CRITICAL CARE

REVIEW

Year in review 2010: *Critical Care* – infection

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Abstract

Infections remain among the most important concerns in critically ill patients. Early and reliable diagnosis of infection still poses difficulties in this setting but also represents a crucial step toward appropriate antimicrobial therapy. Increasing antimicrobial resistance challenges established approaches to the optimal management of infections in the intensive care unit. Rapid infection diagnosis, antibiotic dosing and optimization through pharmacologic indices, progress in the implementation of effective antimicrobial stewardship and infection control programs, and management of fungal infections are some of the most relevant issues in this special patient population. During the last 18 months, *Critical Care* and other journals have provided a wide array of descriptive and interventional clinical studies and scientific reports helping clinical investigators and critical care physicians to improve diagnosis, management, and therapy of infections in critically ill patients.

Introduction

Infections remain among the most important concerns in critically ill patients. Early and reliable diagnosis of infection still poses difficulties in this setting but also represents a crucial step toward an appropriate antimicrobial therapy that avoids the perils of excessive antibiotic exposure. Increasing antimicrobial resistance challenges established approaches to the optimal management of infections in the intensive care unit (ICU). Rapid infection diagnosis, antibiotic dosing and optimization through pharmacologic indices, progress in the implementation of effective antimicrobial stewardship programs, and management of fungal infections are some of the most relevant issues in this special patient population. Here, we briefly review the results from selected studies published on those topics in 2010 and take a special interest in articles published in *Critical Care*. Other important subjects like H1N1 influenza virus infection and prevention of nosocomial infection were discussed in last year's review in *Critical Care* [1] and will be summarized only briefly.

Rapid infection diagnosis: novel technologies and biomarkers

Since they detect viable microorganisms that can be further characterized by molecular or biochemical techniques, blood cultures are still considered the gold standard to diagnose bloodstream infection (BSI) and to identify the species and determine their antimicrobial susceptibility. However, blood cultures are far from being an ideal gold standard as they often provide results with delay, are incomplete, and may not reflect all microbiological evidence important for clinical decision making [2]. Recent technological advances such as the development of fully automated instruments and the application of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) have reduced identification time to 4 hours, once blood cultures have become positive [3]. Various technologies based on nucleic acid extraction (nucleic acid testing) from positive blood cultures hold some promise [4]. A microarray-based, commercially available molecular assay for sepsis detection (Prove-it Sepsis; Mobidiag, Helsinki, Finland) was recently evaluated in a large observational multicenter study [5]. The main shortcomings of these techniques are the inability to be applied directly to biological samples, the need for prior cultivation of the pathogen, and the relatively high costs.

Several automated platforms that are either commercially available or under development aim to directly detect bacteria or fungi in blood without prior cultivation [6]. Multiplex real-time polymerase chain reaction (PCR) assays and microarrays are the most promising approaches for rapid direct identification of pathogens from blood. A real-time multiplex PCR-based assay widely available for BSI diagnosis is the SeptiFast kit (Roche, Basel, Switzerland), which can detect 25 clinically important bacteria and fungi at the species level directly from whole blood in about 6 hours. However, this kit requires a great deal of labor and expertise and is

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expensive (€150 to €200 per test). Moreover, it provides no information on antimicrobial susceptibility except for methicillin-resistant *Staphylococcus aureus* (MRSA). A recent cohort study from Japan [7] showed that SeptiFast could complement traditional culture-based methods, particularly in antibiotic-treated patients. However, in that study, the SeptiFast system missed five episodes of clinically significant BSI with MRSA, *Pseudomonas aeruginosa*, *Klebsiella* spp, and *Enterococcus* spp. Thus, the existing molecular methods still lack sensitivity and a sufficiently broad panel of markers of antibiotic resistance. For instance, no rapid test to detect ESBL (extended-spectrum beta-lactamase)-producing bacteria in blood is currently available, and this represents a true challenge to clinicians given the rapidly increasing rates of ESBL-producing *Enterobacteriaceae* [8]. Most importantly, the clinical evaluation of these rapid molecular systems has been rather poor so far since none of the published clinical studies has clearly established the added value for clinical decision making, antimicrobial management, and patient outcomes.

More than 150 biomarkers have been tested as potential diagnostic and prognostic markers of infection but very few of them have been introduced into daily clinical practice [9,10]. In this journal, Christ-Crain and Opal [11] recently reviewed the role of biomarkers in the diagnosis and management of community-acquired pneumonia. The authors summarized in detail the strengths and limitations of available biomarkers and concluded that biomarkers act as merely an aid in clinical judgment that is based upon a synthesis of additional clinical, physiological, and laboratory features in each patient. This is clearly illustrated by the ongoing controversy surrounding procalcitonin (PCT) as many dispute its clinical usefulness, except for guiding antimicrobial treatment duration in respiratory tract infections and severe sepsis [12,13]. van Nieuwkoop and colleagues [14] evaluated PCT in 136 patients with urosepsis; the findings of this prospective observational study suggest that PCT may accurately predict the presence of BSI and bacterial load in patients with febrile urinary tract infection.

Pharmacokinetics and pharmacodynamics for optimized antimicrobial dosing

Knowledge of pharmacokinetics (PK) and pharmacodynamics (PD) is important for antimicrobial dosing regimens that can maximize the therapeutic effects and conceivably reduce the development of antimicrobial resistance. This knowledge is required mostly for patients in the ICU. A few years ago, Pea and colleagues [15] demonstrated that many physiopathological factors may affect antimicrobial plasma concentration in critically ill patients: overexposure to hydrophilic or lipophilic antimicrobials may occur during acute renal failure or severe liver insufficiency; conversely, underexposure may be due to increased volume of distribution (for example, ascites, edema, and mediastinitis) or to increased renal filtration (for example, hyperdynamic conditions during sepsis or hypoalbuminemia). Indeed, Giannoni and colleagues [16] showed that up to 30% of patients may be underdosed and thus successful outcomes may be impaired and antimicrobial resistance promoted. For example, in patients with severe sepsis, hypoalbuminemia occurs frequently as a consequence of either increased capillary escape rate through leaky endothelium or fluid overload. By increasing the unbound fraction, hypoalbuminemia may promote not only a more extensive distribution but also greater renal clearance [17]. This may lead to underdosing in critically ill patients whenever highly protein-bound antimicrobials (that is, teicoplanin, ertapenem, or ceftriaxone) are used.

The increased importance of PK and PD parameters strengthens the relationship with prospective monitoring of minimal inhibitory concentration (MIC) of bacterial strains at the local level. Indeed, to achieve better clinical outcomes, the target concentration attainment should be based on the ratio between optimized antimicrobial dosing and the MIC of the pathogen involved in the infection [18]. According to the two most important mechanisms of action of antimicrobials (that is, concentration-dependent and time-dependent), maximal drug efficacy could be achieved through an optimized peak concentration (C_{max})/MIC ratio for the former (aminoglycosides and quinolones) and a time-curve over MIC (t >MIC) for the latter (β-lactams, carbapenems, and vancomycin).

Optimal antibacterial activity of concentration-dependent antimicrobials is achieved when the C_{max} is 8 to 10 times greater than the MIC. Taccone and colleagues [19] confirmed the hypothesis that, in critically ill patients, increased volume of distribution (V_d) of hydrophilic drugs affects the disposition of aminoglycosides and therefore a revisited amikacin loading dose of 25 mg/kg should be required to attain the target concentration and the optimized C_{max}/MIC ratio. These findings parallel a recent experience by the same group [20], in which sepsis due to panresistant *P. aeruginosa* (amikacin MIC = 16 mg/L) was successfully treated with amikacin monotherapy once amikacin C_{max} attained 160 mg/L under continuous venovenous hemodiafiltration (C_{max}/MIC ratio = 10). Other recent papers on aminoglycoside dosing and disposition seem to confirm those findings [21,22]. Lastly, high-dosage, short-course therapy regimens with concentration-dependent antibiotics through a once-daily administration schedule may yield a more rapid bacterial killing or prevention of resistance development.

For time-dependent antimicrobials, the PD parameter most predictive of maximal bactericidal activity is the

duration of time in which free drug concentrations remain above the MIC during the dosing interval (fT >MIC). Time-dependent antimicrobials – β-lactams, carbapenems, and vancomycin – are hydrophilic substances, and their disposition is greatly affected by several factors that are frequently encountered in critically ill patients [17,23-25]: variation in V_d by capillary leak syndrome, massive fluid replacement, and hypoalbuminemia or by increased third space (for example, drainages, ascites, pleural effusions, and mediastinitis) as well as hyperdynamic status, vasoactive and diuretic drugs, and variation in glomerular filtration rate. Even though adjusting the meropenem dosage for renal function and prolonging the infusion in such patients may provide an improved target attainment of fT >MIC [26], other recent experiences have confirmed how most of the aforementioned conditions may substantially impair the effective concentration of hydrophilic antimicrobials [27-32]. By optimizing antibiotic doses to achieve PD targets predictive of efficacy, clinicians can improve care and minimize drug toxicity provided that careful therapeutic drug monitoring is carried out [33]. Unfortunately, the conventional intermittent β-lactam dosing schemes often used in ICU practice have suboptimal PD profiles. Prolonging the infusion time of β-lactams is one method to maximize the probability of achieving concentrations in excess of the MIC for the majority of the dosing interval, especially against pathogens with elevated MIC values [17,28,29]. Prolonged infusions of intravenous β-lactams not only are associated with improved probability of target attainment profiles but offer possible cost savings and greater potential for reducing the emergence of resistance relative to intermittent infusions [34].

Since these new approaches are not yet firmly confirmed, several ongoing clinical studies are now applying the clinical pharmacology parameters to real practice; probably, these studies will offer new insights into the appropriateness of antimicrobial therapy in the ICU. Until the results of these studies are published, it is mandatory that ICU physicians conduct a daily reassessment of antimicrobial regimens in accordance with the daily measurement of creatinine clearance and other variables affecting PK and keep in mind that the assessment of renal function can identify not only patients with renal impairment at risk for drug toxicity but also those with glomerular hyperfiltration or increased V_d, in whom higher dosages are bound to be administered.

Antimicrobial resistance, infection control, and antimicrobial stewardship programs

Antimicrobial resistance (AMR) is increasing worldwide [35]. In a multicenter study performed by Meyer and colleagues [8] between 2001 and 2008 in 53 German ICUs, carbapenem use almost doubled despite the absence of significant change in total antibiotic use expressed as defined daily doses per 1,000 patient-days. The exponential increase of third-generation cephalosporin resistance in *Escherichia coli* and other *Enterobacteriaceae* reported in that study led to switching empirical therapy to carbapenems to treat infections, and carbapenem-resistant *Klebsiella pneumoniae*, carbapenemase-producing Gram-negative pathogens, and imipenem-resistant *Acinetobacter baumannii* emerged as a direct consequence. This scenario will affect many ICUs in Europe in the near future. However, resistance trends and antibiotic consumption rates will depend on different factors, including ICU characteristics (medical, surgical, and general), local antibiotic policies, and physicians' level of education. The heterogeneity of antibiotic prescriptions within ICUs, as recorded by Meyer and colleagues [8], seems to indicate that antimicrobial use can be improved in ICU settings by shortening the duration of treatment or antibiotic prophylaxis without affecting patient outcome. In this respect, Morel and colleagues [36] showed how de-escalation could be one of several effective strategies for a more appropriate empirical therapy. However, the retrospective design of the study and the delay in de-escalation (more than 3 days on average) from the onset of infection limit the power of the study. Moreover, as clearly pointed out in the same study, it was not possible to draw firm conclusions on the impact of this strategy on AMR. Adherence to shared protocols or local guidelines, on the basis of local epidemiology of resistance and control of antibiotic prescriptions, may reverse the trend of AMR (especially in MRSA), whereas it appears more difficult for Gram-negative pathogens [37-40]. The findings of Meyer and colleagues [8] reaffirm the concern that Gram-negative pathogens could become even more intractable day by day and are paralleled by the findings of Augustin and colleagues [41], indicating that, at this time, only imipenem/cilastatin can be considered an adequate single-drug empirical therapy for postoperative peritonitis. Not surprisingly, in the latter study, use of broad-spectrum antimicrobials between initial intervention and reoperation was the only significant risk factor for the emergence of multidrug-resistant pathogens in critically ill patients with postoperative peritonitis [41].

To challenge such situations, a multitasked approach is needed [42,43]. The combination of a comprehensive infection control strategy and an effective antimicrobial stewardship program (ASP) may lead to the prevention of emergence and transmission of resistant pathogens [42]. This includes multimodal strategies, variably combined, such as hand hygiene promotion, barrier precautions and asymptomatic patient decolonization, prevention bundles, and environmental decontamination [44]. Recently, two important studies have highlighted not

only the efforts in prevention of resistant pathogens but also the difficulties in gaining sustained and reproducible results [45,46]. Jain and colleagues [45] evaluated the effectiveness of a quality improvement initiative in preventing the acquisition and spread of MRSA among nearly 2 million patient admissions; the study included data from 196 ICUs in the US. During the intervention period – with increased attention to MRSA admission screening, contact precautions, hand hygiene, and emphasis on the responsibility of all health-care workers in prevention procedures – an important decrease in infections caused not only by MRSA but also by other pathogens was observed [45]. Huskins and colleagues [46] evaluated more than 9,000 patients in 18 ICUs with an intervention aimed at implementing barrier precautions (such as universal gloving until a patient's colonization status was known to be negative), carrying out active surveillance culturing, and feeding back adherence information to personnel; however, the net result of the intervention has been that, despite the improvement in compliance with precautions and procedures, no effect on colonization or infection rates was observed.

ASP may be another important tool to reduce and prevent AMR by selecting the most appropriate antibiotic choice with the least impact on microbial environment. Early diagnostic markers, information on the local epidemiology of AMR, and PK/PD indices for appropriate dosing and duration of antimicrobial therapy are among the elements of an established ASP. Strictly interconnected with the infection control policy, these approaches represent the pillars of antimicrobial stewardship not only in the ICU but in the entire health-care systems. Some interesting papers showing the importance and positive results of ASP carried out in different settings have been reviewed in the last 2 years [42,47]. Although the role of infectious disease specialists such as antimicrobial therapy experts within the ICU appears relevant in promoting and improving the quality of antibiotic prescription, clinical results of such approaches in terms of better patient outcome, reduction of AMR, and prevention of nosocomial transmission are still scanty. The excellent pro/con debate by George and Morris [48] in *Critical Care* clearly summarizes both the robust evidence to support the implementation of ASP and the difficulty of demonstrating a real impact in terms of reduction of length of stay or mortality.

Fungal infections in the intensive care unit

Despite the availability of effective antifungal drugs, fungal infections remain a major concern in critically ill patients, mostly because of several predisposing factors occurring in ICU patients. Advances in medical care warrant improved survival to an ever-wider patient population with severe diseases while creating new subsets of patients at high risk for fungal infections. Both invasive candidiasis and aspergillosis often need surrogate markers of infection since proven diagnosis is still far from being the rule [49]. In addition, delaying the targeted antifungal treatment has been shown to further increase morbidity and mortality.

In an article in *Critical Care*, Bassetti and colleagues [50] reviewed the management of *Candida* infection in the ICU, providing updated considerations about issues in diagnosis, risk factors, adequate treatment, and the potential shift from *Candida albicans* to non-*albicans* strains because of widespread prophylactic use of fluconazole in the ICU. This shift may lead to inappropriate antifungal therapy whenever epidemiological data at the local level are lacking. In France, Leroy and colleagues [51] conducted a multicenter study aiming at identifying clinical factors that could help distinguish between *C. albicans* and non-*albicans* fungemia episodes, thus guiding the choice of appropriate empirical antifungal treatment. Only a few significant differences were observed among the 136 patients analyzed: severity of underlying disease, the time to candidemia onset, and the rate of neutropenia. Accordingly, the authors concluded that it was not possible to identify a reliable parameter to allow a binary distinction between *albicans* and non-*albicans* candidemia or to guide the choice of antifungal therapy thereafter.

A shift in the paradigm of patient populations at risk for invasive aspergillosis has recently been described. For instance, a rising incidence of invasive bronchial-pulmonary aspergillosis (IBPA) in non-neutropenic critically ill patients has been reported [52]. Critically ill patients are prone to develop impairments in immunoregulation during a stay in the ICU and thus are rendered more vulnerable to mold infections. Risk factors such as chronic obstructive respiratory disease (CORD), prolonged use of steroids, advanced liver disease, chronic renal replacement therapy, near-drowning, and diabetes mellitus have been described. Diagnosis of IBPA may be difficult, and obtaining histologic confirmation to meet the gold standard for IBPA diagnosis is not always feasible in these patients, nor is the galactomannan test really useful in monitoring the development of IBPA in these patients. Recently, however, He and colleagues [53] prospectively evaluated 55 critically ill patients with CORD, including 13 who had IBPA. The authors' findings indicate that more than three kinds of antibiotics used before ICU admission, high-dose steroids received before ICU admission, and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of greater than 18 were significant independent risk factors for IBPA in the multivariate analysis. In such patients, IBPA may present as respiratory failure and clinical and bronchoscopic features of severe infection, bronchospasm, and rapid

progression of radiologic lesions unresponsive to steroids and antibiotics. Despite the weaknesses of this study because of the small dataset (three predictor variables for 13 IBPA cases analyzed), the recommendations by the authors to perform early bronchoscopy and tight radiologic follow-up in order to avoid misdiagnosis and achieve microbiological confirmation may be extended to other subsets of critically ill patients in the ICU with identified risk factors for IBPA. Prospective studies aimed at improving the diagnosis and treatment of invasive fungal infections would certainly be welcomed by intensive care physicians.

Influenza A (H1N1) infection

Many data about the influenza A H1N1 pandemic were reported last year in *Critical Care* [1]; however, some important advances on the topic have been described lately. First of all, the Global Influenza Programme of the World Health Organization analyzed and published pooled data collected from 19 countries or administrative regions [54], including data from approximately 70,000 hospitalized patients with laboratory-confirmed H1N1 diagnosis, 9,700 of whom were admitted to ICU and 2,500 of whom died. Risk factors were found to be similar to those for seasonal influenza but with some notable differences: cardiac or chronic respiratory illnesses and diabetes were important risk factors for severe disease, and the proportion of patients with H1N1 with one or more pre-existing chronic diseases increased with severity of infection. The proportion of H1N1 patients with one or more reported chronic conditions increased with severity (median = 31.1%, 52.3%, and 61.8% of hospitalized, ICU-admitted, and fatal H1N1 cases, respectively). Moreover, the analysis identified obesity and younger age in comparison with seasonal influenza as additional risk factors. An important study from six Toronto hospitals [55] provided a multivariable logistic regression analysis to estimate the likelihood of H1N1 influenza in patients admitted to ICUs during pandemic waves: an admission temperature of at least 38°C and an admission diagnosis of pneumonia or respiratory infection were found to be independent predictors for influenza, and odds ratios for H1N1 were remarkably higher than those for seasonal influenza. Finally, researchers from the Guangdong Center for Disease Control and Prevention (China) [56] showed that early glucocorticoid treatment tripled the hazard of developing critical disease in hospitalized patients with confirmed H1N1 influenza, once again highlighting the debated issue of glucocorticoid treatment in pulmonary infections.

Conclusions

During the last 18 months, *Critical Care* and other journals have provided a wide array of descriptive and interventional clinical studies and scientific papers helping clinical investigators and ICU clinicians to improve diagnosis, management, and therapy of infections in the ICU setting. We are confident that exciting progress will continue to be made, especially in the field of rapid diagnostics of infections in critically ill patients.

Abbreviations

AMR, antimicrobial resistance; ASP, antimicrobial stewardship program; BSI, bloodstream infection; C_{max}, optimized peak concentration; CORD, chronic obstructive respiratory disease; ESBL, extended-spectrum beta-lactamase; IBPA, invasive bronchial-pulmonary aspergillosis; ICU, intensive care unit; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction; PCT, procalcitonin; PD, pharmacodynamics; PK, pharmacokinetics; V_d, volume of distribution.

Competing interests

SH has received consultant and speaker honoraria from bioMérieux (Marcy l'Etoile, France), Da Volterra (Paris, France), and Destiny Pharma (Brighton, UK). AA and LP declare that they have no competing interests.

Authors' statement

All authors state that they have read and approved the manuscript. It has not been published nor is it under consideration for publication elsewhere.

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