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Impact of infectious diseases consultation on the outcome of patients with bacteraemia

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***Abstract*:** Bacteraemia or bloodstream infections (BSI) are associated with much morbidity and mortality. Management of patients with bacteraemia is complex, and the increase in immunosuppressed patients and multidrug-resistant organisms poses additional challenges. The objective of this review is to assess the available published information about the impact of different aspects of management on the outcome of patients with BSI, and, specifically, the importance of infectious diseases specialists (IDS) consultation. The impact of management by IDS on different aspects, including interpretation of newer rapid techniques, early evaluation and treatment, and follow up, are reviewed. Overall, the available data suggest that IDS intervention improves the management and outcome of patients with BSI, either through consultation or structured unsolicited interventions in the context of multidisciplinary bacteraemia programmes.

Keywords: bacteraemia, infectious diseases, bacteraemia programs

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Introduction

Bloodstream infection (BSI) are very frequent events and are associated with high morbidity and mortality. The population-based incidence of BSI has been estimated to range between 113 and 204 episodes per 100,000 person-years,[1] and has increased over the last decades, possibly as a consequence of the higher proportion of elderly and immunocompromised persons, increased use of invasive procedures and better diagnosis.[2] BSI is classified according to acquisition type into community and nosocomial onset; community-onset BSI are those presenting in patients not admitted to a hospital, or less than 72 h after admission. However, community-onset BSI are considered as healthcare-associated if occurring in patients receiving specialized home care, intravenous ambulatory treatment, haemodialysis or living in a long-term care facility.[3,4] Thus, the mortality of strict community-acquired BSI (10–16%) is usually lower than that of healthcare-associated (20–25%) or nosocomial episodes (25–35%).[3–5] In addition, antimicrobial-resistant pathogens are more frequent among healthcare-associated and nosocomial episodes.

In fact, the rate of BSI caused by microorganisms usually considered as multidrug-resistant (MDR), showing resistance to three or more families of antimicrobials, has increased considerably during recent decades. These include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), enterobacteria producing extended-spectrum beta-lactamases (ESBL), AmpC beta-lactamases or carbapenemases, *Pseudomonas aeruginosa* showing resistance to multiple antipseudomonal agents, or *Acinetobacter baumannii*.[6] However, the rate of MDR organisms in general, and causing BSI in particular, is heterogeneous in different hospitals and geographical areas. This increase in bacterial resistance, as well as in other infectious processes, has been associated with a rise in recurrence, and both hospital stays and costs.[7–10]

Beyond acquisition and resistance, BSI are heterogeneous. Treating patients with bacteraemia is challenging. Importantly, identifying and appropriately removing the source of infection when feasible, early detection of complications or secondary foci, providing early appropriate treatment

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according to source, and administering the adequate duration of treatment may impact patient outcomes. It is well known that the input of an infectious diseases consultant improves the prognosis of patients with infections.[11,12]

Bloodstream infections are classified according to the microbiological diagnosis and the source of infection, which helps to standardise clinical management. Bacteriemia programmes have led to a better optimisation of antimicrobial treatments and a better prognosis.

As reviewed here, the best way to achieve the best quality of treatment for patients with BSI is through specialized care by infectious diseases specialists (IDS), either directly or through consultation.[13]

Rapid detection of bacteraemia and information

Growth of bacteria in blood cultures usually takes around 10–20 h, depending on the organism, blood volume and bacterial inoculum; once growth is detected, a Gram stain provides preliminary and crucial information. More recently, the application of matrix-assisted laser desorption-ionization time of flight mass spectrometry (MALDI-TOF) for the direct identification of pathogens from positive blood culture is used in many hospitals. In addition, the presence of bacteria (and some resistance mechanisms) in blood may be demonstrated more rapidly and directly using molecular methods.[14,15] A discussion about the accuracy and clinical impact of these rapid tests is beyond the objectives of this review. Rapid techniques have a positive impact on the appropriate use of antibiotics and outcome of patients when accompanied by rapid communication to IDS or when applied in the context of an antimicrobial stewardship progra mme.[16–27] Without such support, rapid results may not result in substantial improvements because of the complexity of integrating the microbiological information and clinical data, which frequently must be reassessed by carefully and directly re-examining the patient in order to take appropriate decisions in a timely manner.

Early clinical evaluation of patients with bacteraemia

A first consideration is whether any positive result from a blood sample may reflect a contamination during blood sample extraction. A careful evaluation is needed in these circumstances. Furthermore, there are some microorganisms that, when isolated, suggest certain infections.[28] The situations and aspects to consider are summarized in Table 1. Repetition of blood cultures is usually recommended; in case of a potential contamination, the drugs covering the potential contaminant can be withdrawn until more data are available in stable, low risk patients.

All patients with BSI must be evaluated carefully as soon as the bacteraemia is detected. A full medical history is needed, including underlying conditions or procedures potentially predisposing to BSI and symptoms orientating about the potential source of entry/source of bacteraemia (see below), together with a complete medical examination evaluating the severity of infection and seeking the potential source of infection. At that moment, it is useful to measure some outcome predictive scores such as the Charlson index, Pitt bacteraemia score and SOFA,[29–31] and stating the presence of sepsis or septic shock is mandatory.[32] Timely support therapy is needed in case of sepsis with organ failure.

The evaluation of patients with BSI by an IDS has proved to obtain better clinical results and higher efficiency thanks to BSI programmes, as will be detailed below.

Identification of the source of infection

Identifying the source of infection (and if needed, secondary foci) is an essential aspect in the evaluation of patients with BSI because early source control is considered a keystone in the management of patients with sepsis.[33] This includes abscess debridement or drainage, drainage of close-space purulent infections (e.g. peritonitis, empyema, arthritis), resolution of obstruction in urinary or biliary tract infections and removal of an infected device. For example, early catheter removal in short-term catheter-related infections has been associated with lower mortality in patients with bacteraemia and in candidaemia,[34,35] with removal being more frequent when patients were assessed by the IDS.[36,37]

The source of infection is sometimes clinically evident, but this is not the case in many patients. Typically, the source of infection may not be

Table 1. Evaluation of potential contamination of blood cultures.

Situations in which contamination of blood cultures are suspected
Isolation/detection of a typical contaminant from only one blood extraction in patients with low risk of infection caused by that microorganism (e.g. no vascular catheter or prosthetic valve). Isolation/detection of a typical contaminant together with a true pathogen in patients with a high suspicion of infection due to the true pathogen but low for the contaminant). Isolation of different morphologies of a typical contaminant(s) in different blood extractions.
Aspects to evaluate for decisions
The microorganism(s) The number of extractions in which the potential contaminant is present The predisposing factors of the patient for infection due to the potential contaminant The clinical situation of the patient (severity of infection, underlying conditions)
Diagnostic implications of bacterial species identified from blood cultures
Staphylococcus aureus: IE and vertebral osteomyelitis *Staphylococcus epidermidis*: Device-related BSI and IE *Streptococcus anginosus*: Abscess (brain, lung, liver, or gastrointestinal) *Streptococcus sanguinis*: IE *Streptococcus bovis*: IE *Enterococcus faecalis*: IE, urinary tract infection, and intra-abdominal source *Clostridium septicum*: Fatal sepsis in immunocompromised patients *Burkholderia pseudomallei*: Melioidosis *Salmonella enteritidis*: Gastrointestinal tract infection and extraintestinal focus of infection, such as osteomyelitis, abscess, or mycotic aneurysm *Fusobacterium necrophorum*: Lemiérre syndrome (often fatal)
IE, infective endocarditis.

readily apparent in neutropenic or other immunodepressed patients, children, elderly patients and in those with altered mental status; this is also the case for certain sources such as deep-seated abscesses (e.g. liver abscess), central line catheter infections or endocarditis. Therefore, the source of infection must be actively looked for in all cases. Clinical skill and experience are important. Even in patients with a clear predisposing factor for a specific infection (e.g. a urinary catheter for a urinary tract infection), alternative sources must always be considered. Also, in patients with transitory bacteraemia after an invasive procedure, the portal of entry may be suspected (e.g. the digestive tract after a gastroscopy), and a source of infection may not exist unless a secondary focus appears during the evolution.

Episodes of BSI without an identifiable source of infection were found to have a worse prognosis in some studies,[38,39] which may be due to the fact that these episodes sometimes occur in patients with severe underlying conditions and also because empirical treatment may also be more frequently inadequate in these patients. In this context, it has been demonstrated that patients followed by an infectious diseases consultant during the episode of bacteraemia achieve a higher identification of the source of infection and better control of it.[40] In studies that analyse potentially serious BSI, such as *S. aureus* bacteraemias (SAB), a higher number of echocardiographies were performed in those assessed by an infectious diseases specialist.[41]

Up to 25% of bacteraemia cases are considered to have a nonidentifiable source of infection and mortality can exceed 20% depending on the series.[42,43] In these cases, techniques such as scintigraphies with marked leucocytes or PET-CT-scan, may be of help for diagnosis.[44]

Early administration of active antibiotic treatment

Early administration of active antimicrobials has been shown to be associated with lower mortality in patients with severe infections.[45,46] Several

Table 2. Situations in which antimicrobial treatment may be reconsidered with availability of preliminary microbiological results for blood cultures. All decisions must follow a careful clinical evaluation.

Situation	Decision(s)
Positive blood cultures; empirical therapy not administered; contamination improbable	Start a drug appropriate for the suspected source and the type of microorganism according to preliminary microbiological information
Bacteria identified or mechanism of resistance detected, but not covered	Start/change to a drug appropriate for the suspected source and the type of microorganism or resistance mechanisms, according to preliminary microbiological information
Negative results for mechanism(s) of resistance, which are covered by the empirical therapy	Consider if de-escalation can be safely performed pending confirmatory results; be aware that other not-studied mechanisms of resistance may be present. Consider clinical stability
Combination therapy, one drug covering Gram-positive and the other covering Gram-negative bacteria	Stop the unnecessary drug if monomicrobial infection is highly probably; adjust the other drug as above.
Redundant combination therapy	Stop the unnecessary drug according to additional microbiological information, local susceptibility patterns and clinical stability

studies have also found that appropriate empirical therapy is associated with better outcomes in patients with BSI; the impact may be higher for patients with severe presentation, high-risk sources (e.g. pneumonia) and Gram-negative bacteria.[39,47–50] Therefore, adequate empirical antimicrobial coverage of patients with suspicion of bacteraemia is important but should always be tailored to avoid the overuse of broad-spectrum antimicrobial agents. This is far from easy; best decisions are taken considering the severity and source of the infection, the features of the patient, knowledge of colonization status of the patients and other specific risk factors for antimicrobial resistance, and local epidemiology. Some algorithms for the coverage of multidrug-resistant bacteria are being developed. In relation to the use of antibiotics with coverage for carbapenemase-producing Enterobacteriacea, the implementation of scores such as Gianella risk score and the Increment score in carbapenemase-producing *Klebsiella pneumoniae* colonised patients have proved useful for starting empirical treatment with those agents.[51]

Early notification of the preliminary results of blood cultures, either from a Gram stain, MALDI-TOF identification or use of a molecular method, provides a unique opportunity to evaluate whether the empirical treatment administered may be continued until more information is available or must be readily changed. The use of rapid methods for detecting resistance mechanisms (e.g. specific beta-lactamases) may allow earlier adequate coverage for bacteria producing them and might also help to de-escalate from very broad to narrow spectrum drugs in some cases,[11–21,52] although the latter is a more difficult and risky decision. The situations and decisions frequently faced by the IDS are summarized in Table 2.

Finally, the use of rapid antimicrobial susceptibility testing as recently recommended by EUCAST may also be very useful for early administration of active drugs and for streamlining therapy.[53] A meta-analysis evaluated the impact of rapid microbiological tests; 31 studies with 5920 patients were included. The mortality risk was lower with the use of rapid methods when the rapid tests were used in the context of an antibiotic stewardship program (OR = 0.64; 95% CI: 0.51–0.79).[54]

Follow up

Once susceptibility tests are available, streamlining of therapy is mandatory. BSI are frequently classified as complicated and uncomplicated. Generally speaking, BSI is considered complicated when

presenting with organ failure or hypoperfusion (sepsis) or in which complications associated with increased mortality or relapse rates are present or are anticipated, such as endocarditis, persistent or recurrent bacteraemia, presence of secondary foci, or occurring in patients with predisposing conditions for the above (such as prosthetic valves in case of bacteria typically causing endocarditis, or severely immunodepressed patients). Some of the data that would classify an episode as complicated must be assessed during the first days of evolution. While all patients with BSI should be followed, those with a complicated infection needs a more careful assessment of their evolution. Specific data are provided according to the pathogens below.

Bacteraemia programmes

The application of the above measures, and those more specific depending on specific pathogens and patients, are better achieve by using structured actions which may be included in bacteraemia programmes or services.[55–57] These programmes are increasingly being implemented in hospitals.[58]

A seminal prospective study analysed 428 BSI episodes in order to evaluate the impact of IDS consultation. IDS consultation was associated with appropriate empirical treatment, which in turn was associated with improved survival. After susceptibility testing, IDS intervention was also associated with earlier administration of active drugs, with lower use of broad spectrum drugs and higher prescription of sequential oral treatment.[59] A later quasiexperimental study evaluated the proportion of major errors (delay in diagnosis of sepsis >48 h, delay in administration of appropriate antibiotics in critically ill patients >6 h, and no administration of active drugs after susceptibility test data were available) in the management of BSI before and after an intervention based on the actions of a bacteraemia team and the elaboration of a local guideline. The intervention reduced the major errors from 30% to 8%.[57] Fluckiger and colleagues found that IDS more frequently de-escalated from broad spectrum drugs, and were associated with reduced length of hospital stay.[60] Bouza and colleagues evaluated different ways to communicate the Gram stain results of blood cultures using a randomised trial design; reporting the results by an IDS improved the average number of days of appropriate therapy.[61] Recently, a prospective cohort study investigated the impact of unsolicited consultation with IDS in patients with BSI. The results showed that IDS consultation was independently associated with an increase in the proportion of appropriate antibiotic therapy. When the specific aspects of therapy were analysed, IDS provided a more adequate duration of therapy, more frequent and earlier de-escalation, changes of empirical regimens and better source identification. Importantly, when the IDS recommendations were fully followed, lower mortality was also shown.[40] As described above, the results of a meta-analysis suggested the importance of using rapid microbiological methods with an antimicrobial stewardship programme in patients with BSI.[54]

Therefore, implementation of bacteraemia programmes, in which IDS, clinical microbiologists and pharmacists works together to actively provide recommendations for the management of all patients with BSI without waiting for being consulted would seem advisable in all hospitals.

Staphylococcus aureus *bacteraemia*

Because of its intrinsic complexity, many studies have evaluated the impact of IDS consultation in the outcome of patients with SAB. In these studies, IDS consultation has been associated with improved management and sometimes lower mortality.[62–67] A meta-analysis if studies evaluating the impact of IDS consultation included 5337 patients from 18 studies.[68] IDS consultation was associated with lower mortality both at day 30 (RR = 0.53; CI 95% 0.43–0.65) and at day 90 (RR = 0.77; 95% CI: 0.64–0.92), as well as lower risk of recurrence (RR = 0.62; 95% CI: 0.39–0.99).

However, the impact of IDS might depend on the specific ability of local specialists. Lopez-Cortés and colleagues took additional steps by first defining the bundle of key evidence-based management aspects that would impact on outcome, and second establishing efficient implementation methods.[69] The bundle of measures included performance of follow-up blood cultures in all cases, early source control, early use of cloxacillin or cefazolin for methicillin-susceptible isolates, measuring vancomycin levels when this drug was used, performing echocardigraphy when indicated and appropriate duration according to

complexity. By using a multicenter quasiexperimental design, they found that implementation of a structured intervention including timely written and oral recommendations based on the bundle was associated with increase in adherence to the measures and reduced mortality. These results have been replicated,[70,71] which reinforces the applicability of this approach. A randomized controlled trial tested an algorithm for the management of *Staphylococcus* spp. bacteraemia, including coagulase-negative staphylococci. The algorithm comprised diagnostic procedures to be performed, drugs according to susceptibility and treatment duration; the algorithm was not inferior in clinical success when compared with usual care; the clinical success rate was somewhat better for patients with SAB treated with the algorithm but the estimations were not precise.[72]

Candidaemia

Candidaemia is associated with 35–75% mortality rates.[73–76] Among patients with septic shock, candidaemia is an independent predictor of mortality.[77] Several aspects in the management are recommended, including early removal of central venous catheter,[35,78] early treatment with active drug (an echinocandin is recommended for neutropenic patients, those with septic shock or risk factors for azole-resistance; fluconazole may be used otherwise), follow-up blood cultures until negative, fundoscopy, sequential therapy with fluconazole (if *in vitro* active) when clinical stability has been reached and appropriate duration of treatment. Because of the complexity of management, IDS consultation is recommended in all cases.[79] In a study, 213 patients with candidaemia were included in order to evaluate whether adherence to five main elements was associated with improved survival. The elements were: appropriate selection of initial therapy, follow-up blood cultures, echocardiography when indicated, ophthalmological examination and removal of a central venous catheter. Multivariate analysis showed that the number of elements achieved was associated with increased survival [hazard ratio (HR) = 0.39; 95% confidence interval (CI): 0.30–0.52].[80] Another study found much room for improvement in the management of candidaemia; adherence of less than 50% of the guideline-based recommendations was independently associated with a higher mortality (HR = 3.55, 95% CI: 2.24–5.64).[81]

With regards to this, in a recent retrospective study where 145 episodes of candidaemia were analysed (77% assessed by the IDS), in the group that received these recommendations, as well as a higher adherence to the IDSA recommendations for the management of candidaemia, there was lower inpatient mortality, at 30- and 60-day follow up (20% *versus* 50%, $p < 0.0001$; 24% *versus* 59%, $p < 0.0001$; 21% *versus* 56%, $p < 0.0001$, respectively).[82]

In a study performed in Japan, 283 episodes of candidaemia were analysed retrospectively in cases where a consultation to the IDS took place (44.5%) and in those where it did not (55.1%). The independent factors associated with the increase of mortality at 30 days were the presence of urinary catheters (adjusted HR = 2.94; 95% CI = 1.48–5.87; $p = 0.002$) and the severity of the infection (adjusted HR = 2.10; 95% CI = 1.20–3.65; $p = 0.009$). The consultation to the ID consultant meant a reduction in mortality in this group (adjusted HR = 0.54; 95% CI = 0.32–0.90; $p = 0.017$). Although the study has some limitations due to its retrospective nature, the lack of other confusing factors not included in the analysis, as well as not including the time analysis in the infectious disease specialist intervention from the positive result of the blood culture, these results demonstrate the benefits derived from this counselling on infectious events.[36]

Bacteraemia due to Gram-negative bacteria

Delay in administering active treatment has been associated with increased mortality in patients with bacteraemia due to Gram-negative bacteria.[83–86] However, avoiding the use of broad-spectrum drugs in these patients is important from an antibiotic stewardship perspective.

De-escalation from antipseudomonal agents has been shown to be safe in a recent multicentre cohort study.[87] In this sense, a quasiexperimental study evaluated an antibiotic stewardship intervention including rapid techniques (MALDI-TOD and FilmArray blood culture identification) in patients with bacteraemia due to Gram negative bacteria. The intervention was associated with lower combination regimens, less use of antipseudomonal/carbapenems and shorter time until de-escalation.[23] Another study evaluated an stewardship programme associated with rapid identification with MALDI-TOF in patients with

bacteraemia due to multidrug-resistant Gram negatives; again the intervention was associated with shorter time until appropriate therapy, shorter hospital stay and lower mortality.[18]

In another recent trial, 4214 patients with multiresistant microorganisms isolated in blood, bronchoalveolar lavage and other sterile sites were analysed retrospectively, with the primary objective of evaluating the impact on mortality and rate of readmissions when these were assessed by the IDS. In patients assessed with resistant *S. aureus* infections, mortality at day 30 and a year was lower (HR, 0.48; 95% CI, 0.36–0.63; and HR,0.73, 95% CI, 0.61–0.86), the same as in resistant enterobacteriaceae (HR, 0.41; 95% CI, 0.27–0.64; and HR, 0.74; 95% CI, 0.59–0.94) and in the case of patients with polymicrobial infections mortality was lower at day 30 (HR, 0.81; 95% CI, 0.62–1.06). Furthermore, there were fewer readmissions in those patients with resistant enterobacteriaceae. Although the study has limitations, such as its retrospective nature, the loss to follow up of some patients and the lack of analysis of suitable antimicrobial therapy as factors that may influence mortality, the data suggest, as in previous studies, the beneficial effect of consultations with IDS on infections caused by resistant pathogens.[88]

The increase in resistance to multiple antibiotics in these bacteria pose an additional challenge for their treatment. This is particularly relevant in the case of carbapenemase-producing Enterobacteriacae and extensively-drug resistant *P. aeruginosa* or *A. baumannii*, for which the available therapeutic options are very limited. Early active therapy has been associated with improved survival in a multinational cohort study of BSI due to carbapenemase-producing Enterobacteriaceae.[89] In that study, patients with high probability of death measured by the predefined INCREMENT score had lower mortality if treated with a combination of two active drugs.[90] The selection of the more appropriate drugs to be used must be done by considering the available drugs, the severity and source of infection, and patient characteristics; also the dosing must be optimized to maximize exposure.[91]

Conclusion

BSI are potentially serious frequent events in our daily clinical practice, to which complexity is added the emergence of multidrug-resistant pathogens, which are becoming more and more frequent and difficult to treat.

As we have seen, enough evidence exists to support the benefits of stewardship programs on bacteraemias performed by a consultant on infectious diseases with the support of the new systems of microbiological diagnosis. This leads to more appropriate use of antibiotics and better management of these patients as well as higher numbers of identification and control of the source of infection, which means getting better clinical results without an impact on stays or costs. All these advantages make implementation of IDS consultation advisable for all hospitals.

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Conflict of interest statement

JR-B participated as a speaker in accredited educational activities funded by Merck. LELC has been a speaker for Merck, Sharp and Dohme, Pfizer, and Angelini, has received funding from Novartis for research activities, and has served as a trainer for Merck, Sharp and Dohme. PAJ has no conflicts of interest.

Ethical statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

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