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DIAGNOSIS AND THERAPY FOR BACTERIAL BLOOD STREAM INFECTION

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Abstract

The rising incidence of bloodstream infections (BSI) due to Gram-negative bacteria (GNB) with di cult-to-treat resistance (DTR) has been recognized as a global emergency. The aim of this review is to provide a comprehensive assessment of the mechanisms of antibiotic resistance, epidemiology and treatment options for BSI caused by GNB with DTR, namely extended-spectrum Beta-lactamase-producing Enterobacteriales; carbapenem-resistant Enterobacteriales; DTR Pseudomonas aeruginosa; and DTR Acinetobacter baumannii Bloodstream infection (BSI) is defined by positive blood cultures in a patient with systemic signs of infection and may be either secondary to a documented source or primary-that is, without identified origin. Community acquired BSIs in immunocompetent adults usually involve drug susceptible bacteria, while healthcare associated BSIs are frequently due to di cult-to-treat resistance (DTR) strains. Early adequate antimicrobial therapy is a key to improve patient outcomes, especially in those with criteria for sepsis or septic shock, and should be based on guidelines and direct examination of available samples. Local epidemiology, suspected source, immune status, previous antimicrobial expo sure, and documented colonization with MDR bacteria must be considered for the choice of first line antimicrobials in healthcare associated and hospital acquired BSIs.. Initial antimicrobial dosing should take into account the pharmacokinetic alterations usually observed in ICU patients, with a loading dose in case of sepsis or septic shock. Source identification and control should be performed as soon as the hemodynamic status is stabilized.

***Keywords*:** Bloodstream Infection, Gram-Negative Bacteria, Gram-Positive Bacteria, Di Cult-To-Treat Resistance (DTR), Multi Drug Resistance (MDR).

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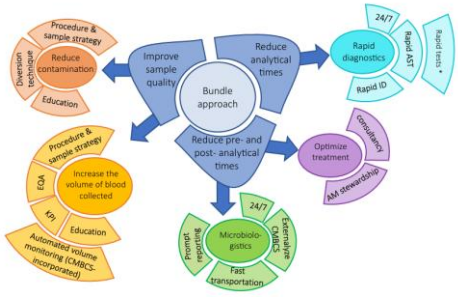
Introduction

With an estimated burden of 1200 000 episodes of bloodstream infection (BSI) each year in Europe and long-term sequelae, BSI represents an increasing public health concern. Delayed effective therapy is associated with worse outcome. Fast and ac curate diagnosis of the causing microorganism and a correct susceptibility testing improves the care of patients with BSI/sepsis and leads to a more precise therapy which grows in importance with antimicrobial resistance increase. The detection of the causing pathogen with molecular techniques has, so far, been proven suboptimal and blood culture (BC) remains the reference standard and first line tool in the pathogen diagnostics of BSIs and sepsis [1]. The introduction of continuous monitoring blood culture systems (CMBCs) in the 1990s led to an improved standardization of BC diagnostics with easier ordering and optimized culture media yield. However, this development was not followed by other improvements in the area for the next decades while CMBCSs partly obscured the fact that pre-analytics are critical to detect BSI pathogen. During the last decade, however, a dramatic progress in the development of rapid diagnostic tests relying on innovative technologies has occurred. Also, the importance of the Summary of all the actions to improve the bloodstream infection pathogen diagnostics logistics and the improvement of quality management of BC diagnostics are increasingly recognized [2].

This resulted in a multifaceted range of actions to improve the microbiological diagnosis of BSI (Fig. 1), and many of them are complementary. Here, we review the

standards of BSI pathogen diagnostics, the progress in this area, interns of reduced time to result (TTR) and quality of results and propose new timelines to aim for in modern BC diagnostics. deeply rushed practices during the latest decade and outdates the classical process. The high variability in utility, dissemination and cost of the new techniques (such as matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS)) makes it challenging to define the current standard of BSI pathogen diagnostics [3].



Bacterial blood stream infections

In the clinical microbiology laboratory blood cultures are a vital technology for isolating bacteria and fungi. They are the reference standard for diagnosing bloodstream infection and are considered a prerequisite for targeted antibiotic treatment. Diagnostics with blood cultures can reduce mortality, length of hospital stay, and hospital expense. It is not known exactly when the blood culture technique was 'invented'. The first practice of microbiological culture of blood occurred prior 1880 (mostly for puerperal fever and endocarditis) and was limited to one drop of blood obtained from the fingertip pricked with a sting. It was acknowledging das early as 1880, at least from Pasteur's comments, that microorganisms in blood were likely to be very few in number and that the volume of blood was critical for detecting them, suggesting that the number of pricks should be multiplied [4]

Progress occurred when physicians were able to draw aseptically a volume of blood greater than a few drops. This was made possible when the sterilizable syringe was invented (1886, thanks to elderberry made syringe plunger), and then when improved syringes were developed in Germany by Sittmann (the Lu€ er syringe) and by Malassez in France in 1891[5]

Gram positive blood stream infection

Staphylococcus aureus bacteremia (SAB) is associated with high mortality. Areas of uncertainty about antibiotic treatment of SAB regard the optimal first-choice drug for methicillin-susceptible and methicillin-resistant strains, and the usefulness of combination therapy over monotherapy. Another important cause of Gram-positive BSI is Enterococcus spp., ranking fourth among causative pathogens of BSI in Europe, and being an important cause of infective endocarditis. Areas uncertainty about antibiotic treatment of enterococcal BSI include the optimal drug for vancomycin-resistant strains and the need for combination therapy [6].

Drugs

Anti-staphylococcal penicillin's (ASPs) (methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin and flucloxacillin) are considered the treatment of choice for methicillin-susceptible SAB (MSSAB) Cefazolin is considered an alternative regime .Concern in using cefazolin as frontline treatment is related to a possible failure in high-inoculum infections However, in the majority of recent studies comparing the efficacy of cefazolin versus ASPs, cefazolin showed higher efficacy and a lower rate of adverse events than ASP [6e19]. Nevertheless, none of these studies was randomized and bias may have occurred. Indeed, in most of them the number of patients with complicated MSSAB including endocarditis was limited. An ongoing randomized trial (NCT03248063) may resolve this uncertainty. Vancomycin is considered the treatment of choice for methicillin-resistant SAB (MRSAB). Though no randomized controlled trials (RCT) comparing other drugs with vancomycin for MRSAB are available, observational studies suggest that daptomycin could be associated with improved outcome in specific situations. Trimethoprim/sulfamethoxazole did not reach the non-inferiority margin compared with vancomycin in a multicenter RCT of individuals with severe MRSA infection. Additionally, the unfavorable outcome was enhanced in the subgroup of individuals with BSI [23]. Ceftaroline and ceftobiprole are fifth-generation cephalosporins with intrinsic MRSA activity related to their affinity for penicillin binding protein 2a. Ceftaroline has been demonstrated to be safe and effective in the treatment of MRSAB, though data are limited;

it has been proposed as salvage treatment for persistent MRSAB. Among the novel lipoglycopeptides, dalbavancin allows the management of serious infections with once-weekly or biweekly administration. The proposed dosing regimen of two 1500-mg infusions 1 week apart, resulting in dalbavancin exposure well-above the MRSA MIC up to 8 weeks, and its effectiveness in reducing biofilm production, make dalbavancin a promising option for the treatment of catheter-related BSI, complicated bacteremia or endocarditis. However, the body of evidence for dalbavancin in the treatment of SAB is limited to small pilot RCTs or post-marketing case series. In these studies, the number of included MSSAB was low, further limiting the evidence [7]

Gram negative blood stream infection

The current challenge in the treatment of patients with Gramnegative BSI is antibiotic resistance. Treatment of extended spectrum b-lactamase-producing Enterobacteriaceae has been recently addressed in a review. We will address the other main causes of multidrug-resistant Gram-negative BSI: carbapenems producing Enterobacteriaceae (CPE), Pseudomonas aeruginosa and carbapenem-resistant Acinetobacter

baumannii focusing on available new drugs, combination regimens and optimal dosing schedules [8].

Antibiotics	Normal renal function	Augmented renal clearance (≥130 mL/min)	Hypoalbuminaemia (<2.5 g/dL)	CRRT (Q_{ef} ≥2.5 L/h)
Gram-positive BSIs				
Daptomycin				8 mg/kg/day (MIC <0.5 mg/L)
MRSA	≥8 mg/kg/day	12 mg/kg/day (MIC ≤0.5 mg/L)	12 mg/kg/day + TDM	10–12 mg/kg/day (MIC ≥1 mg/L)
				10–12 mg/kg/day
VRE	≥10 mg/kg/day	12 mg/kg/day + TDM	12 mg/kg/day + TDM	
Dalbavancin	1500 mg once 1500 mg twice 1 week apart	NA	NA	NA
Gram-negative BSIs				
Ceftolozane/tazobactam	3 g q8h EI/CI (MIC >4 mg/L)	3 g q8h EI/CI	No change	3 g q8h[a]
Ceftazidime/avibactam	2.5 g q8h EI/CI[b]	NA (high-dose EI/CI should be considered)	No change	1.25 g q8h[a] (Q_{ef} 2 L/h)
Meropenem/vaborbactam	4 g q8h EI/CI[b]	NA (high-dose EI/CI should be considered)	No change	2 g q8h[a]

Abbreviations: BSIs, bloodstream infections; CI, continuous infusion; CRRT, continuous renal replacement therapy; EI, extended infusion; MRSA, methicillin-resistant Staphylococcus aureus; NA, not available; q8h, every 8 h; Q_{ef}, effluent flow rate; TDM, therapeutic drug monitoring; VRE, vancomycin-resistant Enterococci.

[a] Dosing schedule reported in single case reports.

[b] No evidence for extended infusion/continuous infusion.

Table 1. Dosing schedule proposed for newer agents used in management of Gram-positive and Gram-negative bloodstream infections in different challenging situations based on clinical studies

3.2.1 New Drugs

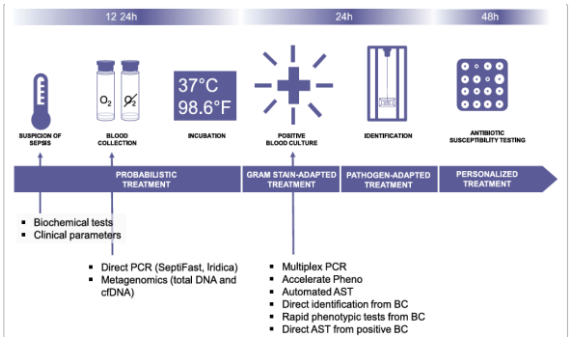
I. Ceftolozane/tazobactam
II. Ceftazidime/avibactam
III. Combination regimens
IV. Optimal dosing schedules in Gram-negative BSIs

Search Strategy

A literature search was conducted on PubMed, limited to articles published in English and in the last 5 years (until 31 July 2019)

5. Diagnosis of Bacterial Blood Stream Infection

Culture-based methods remain the gold standard to identify the causative microorganism in sepsis, with a recommended sampling of at least two sets of aerobic and anaerobic blood cultures (10–20 mL per bottle) following rigorous skin disinfection; yet the rhythm imposed by the growth time requirements of the latter is barely compatible with the 'need for speed' in the con text of sepsis. It should be kept in mind that the initiation of empirical antimicrobial therapy significantly reduces the sensitivity of blood cultures drawn shortly after treatment initiation [9].



Name	Manufacturer	Method	Input	TAT	Sensitivity	Specificity	References
Magicplex™ Sepsis Test	Seegene	RT-PCR	Blood sample	5 h	0.65	0.92	Carrara et al. [135]
					0.29	0.95	Zboromyrska et al. [136]
					0.47	0.66	Ziegler et al. [137]
T2Bacteria® Panel	T2Biosystems	Magnetic resonance	Blood sample	3.5	0.9% (95% CI, 0.76–0.96)	0.9 (95% CI, 0.88–0.91)	Nguyen et al. [28]
FilmArray® Blood Culture	bioFire	PCR	Positive BC	1 h	0.92-1[a]	0.76-1[a]	Altun et al. [138]
					0.95	ND	Bhatti et al. [139]
Verigene® Blood culture tests	Luminex	PCR	Positive BC	2.5 h	0.99	ND	Bhatti et al. [139]
					0.95	ND	Kim et al. [140]
Accelerate Pheno™	Accelerate Diagnostics	FISH and microscopy	Positive BC	1.5 h (identification) 7 h (AST)	0.95	0.99	Lutgring et al. [141]
					0.96	0.99	Charnot-Katsikas et al. [142]
VitekMS Biotyper	bioMérieux Bruker	MALDI-TOF	Positive BC	<1 h (identification), < 1 h-4 h (AST)	Concordance for Gram-negative[b]: 0.83–1 Concordance for Gram-positive[b]: 0.32–0.89		Faron [31]

Figure 2: Current workflow of microbiological diagnosis in bloodstream infection. PCR polymerase chain reaction, CfDNA cell-free DNA, AST antibiotic susceptibility testing, BC blood culture.

Biochemical tests such as C-reactive protein of Procalcitonin is most of time elevated in case of BSI but not sufficiently accurate to discard the diagnosis. A significant decrease of these biomarkers should be used to shorten the duration of antimicrobial therapy

Treatment of Bacterial Blood Stream Infection

In 2008, the US and European Centers for Disease Control and Prevention (CDC and ECDC) proposed a classification of resistance based on the phenotypic profiles of resistance to antimicrobials. Three resistance phenotypes were defined: multidrug resistance (MDR), defined as non-susceptibility to 1agents in 3 antimicrobial categories; extensive drug resistance (XDR), susceptibility limited to 2categories; and pan-drug resistance (PDR), non-susceptibility to all agents in all antimicrobial categories [18]. This classification has been extensively used in the literature, but its usefulness in clinical practice has been recently questioned [19]. Despite their advantages for epidemiological studies, these definitions share several limitations, as they do not dibranchiate between or prioritize antibiotic classes according to their ecacy or toxicity and mean that very broad classes of antibiotics

must be tested. Above all, the problem is that their use does not correlate with clinical outcomes [10]

Novel Treatment

Ceftolozane/Tazobactam

Ceftolozane/tazobactam (C/T) is a novel-lactam/-lactamase inhibitor (BL/BLI), which exhibits excellent in vitro activity against Pseudomonas aeruginosa, including drug-resistant strains, and other Enterobacteriales including most ESBL. This new drug is currently EMA and FDA approved for the treatment of complicated intra-abdominal infections (cIAI) (in combination with metronidazole) and complicated urinary tract infections (cUTI) on the strength of the results of the ASPECT-claim and ASPECT-cut trials. Recently, C/T has also been approved for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), since high-dose ceftolozane/tazobactam (3 g q 8 h) achieved non-inferiority vs. meropenem in the ASPECT-nosocomial pneumonia (NP) trial [11].

ESBL

Carbapenemsremain the treatment of choice for severe ESBL infections. The role of carbapenem sparing regimens for ESBL infections in order to reduce selective antimicrobial pressure is unclear. The data available on the use of ceftolozane–tazobactam for ESBL pathogens are limited, and are mainly extrapolated from pivotal clinical trials. Regarding ESBL producers, the activity of C/T has been shown to be superior overall to that of piperacillin/tazobactam, but meropenem showed better in vitro activity against Enterobacteriales, especially against ESBL-producing strains. Nonetheless, when patients with ESBL infections treated with ceftolozane–tazobactam were compared to those receiving meropenem, there were no dierences in terms of clinical outcomes between treatment groups [12].

CRE

In real-life experience, high favorable response rates have been reported in patients with infections due to KPC-producing Enterobacteriales treated with ceftazidime-avibactam, with an overall success rate around 70%. Among patients with KPC-KP BSI, 30-day mortality rates were significantly lower in the ceftazidime/avibactam group than in a matched group of patients receiving other treatments (36.5% versus 55.7%, p = 0.005). The reports of the emergence of resistance during therapy to this new combination due to black mutations are a matter of concern. Interestingly, pneumonia and renal replacement therapy have been associated with clinical failure and with the emergence of resistance during therapy among patients with CRE infections. Despite few clinical data, ceftazidime/avibactam has shown promising results for salvage treatment of patients with severe infections due to OXA-48-producing Enterobacteriales and with limited therapeutic options, with no evidence of the emergence of resistance to ceftazidime/avibactam [13]

DTR P. Aeruginosa

CAZ-AVI has shown high invitro potency against clinical isolates of P. aeruginosa collected in European countries, including isolates that exhibit resistance to ceftazidime, meropenem and colistin and combined resistance to agents from multiple drug classes. Overall, P. aeruginosa showed a resistance rate to CAZ-AVI ranging from 2.9 to 18%, and the activity of CAZ-AVI against DTR P. aeruginosa has proven to be slightly lower than that of C/T (i.e., with lower MICs against ESBL isolates). The use of CAZ-AVI in P. aeruginosa infections focuses on strains resistant to C/T by the production of ESBL or class A carbapenemase and to MBL-producing strains, in which combination treatment with aztreonam (+/ colistin) may be one of the few currently available therapeutic options [14]

DTR Acinetobacter

Resistance to CAZ-AVI exceeds 50% in Acinetobacter baumannii, and strains isolated from patients admitted to intensive care units (ICUs) have an even higher resistance rate, at 73.6%. In addition, DTRAcinetobacter spp. expressing blaOXA-51-like genes are completely resistant to CAZ-AVI [15]

8. Other new antibiotics
8.1 Aztreonam/Avibactam
8.2 Plazomicin
8.3 Eravacycline
8.4 Murepavadin
8.5 Cefepime/Zidebactam
8.6 Meropenem/nacubactam
8.7 Ceftaroline/Avibactam
8.8 Cefepime/Enmetazobactam

Conclusion

Technological advances in molecular methods have revolutionized the approach to diagnosis of microbial pathogens in the microbiology laboratory. As these sophisticated methods have become faster, more automated, and simpler to use, they can be easily implemented into the laboratory workflow and have become an integral part of the routine testing repertoire in most diagnostic laboratories

Although conventional culture techniques remain the foundation for diagnosis of BSIs in most microbiology laboratories, a move toward novel technologies that can identify pathogens and resistance markers directly from blood culture is critically important to optimize treatment and improve patient outcomes. Fortunately, several of these technologies have become available in the last decade to aid in diagnosis of BSIs. Rapid molecular tests, such as the VERIGENE Blood Culture Nucleic Acid Tests, which allow direct identification of bacteria and genetic resistance markers from positive blood cultures, have been shown to perform with extremely high sensitivity and specificity.

Author Contributions
All authors are contributed equally

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The Authors have no Conflicts of Interest to Declare.

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