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EDITORIAL

Bloodstream infections: The peak of the iceberg

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Bloodstream infections (BSI) are infectious diseases defined by the presence of viable bacterial or fungal microorganisms in the bloodstream (later demonstrated by the positivity of one or more blood cultures) that elicit or have elicited an inflammatory response characterized by the alteration of clinical, laboratory and hemodynamic parameters. In this sense, the definitions of BSI and that of sepsis are 2 sides of the same phenomenon, since sepsis is an infectious syndrome triggered by an infectious disease, while BSI is a sepsis triggered by viable microorganisms circulating in the bloodstream. Of course, BSI can be preceded, followed or be concomitant to a localized infectious disease, like endocarditis, pneumonia, UTI, meningitis and others. The interest in focalizing on BSI, instead of infection in general, is in the diagnostic certainty inherent a positive blood culture, although contamination is possible.

As a rule, BSI can be categorized in 3 main groups, i.e. if occurring

(i) in immunologically normal hosts, with intact defenses,
(ii) in patients with physiological condition impairing defenses, (newborns, elderly)
(iii) in patients affected by pathological or pharmacological conditions predisposing to infections.

The first group includes for example *N. meningitidis* and *S. pyogenes* diseases, viridans streptococcal BSI during native valve endocarditis in children, adolescent or young adults, post-influenza *S. pneumoniae* and *S. aureus* bacteremias, and *Salmonella typhi* and non-*typhi* in certain areas of the word; in most cases these are community-onset infections, even if sometimes diagnosed a few hours from admission. Community-acquired BSI and meningitis in normal hosts are worrisome, especially in the light of repeated recommendations by many authorities not to use antibiotics without an adequate reason and the consequent risk of not treating an infection that looks banal, but might be dangerous. Indeed, the border in terms of initial differential diagnosis between a viral infection and an insidious more severe bacterial disease may be blurred. Slurred speech or confusion, extreme shivering or muscle pain, oliguria, respiratory problems, a pale skin, with a falling blood pressure are all symptoms potentially associated with initial sepsis that should be recognized.

The second group of BSI encompasses infections in patients with an immature or aged immune system. Pathogens are frequently and surprisingly similar at the 2 extremes of life, and include *Listeria*, group B streptococcal and pneumococcal infections, *E. coli, Klebsiella* spp. and *Candida*.

The third group of BSI, which can be both community and hospital-acquired, can be caused by virtually any pathogen, from Gram-positives to Gram-negatives and fungi. It includes infections in patients with acquired or inherited immunodeficiency, affected with diseases like diabetes, that are associated with an increased risk of infectious complications and those belonging to the big area of health-care associated and nosocomial infections, typical of modern medicine, in which the use of immunosuppressive and cytotoxic therapy or highly invasive surgery has become common practice. Indeed, the progress of modern medicine has obtained unimaginable results in the last decades, in the therapy of many diseases, in medicine, surgery and intensive care, in adults and in children, but not without paying a price. One of the untoward effects of modern medicine has been the creation of a patient population defined as compromised or immunocompromised, with single or multiple defects of defense mechanisms, predisposing to severe infections due to opportunistic pathogens. We have learned that the ability of a microorganism to cause disease is a function not only of its intrinsic virulence, but also of the immunological competence of the host and the disruption of its defense barriers.

Certainly, the above categorizations is imperfect and overlapping exist. One is for example, the cancer patient population, in which the risk of infection is the result of

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an interaction between both the underlying disease, which by itself can alter both mechanical and immunological defense mechanisms, and chemotherapy-related toxicity. However, this categorization is useful for describing the reality in infectious disease nowadays. A couple of interesting reviews on this subject have recently been published.[1,2]

The global epidemiology of BSI is very difficult to assess, because studies were conducted with different methodologies (incidence and prevalence, for example) and included very different patient populations and hospital types. The incidence of BSI varies substantially among the 3 categories that we tried to define above. Especially within the third category the incidence depends on underlying disease, country, type of hospital, type of ward and length of hospitalization, being as high as 30% in the population of Haematopoietic Stem Cell Transplant (HSCT).[3] In terms of community-acquired BSI, Laupland and co-workers,[1] who reviewed several articles on community-onset BSI, found an annual incidence varying from 40 to 154/100.000 population. In terms of health-care-associated infections a pivotal study by Hilmar Wisplinghoff and coworkers in 2003,[4] reported more than 24000 cases of BSI in 49 US hospitals over a 7-year period, with an incidence of 6 cases/100.000 hospital admissions. This article provides important information, including, for example, the very high mortality associated with candidemia. In more recent years, Ani et al, starting from ICD-9-CM codes, identified more than 5.000.000 severe sepsis hospital discharges in the US from 1999 to 2008.[5] A prevalence study by the European CDC (ECDC) found a prevalence of patients with at least one HAI in European hospitals of 6%, with a country range varying from 2.3% to 10.8%. About 10% of the episodes were BSI.[6] Data from the European Antimicrobial Resistance Surveillance System (EARSS) [7] showed that the number of BSI due to *S. aureus, E. coli, S. pneumoniae, E. faecium* or *faecalis* reported between 2002 and 2008 increased by 47% from 46.095 to 67.876. In my hospital, 2 one-day prevalence studies in January 2014 and 2015 identified each year 32 cases of BSI, representing about 20% of all HAI. Interestingly, 30–50% of the cases were in Internal Medicine wards (G. Icardi, MD and A. Orsi, MD, Infection Control and Hospital Epidemiology, University of Genova and IRCCS San Martino-IST, Genova, Italy; personal communication).

Interestingly, the pattern of pathogens causing BSI has been changing over the years, with increasing numbers of Gram-negative and, especially, fungal (C. albicans and non-albicans) infections.[8] However, in the last 2 decades, the most significant change in etiology of BSI has not been the type of infecting organisms, but rather their resistance to antibiotics, especially for Gram-negative rods. Two main mechanisms have put in danger the marvelous antibiotic weapon: (i) the production of ESBL (several different subtypes), for which in some countries we have lost (in others we are losing) the activity of IIIrd generation cephalosporins, at least in hospitals and (ii) the production of carbapenemases and metallo-betalactamases, with consequent spread of multi or pan-resistant organism. In countries where carbapenem-resistant and sometimes colistin-resistant *K. pneumoniae* is endemic, BSI due to this pathogen can have only one or two treatment options.[9] The crude mortality rate in KPC-Kp BSI can vary between 30-and 60% but can approach 50% colistin-resistant strains[10] and can be as high as 80% in recipients of HSCT.[11] It has been shown that mortality is lower if patients are timely treated with combination antibiotic therapy, including, paradoxically, a carbapenem and at least 2 drugs with some *in vitro* some activity against the isolated pathogen.[12]

The source of BSI is controversial. Indwelling devices may be obvious sources, when the patient has no other apparent breakage in defense mechanisms. However, this happens rarely. In cancer patients, for example, the central catheter is just one of the many mechanisms possibly predisposing to BSI. New data actually suggest that 40–50% of bloodstream infections in oncologic settings are due to mucosal barrier injury.[13] This has an impact on the expectations from improvements in proper catheter management as able to decrease BSI in cancer patients and dictate against precipitous catheter replacement, outside of well-defined situation, like candidemia.[14]

As already mentioned, the diagnosis of a BSI is based on the positivity of one or more blood cultures. Two positive blood cultures are preferable for common skin contaminants, to avoid ascribing the etiology to a pathogen that was actually not present in the bloodstream, with obvious therapeutic mistakes and possible dramatic consequences. It follows that advances in therapeutic technologies may have substantial impact on many factors related to BSI, including sensitivity of the procedure and the turnaround time from sample collection to detection of positivity, pathogen identification and susceptibility results. Speeding-up all the procedure of blood culturing is essential for clinicians, because it potentially shortens empirical therapy and allows earlier targeted therapies, with advances in antimicrobial stewardship. In recent years, several new methodologies have been proposed and some of them are already available in many laboratories. It is beyond the purposes of this article to review new microbiological methods. I would only like to mention the MALDI-TOF technology that has certainly been a revolutionary advance in diagnostic microbiology. The topic has been recently reviewed.[15] In any case, so far,

the traditional blood culture technology, based on the detection of bacterial or fungal growth in a medium still remain state of the art. What I am wondering is if, how and to what extent things will change if we will able to accept alternative methods as demonstration of a pathogen in blood, like antigen-detection (already used for *Candida*), and especially molecular biology methods. Will PCR revolutionize the field of diagnosis in mycology and bacteriology as it did already in virology?

The present *Virulence* special issue will extensively focus on BSI in several populations of patients at high risk of infections. We have deliberately chosen to widen the spectrum of clinical settings in order to give the reader an as much as possible complete review of the topic, accepting the unavoidable risk of overlapping. Murat Akova will give us an overview of the microbiological problems, stressing, of course, the issue of antibiotic resistance, which I just touched on in the previous lines.[16] The other papers will focus of specific patient populations, including not only classic populations of patients at high risk of BSI, like those in ICU [17] and hematological wards,[18] but also other patient populations that are rarely dealt with in terms of BSI, like those with solid tumors,[19] liver cirrhosis,[20] HIV,[21] Solid Organ Transplant recipients [22] and the elderly.[23] Several reports [4,24] have raised the issue of the changing population nowadays admitted to internal medicine wards and this is the reason why we also decided to include an article of BSI in Internal Medicine,[25] being aware of possible overlapping with other chapters.

In conclusion, the most remarkable change in the last two decades in the management of bacterial infections is the dramatically decreasing efficacy of many antibiotics in concomitance with an important shortage of new molecules. Bacteria have shown extraordinary resilience capabilities. Infection control measures, improvements in diagnostics, more judicious use of old antibiotics and availability of new molecules are all urgently needed to control the spread of resistance. BSI remain a formidable challenge for the infectious disease physician, but may become a mission impossible if we will not efficiently contrast the development of resistance.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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