Bloodstream infections (BSI) carry a heavy burden of morbidity and mortality in modern internal medicine wards (IMW). These wards are often filled with elderly subjects with several risk factors for BSI, such as multiple comorbidities, polypharmacy, immunosuppression, and indwelling devices. Diagnosing BSI in such a setting might require a high degree of suspicion, since the clinical presentation could be affected by underlying conditions and concomitant medications, which might delay the administration of an appropriate antimicrobial therapy, an event strongly and unfavorably influencing survival. Furthermore, selecting the appropriate antimicrobial therapy to treat these patients is becoming an increasingly complex task in which all possible benefits and costs should be carefully analyzed from patient and public health perspectives. Only a specialized, continuous, and interdisciplinary approach could really improve the management of IMW patients in an era of increasing antimicrobial resistance and complexity of care.

Background

During the last decades, unprecedented improvements in medicine and surgery have led to a substantial increase in the average life span of human beings, with currently as many as 23% of individuals being adults aged 60 y or older. However, such a health improvement is not always completely cost-free. Population aging is associated with increasing prevalence of comorbidities such as cardiovascular diseases, type 2 diabetes mellitus, chronic obstructive pulmonary disease, liver cirrhosis, and cancer, all medical conditions that may lead to prolonged and recurrent hospitalizations and also predispose to infection. As a consequence, modern internal medicine wards (IMW) are often filled with aged subjects, whose risk for infection is further increased by polypharmacy, immunosuppressive therapies, and presence of indwelling devices. Among the possible infectious syndromes, bloodstream infections (BSI) are particularly worrisome, since they carry a heavy burden in terms of morbidity and mortality in this complex population. The purpose of this narrative review is to summarize current concepts and evidence about the epidemiology, risk factors, clinical features, and management of BSI in IMW.

Methods

We reviewed existing literature using the inductive approach of grounded theory. First, we performed an updated MEDLINE/PubMed search (from 1 January 2000 to 15 August 2015; search terms: "bloodstream infections" OR "sepsis") AND ("internal medicine" OR "medical wards"). Then, we discussed the initial findings and iteratively selected pertinent articles and references.

Epidemiology

BSI occur when one or more viable pathogens invade the bloodstream, usually causing a systemic inflammatory response syndrome (SIRS). BSI are still one of the most common causes of hospital admission, even more than acute myocardial infarction, and they are also a leading cause of mortality among hospitalized patients, especially when presenting or progressing to severe sepsis or septic shock.

Although more than half of BSI episodes do not occur in intensive care units (ICU), the epidemiology of BSI in wards outside ICU has seldom been investigated in depth. Among 24,179 episodes of BSI in 49 US hospitals over a 7-year period, as many as 9,088 episodes...
(37.6%) occurred in IMW. More than 60% of these cases were due to gram-positive bacteria, such as coagulase-negative staphylococci (27.1%), Staphylococcus aureus (27.0%), and enterococci (9.9%).14 This predominance of gram positives has been confirmed in several studies from different geographic areas, although a relative increase in the incidence of healthcare-associated BSI due to gram negatives has also been signaled in recent years, both in United States and in Europe.15-19 In addition, two recent studies have reported an equal prevalence of gram-positive and gram-negative bacteria as a cause of BSI in medical wards.7,13 In the first of these studies, an equal prevalence of gram-positive and gram-negative organisms was observed among 64 patients with BSI mainly hospitalized in medical wards.7 These results are consistent with those of a Spanish study on 702 patients with BSI, which reported a high prevalence of gram negatives in wards other than ICU.13 Although the small sample size of these studies does not allow any definite conclusion, such findings - if reproduced in larger surveys - might be of particular concern in those countries endemic for multidrug resistant (MDR) gram negatives. Indeed, these organisms are frequently resistant to most antibacterials available in the present time.20-22 In particular, extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, which are able to inactivate third generation cephalosporins, have rapidly spread around the world during the last 15 years, both because of the dissemination of successful clones and because of the ease of inter-bacterial transferability of resistance through plasmid-encoded enzymes.22-26 Similar mechanisms underlie the growing diffusion of carbapenemase-producing Enterobacteriaceae (CPE), which might dramatically threaten the effective treatment of healthcare-associated infections in the 21st century.20,21,27 Although these carbapenem-resistant organisms are currently endemic only in a few countries, mostly in Southern Europe, their diffusion is increasingly reported worldwide.28-30 With regard to IMW, Corcione et al. recently observed that carbapenemase-producing Klebsiella pneumoniae (CPKP) was responsible for BSI at the same rate in medical wards and in ICU in a multicenter survey in North-West Italy.31 Consistently with these findings, we recently provided observational data suggesting a worrisome diffusion of CPKP in clinical wards (mainly medical) which were not considered at risk for CPKP spread, raising concern as to whether current infection-control efforts are sufficient to counteract CPKP diffusion, at least in some endemic hospitals.32,33

Besides bacteria, fungi, namely Candida spp., are another important cause of healthcare-associated BSI both in United States and in Europe.34-37 The number of IMW patients with BSI due to these yeasts has considerably increased during the last decades.5,34,38 In a recent combined Italian and Spanish survey, 448 out of 995 patients with BSI due to Candida spp were hospitalized in medical wards (46%).34 An even more impressive rate was reported in another Italian study focused on elderly patients, with as many as 98/145 episodes occurring in medical departments (67.6%).39 Although this trend toward a higher incidence of Candida spp. infections in medical wards has not been confirmed so far in other countries,40,41 a global increase in the incidence of fungal BSI in IMW is expected in the near future, due to the increasing size of the population at risk. Indeed, several risk factors for invasive fungal diseases such as increasing age, immunosuppression, solid tumors, and indwelling devices are becoming increasingly common in IMW.39,42-45

Worth of note is the fact that epidemiological surveys such as those cited above usually rely on culture-proven episodes (i.e., bacteremia or candidemia), thus including only patients with blood cultures positive for the causative agent of BSI. The obvious benefit of this approach is the exclusion from the analyses of patients with non-infection-related SIRS. However, considering that the frequent atypical clinical presentation of BSI in IMW patients (see below) might not be consistent with the classical indications for collecting blood cultures,46 the real burden of BSI in IMW may be considerably underestimated.

**Risk factors**

In IMW patients, some common comorbidities and their complications per se predispose to BSI. Several leukocytes defects capable of impairing host defenses have been described in patients with diabetes mellitus.47-49 Bedridden patients with diabetes mellitus and peripheral vascular insufficiency are also at high risk for the development of cutaneous ulcers, with subsequent superimposed infections by gram-positive and gram-negative bacteria.47-50 Another example is decompensated liver cirrhosis, which might predispose to BSI by gram negatives, gram positives and obligate anaerobes.51,54 Indeed, a severe liver impairment is associated with an increased intestinal patency and a reduced expression of intestinal antimicrobial peptides, which favor bacterial translocation from the intestinal lumen to the bloodstream.55-57 In addition, also IMW patients with autoimmune or neoplastic diseases should always be considered at increased risk of BSI, either because of inherent perturbations of the innate and adaptive responses to infection or because of the frequent administration of immunosuppressive and cytotoxic therapies targeting the underlying disease.52,54,58,59 In this regard, the risk of developing BSI
appears to be considerably increased in neutropenic patients with hematological malignancies (up to 8-fold higher than in those with solid neoplasms).60-61 Furthermore, disturbances of differentiation and maturation of neutrophils that might favor the development of BSI are also present in non-neutropenic hematological conditions (e.g., most of myelodysplastic syndromes).62 These conditions, which are increasingly seen in modern IMW, should thus be viewed as a potential risk factor for BSI, although the actual increase in risk remains unclear because of the high heterogeneity of diseases and treatments.53

Another important risk factor for the development of BSI in IMW patients is the presence of a central venous catheter (CVC).64-66 Although the rate of CVC utilization, expressed as catheter-days/patient-days, is generally lower in IMW than in ICU, some studies have reported a markedly higher incidence of CVC-related BSI (i.e., episodes/1000 catheter-days) in non-ICU wards in comparison with ICU.66,67 The reason for this finding might rely on a suboptimal care of CVC in the non-ICU setting. Indeed, prevention efforts to optimize indications and rules for CVC placement and maintenance (and thus reduce the incidence of CVC-related BSI) have been classically focused on ICU patients, due to the high CVC utilization rate and the high mortality of BSI in such a setting.68 In support of this hypothesis, the number of clinically unjustified CVC was higher in non-ICU departments than in ICU wards in a cross-sectional survey in a 600-bed US teaching hospital.69 With regard to the type of CVC, it should be noted that the use of peripherally-inserted CVC (PICC) has considerably increased in medical wards in recent years.65,70 Despite a theoretical reduced risk of infections due to PICC relative ease of insertion and its management by well-trained, dedicated nursing teams, a recent meta-analysis of 23 studies showed no difference in the incidence of device-related infections between patients with PICC and traditional CVC.70 Although some inter-hospital variability in the PICC management might explain these findings, we think PICC patients should better be considered at the same risk for device-related infections of those with classical CVC, at least until further studies will be available on this matter.

Besides CVC, several other types of indwelling devices frequently used in IMW patients might also predispose to the development of BSI. The occurrence of fever in patients with prosthetic joints, prosthetic cardiac valves, cardiac electronic devices, or urinary catheters could be the expression of a systemic infection starting from the foreign body, a clinical event that should be promptly suspected to avoid perilous delays in diagnosis and treatment.3,71,72 In particular, urinary catheters are frequently used in elderly patients in IMW, further increasing their high baseline risk for BSI related to obstructive uropathy, neurological disorders, and age itself.4,73-75

Finally, some important risk factors for the development of BSI due to Candida spp should also be mentioned. Besides CVC, diabetes mellitus, liver cirrhosis, cancer, treatment with cytotoxic and/or immunosuppressive drugs, all predisposing factors to bacterial and fungal BSI, additional risk factors for the development of Candida infections should be taken into account at the bedside of IMW patients.32,44,76,77 Among them, total parenteral nutrition (TPN) is an independent risk factor for the development of fungal BSI.78 Indeed, both glucose-containing solutions and lipid emulsions favor the formation of Candida biofilms within catheters used to administer TPN.79,80 In addition, hospital-dependent IMW patients often receive multiple courses of antibacterial therapies, that also predispose to fungal BSI by reducing the bacterial microbiome that usually prevents Candida overgrowth.5,81,82

**Clinical features**

The diagnosis of BSI may pose particular challenges in IMW patients. Indeed, they are often old individuals with nonspecific signs and symptoms of infection such as weakness, anorexia, malaise, or confusion, that may be considered manifestations of underlying comorbidities rather than expression of BSI.4,83,84 In addition, the most frequent clinical sign in BSI, fever, may be absent or blunted in up to one third of old subjects with BSI.85 This possibly reflects age-related changes both in body temperature regulation and in the biological response to infection.86 In this regard, aging has been associated with an increased generation of anti-inflammatory markers such as IL-10, IL-1 receptor antagonist, and soluble TNF receptors.87,88 However, even higher levels of circulating pro-inflammatory cytokines (e.g., TNF-α, IL-1, and IL-6) have been reported in old subjects in comparison with younger individuals with BSI.87,89,90 Although the underlying biologic response during BSI is still far to be completely understood, it is conceivable that aging is associated with complex and dynamic imbalances between anti- and pro-inflammatory stimuli, which involve both the humoral and the cellular phases of the host response to infection.91,92

Aside from aging, several other factors might contribute to the atypical presentation of BSI in IMW patients. A considerable number of IMW patients receive chronic treatment for systemic inflammatory diseases and tumors, using drugs - glucocorticoids and immunosuppressants - capable of blunting the biological response to infection and attenuating the clinical manifestations of
BSI. On the other hand, systemic inflammatory diseases themselves and other comorbidities like neoplasms or chronic respiratory failure might mimic fever, dyspnea, or other symptoms of infection. This might prevent clinicians from recognizing the possible development of BSI, by erroneously attributing the responsibility for the clinical picture to the underlying medical condition. In turn, this might delay the administration of an adequate antimicrobial treatment, a factor that is strongly and unfavorably associated with the outcome in subjects with BSI.

Some laboratory markers might help IMW clinicians in suspecting BSI pending blood culture results. Serum C-reactive protein (CRP) and serum procalcitonin (PCT) are currently the most widely used laboratory markers to assist the diagnosis of BSI. PCT has some advantages over CRP, being not influenced by the use of corticosteroids and by several systemic inflammatory diseases, although it might moderately increase after major trauma, surgery, and in case of end-stage renal disease. In addition, no or only mild increase in PCT usually occurs in case of fungal BSI or viral infections. In a recent systematic review and meta-analysis, PCT has been demonstrated to have a sensitivity of 76% and a specificity of 69% in the diagnosis of bacterial BSI. Discrepancies between high CRP levels and low PCT levels have also been proposed as a diagnostic tool to help distinguishing between fungal and bacterial BSI in patients with risk factors for candidemia, although no large studies have been conducted so far to clearly balance benefits and risks of this approach.

Blood cultures have both poor sensitivity and slow turn-around time in the diagnosis of candidemia. Therefore, specific tests to detect serum fungal antigens have been developed to be used in patients with signs and symptoms of infections and risk factors for invasive fungal diseases. Among them, the detection of serum (1,3)-β-D-glucan (BDG), a wall component of Candida and other fungi, has been recommended by the European Society for Clinical Microbiology and Infection (ESCMID) as an important aid in the early diagnosis (with >65% sensitivity and >80% specificity) and as a useful tool to rule out Candida BSI (with 85% negative predictive value). A combined serum mannan-antimannan testing has also been studied as a potential surrogate marker for the early diagnosis of candidemia, showing variable specificity and sensitivity in different studies. However, although possibly being either an alternative or a complement to BDG, the optimal way to use this test in clinical practice remains unclear.

Finally, although promising, the use of molecular methods (e.g., Candida real-time polymerase chain reaction) deserves further investigation, in view of the lack of standardized methodology and reproducibility of results.

Management

Different aspects should be taken into account when caring for IMW patients with BSI. First, resuscitation measures should be rapidly adopted in severe cases, and, whenever possible, the source of infection (e.g., CVC) should be removed. Second, antimicrobials active against the most probable pathogens should be administered early and empirically, pending blood cultures results, due to the favorable impact on survival of an appropriate initial antimicrobial therapy. The choice of the initial regimen should be guided by means of several clues, such as patient’s characteristics, patient’s medical history, and the microbiological epidemiology of the hospital/ward where BSI develop. Among the patient’s characteristics to be considered are the presence of indwelling devices, the type of comorbidities, and the presence of proven/suspected primitive foci of infection. An attempt at describing the most common causative agents of BSI on the basis of these characteristics is shown in Table 1, which also shows commonly administered antimicrobial agents with activity against susceptible phenotypes.

With regard to antimicrobial resistance, it is worth noting that standard empirical choices such as semi-synthetic penicillins, third generation cephalosporins, or carbapenems are inactive against methicillin-resistant Staphylococcus aureus (MRSA), as well as against the majority of MDR gram negatives (e.g., CPE, carbapenem-resistant Pseudomonas aeruginosa). Since survival from BSI is adversely influenced by an inappropriate initial antimicrobial therapy, the coverage of these pathogens should be ensured when the MDR etiology can be suspected on the basis of the local microbiological epidemiology (perhaps the main factor influencing the choice of antibiotics) and/or of the patient’s medical history (i.e., previous colonization/infection with MDR organisms, previous stay in hospitals or long-term care facilities endemic for MDR organisms, previous administration of broad-spectrum antibacterials, previous contact with known MDR carriers). Currently available antimicrobials that could be administered to treat infections caused by the most diffuse MDR bacteria are detailed in Table 2. As shown in the table, while dependable alternatives exist against MRSA, a few options remains to treat sepsis caused by MDR gram negatives, especially CPE. In such a case, 2- or 3-drug combinations are often administered, for
Table 1. Most common causative agents of bloodstream infections in internal medicine wards according to patients’ characteristics.

| Causative agent       | Predisposing factors                                                                 | Commonly administered antimicrobial agents with activity against susceptible phenotypes                                                                 |
|-----------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| *Staphylococcus aureus* | Skin/soft tissue infections, prosthetic joints, prosthetic cardiac valves, cardiac electronic devices, central venous catheters | Oxacillin, cefazolin (in case of MRSA: vancomycin, daptomycin, or linezolid)                                                                                                                                   |
| Coagulase-negative    | Central venous catheters, cardiac electronic devices, prosthetic joints, prosthetic cardiac valves | Oxacillin, cefazolin (if resistant to β-lactams: vancomycin, daptomycin, or linezolid)                                                                                                                           |
| *Staphylococcus*      | Inflammatory bowel diseases, colorectal cancer, cirrhosis, aging, urinary tract infections | Ampicillin, ampicillin/sulbactam, vancomycin (if resistant to penicillins)                                                                                                                                       |
| Enterococci           | Urinary tract infections, diabetes, aging, solid and hematologic cancers, inflammatory bowel diseases, cirrhosis | Ureidopenicillins, third generation cephalosporins, gentamicin, fluoroquinolones (high rates of resistance have been reported in both community and hospitals worldwide), carbapenems (in case of ESBL-PE) |
| Pseudomonas aeruginosa| Bedridden patients, chronic obstructive pulmonary disease, solid and hematologic cancer, aging, prolonged hospital stay | Ureidopenicillins, anti-pseudomonal cephalosporins (ceftazidine, cefepime), amikacin, ciprofloxacin (usually not as single agent), carbapenems (usually not as single agent) |
| Candida spp.          | Elderly, solid and hematologic cancer, immunosuppressive therapies, broad spectrum antibiotics, total parenteral nutrition, diabetes, central venous catheters, prolonged hospital stay | Echinocandins, polyenes, azoles (see Table 3 for specific indications)                                                                                                                                       |

Notes. MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL-PE, extended-spectrum β-lactamases-producing Enterobacteriaceae. With the exception of ertapenem which is inactive against *Pseudomonas* spp.

Table 2. Currently available antimicrobials against multidrug resistant (MDR) bacteria causing bloodstream infections.

| Drug          | Class       | Spectrum of activity against MDR bacteria | Possible disadvantages                                           |
|---------------|-------------|-------------------------------------------|-----------------------------------------------------------------|
| Vancomycin    | Glycopeptides | MRSA                                      | Nephrotoxicity; “slow” bactericidal activity; increased MIC values within the susceptibility range associated with poor outcomes; possible red neck syndrome |
| Teicoplanin   | Glycopeptides | MRSA                                      | Not available in US, nephrotoxicity; “slow” bactericidal activity; possible thrombocytopenia |
| Oritavancin   | Lipoglycopeptides | MRSA, VRE                                | Approved only for skin and skin structure infections; limited clinical experience |
| Telavancin    | Lipoglycopeptides | MRSA, VRE*                                | Nephrotoxicity; possible QTc prolongation, interference with laboratory coagulation tests; dysgeusia and nausea as frequent adverse events |
| Daptomycin    | Lipopeptides | MRSA, VRE                                 | Limited clinical experience; cross-allergenicity with other cephalosporins |
| Ceftaroline   | Cephalosporins | MRSA, VISA, HVISA, VRSA                   | Limited clinical experience; cross-allergenicity with other cephalosporins |
| Ceftobiprole  | Cephalosporins | MRSA, VISA, HVISA, VRSA                   | Limited clinical experience; cross-allergenicity with other cephalosporins |
| Linezolid     | Oxazolidinones | MRSA, VISA, HVISA, VRSA                   | Limited clinical experience; cross-allergenicity with other cephalosporins |
| Tedizolid     | Oxazolidinones | MRSA, VRE                                 | Limited clinical experience; cross-allergenicity with other cephalosporins |
| Tigecycline   | Glycylcyclines | MRSA, VRE, ESBL-PE, CPE                   | Bacteriostatic; low lung and serum concentrations (tigecycline should not be used for BSI, although a possible role in combination regimens for BSI due to CPE has been proposed); nausea and vomiting as frequent adverse events; FDA safety warning of higher risk of mortality than comparator agents in meta-analyses; inactive against Pseudomona and Proteus spp. |
| Meropenem     | Carbapenems  | ESBL-PE                                    | Inactive against CPE, although a possible role in combinations regimens has been proposed for CPE with meropenem MIC ≤ 8 mg/L |
| Colistin      | Polymyxins   | ESBL-PE, CPE, CRPA                        | Nephrotoxicity, neurotoxicity, emergence of resistance and increased mortality reported when administered as monotherapy |
| Gentamicin    | Aminoglycosides | ESBL-PE, CPE                              | Nephrotoxicity, ototoxicity                                    |
| Ceftolozane/Tazobactam | B-lactams inhibitor | ESBL-PE, CPE                              | Limited clinical experience; inactive against CPE |
| Ceftazidine/Avibactam | B-lactams inhibitor | ESBL-PE, CPE                              | Limited clinical experience                                    |

Notes. MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococci; VISA, vancomycin-intermediate *Staphylococcus aureus*; HVISA, heteroresistant vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; ESBL-PE, extended-spectrum β-lactamases-producing Enterobacteriaceae; CPE, carbapenemase-producing Enterobacteriaceae, CRPA, carbapenem-resistant *Pseudomonas aeruginosa*, MIC, minimum inhibitory concentration.

*Less active against Van-A phenotype.
**With the exception of strains producing metallo-β-lactamases.
several reasons: to reduce the emergence of resistance to the last available active agents (often colistin and/or gentamicin), to take advantage of possible synergistic effects, and, above all, because of a survival benefit of combinations over monotherapy that has been suggested by several observational studies. However, although ultimately it appears reasonable to encourage the use of combination regimens, no large randomized clinical trials exist in this setting that clearly define the right balance between benefits and risks of each specific combination (NCT01732250 and NCT01597973 are ongoing). Indeed, combinations are not completely free from risks, being associated with an increase in adverse events, a large disruption of the human microbiome that favors Candida and Clostridium difficile infections, and a self-perpetuating selection of resistant strains both in the patient and in the hospital environment.

In IMW patients with BSI and risk factors for candidemia, an empirical antifungal therapy should also be considered. Table 3 reports the characteristics of the different classes of antifungals, as well as the recommendations for their use in the treatment of candidemia according to guidelines.

In addition to antimicrobials, also immunoglobulins (particularly if IgM-enriched) have been suggested to possibly increase survival of patients with sepsis. However, conflicting results have been reported so far in high-quality studies, and the definite existence of any related survival benefit is still a matter of debate. Furthermore, available data is limited to critically ill patients, and dedicated studies are still lacking in settings other than ICU.

Empiric antimicrobial therapies should be reassessed once blood cultures results become available (usually within 48–72 h from the blood drawn). If cultures yield a bacterial or fungal pathogen, the initial therapy should be either changed or de-escalated to a tailored regimen, according to the nature of the isolate. In case of negative blood cultures, the clinical judgment dictates the choice. Indeed, if there is improvement of patient’s conditions, the initial therapy can be confirmed. Conversely, if there is no improvement, different possibilities should be taken into consideration: (a) presence of infection due to an unusual or resistant pathogen not covered by the initial regimen; (b) presence of complications such as infection of indwelling devices or abscess formation; (c) presence of drug-resistant organisms; (d) infection due to an organism resistant to the initial therapy; (e) infection due to a polymicrobial infection; (f) infection due to an organism with a unique antimicrobial susceptibility pattern; (g) infection due to an organism with a high likelihood of multidrug resistance; (h) infection due to an organism with a high likelihood of resistance to the initial therapy. In this setting, the use of combination regimens is generally recommended, especially if the initial therapy did notwork or was stopped due to adverse effects. The choice of the second and third therapy should be determined by the nature of the isolate and the susceptibility pattern.

**Table 3. Recommendations for the treatment of candidemia in non-neutropenic adults.**

| Class       | Notes                                                                 | Drug                                      | ESCMID (2016) | IDSA (2016) |
|-------------|------------------------------------------------------------------------|-------------------------------------------|---------------|-------------|
| Echinocandins | Good efficacy and favorable safety profile in clinical trials, few drug interactions, fungicidal, highly active against biofilm (e.g., CVC-related infections). Activity against all Candida spp, but reduced in vitro susceptibility of C. parapsilosis. Possible development of resistance in C. glabrata due to mutation in FKS1 or FKS2 genes. | - Anidulafungin A (I) Strong (high)       |               |             |
|             |                                                                      | - Caspofungin A (I) Strong (high)         |               |             |
|             |                                                                      | - Micafungin A (I) Strong (high)          |               |             |
| Polyenes    | Renal and infusion-related toxicity. Recommended as initial therapy when there is a history of intolerance to echinocandins, when the infection is refractory to other therapies, and when the Candida isolate is resistant to other agents. Better safety profile of amphotericin B lipid formulations (liposomal, lipid complex, and colloidal dispersion) over amphotericin B deoxycholate. | - Amphotericin B liposomal B (I) Strong (high) |               |             |
|             |                                                                      | - Amphotericin B lipid complex C (III) Strong (high) |               |             |
|             |                                                                      | - Amphotericin B colloidal dispersion D (III) Strong (high) |               |             |
|             |                                                                      | - Amphotericin B deoxycholate A (I) Strong (high) |               |             |
| Azoles      | Narrower spectrum and inferiority of fluconazole vs. echinocandins in clinical trials (especially in patients with severe disease), poor activity against biofilms, fungistatic. Possible better activity than echinocandins against C. parapsilosis. In IDSA guidelines, fluconazole is suggested as an alternative to echinocandins for patients who have mild to moderate illness, who have no previous exposure to azoles, and who are not at risk of resistant Candida spp. (C. krusei, C. glabrata, or other Candida spp according to local resistance patterns), while ESCMID considers echinocandins as the preferred initial choice. Step-down therapy to fluconazole appears reasonable for patients improved after initial therapy with an echinocandin or amphotericin B (in the case of Candida spp, susceptible to fluconazole). Voriconazole has a limited spectrum of activity compared to echinocandins, more drug interactions, and necessity of therapeutic drug monitoring. Posaconazole has good in vitro activity against most Candida species, but few clinical data to support its use among patients with candidemia. Itraconazole has similar antifungal spectrum of fluconazole, but inferior pharmacokinetics and less tolerability. | - Fluconazole C (I) Strong (high)          |             |             |
|             |                                                                      | - Voriconazole B (I) Strong (moderate)     |               |             |
|             |                                                                      | - Posaconazole D (III) —                  |               |             |
|             |                                                                      | - Itraconazole D (III) —                  |               |             |

Notes. ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; CVC, central venous catheter.

*Expressed as: strength of recommendation (quality of evidence), according to IDSA and ESCMID classifications.**
of a non infectious condition as responsible for the clinical picture.

Once the infectious process is under control and the maximum benefit has been obtained, antimicrobial therapy should be discontinued.\textsuperscript{130} In this regard, a strong and early decrease during treatment of serum CRP and PCT, especially the latter, might strengthen the decision of discontinuing antimicrobials once the resolution of the infectious process has been detected on a clinical basis.\textsuperscript{99} Conversely, although BDG has been shown to possibly have a prognostic role in candidemia, it should not be used as a single tool to guide prosecution or discontinuation of antifungals.\textsuperscript{131,132}

Finally, the application of antimicrobial stewardship programs in IMW, in addition to effective infection-control interventions (including not only contention measures, but also a detailed assessment of the local microbiological epidemiology), might reduce the rates of inappropriate antimicrobial treatment and prevent the further emergence of resistance.\textsuperscript{133,134} Indeed, such programs rely on coordination and collaboration among different healthcare professionals to ensure consistency and coherence in prescribing, sharing knowledge, and educating.\textsuperscript{134} We think both infectious diseases specialists and IMW physicians should play a key role in this setting, since an effective specialist support cannot be separated from a continuous and proactive collaboration of a motivated ward staff.

Conclusions

BSI have particular diagnostic and therapeutic features in IMW patients. Recognizing the onset of BSI might sometime require a high degree of suspicion, since the clinical picture could be affected by underlying conditions and concomitant medications. Furthermore, selecting the appropriate antimicrobials to treat BSI in IMW is becoming an increasingly complex task in which all possible benefits and costs should be carefully analyzed, also from a public health standpoint. Under this light, IMW clinicians should be actively involved in infection-control and antimicrobial stewardship programs, together with infection-control experts, infectious diseases consultants, microbiologists, and pharmacists. Indeed, only a specialized, continuous, and interdisciplinary approach could really improve the management of patients in an era of increasing antimicrobial resistance and complexity of care.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2012 Revision, Press Release (13 June 2013). http://esa.un.org/unpd/wpp/Documentation/pdf/ WPP2012_Press_Release.pdf 2013
[2] Heppner HJ, Cornet S, Peter W, Philipp B, Katrin S. Infections in the elderly. Crit Care Clin 2013; 29:757-74; PMID:23830661; http://dx.doi.org/10.1016/j.ccc.2013.03.016
[3] Juthani-Mehta M, Quagliarello VJ. Infectious diseases in the nursing home setting: challenges and opportunities for clinical investigation. Clin Infect Dis 2010; 51:931-6; PMID:20822459; http://dx.doi.org/10.1086/656411
[4] Beckett CL, Harbarth S, Huttner B. Special considerations of antibiotic prescription in the geriatric population. Clin Microbiol Infect 2015; 21:3-9; PMID:25636920; http://dx.doi.org/10.1016/j.cmi.2014.08.018
[5] Bassetti M, Molinari MP, Mussap M, Viscoli C, Righi E. Candidaemia in internal medicine departments: the burden of a rising problem. Clin Microbiol Infect 2013; 19:E281-4; PMID:23414070; http://dx.doi.org/10.1111/1469-0691.12155
[6] Odden AJ, Rohde JM, Bonham C, Kuhn L, Malani PN, Chen LM, Flanders SA, Iwashyna TJ. Functional outcomes of general medical patients with severe sepsis. BMC Infect Dis. England 2013; 13:588
[7] Rohde JM, Odden AJ, Bonham C, Kuhn L, Malani PN, Chen LM, Flanders SA, Iwashyna TJ. The epidemiology of acute organ system dysfunction from severe sepsis outside of the intensive care unit. J Hosp Med 2013; 8:243-7; PMID:23401431; http://dx.doi.org/10.1002/jhm.2012
[8] Pope C, Ziebland S, Mays N. Qualitative research in health care. Analyzing qualitative data. BMJ 2000; 320:114-6; PMID:10625273; http://dx.doi.org/10.1136/bmj.320.7227.114
[9] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101:1644-55; http://dx.doi.org/10.1378/chest.101.6.1644
[10] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29:1303-10; PMID:11445675; http://dx.doi.org/10.1097/00003246-200107000-00002
[11] Karlsson S, Ruokonen E, Varpula T, Ala-Kokko T, Pettita V. Long-term outcome and quality-adjusted life years after severe sepsis. Crit Care Med 2009; 37:1268-74; PMID:19242321; http://dx.doi.org/10.1097/CCM.0b013e31819c13ac
[12] Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med 2010; 38:1276-83; PMID:20308885
[13] Esteban A, Frutos-Vivar F, Ferguson ND, Penuelas O, Lorente JA, Gordo F, Honrubia T, Algara A, Bustos A, Garcia
G, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. Crit Care Med 2007; 35:1284-9; PMID:17414725; http://dx.doi.org/10.1097/01.CCM.0000260960.94300.DE

[14] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004; 39:1093; http://dx.doi.org/10.1086/421946

[15] Pfaffer MA, Jones RN, Doern GV, Kugler K. Bacterial pathogens isolated from patients with bloodstream infection: frequencies of occurrence and antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program (United States and Canada, 1997). Antimicrob Agents Chemother 1998; 42:1762-70; PMID:9661018

[16] Rodriguez-Crêixems M, Alcalá L, Muñoz P, Cercedano E, Vicente T, Bouza E. Bloodstream infections: evolution and trends in the microbiology workload, incidence, and etiology, 1985-2006. Medicine (Baltimore) 2008; 87:234-49; http://dx.doi.org/10.1097/MD.0b013e318182119b

[17] Sader HS, Jones RN, Andrade-Baiocchi S, Biedenbach DJ, SENTRY Participants Group (Latin America). Four-year evaluation of frequency of occurrence and antimicrobial susceptibility patterns of bacteria from bloodstream infections in Latin American medical centers. Diagn Microbiol Infect Dis 2002; 44:273-80; PMID:12493175; http://dx.doi.org/10.1016/S0732-8893(02)00469-8

[18] Lai CC, Chen YH, Lin SH, Chung KP, Sheng WH, Ko WC, Hsueh PR. Changing aetiology of healthcare-associated bloodstream infections at three medical centres in Taiwan, 2000-2011. Epidemiol Infect 2014; 142:2180-5; PMID:25116133; http://dx.doi.org/10.1017/C19.0139152

[19] Albrecht SJ, Fishman NO, Kitchen J, Nachamin I, Bilker WB, Hoegg C, Samel C, Barbagallo S, Arentzen J, Lautenbach E. Reemergence of gram-negative healthcare-associated bloodstream infections in the ICU. Clin Microbiol Infect 2015; 21:e11-3; PMID:25682279; http://dx.doi.org/10.1016/j.cmi.2014.09.012

[20] Nordmann P, Dortet L, Poirel L. Carbapenem resistance in Enterobacteriaceae: here is the storm! Trends Mol Med 2012; 18:263-72; PMID:22480775; http://dx.doi.org/10.1016/j.molmed.2012.03.003

[21] Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, Luzzati R, Novais A, Valverde A, Machado E, Peixe L, Baquero F, Coque TM. Prevalence and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae in Europe. Clin Microbiol Infect 2008; 14 S1:144-53; PMID:Can’t; http://dx.doi.org/10.1111/j.1469-0691.2007.01850.x

[22] Bush K. Extended-spectrum β-lactamases in North America, 1987-2006. Clin Microbiol Infect 2008; 14 S1:134-43; PMID:18154537; http://dx.doi.org/10.1111/j.1469-0691.2007.01848.x

[23] Cantón R, Novais A, Valverde A, Machado E, Peixe L, Baquero F, Coque TM. Prevalence and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae in Europe. Clin Microbiol Infect 2008; 14 S1:144-53; PMID:Can’t; http://dx.doi.org/10.1111/j.1469-0691.2007.01850.x

[24] Hawkey PM. Prevalence and clonality of extended-spectrum β-lactamases in Asia. Clin Microbiol Infect 2008; 14 S1:159-65; PMID:18154540; http://dx.doi.org/10.1111/j.1469-0691.2007.01855.x

[25] Giani T, Pini B, Arena F, Conte V, Bracco S, Migliavacca R, Pantosti A, Pagani L, Luzzaro F, Rossolini GM. AMCLI-CRE Survey Participants. Epidemic diffusion of KPC carbapenemase-producing Klebsiella pneumoniae in Italy: results of the first countrywide survey, 15 May to 30 June 2011. Euro Surveill 2013; 18 pii:20489; PMID:23787077

[26] Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, Cornaglia G, Garau J, Giannakouski M, Hayden MK, et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis 2013; 13:785-96; PMID:23969216; http://dx.doi.org/10.1016/S1473-3099(13)70190-7

[27] Endimiani A, Hujer AM, Perez F, Bethel CR, Hujer KM, Kroeger J, Oethinger M, Paterson DL, Adams MD, Jacobs MR, et al. Characterization of blaKPC containing Klebsiella pneumoniae isolates detected in different institutions in the eastern USA. J Antimicrob Chemother 2009; 64:327-37; PMID:19155227; http://dx.doi.org/10.1093/jac/dkn547

[28] Ma L, Wang JT, Wu TL, Siu HK, Chuang YC, Lin JC, Lu MC, Lu PL. Emergence of OXA-48-Producing Klebsiella pneumoniae in Taiwan. PLoS ONE 2015; 10:e0139152; PMID:26414183; http://dx.doi.org/10.1371/journal.pone.0139152

[29] Corcione S, Rocchetti A, Argentaro PA, Raso R, Zotti CM, De Rosa FG, Ghisetti V. A one-year survey of carbapenemase-producing Klebsiella pneumoniae in Italy: beyond the ICU. Clin Microbiol Infect 2015; 21:e11-3; PMID:25682279; http://dx.doi.org/10.1016/j.cmi.2014.09.012

[30] Giacobbe DR, Del Bono V, Marchese A, Viscoli C. Early carbapenem-resistant Klebsiella pneumoniae bacteremia: should we expand the screening? Clin Microbiol Infect 2014; 20(12):O1157-8

[31] Alcalá L, Muñoz P, Cercedano E, Vicente T, Bouza E. Bloodstream infections: evolution and trends in the microbiology workload, incidence, and etiology, 1985-2006. Medicine (Baltimore) 2008; 87:234-49; http://dx.doi.org/10.1097/MD.0b013e318182119b
Rychly DJ, DiPiro JT. Infections associated with tumor necrosis factor-α antagonists. Pharmacotherapy 2005; 25:1181-92; PMID:16164393; http://dx.doi.org/10.1592/phco.2005.25.9.1181

Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? JAMA 2012 Aug 1; 308:502-11; http://dx.doi.org/10.1001/jama.2012.8262

Stojadinovic O, Brem H, Younghounis C, Lee B, Fallon J, Staluppi M, Merchant A, Galiano RD, Tomic-Canic M. Molecular pathogenesis of chronic wounds: the role of β-catenin and c-myc in the inhibition of epithelialization and wound healing. Am J Pathol 2005; 167:59-69; PMID:15972952; http://dx.doi.org/10.1016/S0002-9440(10)62953-7

van der Pouw Kraan TC, Chen WJ, Bunck MC, van Raalte DH, van der Zijl NJ, van Genugten RE, van Bloe mendaal L, Baggen JM, Serné EH, Diamant M, et al. Metabolic changes in type 2 diabetes are reflected in peripheral blood cells, revealing aberrant cytoxicity, a viral signature, and hypoxia inducible factor activity. BMC Med Genomics 2015; 8:20; PMID:25956355; http://dx.doi.org/10.1186/s12920-015-0096-y

Wong SL, Demers M, Martinod K, Gallant M, Wang Y, Goldfine AB, Kahn CR, Wagner DD. Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. Nat Med 2015; 21(7):815-9

LoGerfo FW, Coffman JD. Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. N Engl J Med 1984; 311:1615-9; PMID:6390204; http://dx.doi.org/10.1056/NEJM198412203112506

Noor S, Zubair M, Ahmad J. Diabetic foot ulcer-A review on pathophysiology, classification and microbial etiology. Diabetes Metab Syndr 2015; 9(3):192-9; PMID:25982677

Tooke JE, Brash PD. Microvascular aspects of diabetic foot disease. Diabet Med 1996; 13 Suppl 1:S26-9; PMID:8741825

Borelli M. Epidemiology and outcome of nosocomial infections due to Candida spp. in the USA: species distribution and resistance to echinocandin and azole antifungal agents. Pharmacotherapy 2005; a

25:1181-92; PMID:16164393; http://dx.doi.org/10.1592/phco.2005.25.9.1181

Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? JAMA 2012 Aug 1; 308:502-11; http://dx.doi.org/10.1001/jama.2012.8262

Stojadinovic O, Brem H, Younghounis C, Lee B, Fallon J, Staluppi M, Merchant A, Galiano RD, Tomic-Canic M. Molecular pathogenesis of chronic wounds: the role of β-catenin and c-myc in the inhibition of epithelialization and wound healing. Am J Pathol 2005; 167:59-69; PMID:15972952; http://dx.doi.org/10.1016/S0002-9440(10)62953-7

van der Pouw Kraan TC, Chen WJ, Bunck MC, van Raalte DH, van der Zijl NJ, van Genugten RE, van Bloe mendaal L, Baggen JM, Serné EH, Diamant M, et al. Metabolic changes in type 2 diabetes are reflected in peripheral blood cells, revealing aberrant cytoxicity, a viral signature, and hypoxia inducible factor activity. BMC Med Genomics 2015; 8:20; PMID:25956355; http://dx.doi.org/10.1186/s12920-015-0096-y

Wong SL, Demers M, Martinod K, Gallant M, Wang Y, Goldfine AB, Kahn CR, Wagner DD. Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. Nat Med 2015; 21(7):815-9

LoGerfo FW, Coffman JD. Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. N Engl J Med 1984; 311:1615-9; PMID:6390204; http://dx.doi.org/10.1056/NEJM198412203112506

Noor S, Zubair M, Ahmad J. Diabetic foot ulcer-A review on pathophysiology, classification and microbial etiology. Diabetes Metab Syndr 2015; 9(3):192-9; PMID:25982677

Tooke JE, Brash PD. Microvascular aspects of diabetic foot disease. Diabet Med 1996; 13 Suppl 1:S26-9; PMID:8741825

Bruns T, Zimmermann HW, Stallmach A. Risk factors and outcome of bacterial infections in cirrhosis. World J Gastroenterol 2014; 20:2542-54; PMID:24627590; http://dx.doi.org/10.3748/wjg.v20.i10.2542

Steffen EK, Berg RD, Deitch EA. Comparison of translocation of gut bacteria in rats with cirrhosis to mesenteric lymph nodes partially explains the pathogenesis of spontaneous bacterial peritonitis. J Hepatol 1994; 21:792-6; PMID:7890896; http://dx.doi.org/10.1016/S0168-8278(94)80241-6

Scarpetella V, Melia J, Lauritano EC, Perotti G, Merra G, Dal Lago A, Ojetti V, Ainaro ME, Santoro M, et al. Intestinal permeability in cirrhotic patients with and without spontaneous bacterial peritonitis: is the ring closed? Am J Gastroenterol 2010; 105:323-7; PMID:19844200; http://dx.doi.org/10.1038/ajg.2009.558

Teltschik Z, Wiest R, Beisner J, Nuding S, Hofmann C, Schoelcher J, Bevins CL, Stange EF, Wehkamp J. Intestinal bacterial translocation in rats with cirrhosis is
related to compromised Paneth cell antimicrobial host defense. Hepatology 2012; 55:1154-63; PMID:22095436; http://dx.doi.org/10.1002/hep.24789

[58] Alarcon GS. Infections in systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis. Infect Dis Clin North Am 2006; 20:849-75; PMID:17118293; http://dx.doi.org/10.1016/j.idc.2006.09.007

[59] Marin M, Gudiol C, Garcia-Vidal C, Ardanuy C, Carratala J. Bloodstream infections in patients with solid tumors: epidemiology, antibiotic therapy, and outcomes in 528 episodes in a single cancer center. Medicine (Baltimore) 2014; 93:143-9; PMID:24797169; http://dx.doi.org/10.1097/MD.0000000000000026

[60] Schelenz S, Nwaka D, Hunter PR. Longitudinal surveillance of bacteremia in haematology and oncology patients at a UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. J Antimicrob Chemother 2013; 68:1431e8; http://dx.doi.org/10.1093/jac/dkt002

[61] Marin M, Gudiol C, Ardanuy C, Garcia-Vidal C, Calvo M, Arnau M, Carratalà J. Bloodstream infections in neutropenic patients with cancer: differences between patients with haematological malignancies and solid tumours. J Infect 2014; 69:417-23; PMID:24960295; http://dx.doi.org/10.1016/j.jinf.2014.05.018

[62] Goasguen JE, Bennett JM, Bain BJ, Brunning R, Vallespi MT, Tomonaga M, Zini G, Renault AS. Proposal for refining the definition of dysgranulopoiesis in acute myeloid leukemia and myelodysplastic syndromes. Leuk Res 2014; 38:447-53; PMID:24439566; http://dx.doi.org/10.1016/j.leukres.2013.12.020

[63] Steensma DP, Tefferi A. The myelodysplastic syndrome (s): a perspective and review highlighting current controversies. Leuk Res 2003; 27:95-120; PMID:12526916; http://dx.doi.org/10.1016/S0145-2126(02)00098-X

[64] Marschall J. Catheter-associated bloodstream infections: looking outside of the ICU. Am J Infect Control. United States 2008:S172 e5-8

[65] Rhee Y, Heung M, Chen B, Chenoweth CE. Central line-associated bloodstream infections in non-ICU inpatient wards: a 2-year analysis. Infect Control Hosp Epidemiol 2015; 36:424-30; PMID:25782897; http://dx.doi.org/10.1017/ice.2014.86

[66] Tedja R, Gordon SM, Fatica C, Fraser TG. The descriptive epidemiology of central line-associated bloodstream infection among patients in non-intensive care unit settings. Infect Control Hosp Epidemiol 2014; 35:164-8; PMID:24442079; http://dx.doi.org/10.1086/647845

[67] Vonberg RP, Behnke M, Geffers C, Sohr D, Ruden H, Dettenkofer M, Gastmeier S. Device-associated infection rates for non-intensive care unit patients. Infect Control Hosp Epidemiol 2006; 27:357-61; PMID:16622812; http://dx.doi.org/10.1086/503339

[68] Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, Sexton B, Hyzy R, Welsh R, Roth G, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006; 355:2725-32; PMID:17192537; http://dx.doi.org/10.1056/NEJMoa061115

[69] Trick WE, Vernon MO, Welbel SF, Wisniewski MF, Jernigan JA, Weinstein RA. Unnecessary use of central venous catheters: the need to look outside the intensive care unit. Infect Control Hosp Epidemiol 2004; 25:266-8; PMID:15061422; http://dx.doi.org/10.1086/502390

[70] Chopra V, O’Horo JC, Rogers MA, Maki DG, Saïd Dar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2013; 34:908-18; PMID:23917904; http://dx.doi.org/10.1086/671737

[71] Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi MF, Barsic B, Bouza E, Cabell CH, Ramos AI, Fowler V, Jr, Hoen B, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med 2008; 168:2095-103; PMID:18955638; http://dx.doi.org/10.1001/archinte.168.19.2095

[72] Wang L, Lansing B, Symons K, Flannery EL, Fisch J, Cherian K, McNamara SE, Mody L. Infection rate and colonization with antibiotic-resistant organisms in skilled nursing facility residents with indwelling devices. Eur J Clin Microbiol Infect Dis 2012; 31:1797-804; PMID:22274858; http://dx.doi.org/10.1007/s10096-011-1504-7

[73] Cornejo-Dávila V, Palmeros-Rodríguez MA, Uberoygoyena-Tello de Meneses I, Mayorga-Gómez E, Garza-Sáinz G, Osornio-Sánchez V, et al. Management of complicated urinary tract infections in a referral center in Mexico. Int Urol Nephrol 2015; 47:229-33; http://dx.doi.org/10.1007/s10096-014-0883-y

[74] Lee CC, Chen SY, Chang IJ, Chen SC, Wu SC. Comparison of clinical manifestations and outcome of community-acquired bloodstream infections among the oldest old, elderly, and adult patients. Medicine (Baltimore) 2007; 86:138-44; PMID:17505253; http://dx.doi.org/10.1097/SHK.0b013e318067da56

[75] Wagenlehner FM, Lichtenstern C, Rolfs C, Mayer K, Uhle F, Weidner W, Weigand MA. Diagnosis and management for urosepsis. Int J Urol 2013; 20:963-70; PMID:23714209

[76] Bassetti M, Taramasso L, Nicco E, Molinari MP, Musiap M, Viscoli C. Epidemiology, species distribution, antifungal susceptibility and outcome of nosocomial candidemia in a tertiary care hospital in Italy. PLoS One 2011; 6:e24198; PMID:21935385; http://dx.doi.org/10.1371/journal.pone.0024198

[77] Rajagopalan S. Serious infections in elderly patients with diabetes mellitus. Clin Infect Dis 2005; 40:990-6; PMID:15824991; http://dx.doi.org/10.1086/427690

[78] Luzzati R, Cavinato S, Giangreco M, Grana G, Centonze Deiana ML, Biolo G, Barbone F. Peripheral and total parenteral nutrition as the strongest risk factors for nosocomial candidemia in elderly patients: a matched case-control study. Mycoses 2013; 56:664-71; PMID:23675641; http://dx.doi.org/10.1111/myc.12090

[79] Branchini ML, Pfaller MA, Rhine-Chalberg J, Frempong T, Isenberg HD. Genotypic variation and slime production among blood and catheter isolates of Candida parapsilosis. J Clin Microbiol 1994; 32:452-6; PMID:8150956

[80] Swindell K, Lattiff AA, Chandra J, Mukherjee PK, Ghannoum MA. Parenteral lipid emulsion induces
germination of Candida albicans and increases biofilm formation on medical catheter surfaces. J Infect Dis 2009; 200:473-80; PMID:19552524; http://dx.doi.org/10.1086/600106

[81] Samonis G, Galanakis E, Ntaoukas M, Sarchianaki E, Spathopoulou T, Dimopoulou D, Kofteridis DP, Maraki S. Effects of carbapenems and their combination with amikacin on murine gut colonization by Candida albicans. Mycoses 2013; 56:105-9; PMID:22680984; http://dx.doi.org/10.1111/j.1439-0507.2012.02212.x

[82] Samonis G, Gikas A, Anaissie EJ, Vrenzos G, Maraki S, Tsleentis Y, Bodey GP. Prospective evaluation of effects of broad-spectrum antibiotics on gastrointestinal yeast colonization of humans. Antimicrob Agents Chemother 1993; 37:51-3; PMID:8431017; http://dx.doi.org/10.1128/AAC.37.1.51

[83] Chassagne P, Perol MB, Doucet J, Trivalle C, Menard JF, Manchon ND, Muynot Y, Humbert G, Bourreille J, Bercoff E. Is presentation of bacteremia in the elderly the same as in younger patients? Am J Med 1996; 100:65-70; PMID:8579089; http://dx.doi.org/10.1016/S0002-9343(96)90013-3

[84] Jeong SJ, Yoon SS, Han SH, Yong DE, Kim CO, Kim JT. Evaluation of humoral immune response to nosocomial pathogen and functional status in elderly patients with sepsis. Arch Gerontol Geriatr 2014; 58:10-4; PMID:23998496; http://dx.doi.org/10.1016/j.archger.2013.07.001

[85] Gavazzi G, Krause KH. Ageing and infection. Lancet 1998; 351:1155-9; PMID:9583134; http://dx.doi.org/10.1016/S0140-6736(98)00892-0

[86] Blatteis CM. Age-dependent changes in temperature regulation - a mini review. Gerontology 2012; 58:289-95; PMID:22085834; http://dx.doi.org/10.1159/2012.00333148

[87] Gabriel P, Cakman I, Rink L. Overproduction of monokines by leukocytes after stimulation with lipopolysaccharide in the elderly. Exp Gerontol 2002; 37:235-47; PMID:11772509; http://dx.doi.org/10.1016/S0531-5565(01)00189-9

[88] Grubeck-Loebenstein B, Berger P, Saurwein-Teissl M, Zisterer K, Wick G. No immunity for the elderly. Nat Med 1998; 4:870; PMID:9701220; http://dx.doi.org/10.1038/nm0898-870b

[89] Born J, Uthgenannt D, Dott C, Nunninghoff D, Ringvolt E, Wagner T, Fehm HL. Cytokine production and lymphocyte subpopulations in aged humans. An assessment during nocturnal sleep. Mech Ageing Dev 1995; 84:113-26; PMID:8788239; http://dx.doi.org/10.1016/000333148

[90] Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol 2004; 39:687-99; PMID:15130663; http://dx.doi.org/10.1016/j.exger.2004.01.009

[91] Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369:840-51; PMID:23984731; http://dx.doi.org/10.1056/NEJMra1208623

[92] Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis 2005; 41Suppl 7:S504-12; PMID:16237654; http://dx.doi.org/10.1086/432007

[93] Richardson MD. Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother 2005; 56Suppl 1:i5-i11; PMID:16120635; http://dx.doi.org/10.1093/jaac/jdl218

[94] Chen HC, Lin WL, Lin CC, Hsieh WH, Hsieh CH, Wu MH, Wu JY, Lee CC. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. J Antimicrob Chemother 2013; 68:947-53; PMID:23264512; http://dx.doi.org/10.1093/jac/dks475

[95] Retamar P, Portillo MM, Lopez-Prieto MD, Rodriguez-Lopez F, de Cueto M, Garcia MV, Gómez MJ, Del Arco A, Muñoz A, Sánchez-Porto A, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother 2012; 56:472-8; PMID:22005999; http://dx.doi.org/10.1128/AAC.00462-11

[96] Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marches A, Spanu T, Ambretti S, Ginocchio F, Cristini F, et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: importance of combination therapy. Clin Infect Dis 2012; 55:943-50; PMID:22725216; http://dx.doi.org/10.1093/cid/cis588

[97] Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. Crit Care Med 2008; 36:941-52; PMID:18431284; http://dx.doi.org/10.1097/CCM.0b013e318165BABB

[98] Dahaba AA, Rehak PH, List WF. Procalcitonin and C-reactive protein plasma concentrations in nonseptic uremic patients undergoing hemodialysis. Intensive Care Med 2003; 29:579-83; PMID:12652350

[99] Foushee JA, Hope NH, Grace EE. Applying biomarkers to clinical practice: a guide for utilizing procalcitonin assays. J Antimicrob Chemother 2012; 67:2560-9; PMID:22833636; http://dx.doi.org/10.1093/jac/dks265

[100] Burkhardt O, Ewig S, Haagen U, Giersdorf S, Hartmann O, Wegscheider K, Hummers-Pradier E, Welte T. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. Eur Respir J 2010; 36:601-7; PMID:20185423; http://dx.doi.org/10.1183/09031936.0016309

[101] Charles PE, Dalle F, Aho S, Quenot JP, Doise JM, Aube AB. The diagnostic accuracy of procalcitonin for bacteremia in critically ill patients. Intensive Care Med 2003; 29:579-83; PMID:12652350

[102] Hoeboer SH, van der Geest PJ, Nieboer D, Groenevelt AB. The diagnostic accuracy of procalcitonin for bacteremia: a systematic review and meta-analysis. Clin Microbiol Infect 2015; 21:474-81; PMID:25726038; http://dx.doi.org/10.1016/j.cmi.2014.12.026

[103] Martini A, Gotti L, Menestrina N, Schweiger V, Simion D, Vincent JL. Procalcitonin levels in surgical patients at risk of candidemia. J Infect 2010; 60:425-30; PMID:20226210; http://dx.doi.org/10.1016/j.jinf.2010.03.003

[104] Clancy CJ, Nguyen MH. Finding the “missing 50%” of invasive candidiasis: how nonculture diagnostics will
improve understanding of disease spectrum and transform patient care. Clin Infect Dis 2013; 56:1284-92; PMID:23315320; http://dx.doi.org/10.1093/cid/cit006

[105] Del Bono V, Delfino E, Furaro E, Mikulska M, Nicco E, Bruzzì P, Mularoni A, Bassetti M, Viscoli C. Technical Performance of the (1,3)-β-D-Glucan Assay in Early Diagnosis of Nosocomial Candida Bloodstream Infections. Clin Vaccine Immunol 2011; 18:2113-7; PMID:21994353; http://dx.doi.org/10.1128/CVI.05408-11

[106] Posteraro B, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, Maviglia R, Fadda G, Sanguinetti M, Antonelli M. Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, Candida score, and colonization index. Crit Care 2011; 15:R249; PMID:22018278; http://dx.doi.org/10.1186/cc10507

[107] Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Andes DR, Safdar N, Baddley JW, Playford G, Reboli MP, Cauda R, et al. Risk factors and mortality of healthcare-associated and community-acquired Staphylococcus aureus bacteraemia. Clin Microbiol Infect 2012; 18:862-9; PMID:21999245; http://dx.doi.org/10.1111/j.1469-0691.2011.03679.x

[111] Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psychogios M, Argyropoulou A, Stefanou I, Syspa V, Miragou V, Nepka M, et al. Carbapenem-producing Klebsiella pneumoniae Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapensems. Antimicrob Agents Chemother 2014; 58:2322-8; PMID:24514083; http://dx.doi.org/10.1128/AAC.02166-13

[116] Tumbarello M, De Pascale G, Trecarichi EM, Spanu T, Antonicelli F, Maviglia R, Pennisi MA, Bello G, Antonelli M. Clinical outcomes of Pseudomonas aeruginosa pneumonia in intensive care unit patients. Intensive Care Med 2013; 39:682-92; PMID:23370828; http://dx.doi.org/10.1007/s00134-013-2828-9

[117] Papadimitriou-Oliveris M, Christofidou M, Flogou F, Bartzavali C, Vrettos T, Filos KS, Marangos M, Anastasiou ED. The role of colonization pressure in the dissemination of colistin or tigecycline resistant KPC-producing Klebsiella pneumoniae in critically ill patients. Infection 2014; 42:883-90; PMID:25008195; http://dx.doi.org/10.1007/s10156-014-0653-x

[118] Tumbarello M, Trecarichi EM, Tumietto F, Del Bono V, De Rosa FG, Bassetti M, Lusito AR, Tedeschi S, Saffioti C, Corcione S, et al. Predictive models for identification of hospitalized patients harboring KPC-producing Klebsiella pneumoniae. Antimicrob Agents Chemother 2014; 58:3514-20; PMID:24733460; http://dx.doi.org/10.1128/AAC.02373-13

[119] Giacobbe DR, Del Bono V, Trecarichi EM, De Rosa FG, Giannella M, Bassetti M, Bartoloni A, Lusito AR, Corcione S, Bartoletti M, et al. Risk factors for bloodstream infections due to colistin-resistant KPC-producing Klebsiella pneumoniae: results from a multicenter case-control-control-study. Clin Microbiol Infect 2015; 21:106.e1-8; PMID:26278669

[120] Kontopidou F, Giamarello H, Katerelos P, Maragos A, Kiounis I, Trikká-Graphakos V, Valakis C, Maltezou HC. Infections caused by carbapenem-resistant Klebsiella pneumoniae among patients in intensive care units in Greece: a multi-centre study on clinical outcome and therapeutic options. Clin Microbiol Infect 2013; 20(2):O117-23

[121] Qureshi ZA, Paterson DL, Potsoki BA, Kilayko MC, Sondovský G, Sordillo E, Polsky B, Adams-Haduch JM, Doi Y. Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother 2012; 56:2108-13; PMID:22252816; http://dx.doi.org/10.1128/AAC.00628-11

[122] Paul M, Carmeli Y, Durante-Mangoni E, Mouton JW, Tacconelli E, Theuretzbacher U, Mussini C, Leibovici L. Combination therapy for carbapenem-resistant Gram-negative bacteria. J Antimicrob Chemother 2014; 69:2305-9; PMID:24872346; http://dx.doi.org/10.1093/jac/dku168

[123] De Rosa FG, Corcione S, Pagani N, Di Perri G. From ESKEAPE to ESCAPE, from KPC to CCC. Clin Infect
[124] Papadimitriou-Olivgeris M, Spiliopoulou A, Fligou F, Manolopoulou P, Spiliopoulou I, Vrettos T, Dodou V, Filos KS, Anastassiou ED, Marangos M, et al. Association of KPC-producing Klebsiella pneumoniae colonization or infection with Candida isolation and selection of non-albicans species. Diagn Microbiol Infect Dis 2014; 80:227-32; PMID:25175179; http://dx.doi.org/10.1016/j.diagmicrobio.2014.07.012

[125] Schechner V, Kotlovsky T, Kazma M, Mishali H, Schwartz D, Navon-Venezia S, Schwaber MJ, Carmeli Y. Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected? Clin Microbiol Infect 2013; 19:451-6; PMID:22563800; http://dx.doi.org/10.1111/j.1469-0691.2012.03888.x

[126] Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother 2008; 52:1028-33; PMID:18086836; http://dx.doi.org/10.1128/AAC.01020-07

[127] Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, Meersseman W, Akova M, Arendrup MC, Arikan-Akdagli S, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012; 18 Suppl 7:19-37; PMID:23137135; http://dx.doi.org/10.1111/1469-0691.12039

[128] Laupland KB, Kirkpatrick AW, Delaney A. Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: a systematic review and meta-analysis. Crit Care Med 2007; 35:2686-2692; PMID:18074465; http://dx.doi.org/10.1093/cid/ciu1170

[129] Vincent JL. Emerging therapies for the treatment of sepsis. Curr Opin Anaesthesiol 2015; 28:411-6; PMID:26087275; http://dx.doi.org/10.1097/ACO.000000000000210

[130] Deresinski S. Principles of antibiotic therapy in severe infections: optimizing the therapeutic approach by use of laboratory and clinical data. Clin Infect Dis 2007; 45 Suppl 3:S177-83; PMID:17712744; http://dx.doi.org/10.1086/519472

[131] Giacobbe DR, Esteves P, Bruzzi P, Mikulska M, Furfaro E, Mesini A, Tatarelli P, Grignolo S, Viscoli C, Colombo AL, et al. Initial serum (1,3)-β-D-glucan as a predictor of mortality in proven candidemia: findings from a retrospective study in two teaching hospitals in Italy and Brazil. Clin Microbiol Infect 2015; 21:954.e9-954.e17; PMID:26070961

[132] Jaijakul S, Vazquez JA, Swanson RN, Ostrosky-Zeichner L. (1,3)-β-D-glucan as a prognostic marker of treatment response in invasive candidiasis. Clin Infect Dis 2012; 55:521-6; PMID:22573851; http://dx.doi.org/10.1093/cid/cis456

[133] Hamilton KW, Fishman NO. Antimicrobial stewardship interventions: thinking inside and outside the box. Infect Dis Clin North Am 2014; 28:301-13; PMID:24857395; http://dx.doi.org/10.1016/j.idc.2014.01.003

[134] Charani E, Cooke J, Holmes A. Antibiotic stewardship programmes—what’s missing? J Antimicrob Chemother 2010; 65:2275-7; PMID:20851812; http://dx.doi.org/10.1093/jac/dkq357