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EDITORIAL

Focus on infection

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Infections in critically ill patients remain a bedside challenge for Intensive Care Units (ICU) physicians. The scope of this editorial article is to highlight the most recent evidence and the clinical practice about infection diagnosis, prevention and therapy, supported by new epidemiological data.

Three large studies provided new epidemiological data. The AbSeS (Epidemiology of intra-abdominal infection and sepsis in critically ill patients), a multicenter, observational study in adult ICU patients diagnosed with intra-abdominal infection (IAI) in the year 2016, included 2621 patients from over 300 ICUs and 42 countries [1]. IAI was community-acquired in 31%, mortality was almost 30% and prevalence of multidrug-resistance 26.3% (with great variation according to geographic region but without difference between community-acquired and hospital-acquired IAI). Madsen et al. conducted a Scandinavian, multicentre, prospective cohort study in 409 adults with necrotising soft-tissue infections NSTI [2]. The main finding was the surprisingly low (18%) 90-day mortality despite the presence of septic shock in half of the population, acute kidney injury in 20% and comorbidity in 70%. Monomicrobial group A streptococcus infection, mostly in NSTI of the extremities, was associated with lower mortality compared with polymicrobial infection, mostly in abdominal/anogenital NSTI. Miailhe et al. reported one of the largest registries for severe leptospirosis in metropolitan France (a non-tropical area) [3]. They reported on 160 patients with a very low rate for ICU admission (0.04%) and a moderately low hospital mortality (9%) despite a high severity and organ failure score. Among four phenotypes, mortality was worst in neurologic leptospirosis. The main risk factors for leptospirosis contamination were contact with animals, contact with river or lake water, and specific occupations.

A pre-planned subanalysis of a large prospective cohort of mechanically ventilated patients by the TVeM group demonstrated that inappropriate antibiotic treatment was not an independent risk factor for ICU mortality in patients with cardiovascular failure. In patients without cardiovascular failure, the survival benefit was limited to those with VAP, but not with VAT [4].

Respiratory tract Candida spp. colonization has been associated with more frequent bacterial ventilator-associated pneumonia (VAP), but causality was questioned in the context of immunoparalysis associated with multiple organ failure. FUNGIBACT, a prospective cohort study in 213 mechanically ventilated patients with multiple organ failure, showed no association between Candida spp. colonization and bacterial VAP, even after adjustment for immune function [5].

During winter months, there is a constant burden of patients with influenza being admitted to ICU, frequently featuring bacterial co-infection, with immunosuppression being an important risk factor [6]. A prospective cohort study in 16 countries analyzing 1611 immunocompromised patients with hypoxic respiratory failure did not show an association of influenza infection with hospital mortality [7]. Immunosuppressed patients are also at risk of fungal infection. Invasive pulmonary aspergillosis (IPA) was found in 219 patients with hematologic malignancies, most of these being probably IPA. Despite advances in diagnosis, prophylactic and curative therapy, the high 90-day mortality (85%) did not appear to improve over time. Delayed ICU admission was associated with worse outcome [8].

The role of procalcitonin to distinguish viral from bacterial infection was analyzed in a systematic review and meta-analysis: the biomarker appeared not sufficiently sensitive nor specific [9]. Another controversial topic in the filed in infection diagnosis is ventilator-associated lower respiratory tract infections (VA-LRTIs), either

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ventilator-associated pneumonia (VAP) or tracheobronchitis (VAT). The VAPrapid2 trial, a prospective randomized trial in patients with suspected VAP, assessed the impact of measuring IL-1β and IL-8 in bronchoalveolar lavage fluid on antibiotic prescription [10]. Although low biomarker levels had a negative predictive value of 100%, the antibiotic consumption in the first 7 days after BAL was not affected by biomarker-guided recommendations. Another interesting study showed that 16S rRNA taxonomic profiling of bacteria in respiratory specimen early after intubation in antibiotic-naive patients recovered more VAP pathogens compared with conventional cultures with the abundance of Bacilli being associated with subsequent VAP in a matched case–control study. This promising diagnostic approach requires further investigation [11].

Patients in ICU can develop some forms of immunoparalysis, potentially contributing to opportunistic infections such as cytomegalovirus (CMV) and herpes simplex virus (HSV) reactivation. Luyt et al. conducted a placebo-controlled randomized trial of pre-emptive therapy with intravenous acyclovir in patients with HSV oropharyngeal reactivation that were on mechanical ventilation for at least 96 h. The authors could not find a benefit of acyclovir regarding the number of ventilator-free days at day 60 [12].

One of the features of immunoparalysis in sepsis is T cell exhaustion syndrome that is characterized by the overexpression of programmed cell death protein (PD-1) and its corresponding ligand (PD-L1) markers. Hotchkiss et al. performed a phase-1b RCT with nivolumab (anti-PD-L1 monoclonal antibody) in patients with sepsis and lymphocytopenia. Nivolumab seemed to be well tolerated and safe. A confirmation of these results in larger RCTs targeting the PD-1/PD-L1 pathway could enable clinicians to do a more personalized medicine [13].

INHALE 1 and 2 trials involving 725 patients randomly assigned to Amikacin Inhale or aerosolized placebo showed no between-group difference in survival between days 28 and 32 [14]. The results, in line with other recent RCTs, do not support the use of inhaled amikacin adjunctive to standard-of-care intravenous therapy in mechanically ventilated patients with Gram-negative pneumonia.

In a post-hoc analysis of four randomized-controlled trials (RCT) including over 3000 patients, the authors found that, compared to central venous catheters (CVC), short-term dialysis catheters were associated with a higher risk of colonization and major CRIs within the first 7 days of catheter maintenance, stressing the need for preventive measures [15]. Eggimann et al., in a population of 18,286 patients from 2006 to 2014, showed that applying chlorhexidine dressings to all CVC and arterial lines, when added to an ongoing catheter bundle, was associated with a sustained reduction in catheter-associated bloodstream infections from 1.48 to 0.23 episodes per 1000 catheter days [16].

Vaccination may be another type of infection prevention. A Danish study found that ICU survivors with age above 65 had a better 1-year outcome when they received an influenza vaccination. Interestingly, while vaccinated patients had a lower risk for stroke and death at 1 year after discharge, other complications such as pneumonia, congestive heart failure and ischemic heart disease were comparable [17].

We are living in an era of rare therapeutic innovations, and multidrug resistant (MDR) pathogens are an increasing problem. The EPIC trial demonstrated that plazomicin, an aminoglycoside given as monotherapy once daily, was non-inferior to meropenem for the treatment of complicated urinary tract infections and acute pyelonephritis even when caused by MDR strains [18]. Pneumococcal CAP remains a severe infection. In a first-in-human, double-blind, dose-escalation, placebo-controlled, randomized trial including a small sample size, the authors assessed safety of CAL02 as an add-on therapy to antibiotics. CAL02 is an antitoxin agent that consists of liposomes that capture bacterial toxins [19]. The drug showed a good safety and tolerance profile, and potential clinical benefits, which should be further studied in a larger study.

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Compliance with ethical standards

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