Blood Stream Infections

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Blood Stream Infections (BSIs) are defined by positive blood culture or cultures (with an isolate of the same species grown in at least one blood culture bottle) in a patient with systemic signs of infection (i.e., a patient who has evidence of one or more of the symptoms or signs, which are fever (body temperature > 38 °C), hypothermia (body temperature < 36 °C), chills, hypotension, oliguria, or high lactate levels).

Keywords: bloodstream infections ; intensive care unit ; multidrug-resistant pathogens ; septic shock

1. Introduction

This entry summarizes the epidemiological and microbiological characteristics of bloodstream infections (BSIs) with a particular focus on intensive care unit (ICU) acquired BSIs (ICU-BSIs) caused by multidrug-resistant (MDR) pathogens, the development of resistance to antimicrobial drugs, and therapeutic strategies for empirical and targeted therapy of MDR BSIs.

BSIs are defined by positive blood culture or cultures (with an isolate of the same species grown in at least one blood culture bottle) in a patient with systemic signs of infection (i.e., a patient who has evidence of one or more of the symptoms or signs, which are fever (body temperature > 38 °C), hypothermia (body temperature < 36 °C), chills, hypotension, oliguria, or high lactate levels) [1].

BSIs constitute a growing public health concern, a life-threatening nosocomial pathology, and a worldwide primary cause of morbidity and mortality, increasing treatment costs and diagnostic uncertainties [2].

Mortality associated with BSI is 14% for BSIs developed in the community, while the rate grows to 30% in case of patients with severe comorbidities (i.e., cirrhosis, onco-hematologic diseases, or solid-organ transplants) [3][4][5].

In the case of critically ill patients, due to their high predisposition to BSIs, in the first month of hospitalization in ICUs a 7% incidence of BSIs has been reported [6].

Among this specific patient population, BSIs caused by multidrug-resistant (MDR) bacteria are a worrisome phenomenon because if they are not adequately and promptly treated, these infections are correlated with prolonged ICU stays, high costs, and poor outcomes [7].

The mortality rates are between 40% and 60%, increasing the risk of hospital death due to organ dysfunction such as sepsis or septic shock by three times. [6]

Considering that sepsis has recently been included in the global health priorities by the World Health Organization, it is our obligation to prevent this severe and unfaithful clinical evolution of BSIs [8].

2. Epidemiology

The epidemiology of BSIs is complex, since ICU-BSIs present unique epidemiologic characteristics when compared with the BSIs that complicate both community-acquired- (CA) and hospital-acquired-(HA) infections [9].

The uniqueness of the epidemiology of BSIs, even those caused by MDR pathogens, is related to numerous factors. A mixture of different ICUs, geographical locations, antimicrobial management approaches, and the applied policies of infection control influence a BSI's characteristics.

Worldwide, in the range of 5–7% of ICU admissions are reported to have developed a BSI there. This corresponds to a mean of 6–10 episodes per 1000 patient-days [2].

HA-BSIs in critically ill patients are community imported (i.e., documented at ICU admission) in 25% of cases, while most HA-BSI cases (75%) are acquired after admittance to the ICU [10][11].

Table 1 synthesizes the prevalence of BSIs recently reported on the SENTRY database, describing the prevalence of each pathogen in different geographical regions.

Table 1. Number of reported cases of BSIs according to pathogens and geographical distribution.

Pathogens Causing BSIs	Reported Cases of BSIs for Country (n = Number of Cases)					
	World n. BSIs/n. Tot (66,729/319,581)	Asia n. BSIs/n. Tot (6914/29,359)	West Europe n. BSIs/n. Tot (20,897/77,554)	East Europe n. BSIs/n. Tot (6689/29,313)	South America n. BSIs/n. Tot (5188/19,462)	North A n. BSI (27,041/
K. pneumoniae	1882	150	551	561	335	2
Escherichia coli	1747	266	612	285	164	4
Acinetobacter baumannii-calcoaceticus species complex	855	98	188	345	155	6
Pseudomonas aeruginosae	612	41	172	175	75	1
Proteus mirabilis	351	13	142	50	14	1
E. cloacae species complex	180	22	22	18	48	7
S. marcescens	124	2	33	34	32	2
E. cloacae	114	12	44	23	14	2
Morganella morganii	87	3	23	10	6	4
K. oxytoca	59	1	21	8	8	2
P. stuartii	54		12	9	4	2
Klebsiella aerogenes	41	5	15	5	3	1
C. freundii species complex	25	3	8	1	1	1
Citrobacter freundii	14		7			
Hafnia alvei	14		9	1		
A. lwoffii	7			2	2	
A. pittii	7	1	2	2		
Providencia rettgeri	5				1	
Unspeciated acinetobacter	5	1		2		
A. berezinae	4			3	1	
A. nosocomialis	3	1	1			
A. ursingii	3					
Enterobacter asburiae	3	1		1		
A. johnsonii	2	1	1			
C. koseri	2		1			
P. vulgaris group	2		2			
Acinetobacter baumannii	1				1	
A. radioresistens	1					
E. hormaechei	1		1			
K. variicola	1	1				
Pluralibacter gergoviae	1		1			
P. vulgaris	1					
Raoultella ornithinolytica	1					
Serratia liquefaciens	1				1	
S. rubidaea	1					
Providencia (unspeciated)	1				1	
Raoultella (unspeciated)	1					
Salmonella (unspeciated)	1	1				
Serratia (unspeciated)	1				1	

Among the pathogens causing BSIs reported in **Table 1**, listed in order of prevalence, we found in the first positions *K. pneumoniae* and *E. coli* with 1882 and 1747 cases of BSIs, respectively, followed by the *A. baumannii calcoaceticus* species complex and *P. aeruginosae* with 855 and 612 cases of BSIs, respectively. Proteus mirabiliswas isolated among 315 cases, *E. cloacae* species complex in 180 cases, and *S. marcescens* in 124 cases.

According to geographical distribution in West Europe, North America, and Asia, the major prevalence is for *E. coli* BSIs, while in East Europe and South America the leader is *K. pneumoniae*.

Comparing the data reported in **Table 1** with the data collected prior to 2008, the epidemiological trend of BSIs has dramatically changed. Between 1997 and 2004, the most common pathogen overall was *S. aureus*. Furthermore, from 2005 the prevalence of *S. aureus* resistant to methicillin (MRSA) or oxacillin (ORSA) grew until 2008 before declining from that year among community settings in all geographical regions [1].

Meanwhile, BSIs caused by extended-spectrum beta-lactamase-producingEnterobacteriaceae(ESBL-PE) are spreading massively worldwide.

The epidemiology of BSIs changes even according to the setting of their development.

Escherichia coli,Staphylococcus aureus, *Klebsiella pneumoniae*, and *Streptococcus pneumoniaeare* the pathogens causing the largest portions of community acquired BSIs, while *Pseudomonas aeruginosae* is the cause of only 5% of community BSIs, especially in compromised patients. Patients who are immunosuppressed, who have had recent urinary tract infections, or recent pneumonia are most predisposed to *P. aeruginosae* BSIs. In this population, the prevalence of multidrug-resistant (MDR) isolates has been reported.

In the case of BSIs acquired in a hospital setting, according to the data collected from 1997 to 2016 (SENTRY network), 22% were caused by *S. aureus*, 16% by *E. coli*, 9% by *K. pneumoniae*, and 8% by *P. aeruginosae*[12].

The SENTRY Antimicrobial Surveillance Program, established in 1997, is one of the longest running antimicrobial surveillance networks in the world. It monitors worldwide pathogens and the changes in resistance patterns over time. The network is composed of numerous medical centers and hospital sites that participate in the program and collect data on the prevalence of different types of infections and microorganisms in their daily clinical practice. All data collected from the network are then made available and organized in the free SENTRY database.

Among the pathogens causing BSIs, the MDR species are listed in **Table 2**.

Table 2. MDR bacteria causing BSIs from SENTRY database.

MDR Bacteria Causing BSIs Form SENTRY Database						
Pathogen	**World**	**Asia**	**West Europe**	**East Europe**	**North America**	**South An**
K. pneumoniae	1882	150	551	561	285	335
Escherichia coli	1747	266	612	285	420	164
A. baumannii-calcoaceticus species complex	855	98	188	345	69	155
Pseudomonas aeruginosae	612	41	172	175	149	75
Proteus mirabilis	351	13	142	50	132	14
E. cloacae species complex	180	22	22	18	70	48
Serratia marcescens	124	2	33	34	23	32
E. cloacae	114	12	44	23	21	14
Morganella morganii	87	3	23	10	45	6
K. oxytoca	59	1	21	8	21	8
Providencia stuartii	54		12	9	29	4
Klebsiella aerogenes	41	5	15	5	13	3
C. freundii species complex	25	3	8	1	12	1
Citrobacter freundii	14		7		7	
Hafnia alvei	14		9	1	4	
A. lwoffii	7			2	3	2
A. pittii	7	1	2	2	2	
Providencia rettgeri	5				4	1
unspeciated Acinetobacter	5	1		2	2	
A. berezinae	4			3		1
A. nosocomialis	3	1	1		1	
A. ursingii	3				3	
Enterobacter asburiae	3	1		1	1	
A. johnsonii	2	1	1			
C. koseri	2		1		1	
P. vulgaris group	2		2			
Acinetobacter baumannii	1					1
A. radioresistens	1				1	
E. hormaechei	1		1			
K. variicola	1	1				
Pluralibacter gergoviae	1		1			
P. vulgaris	1				1	
Raoultella ornithinolytica	1				1	
Serratia liquefaciens	1					1
S. rubidaea	1				1	
Providencia (unspeciated)	1					1
Raoultella (unspeciated)	1				1	

MDR Bacteria Causing BSIs Form SENTRY Database						
Pathogen	**World**	**Asia**	**West Europe**	**East Europe**	**North America**	**South An**
Salmonella (unspeciated)	1	1				
Serratia (unspeciated)	1					1

Between 1997 and 2016, the prevalence of MDR *Enterobacteriaceae* has increased from 6.2% to 15.8%, with a high rate of non-fermentative Gram-negative bacilli (GNB). Colistin was the only antimicrobial with a predictable 97% efficacy against *Acinetobacter Baumannii-Acinetobacter calcoaceticus complex*.

Data collected from 2013 until 2019 and available on the SENTRY database report that the most frequent MDR pathogen causing BSIs is *K. pneumoniae* with 1882 global cases (high prevalence in West Europe, East Europe and South America), followed by *Escherichia coli* with 1747 global cases (high prevalence in West Europe and North America). *A. baumannii-calcoaceticus species complex* is reported to be responsible for 855 global cases, the majority of which were in East Europe. The MDR *P. aeruginosae* caused 612 cases of BSIs, predominantly in West Europe, East Europe, and North America.

The paragraph beneath describes the MDR mechanisms and MDR species related to BSIs with a special focus on ICU acquired BSIs.

3. Early Microbiological Diagnosis in BSI

Even if culture methods represent the best choice for detecting an infection, the methodology based on molecular assays is achieving remarkable results in terms of specificity and execution times. In the context of sepsis, in fact, timing is crucial and antibiotic therapy should be changed abruptly based on laboratory results. Molecular assays offer rapid results on blood samples without prior incubation. These new techniques are able to determine pathogens and related resistances but, unfortunately, still show a medium sensitivity for pathogens and have a limited number of antibiotic resistances [13];

Besides, a prompt initiation of empirical antimicrobial therapy may be the only chance for a septic patient, but may also significantly reduce the sensitivity of blood cultures drawn, even shortly after treatment initiation [14].

The choice of antimicrobial agent for empirical therapy must take into account several factors such as: the type of pathogen suspected of being involved, any suspicion of resistance or the onset of fungal infection [15][16].

Leukopenia and immunosuppression are other factors to consider because they increase the risk of MDR and fungal infections [17].

Recently, new magnetic resonance-based tests have been introduced that show good sensitivity and short execution times (T2Bacteria Panel, T2Biosystems) [18].

Other very promising, but in development, methods to obtain quickly an etiological accurate diagnosis are next-generation sequencing (NGS) and application of machine-learning [19][20][21].

These techniques may effectively improve treatment optimization in the ICU, reducing the percentage of empirically treated infections [17], anticipating the timing of de-escalation treatment, and improving critically ills patients' outcomes [22].

In this scenario, a thrifty use of recently approved drugs active against MDR organisms is fundamental. The objective of treatment should be to promptly administrate an effective treatment, not improving the selection of antimicrobial resistance using the most recent and high spectrum drugs indiscriminately [23]. Therefore, the prevalence of carbapenemases in each clinical environment should now be taken into account when prompting empirical therapies. The availability of novel beta-lactams/beta-lactamases inhibitor (BL-BLI) combinations, active against MDR Gram-negative bacteria expressing different determinants of resistance, is already changing the approach to management of septic patients [24].

4. Rationale of Treatment

Nowadays, in the case of a patient with a diagnosis of a blood stream infection the primary object when planning a first line empirical treatment regimen is to combine multiple antimicrobial molecules to maximize the likelihood of efficacy against the hypothesized pathogen due to the high rates of antimicrobial resistance. The lack of clinical reports confirming the data collected from in vitro models leaves unsettled the utility of combination therapy to prevent antimicrobial resistance development. Furthermore, numerous studies and meta-analyses were not able to demonstrate that the association of beta-lactam and aminoglycosides or fluoroquinolones in comparison to beta-lactam monotherapy can reduce fatality rates in patients, including those with sepsis or neutropenia [25]. Moreover, in a regimen that uses a beta-lactam antibiotic, the introduction of an aminoglycoside has frequently increased the rate of acute renal failure in the acute phase of infection [25][26].

Even on a pathogen-specific analysis, in the case of BSI due to methicillin-susceptible *S. aureus*(except in those with implanted devices) or *Enterobacterales*, including AmpC-hyperproducers and ESBL-PE, there is poor data to demonstrate that a double antimicrobial regimen favorably impacts patient outcomes [1].

In the case of carbapenem-resistant *A. baumanni*, a polymyxin-based combination may perform better than polymyxin alone only when a high-dose colistin regimen is administered.

Concerning BSIs caused by *P. aeruginosae*, strong doubts as to the advantages of combination therapy persist, because no rise in survival rates has been detected yet [1].

Recently, two systematic reviews evaluated combination therapy based on Ceftolozane-Tazobactam or Ceftazidime-Avibactam compared to monotherapies for the Treatment of Severe BSIs [27].

In conclusion, combination therapy is still an indicated approach for patients with septic shock, but should not be prescribed as routine treatment. Conditions other than severe infections, including sepsis without circulatory failure, may not benefit from antimicrobial combination but may suffer from cumulative side effects [28].

In the contest of antimicrobial stewardship strategies (AMS), antimicrobial de-escalation (ADE) is a strategy that aims to reduce the spectrum of the chosen antibiotic, narrowing its spectrum but not reducing treatment efficacy, and to decrease the emergence of antimicrobial resistance—even reducing the number of antimicrobials involved in treatment [29]. The ADE should be started 2–3 days after diagnosis of an infection; with the availability of microbiological specimens, the re-evaluation of antimicrobial regimens can be performed. Considering that in all BSIs, the pathogen or the pathogens are always known, these infections are perfect candidates for re-evaluation. According to ADE strategy, the source and the pathogen responsible of the BSI are isolated, and it is strictly recommended, even in immunocompromised patients [30], to stop broad spectrum combination therapy and to re-evaluate the treatment regimen.

In the case of ADE, regarding the antibiotic chosen empirically as a first line molecule, the management will be more complex due to multiple factors.

The antibiotics' spectrum of action is variable according to the region of the world, and the ranking depends on the priorities that are considered [31].

The period of in-hospital stay and the comorbidities of the patient are factors that surely will influence the development of antimicrobial resistance. The employment of ADE usually lengthens the duration of antimicrobial therapy [32]. Since multiple recent studies on different sources of infection have recommended a shorter duration of antimicrobial therapy as a target of treatment because longer exposure to antimicrobials predisposes one to the development of MDR pathogens [33].

Sometimes the switching from beta-lactam to oral fluoroquinolones may be useful at ward dismissal to reduce in-hospital patient stay, but this strategy may not be so useful in the ICU due to the high rate of resistance that has emerged from using those therapeutic regimens.

Carbapenems are the most used antimicrobials in ICU therapeutics regimens, however the incidence of resistance has increased, especially in the case of long course treatment and, unfortunately, most pathogens that have become endemic in ICUs have developed multiple resistance mechanisms to this class of antimicrobials, therefore MDR pathogens have been found even after only 1–3 days of in-ICU therapy [34]. According to what was said before about the early development of resistance, this renders ADE useless.

In some cases, another factor that influences antimicrobial management is patients' antimicrobial flora, which may conditionate the emergence of resistance and the response to treatment [35].

In the case of polymicrobial infections (i.e., intra-abdominal infections), it is important to be cautious because not all pathogens are evidenced by blood cultures, and drugs not continued according to ADE may have been required.

Using in silico pharmacokinetic–pharmacodynamic (PK/PD) modeling, it has been shown that the conventional dosing strategy of using a narrow spectrum beta-lactam may have higher risks of not attaining the target compared to broad spectrum regimens [36].

Furthermore, it must be considered that some narrower spectrum alternatives are sometimes more effective than broad-spectrum regimens (i.e., oxacillin or cephazolin are superior to piperacillin/tazobactam in *S. aureus* BSIs) [37].

It is strictly recommended that one consider all the points described above before deciding whether narrowing the first line antimicrobial is the adequate decision to take in the case of BSIs in critically ill patients. The ADE is spreading among clinicians as a main part of the global AMS re-evaluation plan, with the objective of the optimization of the treatment in patients with a severe infection. The ADE consent to adapt antimicrobial treatment of BSIs every time the laboratory data elaboration provides new information on the profile of the pathogens that are the cause of infections.

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