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FOCUS EDITORIAL

Focus on infection and sepsis in intensive care patients

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Over the last year, several papers have shed light on the management of severe infections and sepsis in intensive care units (ICU). With this overview, we will highlight the important new findings with a focus on infectious disease and sepsis in critically ill patients.

The concept of healthcare-associated pneumonia (HCAP) tried to highlight the increasing prevalence of multidrug-resistant pathogens [1]. The majority of the studies have been conducted outside Europe. Vallés et al. conducted a prospective, multicentre study in Spain [2] in which the etiology of community-acquired pneumonia (CAP) and HCAP was comparable, as *S. pneumoniae* was the most frequently found pathogen. Therefore, based on this European study, empirical antibiotic therapy recommended for CAP would be appropriate for 90 % of patients with HCAP, at least in that population, and clearly differs from experiences in countries with higher rates of resistant pathogens.

One important element over the last year in infectious diseases in critically ill patients has been the development of both less invasive and more sensitive diagnostic techniques in pneumonia [3]. A "What's new in intensive care" paper highlighted the innovative technologies that could result in a more timely recognition of respiratory infections [4] in critically ill patients through the detection of bacterial colonization (colorimetric endotracheal tubes) and the interaction between bacterial growth and host response (exhaled breath analysis) [5]. These technologies are still promising but not fully validated yet. Another promising area of research is the right use of biomarkers [6] in either decision-based algorithms like CHAID (Chi-squared Automatic Interaction Detection) [7] or biomarker combinations to increase diagnostic accuracy [8].

An important "My paper 10 years later" described the trends in infective endocarditis in the ICU [9]. The authors pointed to sustained high mortality rates in patients with infective endocarditis, rates that may exceed 60 % mortality in ICU. They suggested a standardized approach to bacteriological testing including broad-range polymerase chain reaction (PCR) because of the high rates of culture-negative bacteraemia. SeptiFast is the first real-time PCR-based system and, to date, the most intensively investigated in clinical cohort studies. To this end, two papers have provided evidence regarding the new rapid diagnostic tests in bacteraemia. Warhurst et al. [10] conducted a phase III prospective multicentre diagnostic accuracy study of SeptiFast against microbiological culture in critical care settings. SeptiFast had a significantly greater specificity (0.86) than sensitivity (0.50) for bacteraemia. The most interesting finding was that despite the potential benefit of such a technique, there was a low prevalence of blood culture-proven pathogens (9.2 %), acknowledging the potential limitations of this technology in diagnosing bloodstream infection when compared with bloodstream infection at the species/genus level. An updated systematic review and meta-analysis [11], including this study, concluded that standard blood culture techniques are currently not a perfect reference standard, but it is the one that has been used as the basis for the SeptiFast platform design (pathogen panel spectrum designed on the basis of the most common bloodstream infection globally) and it has inevitably influenced subsequent clinical diagnostic trials internationally. The main conclusion is that there is a higher specificity than sensitivity compared to blood cultures, but SeptiFast is not ready for implementation in clinical practice. An appraisal for the future would be the

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incorporation of a wider test panel of pathogens, which may be expected to provide greater diagnostic sensitivity (fewer false negative results). The latter could give clinicians greater confidence in a rapid negative test result, which may lead to reduced use of antibiotics.

In regard to fungal infections in critically ill patients, the vast majority of the recent papers were developed in Europe and the USA. A multicentre study on ICU-acquired candidemia in India [12] reported 6.51 cases per 1000 ICU admissions with high prevalence of *C. tropicalis*. This is in contrast to the developed world, where *C. tropicalis* is uniformly less common and *C. albicans* and *C. glabrata* are more prevalent. The report showed a higher proportion of patients who developed candidemia in Brazil [13]; however, the mortality rate of candidemia in ICU patients decreased in recent years. In this cohort, the receipt of an echinocandin as primary therapy was associated with lower 30-day mortality. Interestingly, Bassetti et al. [14] conducted a retrospective multinational study of intra-abdominal candidiasis and found low percentages of concomitant candidemia; however, the mortality rate was high in ICU (39 %). Interestingly, echinocandins were prescribed in two-thirds of the patients included in that study. Whilst this may be appropriate, the main problem is the difficulties in determining true infection and when to de-escalate antimycotic agents. Regarding the first point, Martín-Mazuelos et al. [15] conducted a prospective cohort of 107 unselected, non-neutropenic ICU patients and found that (1→3)-β-D-glucan (BDG) levels were higher in patients with invasive candidiasis and high-grade candida colonization. Two consecutive BDG levels ≥80 pg/mL allowed discrimination between invasive candidiasis and high-grade colonization; however, the AUROC for either BDG or *C. albicans* germ tube antibody (CAGTA) was low (0.67 and 0.55 respectively). Regarding antifungal de-escalation, Bailly et al. [16] found that de-escalation was uncommon (occurred in only 22 % of cases) and was not associated with increased 28-day mortality; it did significantly decrease the use of antifungal agents in invasive candidiasis in non-neutropenic ICU patients.

Up to 70 % of antifungal therapy ordered in the ICU is pre-emptive/empirical [14], most likely because of the diagnostic difficulties of invasive candidiasis and the fact that delays in starting appropriate antifungal treatment have been associated with increased mortality in patients with candidemia [17]. In a recent study, Ferreira et al. [18] found that a pre-emptive strategy of antifungal increased *C. glabrata* colonization without a significant shift of colonization to other *Candida* spp. The results of two recent studies may help clinicians to better understand candida isolates in respiratory samples. Terraneo et al. [19] found that antifungal treatment for patients with *Candida* spp. isolates in airways in patients with hospital-acquired pneumonia admitted to ICU did not influence outcome. Similar results were confirmed by Albert et al. [20] in a multicentre double-blinded, placebo-controlled, pilot randomized trial of antifungal therapy in critically ill patients with clinical suspicion of ventilator-associated pneumonia and positive airway secretion specimens for *Candida* spp.

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