients in the cotrimoxazole arm was confirmed in the subgroup of BSI even in a multivariable analysis [227]. Reappraisal of some RCTs to identify BSI cases in studies comparing linezolid and vancomycin enabled to perform a pooled analysis showing no differences in outcomes, although in a limited number of patients: 24 out of 36 (67%) patients treated with linezolid survived, in comparison to 24 out of 37 (65%) patients who received vancomycin treatment [228].

An intriguing option to replace oral switching is the implementation of long-acting antimicrobials like dalbavancin and oritavancin [229]. Although these drugs are currently licensed only for treating acute bacterial skin and soft tissue infections, their pharmacological characteristics suggest they could be valuable in managing severe or deep-seated infections such as BSI and IE [230]. The utilization of these antimicrobials is particularly attractive in scenarios where extended treatment, prompt hospital discharge, and avoiding or minimizing long-term intravenous catheter use are preferred [230]. If a patient fulfills the criteria of safe discharge (i.e. afebrile, microbiological clearance achieved, clinical stability), transitioning to oral medications is not always possible: the use of oral antibiotics may pose unacceptable safety risks due to patient-specific factors or the pathogen's resistance profile may be not permissive; additionally, concerns may arise regarding the medication's absorption or the patient's ability to adhere to oral administration, particularly for extended treatment periods [231]. In this respect, dalbavancin and oritavancin, with their long half-lives, might replace oral step-down therapy, even though so far no RCT data have been published to support this approach [230]. Moreover, their administration should be based on a well-organized service of outpatient parenteral antibiotic therapy to guarantee appropriate follow-up [231]. Indeed, a proper dose of dalbavancin and oritavancin may ensure a high likelihood of optimal probability of target attainment for 2 weeks, but in case of longer periods of treatment, TDM-driven management is advisable [172]. These long-acting antimicrobials may be used for sequential/consolidation therapy in patients with BSI. A recent experience of dalbavancin from the United States involved 115 cases, of which 54 (47%) were MRSA, both in uSAB and cSAB; the median time-to-administration of the drug was 10 days, the most common regimen was a single 1,500 mg administration, and the 90-day clinical failure rate was just 12.2% [232]. Similarly, in a cohort of 72 patients, of which 12 (17%) had MRSA-BSI, oritavancin was administered after a median of 11 days of prior antibiotic regimens; the most common dosage was 1,200 mg once, and the 90-day success rate was 86% [233]. Results of the dalbavancin as an option for treatment of SAB trial (DOTS, NCT04775953) are eagerly awaited to shed light on the role of the long-acting as consolidation strategy for MSSA- and MRSA-BSI.

9. Conclusion

The management of MRSA-BSI after decades of research still remains complex and characterized by numerous controversial aspects. A series of coordinated actions is required for a correct prognostication and a proper treatment plan; however, both areas require improvement and refinement. Combination therapy seems not to offer tangible advantages as upfront approach for all patients. There are some interesting antimicrobial options to reduce the duration of hospitalization. Further and well-conducted RCTs are necessary to update the current therapeutic paradigm.

10. Expert opinion

Twenty years have elapsed from the publication of the RCT supporting daptomycin as valid alternative to vancomycin for SAB including MRSA-BSI [53] and the ERADICATE study that proved non-inferiority of ceftobiprole versus daptomycin for the same indication [194]. In the meanwhile, no other breakthrough trials have come to light, whereas the field of invasive infections by Gram-negative pathogens has witnessed the advent of numerous novel drugs to keep the pace up with emergent mechanisms of resistance, especially toward carbapenems [234].

Although the stable susceptibility to the standard of care, vancomycin, over the decades, MRSA-BSI continues to pose a notable burden, associated with a mortality rate approaching 30% [27], comparable to the one of BSI by *Klebsiella pneumoniae* carbapenemases-producing or by carbapenem-resistant *Pseudomonas aeruginosa* [235], which represent menace of this century, whereas MRSA looms for a very longer time.

Considering that no revolutionary drugs able to dramatically modify the prognosis are on the horizon, the current efforts should be directed to find a more nuanced approach to MRSA-BSI, aiming at tailoring treatment strategies especially in the dawning era of personalized medicine.

A first step should be the establishment of a universally accepted definition of complicated (and conversely, uncomplicated) infection. Some authors have advocated a neat distinction among clinical endpoints of SAB: i) early death, associated with multi-morbidity and advanced age; ii) metastatic infection, primarily affecting the musculoskeletal system; ii) endocarditis, associated with delayed death in older individuals with multi-morbidity, and iv) bacteremia without complications [236]. Against this backdrop, an upstream assessment should imply that uSAB is represented by an episode without metastatic foci on presentation in a subject lacking host-related risk factors such as advanced age and comorbidities [236]. The treatment approach could be tailored accordingly, since an intensification of antimicrobial treatment (for instance, by a combination regimen, along with aggressive source control) might be more beneficial in cases with high bacterial load and/or impaired microbiological clearance, typically when the infection is already disseminated, than in cases in which patients' factors are predominant in influencing the prognosis [236]. The challenge ahead is also represented by the development of

a prognostic model not relying on the 'time factor,' as it occurs if data from FUBCs are needed, in order to speed up key decisions already on presentation.

To this regard, another avenue of research is the assessment of host biomarkers, which may be used either to better stratify the risk of a complicated/severe course upstream or to guide antimicrobial duration along the patient's path. A potential signature of heightened mortality risk may be identified in the inflammatory pathway, and probably interleukin (IL)-10 is the most promising marker [237]. IL-10 is a cytokine with relevant anti-inflammatory properties that regulates the immune response to pathogens; it prevents the activation of Th1 helper T cells and suppresses pro-inflammatory macrophage and cytokine production [215]. The link between increased risk of persistent BSI or death and the high serum levels of IL-10 may lie in higher intravascular peptidoglycan concentrations, reflecting an elevated *S. aureus* intravascular inoculum, leading to the stimulation of IL-10 production [238]. As matter of fact, some host genetic variations seem protective toward persistent SAB, both by MRSA or by MSSA, and the mechanistic basis should be the reduced production of IL-10 [239]. Other biomarkers appear to be associated with microbiological clearance, such as IL-1beta, in patients with MRSA-BSI: a robust IL-1beta response is elicited by beta-lactams (regardless of susceptibility of the pathogen) either alone or in combination with vancomycin or daptomycin [240]. In the small RCT by Geriak and colleagues that contrasted the association of daptomycin and ceftaroline with vancomycin monotherapy, the majority of patients with unfavorable outcome in the comparator arm (5/6) showed high baseline levels of IL-10 (above the threshold of 5 pg/ml), whereas no patient died in the intervention group, even among the ones with elevated levels of IL-10 [204]. According to some authors, all these data represent the rationale for a strategy entailing an upfront combination therapy based on vancomycin or daptomycin plus a beta-lactam in all patients with upstream high IL-10 concentrations [196]. The reduction of its levels may also guide therapy duration [196]. Of course, it would be interesting to understand if monotherapy with anti-MRSA beta-lactam such as ceftobiprole, approved in the United States for BSI after the ERADICATE results [194], would be more effective of a monotherapy relying on vancomycin or daptomycin in the subgroup of MRSA-BSI patients showing increased IL-10 levels at baseline.

Another way to refine duration of therapy may be related to the use of novel metagenomic next-generation sequencing (mNGS) techniques [241]. Indeed, in a cohort study of 66 patients with SAB (54.5% MRSA), microbial cell-free DNA (mcfDNA) sequencing detected *S. aureus* genetic material with higher sensitivity of 86% compared with conventional blood cultures and for a longer period of time, with each additional day of positivity almost tripling the likelihood of metastatic infection (OR 2.89; 95% CI, 1.53–5.46) [242]. Some authors have proposed to evaluate the feasibility of a trial investigating discontinuation of antibiotics for SAB in case of undetectable mNGS for *S. aureus* in two consecutive samples at 48- or 72-h intervals [241].

Regarding the therapeutic approach, as outlined above, combination therapy has not clearly demonstrated superiority over monotherapy so far, although findings from prevalently observational studies showed promise, especially when associating daptomycin with a beta-lactam (ceftaroline) in populations with high proportion of endocarditis (around one-third) [243]. To reconcile differences between RCTs and non-randomized studies, when addressing the question of combination therapy, probably a crucial factor is the correct definition of the target population, since the large majority of RCTs had very low number of patients with endocarditis (Table 3), the paramount complication of MRSA-BSI. Ideally, RCTs should be based on more homogeneous patients, since the marginal benefit of a combination therapy in subjects with low-risk or uncomplicated MRSA-BSI is likely very low. About the ideal regimen, the rationale backing the association between daptomycin and a beta-lactam such as ceftaroline has been extensively discussed. At any rate, the same reasoning regarding the benefit of the addition a beta-lactam applies to vancomycin, but disappointing results came from the CAMERA-2 trial, early terminated for safety concerns [205]. The RCT compared standard monotherapy (although daptomycin was allowed, 99% of patients in the control arm received vancomycin) with a combination regimen based on vancomycin plus flucloxacillin, cloxacillin, or cefazolin: any potential positive clinical impact was negated and outweighed by high rate of nephrotoxicity in the intervention arm [244]. Even not delving into the issue of the proper assessment of trial participants' true baseline kidney function [245], actually the risk of heightened nephrotoxicity significantly changed between patients adding to vancomycin an antistaphylococcal penicillin and the ones adding cefazolin [196], a difference rooted in the diverse kidney toxicity potential of the various beta-lactams [246]. Therefore, despite the results of CAMERA-2 [205], the research on combination regimens based on vancomycin should not be abandoned [196].

Pending novel studies for a more personalized approach with standard antibiotics as outlined above, another strategy would consist in resorting to adjuvants different from traditional antimicrobials, ideally to achieve more rapid killing, biofilm disruption, and toxin inhibition. A promising agent was exebacase, a first-in-class lysin produced from a bacteriophage-derived gene, a recombinant protein designed to be bactericidal, anti-biofilm, and synergistic with antibiotics: encouraging results stemmed from a proof-of-concept study testing the association of standard therapy plus exebacase versus standard therapy alone, especially for MRSA-BSI [247]. Unfortunately, in the subsequent phase 3 RCT, named DISRUPT, randomizing in a 2:1 ratio 250 patients with SAB (99/250, 36.5%, MRSA), clinical response rates at day 14 (a composite outcome including survival) were 59.4% in the exebacase arm versus 71.8% in the antibiotics alone group, and the same pattern was observed in the MSSA and in the MRSA subgroups [248]. Another weapon in the armamentarium of adjuvants might be phage therapy, although it would not be feasible as first-line approach but a potential resource for persistent infections [249].

Hopefully, some answers to the most urgent questions regarding SAB management will come from the *Staphylococcus aureus Network Adaptive Platform* (SNAP) trial, conceived to address multiple issues as efficiently and as rapidly as possible, both for MSSA and MRSA: about MRSA-BSI, one of the research questions is the benefit of adjunctive cefazolin for 7 days to daptomycin or vancomycin [250].

Eventually, in the light of the complexity of SAB management, especially concerning MRSA-BSI, prevention is an aspect that cannot be overlooked: there are vaccines and monoclonal antibodies under investigation to prevent hospital-acquired infections including the ones brought about by *S. aureus* [251], although no new drugs are anticipated to enter clinical practice in the very near future.

Instead, in the upcoming months, the publication of the joint guidelines between IDSA and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) on SAB management should occur. Some recommendations were presented as preview at the 2024 ESCMID global and the final version of the document is eagerly awaited to provide a high-profile guidance in this setting.

Funding

This paper was not funded.

Declaration of interest

Outside the submitted work, A.E. Maraolo reports participation in advisory boards for Angelini and Advanz Pharma as well as participation in speaker's bureau for Viatris. Outside the submitted work, M. Gatti reports personal fees from Angelini and participation in advisory boards for Advanz Pharma and Viatris. The remaining authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Tong SYC, Davis JS, Eichenberger E, et al. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603–661.

•• **A seminal review on all the most important aspects of Staphylococcus aureus infections.**

2. Shah RJ, Baltas I. Staphylococcus aureus bacteraemia for the general physician: a narrative review of a metastatic infection with malignant complications. Clin Med. 2024;24(6):100265. doi: 10.1016/j.clinme.2024.100265
3. Vestergaard M, Frees D, Ingmer H. Antibiotic resistance and the MRSA problem. Microbiol Spectr. 2019;7(2):7.2.18. doi: 10.1128/microbiolspec.GPP3-0057-2018
4. Jesudason T. WHO publishes updated list of bacterial priority pathogens. Lancet Microbe. 2024;5(9):100940. doi: 10.1016/j.lanmic.2024.07.003
5. Minter DJ, Appa A, Chambers HF, et al. Contemporary management of *Staphylococcus aureus* bacteremia—controversies in clinical practice. Clin Infect Dis. 2023;77(11):e57–e68. doi: 10.1093/cid/ciad500

•• **A very updated state-of-the-art review addressing the controversies of Staphylococcus aureus bloodstream infections.**

6. Holmes CL, Albin OR, Mobley HL, et al. Bloodstream infections: mechanisms of pathogenesis and opportunities for intervention. Nat Rev Microbiol. 2025;23(4):210–224. doi: 10.1038/s41579-024-01105-2

• **A notable review on the pathogenesis of bloodstream infections.**

7. Ikuta KS, Swetschinski LR, Robles Aguilar G, et al. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the global burden of disease study 2019. Lancet. 2022;400(10369):2221–2248.
8. Hassoun A, Linden PK, Friedman B. Incidence, prevalence, and management of MRSA bacteremia across patient populations—a review of recent developments in MRSA management and treatment. Crit Care. 2017;21(1):211. doi: 10.1186/s13054-017-1801-3
9. Turner NA, Sharma-Kuinkel BK, Maskarinec SA, et al. Methicillin-resistant Staphylococcus aureus: an overview of basic and clinical research. Nat Rev Microbiol. 2019;17(4):203–218. doi: 10.1038/s41579-018-0147-4
10. Kern WV, Rieg S. Burden of bacterial bloodstream infection—a brief update on epidemiology and significance of multidrug-resistant pathogens. Clin Microb Infect. 2020;26(2):151–157.
11. Laupland KB, Lyytikäinen O, Søgaard M, et al. The changing epidemiology of Staphylococcus aureus bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect. 2013;19(5):465–471. doi: 10.1111/j.1469-0691.2012.03903.x
12. Gagliotti C, Högberg LD, Billström H, et al. Staphylococcus aureus bloodstream infections: diverging trends of methicillin-resistant and methicillin-susceptible isolates, EU/EEA, 2005 to 2018. Euro Surveill. 2021 Nov;26(46):2002094. doi: 10.2807/1560-7917.ES.2021.26.46.2002094
13. Pezzani MD, Arieti F, Rajendran NB, et al. Frequency of bloodstream infections caused by six key antibiotic-resistant pathogens for prioritization of research and discovery of new therapies in Europe: a systematic review. Clin Microb Infect. 2024;30:S4–S13.
14. Renggli L, Gasser M, Buetti N, et al. Increase in methicillin-susceptible Staphylococcus aureus bloodstream infections in Switzerland: a nationwide surveillance study (2008–2021). Infection. 2023;51(4):1025–1031. doi: 10.1007/s15010-023-01980-6
15. Klevens RM, Edwards JR, Tenover FC, et al. Changes in the epidemiology of methicillin-resistant Staphylococcus aureus in intensive care units in US hospitals, 1992–2003. Clin Infect Dis. 2006;42(3):389–391. doi: 10.1086/499367
16. Kleyman R, Cupril-Nilson S, Robinson K, et al. Does the removal of contact precautions for MRSA and VRE infected patients change health care-associated infection rate? A systematic review and meta-analysis. Am J Infect Control. 2021;49(6):784–791. doi: 10.1016/j.ajic.2020.11.020
17. Almohaya A, Fersovich J, Weyant RB, et al. The impact of colonization by multidrug resistant bacteria on graft survival, risk of infection, and mortality in recipients of solid organ transplant: systematic review and meta-analysis. Clin Microbiol Infect. 2024;30(10):1228–1243. doi: 10.1016/j.cmi.2024.03.036
18. Zhu H, Jin H, Zhang C, et al. Intestinal methicillin-resistant *Staphylococcus aureus* causes prosthetic infection via 'Trojan Horse' mechanism: evidence from a rat model. Bone Joint Res. 2020;9(4):152–161. doi: 10.1302/2046-3758.94.BJR-2019-0205.R1
19. Yasmin M, El Hage H, Obeid R, et al. Epidemiology of bloodstream infections caused by methicillin-resistant Staphylococcus aureus at a tertiary care hospital in New York. Am J Infect Control. 2016;44(1):41–46. doi: 10.1016/j.ajic.2015.08.005
20. Capsoni N, Azin GM, Scarnera M, et al. Bloodstream infections due to multi-drug resistant bacteria in the emergency department: prevalence, risk factors and outcomes—a retrospective observational study. Intern Emerg Med. 2024 [cited 2025 Jan 14];online ahead of print.
21. Libert M, Elkholti M, Massaut J, et al. Risk factors for methicillin resistance and outcome of Staphylococcus aureus bloodstream infection in a Belgian University Hospital. J Hosp Infect. 2008;68(1):17–24. doi: 10.1016/j.jhin.2007.08.021

22. Bello-Chavolla OY, Bahena-Lopez JP, Garciadiego-Fosass P, et al. Bloodstream infection caused by S. aureus in patients with cancer: a 10-year longitudinal single-center study. Support Care Cancer. 2018;26(12):4057–4065.
23. Li Z, Zhuang H, Wang G, et al. Prevalence, predictors, and mortality of bloodstream infections due to methicillin-resistant Staphylococcus aureus in patients with malignancy: systemic review and meta-analysis. BMC Infect Dis. 2021;21(1):74. doi: 10.1186/s12879-021-05763-y
24. Manzur A, Vidal M, Pujol M, et al. Predictive factors of methicillin resistance among patients with Staphylococcus aureus bloodstream infections at hospital admission. J Hosp Infect. 2007;66(2):135–141. doi: 10.1016/j.jhin.2007.03.015
25. Lakhundi S, Zhang K. Methicillin-resistant Staphylococcus aureus: molecular characterization, evolution, and epidemiology. Clin Microbiol Rev. 2018;31(4):e00020–18.
• **An elegant review on the biological aspects of Staphylococcus aureus.**
26. Lang R, Gill MJ, Vu Q, et al. Longitudinal evaluation of risk factors and outcomes of blood stream infections due to Staphylococcus species in persons with HIV: an observational cohort study. EClinicalMedicine. 2021;31:100675. doi: 10.1016/j.eclinm.2020.100675
27. Bai AD, Lo CKL, Komorowski AS, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. Clin Microbiol Infect. 2022;28(8):1076–1084. doi: 10.1016/j.cmi.2022.03.015
•• **The most comprehensive systematic review with meta-analysis of the mortality burden linked with Staphylococcus aureus bloodstream infections.**
28. Bondi A, Dietz CC. Penicillin resistant staphylococci. Exp Biol Med. 1945;60(1):55–58. doi: 10.3181/00379727-60-15089
29. Gallagher LA, Coughlan S, Black NS, et al. Tandem amplification of the staphylococcal cassette chromosome *mec* element can drive high-level methicillin resistance in methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2017;61(9):e00869–17. doi: 10.1128/AAC.00869-17
30. Harrison EM, Ba X, Blane B, et al. PBP2a substitutions linked to ceftaroline resistance in MRSA isolates from the UK: table 1. J Antimicrob Chemother. 2016;71(1):268–269. doi: 10.1093/jac/dkv317
31. Hess KA, Kooda K, Shirley JD, et al. Failure of *mecA/mecC* PCR testing to accurately predict oxacillin resistance in a patient with Staphylococcus aureus infective endocarditis. Antimicrob Agents Chemother. 2023;67(10):e00437–23.
32. Hryniewicz MM, Garbacz K. Borderline oxacillin-resistant Staphylococcus aureus (BORSA) – a more common problem than expected? J Med Microbiol. 2017;66(10):1367–1373. doi: 10.1099/jmm.0.000585
33. Gostev V, Kalinogorskaya O, Ivanova K, et al. In vitro selection of high-level beta-lactam resistance in methicillin-susceptible Staphylococcus aureus. Antibiotics. 2021;10(6):637.
34. Shariati A, Dadashi M, Moghadam MT, et al. Global prevalence and distribution of vancomycin resistant, vancomycin intermediate and heterogeneously vancomycin intermediate Staphylococcus aureus clinical isolates: a systematic review and meta-analysis. Sci Rep. 2020;10(1):12689.
35. Tenover FC, Biddle JW, Lancaster MV. Increasing resistance to vancomycin and other glycopeptides in *Staphylococcus aureus*. Emerg Infect Dis. 2001;7(2):327–332. doi: 10.3201/eid0702.010237
36. Shoji M, Cui L, Iizuka R, et al. *walK* and *clpP* mutations confer reduced vancomycin susceptibility in *Staphylococcus aureus*. Antimicrob Agents Chemother. 2011;55(8):3870–3881. doi: 10.1128/AAC.01563-10
37. Chen H, Liu Y, Sun W, et al. The incidence of heterogeneous vancomycin-intermediate Staphylococcus aureus correlated with increase of vancomycin MIC. Diagn Microbiol Infect Dis. 2011;71(3):301–303. doi: 10.1016/j.diagmicrobio.2011.06.010
38. Gómez Casanova N, Siller Ruiz M, Muñoz Bellido JL. Mechanisms of resistance to daptomycin in Staphylococcus aureus. Rev Esp Quimioter. 2017;30(6):391–396.
39. Mishra NN, Rubio A, Nast CC, et al. Differential adaptations of methicillin-resistant *Staphylococcus aureus* to serial *in vitro* passage in daptomycin: evolution of daptomycin resistance and role of membrane carotenoid content and fluidity. Int J Microbiol. 2012;2012:1–6.
40. Besier S, Ludwig A, Zander J, et al. Linezolid resistance in *Staphylococcus aureus*: gene dosage effect, stability, fitness costs, and cross-resistances. Antimicrob Agents Chemother. 2008;52(4):1570–1572. doi: 10.1128/AAC.01098-07
41. Toh S, Xiong L, Arias CA, et al. Acquisition of a natural resistance gene renders a clinical strain of methicillin-resistant *Staphylococcus aureus* resistant to the synthetic antibiotic linezolid. Mol Microbiol. 2007;64(6):1506–1514. doi: 10.1111/j.1365-2958.2007.05744.x
42. Rafique H, Hussain N, Saeed MU, et al. Linezolid-resistance Staphylococcus aureus – prevalence, emerging resistance mechanisms, challenges and perspectives. J Pure Appl Microbiol. 2022;16(3):1492–1505.
43. Malabarba A, Goldstein BP. Origin, structure, and activity in vitro and in vivo of dalbavancin. J Antimicrob Chemother. 2005;55(suppl_2):ii15–ii20.
44. Citron DM, Tyrrell KL, Goldstein EJC. Comparative in vitro activities of dalbavancin and seven comparator agents against 41 Staphylococcus species cultured from osteomyelitis infections and 18 VISA and hVISA strains. Diagn Microbiol Infect Dis. 2014;79(4):438–440.
45. Werth BJ, Jain R, Hahn A, et al. Emergence of dalbavancin non-susceptible, vancomycin-intermediate Staphylococcus aureus (VISA) after treatment of MRSA central line-associated bloodstream infection with a dalbavancin- and vancomycin-containing regimen. Clin Microbiol Infect. 2018;24(4):.e429.1–.e429.5. doi: 10.1016/j.cmi.2017.07.028
46. Kussmann M, Karer M, Obermueller M, et al. Emergence of a dalbavancin induced glycopeptide/lipoglycopeptide non-susceptible *Staphylococcus aureus* during treatment of a cardiac device-related endocarditis. Emerging Microbes & Infections. 2018;7(1):1–10. doi: 10.1038/s41426-018-0205-z
47. Zhanel GG, Schweizer F, Karlowsky JA. Oritavancin: mechanism of action. Clin Infect Dis. 2012;54(suppl_3):S214–S219. doi: 10.1093/cid/cir920
48. Yee R, Dien Bard J, Simner PJ. The genotype-to-phenotype dilemma: how should laboratories approach discordant susceptibility results? McAdam AJ, editor. J Clin Microbiol. 2021;59(6):e00138–20.
49. Liu C, Bayer A, Cosgrove SE, 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. Clin Infect Dis. 2011;52(3):e18–e55.
•• **The 2011 guidelines from the Infectious Diseases Society of America about Staphylococcus aureus infections.**
50. Naber CK, Baddour LM, Giamarellos-Bourboulis EJ, et al. Clinical consensus conference: survey on Gram-Positive bloodstream infections with a focus on *Staphylococcus aureus*. Clin Infect Dis. 2009;48(s4):S260–S270. doi: 10.1086/598185
51. Hagel S, Bahrs C, Schumann R, et al. Complicated and uncomplicated S. aureus bacteraemia: an international delphi survey among infectious diseases experts on definitions and treatment. Clin Microbiol Infect. 2022;28(7):.e1026.7–.e1026.11.
52. Kuehl R, Morata L, Boeing C, et al. Defining persistent Staphylococcus aureus bacteraemia: secondary analysis of a prospective cohort study. Lancet Infect Dis. 2020;20(12):1409–1417. doi: 10.1016/S1473-3099(20)30447-3
53. Fowler VG, Olsen MK, Corey GR, et al. Clinical identifiers of complicated Staphylococcus aureus bacteremia. Arch Intern Med. 2003;163(17):2066. doi: 10.1001/archinte.163.17.2066
54. Chang F-Y, Peacock JE, Musher DM, et al. Staphylococcus aureus Bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore). 2003;82(5):333–339. doi: 10.1097/01.md.0000091184.93122.09
55. Minejima E, Mai N, Bui N, et al. Defining the breakpoint duration of Staphylococcus aureus bacteremia predictive of poor outcomes. Clin Infect Dis. 2020;70(4):566–573.
• **A relevant study to define the threshold for persistence of bacteraemia by Staphylococcus aureus.**

56. Goodman A, Cook G, Goh V. Imaging in the investigation and management of Staphylococcus aureus bacteraemia: a role for advanced imaging techniques. J Hosp Infect. 2020;105(2):234–241. doi: 10.1016/j.jhin.2020.01.007
57. Holland TL, Arnold C, Fowler VG. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA. 2014;312 (13):1330–1341. doi: 10.1001/jama.2014.9743
- **A useful review on the management of Staphylococcus aureus bloodstream infections.**
58. Rasmussen RV, Høst U, Arpi M, et al. Prevalence of infective endocarditis in patients with Staphylococcus aureus bacteraemia: the value of screening with echocardiography. Eur J Echocardiogr. 2011;12(6):414–420. doi: 10.1093/ejechocard/jer023
59. Kaasch AJ, Fowler VG, Rieg S, et al. Use of a simple criteria set for guiding echocardiography in nosocomial Staphylococcus aureus bacteremia. Clin Infect Dis. 2011;53(1):1–9. doi: 10.1093/cid/cir320
60. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, et al. Clinical management of Staphylococcus aureus bacteraemia. The Lancet Infect Dis. 2011;11(3):208–222.
61. Ringberg H, Thorén A, Lilja B. Metastatic complications of Staphylococcus aureus septicemia. To seek is to find. Infection. 2000;28(3):132–136.
62. Tubiana S, Duval X, Alla F, et al. The VIRSTA score, a prediction score to estimate risk of infective endocarditis and determine priority for echocardiography in patients with Staphylococcus aureus bacteremia. J Infect. 2016;72(5):544–553. doi: 10.1016/j.jinf.2016.02.003
63. Chaudry MS, Gislason GH, Kamper A, et al. Increased risk of Staphylococcus aureus bacteremia in hemodialysis—A nationwide study. Hemodial Int. 2019; 23(2):230–238. doi: 10.1111/hdi.12728
64. Sinclair MR, Souli M, Ruffin F, et al. Staphylococcus aureus bacteremia among patients receiving maintenance hemodialysis: trends in clinical characteristics and outcomes. Am J Kidney Dis. 2022;79 (3):393–403.e1.
65. Finkelstein R, Sobel JD, Nagler A, et al. Staphylococcus aureus bacteremia and endocarditis: comparison of nosocomial and community-acquired infection. J Med. 1984;15(3):193–211.
66. Kouijzer IJE, Fowler VG, ten Oever J. Redefining Staphylococcus aureus bacteremia: a structured approach guiding diagnostic and therapeutic management. J Infect. 2023;86(1):9–13.
•• **A novel proposal for classifying bloodstream infections by Staphylococcus aureus to provide an adequate treatment plan.**
67. Berrevoets MAH, Kouijzer IJE, Slieker K, et al. ^{18} F-FDG pet/ct–guided treatment duration in patients with high-risk *Staphylococcus aureus* bacteremia: a proof of principle. J Nucl Med. 2019;60(7):998–1002.
68. Kim T, Lee S-R, Park SY, et al. Validation of a new risk stratification system-based management for methicillin-resistant Staphylococcus aureus bacteraemia: analysis of a multicentre prospective study. Eur J Clin Microbiol Infect Dis. 2024;43(5):841–851.
69. Nambiar K, Seifert H, Rieg S, et al. Survival following Staphylococcus aureus bloodstream infection: a prospective multinational cohort study assessing the impact of place of care. J Infect. 2018;77(6):516–525.
70. Tiseo G, Brigante G, Giacobbe DR, et al. Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian society of infection and tropical diseases (SIMIT), the Italian society of anti-infective therapy (SITA), the Italian group for antimicrobial stewardship (GISA), the Italian association of clinical microbiologists (AMCLI) and the Italian society of microbiology (SIM). Int J Antimicrob Agents. 2022;60 (2):106611.
- **The Italian guidelines addressing multidrug-resistant pathogens including methicillin-resistant Staphylococcus aureus.**
71. Guimaraes AO, Cao Y, Hong K, et al. A prognostic Model of persistent bacteremia and mortality in complicated Staphylococcus aureus bloodstream infection. Clin Infect Dis. 2019;68(9):1502–1511.
72. Nagao M, Yamamoto M, Matsumura Y, et al. Complete adherence to evidence-based quality-of-care indicators for Staphylococcus aureus bacteremia resulted in better prognosis. Infection. 2017;45 (1):83–91. doi: 10.1007/s15010-016-0946-3
73. Rosa R, Wawrzyniak A, Sfeir M, et al. Performance of processes of care and outcomes in patients with *Staphylococcus aureus* bacteremia. J Hosp Med. 2016;11(1):27–32.
74. ten Oever J, Jansen JL, van der Vaart TW, et al. Development of quality indicators for the management of Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2019;74(11):3344–3351. doi: 10.1093/jac/dkz342
- **A Delphi consensus to identify quality indicators for the management of Staphylococcus aureus bacteraemia.**
75. Lee A, Mirrett S, Reller LB, et al. Detection of bloodstream infections in adults: how many blood cultures are needed? J Clin Microbiol. 2007;45(11):3546–3548. doi: 10.1128/JCM.01555-07
76. Cockerill FR, Wilson JW, Vetter EA, et al. Optimal testing parameters for blood cultures. Clin Infect Dis. 2004;38(12):1724–1730.
77. Fiala J, Palraj BR, Sohail MR, et al. Is a single set of negative blood cultures sufficient to ensure clearance of bloodstream infection in patients with Staphylococcus aureus bacteremia? The skip phenomenon. Infection. 2019;47(6):1047–1053.
78. Van Goethem S, Boogaerts H, Cuykx M, et al. Follow-up blood cultures in Staphylococcus aureus bacteremia: a probability-based optimization. Eur J Clin Microbiol Infect Dis. 2022;41 (10):1263–1268.
79. Berrevoets MAH, Kouijzer IJE, Aarntzen EHJG, et al. ^{18} F-FDG PET/CT optimizes treatment in *Staphylococcus aureus* bacteremia and is associated with reduced mortality. J Nucl Med. 2017;58 (9):1504–1510. doi: 10.2967/jnumed.117.191981
80. Vos FJ, Bleeker-Rovers CP, Sturm PD, et al. ^{18} F-FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. J Nucl Med. 2010;51(8):1234–1240.
81. Ghanem-Zoubi N, Kagna O, Abu-Elhija J, et al. Integration of FDG-PET/CT in the diagnostic workup for *Staphylococcus aureus* bacteremia: a prospective interventional matched-cohort study. Clin Infect Dis. 2021;73(11):e3859–e3866. doi: 10.1093/cid/ciaa929
82. Thottacherry E, Cortés-Penfield NW. Evidence of clinical impact supports a new petition for medicare coverage of 2-[18F]Fluoro-2-deoxy-D-Glucose positron emission tomography/Computed tomography in the evaluation of *Staphylococcus aureus* bacteremia: a focused literature review and call to action. Clin Infect Dis. 2022;75(8):1457–1461.
- **A useful review to quantify the benefit in the management of Staphylococcus aureus bacteraemia linked with the implementation of 2-[18F]Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography/Computed Tomography.**
83. Buis DTP, Sieswerda E, Kouijzer IJE, et al. [18F]FDG-PET/CT in Staphylococcus aureus bacteremia: a systematic review. BMC Infect Dis. 2022;22(1):282.
84. van der Vaart TW, Prins JM, van Werkhoven CH, et al. Positive impact of [18F]FDG-PET/CT on mortality in patients with *Staphylococcus aureus* bacteremia explained by immortal time bias. Clin Infect Dis. 2023;77(1):9–15.
- **An elegant study demonstrating the pitfalls arising from immortal time bias when investigating the impact of 2-[18F] Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography/ Computed Tomography in patients with Staphylococcus aureus bacteraemia.**
85. Kouijzer IJE, Ghanem-Zoubi N. The role of [18F]FDG-PET/CT in *Staphylococcus aureus* bacteremia: a clinical perspective. NPJ Image. 2024;2(1):32. doi: 10.1038/s44303-024-00036-0
86. Goodman AL, Packham A, Sharkey AR, et al. Advanced imaging for detection of foci of infection in Staphylococcus aureus bacteremia-can a scan save lives? Semin Nucl Med. 2023;53(2):175–183.
87. Henkelmann J, Henkelmann R, Denecke T, et al. Simultaneous 18F-FDG-PET/MRI for the detection of periprosthetic joint infections after knee or hip arthroplasty: a prospective feasibility study. Int Orthop (SICOT). 2022;46(9):1921–1928. doi: 10.1007/s00264-022-05445-7
88. Hulsen DJW, Mitea C, Arts JJ, et al. Diagnostic value of hybrid FDG-PET/MR imaging of chronic osteomyelitis. Eur J Hybrid Imag. 2022;6(1):15.

89. Kouijzer IJE, Scheper H, de Rooy JWJ, et al. The diagnostic value of 18F–FDG-PET/CT and MRI in suspected vertebral osteomyelitis – a prospective study. Eur J Nucl Med Mol Imaging. 2018;45(5):798–805.
90. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European society of cardiology (Esc)endorsed by: European Association for cardio-thoracic surgery (EACTS), the European Association of nuclear medicine (EANM). Eur Heart J. 2015;36(44):3075–3128.
91. Palraj BR, Baddour LM, Hess EP, et al. Predicting risk of endocarditis using a clinical tool (PREDICT): scoring system to Guide use of echocardiography in the management of Staphylococcus aureus bacteremia. Clin Infect Dis. 2015;61(1):18–28. doi: 10.1093/cid/civ235
92. Kahn F, Resman F, Bergmark S, et al. Time to blood culture positivity in Staphylococcus aureus bacteraemia to determine risk of infective endocarditis. Clin Microbiol Infect. 2021;27(9):.e1345.7–.e1345.12. doi: 10.1016/j.cmi.2020.11.007
93. van der Vaart TW, Prins JM, Soetekouw R, et al. Prediction rules for ruling out endocarditis in patients with *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2022;74(8):1442–1449. doi: 10.1093/cid/ciab632
94. Sekar P, Johnson JR, Thurn JR, et al. Comparative sensitivity of transthoracic and transesophageal echocardiography in diagnosis of infective endocarditis among veterans with Staphylococcus aureus Bacteremia. Open Forum Infect Dis. 2017;4(2):ofx035.
95. Vogel M, Schmitz RPH, Hagel S, et al. Infectious disease consultation for Staphylococcus aureus bacteremia – a systematic review and meta-analysis. J Infect. 2016;72(1):19–28. doi: 10.1016/j.jinf.2015.09.037
- **A systematic review about the impact of infectious disease consultation on the prognosis of patients with Staphylococcus aureus bacteraemia.**
96. Pea F, Viale P. The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships Be helpful in addressing the issue of appropriate pneumonia treatment in critically Ill patients? Clin Infect Dis. 2006;42(12):1764–1771.
- **A well-structured paper on the role of pharmacokinetics/pharmacodynamics principles in the optimization of antimicrobial therapy.**
97. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis. 2006;42(Supplement_1):S35–S39. doi: 10.1086/491712
98. Albanèse J, Léone M, Bruguerolle B, et al. Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an intensive care unit. Antimicrob Agents Chemother. 2000;44(5):1356–1358.
99. Cruciani M, Gatti G, Lazzarini L, et al. Penetration of vancomycin into human lung tissue. J Antimicrob Chemother. 1996;38(5):865–869. doi: 10.1093/jac/38.5.865
100. LaPlante KL, Rybak MJ. Impact of high-inoculum *Staphylococcus aureus* on the activities of Nafcillin, vancomycin, linezolid, and daptomycin, alone and in combination with gentamicin, in an in vitro pharmacodynamic Model. Antimicrob Agents Chemother. 2004;48(12):4665–4672.
101. Holmes NE, Turnidge JD, Munckhof WJ, et al. Vancomycin AUC/MIC ratio and 30-day mortality in patients with Staphylococcus aureus bacteremia. Antimicrob Agents Chemother. 2013;57(4):1654–63. doi: 10.1128/AAC.01485-12
102. Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet. 2004;43(13):925–942. doi: 10.2165/00003088-200443130-00005
103. Kullar R, Davis SL, Levine DP, et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis. 2011;52(8):975–981. doi: 10.1093/cid/cir124
104. Brown J, Brown K, Forrest A. Vancomycin AUC_{24}/MIC ratio in patients with complicated bacteremia and infective endocarditis due to methicillin-resistant Staphylococcus aureus and its association with attributable mortality during hospitalization. Antimicrob Agents Chemother. 2012;56(2):634–638. doi: 10.1128/AAC.05609-11
105. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American society of health-system pharmacists, the infectious diseases society of America, the pediatric infectious diseases society, and the society of infectious diseases pharmacists. Am J Health Syst Pharm. 2020;77(11):835–864. doi: 10.1093/ajhp/zxaa036
- **The guideline that reset the therapeutic drug monitoring of vancomycin.**
106. Gregoire N, Chauzy A, Buyck J, et al. Clinical pharmacokinetics of daptomycin. Clin Pharmacokinet. 2021;60(3):271–281. doi: 10.1007/s40262-020-00968-x
107. Kim A, Suecof LA, Sutherland CA, et al. In vivo microdialysis study of the penetration of daptomycin into soft tissues in diabetic versus healthy volunteers. Antimicrob Agents Chemother. 2008;52(11):3941–3946. doi: 10.1128/AAC.00589-08
108. Traunmuller F, Schintler MV, Metzler J, et al. Soft tissue and bone penetration abilities of daptomycin in diabetic patients with bacterial foot infections. J Antimicrob Chemother. 2010;65(6):1252–1257. doi: 10.1093/jac/dkq109
109. Montange D, Berthier F, Leclerc G, et al. Penetration of daptomycin into bone and synovial fluid in joint replacement. Antimicrob Agents Chemother. 2014;58(7):3991–3996. doi: 10.1128/AAC.02344-14
110. Tascini C, Di Paolo A, Poletti R, et al. Daptomycin concentrations in valve tissue and vegetation in patients with bacterial endocarditis. Antimicrob Agents Chemother. 2013;57(1):601–602.
111. Piva S, Di Paolo A, Galeotti L, et al. Daptomycin plasma and CSF levels in patients with healthcare-associated meningitis. Neurocrit Care. 2019;31(1):116–124. doi: 10.1007/s12028-018-0657-y
112. Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. Pediatr Drugs. 2013;15(2):93–117.
113. Taylor SD, Palmer M. The action mechanism of daptomycin. Bioorg & Med Chem. 2016;24(24):6253–6268. doi: 10.1016/j.bmc.2016.05.052
114. Louie A, Kaw P, Liu W, et al. Pharmacodynamics of daptomycin in a murine thigh Model of *Staphylococcus aureus* infection. Antimicrob Agents Chemother. 2001;45(3):845–851. doi: 10.1128/AAC.45.3.845-851.2001
115. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother. 2004;48(1):63–68.
116. Bhavnani SM, Rubino CM, Ambrose PG, et al. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis. 2010;50(12):1568–1574. doi: 10.1086/652767
117. Pea F, Cojutti P, Sbrojavacca R, et al. TDM-Guided therapy with Daptomycin and meropenem in a morbidly obese, critically Ill patient. Ann Pharmacother. 2011;45(7–8):1022–1022.
118. Roger C, Roberts JA, Muller L. Clinical pharmacokinetics and pharmacodynamics of oxazolidinones. Clin Pharmacokinet. 2018;57(5):559–575. doi: 10.1007/s40262-017-0601-x
119. Boselli E, Breilh D, Caillault-Sergent A, et al. Alveolar diffusion and pharmacokinetics of linezolid administered in continuous infusion to critically ill patients with ventilator-associated pneumonia. J Antimicrob Chemother. 2012;67(5):1207–1210.
120. Boselli E, Breilh D, Rimmelé T, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. Crit Care Med. 2005;33(7):1529–1533.
121. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal Fluid/Blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev. 2010;23(4):858–883.
122. Villani PB, Regazzi M, Marubbi F, et al. Cerebrospinal fluid linezolid concentrations in postneurosurgical central nervous system infections. Antimicrob Agents Chemother. 2002;46(3):936–937.

123. Beer R, Engelhardt KW, Pfausler B, et al. Pharmacokinetics of intravenous linezolid in cerebrospinal fluid and plasma in neurointensive care patients with staphylococcal ventriculitis associated with external ventricular drains. Antimicrob Agents Chemother. 2007;51(1):379–382. doi: 10.1128/AAC.00515-06
124. Myrianthefs P, Markantonis SL, Vlachos K, et al. Serum and cerebrospinal fluid concentrations of linezolid in neurosurgical patients. Antimicrob Agents Chemother. 2006;50(12):3971–3976. doi: 10.1128/AAC.00051-06
125. Luque S, Grau S, Alvarez-Lerma F, et al. Plasma and cerebrospinal fluid concentrations of linezolid in neurosurgical critically ill patients with proven or suspected central nervous system infections. Int J Antimicrob Agents. 2014;44(5):409–415. doi: 10.1016/j.ijantimicag.2014.07.001
126. Majcher-Peszynska J, Haase G, Saß M, et al. Pharmacokinetics and penetration of linezolid into inflamed soft tissue in diabetic foot infections. Eur J Clin Pharmacol. 2008;64(11):1093–1100.
127. Plock N, Buerger C, Joukhadar C, et al. Does linezolid inhibit its own metabolism?—population pharmacokinetics as a tool to explain the observed nonlinearity in both healthy volunteers and septic patients. Drug Metab And Dispos. 2007;35(10):1816–1823. doi: 10.1124/dmd.106.013755
128. Buerger C, Plock N, Dehghanyar P, et al. Pharmacokinetics of unbound linezolid in plasma and tissue interstitium of critically Ill patients after multiple dosing using microdialysis. Antimicrob Agents Chemother. 2006;50(7):2455–2463. doi: 10.1128/AAC.01468-05
129. Traunmüller F, Schintler MV, Spendel S, et al. Linezolid concentrations in infected soft tissue and bone following repetitive doses in diabetic patients with bacterial foot infections. Int J Antimicrob Agents. 2010;36(1):84–86. doi: 10.1016/j.ijantimicag.2010.03.007
130. Kutscha-Lissberg F, Hebler U, Muhr G, et al. Linezolid penetration into bone and joint tissues infected with Methicillin-Resistant Staphylococci. Antimicrob Agents Chemother. 2003;47(12):3964–3966.
131. Rana B. Linezolid penetration into osteo-articular tissues. J Antimicrob Chemother. 2002;50(5):747–750. doi: 10.1093/jac/dkf207
132. Andes D, van Ogtrop ML, Peng J, et al. In vivo pharmacodynamics of a new oxazolidinone (linezolid). Antimicrob Agents Chemother. 2002;46(11):3484–3489. doi: 10.1128/AAC.46.11.3484-3489.2002
133. Rayner CR, Forrest A, Meagher AK, et al. Clinical pharmacodynamics of linezolid in seriously Ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003;42(15):1411–1423. doi: 10.2165/00003088-200342150-00007
134. Pea F, Cojutti PG, Baraldo M. A 10-year experience of Therapeutic Drug monitoring (TDM) of linezolid in a hospital-wide population of patients receiving conventional dosing: Is there enough evidence for suggesting TDM in the majority of patients? Basic Clin Pharma Tox. 2017;121(4):303–308. doi: 10.1111/bcpt.12797
135. Pea F, Viale P, Cojutti P, et al. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012;67(8):2034–2042.
136. Cojutti PG, Merelli M, Bassetti M, et al. Proactive therapeutic drug monitoring (TDM) may be helpful in managing long-term treatment with linezolid safely: findings from a monocentric, prospective, open-label, interventional study. J Antimicrob Chemother. 2019;74(12):3588–3595.
137. Pea F, Furlanut M, Cojutti P, et al. Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. Antimicrob Agents Chemother. 2010;54(11):4605–4610.
138. Crass RL, Cojutti PG, Pai MP, et al. Reappraisal of Linezolid Dosing in renal impairment to improve safety. Antimicrob Agents Chemother. 2019;63(8):e00605–19.
139. Kiang TKL, Wilby KJ, Ensom MHH. A critical review on the clinical pharmacokinetics, pharmacodynamics, and clinical trials of Ceftaroline. Clin Pharmacokinet. 2015;54(9):915–931. doi: 10.1007/s40262-015-0281-3
140. Torres A, Mouton JW, Pea F. Pharmacokinetics and dosing of Ceftobiprole Medocaril for the treatment of hospital- and community-acquired pneumonia in different patient populations. Clin Pharmacokinet. 2016;55(12):1507–1520.
141. Helfer VE, Zavascki AP, Zeitlinger M, et al. Population pharmacokinetic modeling and probability of target attainment of ceftaroline in brain and soft tissues. Antimicrob Agents Chemother. 2022;66(9):e00741–22.
142. Matzneller P, Lackner E, Lagler H, et al. Single- and repeated-dose pharmacokinetics of ceftaroline in plasma and soft tissues of healthy volunteers for two different dosing regimens of ceftaroline Fosamil. Antimicrob Agents Chemother. 2016;60(6):3617–3625.
143. Barbour A, Schmidt S, Sabarinath SN, et al. Soft-tissue penetration of ceftobiprole in healthy volunteers determined by in vivo Microdialysis. Antimicrob Agents Chemother. 2009;53(7):2773–2776.
144. Riccobene TA, Pushkin R, Jandourek A, et al. Penetration of ceftaroline into the epithelial lining fluid of healthy adult subjects. Antimicrob Agents Chemother. 2016;60(10):5849–5857.
145. Rodvold KA, Nicolau DP, Lodise TP, et al. Identifying exposure targets for treatment of staphylococcal pneumonia with Ceftobiprole. Antimicrob Agents Chemother. 2009;53(8):3294–3301. doi: 10.1128/AAC.00144-09
146. Gatti M, Tedeschi S, Zamparini E, et al. Pharmacokinetic and pharmacodynamic considerations for optimizing antimicrobial therapy used to treat bone and joint infections: an evidence-based algorithmic approach. Expert Opin On Drug Metab & Toxicol. 2023;19(8):511–535. doi: 10.1080/17425255.2023.2255525
147. Helfer VE, Dias BB, Lock GDA, et al. Population pharmacokinetic modeling of free plasma and free brain concentrations of ceftaroline in healthy and methicillin-resistant Staphylococcus aureus-infected Wistar rats. Antimicrob Agents Chemother. 2023;67(7):e00382–23. doi: 10.1128/aac.00382-23
148. Stucki A, Cottagnoud M, Acosta F, et al. Evaluation of ceftobiprole activity against a variety of gram-negative pathogens, including Escherichia coli, Haemophilus influenzae (β-Lactamase positive and β-Lactamase negative), and Klebsiella pneumoniae, in a rabbit meningitis Model. Antimicrob Agents Chemother. 2012;56(2):921–925. doi: 10.1128/AAC.01537-10
149. MacGowan AP, Noel AR, Tomaselli S, et al. Pharmacodynamics of ceftaroline against Staphylococcus aureus studied in an *in vitro* pharmacokinetic Model of infection. Antimicrob Agents Chemother. 2013;57(6):2451–2456.
150. Craig WA, Andes DR. In vivo pharmacodynamics of Ceftobiprole against multiple bacterial pathogens in murine thigh and lung infection models. Antimicrob Agents Chemother. 2008;52(10):3492–3496.
151. Singh R, Almutairi M, Alm RA, et al. Ceftaroline efficacy against high-mic clinical Staphylococcus aureus isolates in an in vitro hollow-fibre infection model. J Antimicrob Chemother. 2017;72(10):2796–2803. doi: 10.1093/jac/dkx214
152. Bhavnani SM, Hammel JP, Van Wart SA, et al. Pharmacokinetic-Pharmacodynamic Analysis for Efficacy of Ceftaroline Fosamil in Patients with Acute Bacterial Skin and Skin Structure Infections. Antimicrob Agents Chemother. 2015;59(1):372–380. doi: 10.1128/AAC.02531-14
153. Muller AE, Punt N, Mouton JW. Exposure to ceftobiprole is associated with microbiological eradication and clinical cure in patients with nosocomial pneumonia. Antimicrob Agents Chemother. 2014;58(5):2512–2519. doi: 10.1128/AAC.02611-13
154. Gatti M, Cojutti PG, Pea F. Impact of attaining aggressive vs. conservative PK/PD target on the clinical efficacy of beta-lactams for the treatment of gram-negative infections in the critically ill patients: a systematic review and meta-analysis. Crit Care. 2024;28(1):123. doi: 10.1186/s13054-024-04911-5
155. Chauzy A, Gregoire N, Ferrandière M, et al. Population pharmacokinetic/pharmacodynamic study suggests continuous infusion of ceftaroline daily dose in ventilated critical care patients with early-onset pneumonia and augmented renal clearance. J Antimicrob Chemother. 2022;77(11):3173–3179.
156. Cojutti PG, Giuliano S, Pascale R, et al. Population pharmacokinetic and pharmacodynamic analysis for maximizing the

effectiveness of ceftobiprole in the treatment of severe methicillin-resistant staphylococcal infections. Microorganisms. 2023;11(12):2964.
157. Molina KC, Miller MA, Mueller SW, et al. Clinical pharmacokinetics and pharmacodynamics of Dalbavancin. Clin Pharmacokinet. 2022;61(3):363–374. doi: 10.1007/s40262-021-01088-w
158. Saravolatz LD, Stein GE. Oritavancin: a Long-Half-Life Lipoglycopeptide. Clin Infect Dis. 2015;61(4):627–632.
159. Nicolau DP, Sun HK, Seltzer E, et al. Pharmacokinetics of dalbavancin in plasma and skin blister fluid. J Antimicrob Chemother. 2007;60(3):681–684.
160. Rappo U, Dunne MW, Puttagunta S, et al. Epithelial lining fluid and plasma concentrations of Dalbavancin in healthy adults after a single 1,500-milligram infusion. Antimicrob Agents Chemother. 2019;63(11):e01024–19. doi: 10.1128/AAC.01024-19
161. Dunne MW, Puttagunta S, Sprenger CR, et al. Extended-duration dosing and distribution of Dalbavancin into bone and articular tissue. Antimicrob Agents Chemother. 2015;59(4):1849–1855. doi: 10.1128/AAC.04550-14
162. Van Matre ET, Teitelbaum I, Kiser TH. Intravenous and intraperitoneal pharmacokinetics of dalbavancin in peritoneal dialysis patients. Antimicrob Agents Chemother. 2020;64(5):e02089–19. doi: 10.1128/AAC.02089-19
163. Solon EG, Dowell JA, Lee J, et al. Distribution of radioactivity in bone and related structures following administration of [^{14} C] Dalbavancin to New Zealand white rabbits. Antimicrob Agents Chemother. 2007;51(8):3008–3010. doi: 10.1128/AAC.00020-07
164. Fetterly GJ, Ong CM, Bhavnani SM, et al. Pharmacokinetics of oritavancin in plasma and skin blister fluid following administration of a 200-milligram dose for 3 days or a single 800-milligram dose. Antimicrob Agents Chemother. 2005;49(1):148–152. doi: 10.1128/AAC.49.1.148-152.2005
165. Lehoux D, Ostiguy V, Cadieux C, et al. Oritavancin pharmacokinetics and bone penetration in rabbits. Antimicrob Agents Chemother. 2015;59(10):6501–6505.
166. Cabellos C, Fernandez A, Maiques JM, et al. Experimental study of LY333328 (oritavancin), alone and in combination, in therapy of cephalosporin-resistant pneumococcal meningitis. Antimicrob Agents Chemother. 2003;47(6):1907–1911. doi: 10.1128/AAC.47.6.1907-1911.2003
167. Guskey MT, Tsuji BT. A comparative review of the lipoglycopeptides: Oritavancin, Dalbavancin, and Telavancin. Pharmacotherapy. 2010;30(1):80–94. doi: 10.1592/phco.30.1.80
168. Lepak A, Marchillo K, VanHecker J, et al. Impact of glycopeptide resistance in Staphylococcus aureus on the dalbavancin *in vivo* pharmacodynamic target. Antimicrob Agents Chemother. 2015;59(12):7833–7836. doi: 10.1128/AAC.01717-15
169. Cojutti PG, Rinaldi M, Gatti M, et al. Usefulness of therapeutic drug monitoring in estimating the duration of dalbavancin optimal target attainment in staphylococcal osteoarticular infections: a proof-of-concept. Int J Antimicrob Agents. 2021;58(5):106445. doi: 10.1016/j.ijantimicag.2021.106445
170. Galfo V, Tiseo G, Riccardi N, et al. Therapeutic drug monitoring of antibiotics for methicillin-resistant Staphylococcus aureus infections: an updated narrative review for clinicians. Clin Microbiol Infect. 2024;31(2):194–200. doi: 10.1016/j.cmi.2024.08.021
171. Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. Intensive Care Med. 2020 Jun;46(6):1127–1153. doi: 10.1007/s00134-020-06050-1
172. Senneville E, Cuervo G, Gregoire M, et al. Expert opinion on dose regimen and therapeutic drug monitoring for long-term use of Dalbavancin: expert review panel. Int J Antimicrob Agents. 2023;62(5):106960.
- **The only available consensus on how use the long-acting dalbavancin for therapy longer than 14 days.**
173. Cojutti PG, Tedeschi S, Gatti M, et al. Population pharmacokinetic and pharmacodynamic analysis of dalbavancin for long-term treatment of subacute and/or chronic infectious diseases: the Major role of Therapeutic Drug monitoring. Antibiotics (Basel). 2022 Jul 24;11(8):996.
174. Gatti M, Viale P, Cojutti PG, et al. A descriptive case series of the relationship between maintenance of conservative PK/PD efficacy thresholds of dalbavancin over time and clinical outcome in long-term treatment of staphylococcal osteoarticular infections. Int J Antimicrob Agents. 2023;61(5):106773. doi: 10.1016/j.ijantimicag.2023.106773
175. Cattaneo D, Fusi M, Galli L, et al. Proactive therapeutic monitoring of dalbavancin concentrations in the long-term management of chronic osteoarticular/periprosthetic joint infections. Leggett JE, editor. Antimicrob Agents Chemother. 2024;68(4):e00023–24.
176. Lafon-Desmurs B, Gachet B, Hennart B, et al. Dalbavancin as suppressive therapy for implant-related infections: a case series with therapeutic drug monitoring and review of the literature. Eur J Clin Microbiol Infect Dis. 2024;43(7):1475–1480.
177. Gatti M, Pea F. The expert clinical pharmacological advice program for tailoring on real-time antimicrobial therapies with emerging TDM candidates in special populations: how the ugly duckling turned into a swan. Expert Rev Clin Pharmacol. 2023;16(11):1035–1051.
178. Schellong P, Joean O, Pletz MW, et al. Treatment of complicated gram-positive bacteremia and infective endocarditis. Drugs. 2024 Dec 25;85(2):193–214. doi: 10.1007/s40265-024-02135-z
179. Gudiol F, Aguado JM, Almirante B, et al. Diagnosis and treatment of bacteremia and endocarditis due to Staphylococcus aureus. A clinical guideline from the Spanish society of clinical microbiology and infectious diseases (SEIMC). Enfermedades Infecciosas y Microbiología Clínica. 2015;33(9):.e625.1–.e625.23. doi: 10.1016/j.eimc.2015.03.015
- **The Spanish guidelines addressing infections by methicillin-resistant Staphylococcus aureus.**
180. Brown NM, Goodman AL, Horner C, et al. Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): updated guidelines from the UK. JAC-Antimicrob Resist. 2021;3(1):dlaa114. doi: 10.1093/jacamr/dlaa114
- **The guidelines from the United Kingdom providing guidance for infections by methicillin-resistant Staphylococcus aureus.**
181. Kalil AC, Van Schooneveld TC, Fey PD, et al. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. JAMA. 2014;312(15):1552.
182. Ishaq H, Tariq W, Talha KM, et al. Association between high vancomycin minimum inhibitory concentration and clinical outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: a meta-analysis. Infection. 2021;49(5):803–811. doi: 10.1007/s15010-020-01568-4
183. Diaz R, Afreixo V, Ramalheira E, et al. Evaluation of vancomycin MIC creep in methicillin-resistant Staphylococcus aureus infections—a systematic review and meta-analysis. Clin Microbiol Infect. 2018;24(2):97–104. doi: 10.1016/j.cmi.2017.06.017
184. Rose W, Volk C, Dilworth TJ, et al. Approaching 65 years: Is it time to consider retirement of vancomycin for treating methicillin-resistant Staphylococcus aureus endovascular infections? Open Forum Infect Dis. 2022;9(5):ofac137. doi: 10.1093/ofid/ofac137
185. Jorgensen SCJ, Spellberg B, Shorr AF, et al. Should therapeutic drug monitoring based on the vancomycin area under the concentration-time curve Be standard for serious methicillin-resistant *Staphylococcus aureus* infections?—no. Clin Infect Dis. 2021;72(9):1502–1506.
186. Davis JS, Petersiel N, Tong SYC. How I manage a patient with MRSA bacteraemia. Clin Microbiol Infect. 2022;28(2):190–194.
187. Fowler VG, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med. 2006;355(7):653–665.
188. Rehm SJ, Boucher H, Levine D, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to Staphylococcus aureus: subset analysis of patients infected with methicillin-resistant isolates. J Antimicrob Chemother. 2008;62(6):1413–1421. doi: 10.1093/jac/dkn372
- **The sub-analysis of a seminal randomized clinical trial demonstrating non-inferiority of daptomycin versus vancomycin for bloodstream infections by methicillin-resistant Staphylococcus aureus.**

189. Maraolo AE, Giaccone A, Gentile I, et al. Daptomycin versus vancomycin for the treatment of methicillin-resistant Staphylococcus aureus bloodstream infection with or without endocarditis: a systematic review and meta-analysis. Antibiotics. 2021;10(8):1014. doi: 10.3390/antibiotics10081014
190. Adamu Y, Puig-Asensio M, Dabo B, et al. Comparative effectiveness of daptomycin versus vancomycin among patients with methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections: a systematic literature review and meta-analysis. PLOS ONE. 2024;19(2):e0293423. doi: 10.1371/journal.pone.0293423
191. Kimmig A, Hagel S, Weis S, et al. Management of Staphylococcus aureus bloodstream infections. Front Med. 2021;7:616524. doi: 10.3389/fmed.2020.616524
192. Jones TW, Jun AH, Michal JL, et al. High-dose daptomycin and clinical applications. Ann Pharmacother. 2021;55(11):1363–1378.
193. Gentile I, Giuliano S, Corcione S, et al. Current role of ceftobiprole in the treatment of hospital-acquired and community-acquired pneumonia: expert opinion based on literature and real-life experiences. Expert Rev Anti Infect Ther. 2025;23(2–4):217–225. doi: 10.1080/14787210.2025.2461552
194. Holland TL, Cosgrove SE, Doernberg SB, et al. Ceftobiprole for treatment of complicated *Staphylococcus aureus* bacteremia. N Engl J Med. 2023;389(15):1390–1401.
• **The latest randomized clinical trial demonstrating non-inferiority of a new drug (ceftobiprole) for bloodstream infections by methicillin-susceptible and methicillin-resistant Staphylococcus aureus.**
195. Gentile I, Buonomo AR, Corcione S, et al. CEFTO-CURE study: CEFTObiprole Clinical Use in Real-lifE – a multi-centre experience in Italy. Int J Antimicrob Agents. 2023;62(1):106817.
196. Rose W, Fantl M, Geriak M, et al. Current paradigms of combination therapy in methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia: does it work, which combination, and for which patients? Clin Infect Dis. 2021;73(12):2353–2360. doi: 10.1093/cid/ciab452
• **Elegant and insightful review on the role of combination therapy against methicillin-resistant Staphylococcus aureus in the setting of bloodstream infections.**
197. Barber KE, Ireland CE, Bukavyn N, et al. Observation of "seesaw effect" with vancomycin, Teicoplanin, daptomycin and ceftaroline in 150 unique MRSA strains. Infect Dis Ther. 2014;3(1):35–43. doi: 10.1007/s40121-014-0023-0
198. Rand KH, Houck HJ. Synergy of daptomycin with oxacillin and other β-lactams against methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2004;48(8):2871–2875. doi: 10.1128/AAC.48.8.2871-2875.2004
199. Falagas ME, Vouloumanou EK, Samonis G, et al. Fosfomycin. Clin Microbiol Rev. 2016;29(2):321–347. doi: 10.1128/CMR.00068-15
200. Campbell AJ, Dotel R, Blyth CC, et al. Adjunctive protein synthesis inhibitor antibiotics for toxin suppression in Staphylococcus aureus infections: a systematic appraisal. J Antimicrob Chemother. 2019 Jan 1;74(1):1–5.
201. Davis JS, Sud A, O'Sullivan MVN, et al. Combination of vancomycin and β-lactam therapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a Pilot multicenter randomized controlled trial. Clin Infect Dis. 2016;62(2):173–180. doi: 10.1093/cid/civ808
202. Pericàs JM, Moreno A, Almela M, et al. Efficacy and safety of fosfomycin plus imipenem versus vancomycin for complicated bacteraemia and endocarditis due to methicillin-resistant Staphylococcus aureus: a randomized clinical trial. Clin Microbiol Infect. 2018;24(6):673–676. doi: 10.1016/j.cmi.2018.01.010
203. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391(10121):634–636. doi: 10.1016/S0140-6736(17)33294-4
204. Geriak M, Haddad F, Rizvi K, et al. Clinical data on Daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of methicillin-resistant Staphylococcus aureus bacteremia. Antimicrob Agents Chemother. 2019;63(5):e02483–18. doi: 10.1128/AAC.02483-18
205. Tong SYC, Lye DC, Yahav D, et al. Effect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial. JAMA. 2020;323(6):527. doi: 10.1001/jama.2020.0103
206. Pujol M, Miró J-M, Shaw E, et al. Daptomycin plus fosfomycin versus daptomycin alone for methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis: a randomized clinical trial. Clin Infect Dis. 2021;72(9):1517–1525.
207. Campbell AJ, Dotel R, Braddick M, et al. Clindamycin adjunctive therapy for severe *Staphylococcus aureus* treatment evaluation (cassette)—an open-labelled pilot randomized controlled trial. JAC-Antimicrob Resist. 2022;4(1):dlac014.
208. Tabah A, Laupland KB. Update on Staphylococcus aureus bacteraemia. Curr Opin Crit Care. 2022;28(5):495–504.
209. Grillo S, Puig-Asensio M, Schweizer ML, et al. The effectiveness of combination therapy for treating methicillin-susceptible Staphylococcus aureus bacteremia: a systematic literature review and a meta-analysis. Microorganisms. 2022;10(5):848.
210. Ruotsalainen E, Järvinen A, Koivula I, et al. Levofloxacin does not decrease mortality in *Staphylococcus aureus* bacteraemia when added to the standard treatment: a prospective and randomized clinical trial of 381 patients. J Intern Med. 2006;259(2):179–190. doi: 10.1111/j.1365-2796.2005.01598.x
211. Cheng MP, Lawandi A, Butler-Laporte G, et al. Adjunctive daptomycin in the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia: a randomized, controlled trial. Clin Infect Dis. 2021;72(9):e196–e203. doi: 10.1093/cid/ciaa1000
212. Grillo S, Pujol M, Miró JM, et al. Cloxacillin plus fosfomycin versus cloxacillin alone for methicillin-susceptible Staphylococcus aureus bacteremia: a randomized trial. Nat Med. 2023;29(10):2518–2525. doi: 10.1038/s41591-023-02569-0
213. Delgado V, Ajmone Marsan N, De Waha S, et al. 2023 ESC guidelines for the management of endocarditis. Eur Heart J. 2023;44(39):3948–4042.
• **The latest version of the European guidelines focused on management of endocarditis.**
214. Ryder JH, Tong SYC, Gallagher JC, et al. Deconstructing the dogma: systematic literature review and meta-analysis of adjunctive gentamicin and rifampin in staphylococcal prosthetic valve endocarditis. Open Forum Infect Dis. 2022 Oct 31;9(11):ofac583.
215. Parsons JB, Westgeest AC, Conlon BP, et al. Persistent methicillin-resistant Staphylococcus aureus Bacteremia: Host, pathogen, and treatment. Antibiotics. 2023;12(3):455.
216. Kullar R, Sakoulas G, Deresinski S, et al. When sepsis persists: a review of MRSA bacteraemia salvage therapy. J Antimicrob Chemother. 2016;71(3):576–586.
217. Schweizer ML, Richardson K, Vaughan Sarrazin MS, et al. Comparative effectiveness of switching to daptomycin versus remaining on vancomycin among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections. Clin Infect Dis. 2021;72(Supplement_1):S68–S73. doi: 10.1093/cid/ciaa1572
218. Lewis PO, Heil EL, Covert KL, et al. Treatment strategies for persistent methicillin-resistant *Staphylococcus aureus* bacteraemia. J Clin Pharm Ther. 2018;43(5):614–625. doi: 10.1111/jcpt.12743
219. Spellberg B, Rice LB. Duration of antibiotic therapy: shorter is better. Ann Intern Med. 2019;171(3):210. doi: 10.7326/M19-1509
• **The paper supporting the new wave of "shorter is better" in the duration of antimicrobial treatment.**
220. Daneman N, Rishu A, Pinto R, et al. (The BALANCE investigators, for the Canadian critical care trials group, the association of medical microbiology and infectious disease Canada clinical research network, the Australian and new Zealand intensive care society clinical trials group, and the Australasian society for infectious diseases clinical research network). Antibiotic treatment for 7 versus 14 days in patients with bloodstream infections. N Engl J Med. 2025;392(11):1065–1078. doi: 10.1056/NEJMoa2404991
221. Maraolo AE, Ceccarelli G, Venditti M, et al. Short course antibiotic therapy for catheter-related septic thrombosis: "caveat Emptor!":

duration of therapy should not Be set a priori. Pathogens. 2024;13 (7):529. doi: 10.3390/pathogens13070529

222. Zanichelli V, Olearo F, Aiken AM. Impact of shorter (<14 days) antibiotic treatment duration in adults with uncomplicated Staphylococcus aureus bacteremia: a systematic review and meta-analysis. Clin Infect Pract. 2024;21:100346. doi: 10.1016/j.clinpr.2023.100336
223. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med. 2019;380(5):415–424.
224. Kaasch AJ, López-Cortés LE, Rodríguez-Baño J, et al. Efficacy and safety of an early oral switch in low-risk Staphylococcus aureus bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial. The Lancet Infect Dis. 2024;24(5):523–534.
225. Jorgensen SCJ, Lagnf AM, Bhatia S, et al. Sequential intravenous-to-oral outpatient antibiotic therapy for MRSA bacteraemia: one step closer. J Antimicrob Chemother. 2019;74(2):489–498. doi: 10.1093/jac/dky452
226. McDonald EG, Aggrey G, Aslan AT, et al. Guidelines for diagnosis and management of infective endocarditis in adults: a WikiGuidelines group consensus statement. JAMA Netw Open. 2023;6(7):e2326366.
227. Paul M, Bishara J, Yahav D, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant Staphylococcus aureus: randomised controlled trial. BMJ. 2015;350(may14 24):h2219–h2219. doi: 10.1136/bmj.h2219
228. Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for Staphylococcus aureus bacteraemia: pooled analysis of randomized studies. J Antimicrob Chemother. 2005;56(5):923–929. doi: 10.1093/jac/dki355
229. Tran TT, Gomez Villegas S, Aitken SL, et al. New perspectives on antimicrobial agents: Long-Acting Lipoglycopeptides. Antimicrob Agents Chemother. 2022;66(6):e02614–20. doi: 10.1128/aac.02614-20
230. 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. doi: 10.1002/phar.2389
231. Bao H, Igwilo-Alaneme R, Sonia F, et al. Dalbavancin as an alternative to traditional outpatient parenteral antimicrobial therapy for deep gram-positive infections – an observational, retrospective review. Ther Adv Infect. 2024;11:20499361241245523.
232. Rebold N, Alosaimy S, Pearson JC, et al. Dalbavancin sequential therapy for gram-positive bloodstream infection: a multicenter observational study. Infect Dis Ther. 2024;13(3):565–579.
233. Texidor WM, Miller MA, Molina KC, et al. Oritavancin as sequential therapy for gram-positive bloodstream infections. BMC Infect Dis. 2024;24(1):127. doi: 10.1186/s12879-023-08725-8
234. Coppola N, Maraolo AE, Onorato L, et al. Epidemiology, mechanisms of resistance and treatment algorithm for infections due to carbapenem-resistant gram-negative bacteria: an expert panel opinion. Antibiotics. 2022;11(9):1263. doi: 10.3390/antibiotics11091263
235. Falcone M, Tiseo G, Carbonara S, et al. Mortality attributable to bloodstream infections caused by different Carbapenem-Resistant Gram-Negative Bacilli: results from a nationwide study in Italy (ALARICO network). Clin Infect Dis. 2023;76(12):2059–2069. doi: 10.1093/cid/ciad100
236. Russell CD, Berry K, Cooper G, et al. Distinct clinical endpoints of *Staphylococcus aureus* bacteraemia complicate assessment of outcome. Clin Infect Dis. 2024;79(3):604–611.
    - **Interesting study defining new endpoints in the course of Staphylococcus aureus bacteraemia.**
237. Rose WE, Eickhoff JC, Shukla SK, et al. Elevated serum interleukin-10 at time of hospital admission is predictive of mortality in patients with Staphylococcus aureus bacteremia. J Infect Dis. 2012;206 (10):1604–1611.
238. Rose WE, Shukla SK, Berti AD, et al. Increased endovascular Staphylococcus aureus inoculum is the link between elevated serum interleukin 10 concentrations and mortality in patients with bacteremia. Clin Infect Dis. 2017;64(10):1406–1412.
239. Mba Medie F, Sharma-Kuinkel BK, Ruffin F, et al. Genetic variation of DNA methyltransferase-3A contributes to protection against persistent MRSA bacteremia in patients. Proc Natl Acad Sci USA. 2019;116(40):20087–20096. doi: 10.1073/pnas.1909849116
240. Volk CF, Burgdorf S, Edwardson G, et al. Interleukin (il)-1β and IL-10 host responses in patients with Staphylococcus aureus bacteremia determined by antimicrobial therapy. Clin Infect Dis. 2020;70 (12):2634–2640. doi: 10.1093/cid/ciz686
    - **Observational study that delves into predictive role of biomarkers in patients with Staphylococcus aureus bacteraemia.**
241. Mourad A, Fowler VG, Holland TL. Which trial do we need? next-generation sequencing to individualize therapy in Staphylococcus aureus bacteraemia. Clin Microbiol Infect. 2023;29 (8):955–958. doi: 10.1016/j.cmi.2023.04.004
242. Eichenberger EM, De Vries CR, Ruffin F, et al. Microbial cell-free DNA identifies etiology of bloodstream infections, persists longer than conventional blood cultures, and its duration of detection is associated with metastatic infection in patients with *Staphylococcus aureus* and gram-negative bacteremia. Clin Infect Dis. 2022;74 (11):2020–2027.
243. Sakoulas G, Tsou EE, Geriak M, et al. Contemporary management of Staphylococcus aureus Bacteremia: some additional considerations for clinicians. Clin Infect Dis. 2024;79(3):800–801. doi: 10.1093/cid/ciae080
244. Petersiel N, Davis JS, Meagher N, et al. Combination of antistaphylococcal β-lactam with standard therapy compared to standard therapy alone for the treatment of methicillin-resistant Staphylococcus aureus bacteremia: a post hoc analysis of the CAMERA2 trial using a desirability of outcome ranking approach. Open Forum Infect Dis. 2024 25;11(5): ofae181.
245. Legg A, Roberts JA, Roberts MA, et al. Avoiding misclassification of acute kidney injury: timing is everything. Nephrology (Carlton). 2024;29(2):100–104. doi: 10.1111/nep.14246
246. Wolman AT, Gionfriddo MR, Heindel GA, et al. Organic anion transporter 3 interacts selectively with lipophilic β-lactam antibiotics. Drug Metab Dispos. 2013;41(4):791–800.
247. Fowler VG, Das AF, Lipka-Diamond J, et al. Exebacase for patients with Staphylococcus aureus bloodstream infection and endocarditis. J Clin Investigation. 2020;130(7):3750–3760.
248. Fowler VG, Das AF, Lipka-Diamond J, et al. Exebacase in addition to standard-of-care antibiotics for *Staphylococcus aureus* bloodstream infections and right-sided infective endocarditis: a phase 3, superiority-design, placebo-controlled, randomized clinical trial (DISRUPT). Clin Infect Dis. 2024;78(6):1473–1481.
249. Fortaleza JAG, Ong CJN, De Jesus R. Efficacy and clinical potential of phage therapy in treating methicillin-resistant Staphylococcus aureus (MRSA) infections: a review. EuJMI. 2024;14(1):13–25. doi: 10.1556/1886.2023.00064
250. Tong SYC, Mora J, Bowen AC, et al. The Staphylococcus aureus network adaptive platform trial protocol: new tools for an old foe. Clin Infect Dis. 2022 Nov 30;75(11):2027–2034.
251. Sauvat L, Verhoeven PO, Gagnaire J, et al. Vaccines and monoclonal antibodies to prevent healthcare-associated bacterial infections. Clin Microbiol Rev. 2024;37(3):e00160–22. doi: 10.1128/cmr.00160-22