FOCUS EDITORIAL

Focus on severe infections

Kevin B. Laupland¹, Jose-Artur Paiva^{2,3} and Jean-Francois Timsit^{4,5*}

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Introduction

The epidemiology of severe infections is changing worldwide. As a result of many complex factors not limited to globalization of economies and increased travel, intensivists are increasingly challenged to manage patients with unusual etiologies and increased resistance profiles with the associated risk of treatment failure. While a comprehensive review of this area is beyond the scope of this series, this article aims to highlight some selected recent publications examining severe tropical viral diseases, early diagnosis of infection, and means to optimize therapies for infected patients admitted to the ICU.

Severe tropical viral diseases

While traditionally geographically constrained, tropical viral diseases are increasingly having an impact in non-tropical areas as a result of globalization of economies and movement of people.

Dengue is a common disease in many tropical jurisdictions worldwide, and it is important for intensivists everywhere to be aware of the potential for severe dengue infection. Jog et al. reported on a prospective observational study among adults with severe dengue admitted to 14 tertiary care ICUs in Pune, India during 2012–2014 [1]. A diagnosis of severe dengue required laboratory confirmation and at least two organ dysfunctions as per SOFA score. The average age of the 113 patients was 40 years and most had no prior medical co-morbidities. Critical care/organ support included vasopressors (27%), mechanical ventilation (26%), and renal replacement therapy (13%). Neurological impairment occurred in 23%. The 28-day all-cause case fatality rate was 27%, and patients with higher lactate and SOFA score, lower serum albumin, and those requiring mechanical ventilation were at highest risk of death.

While Zika virus infection is frequently mild with the majority being asymptomatic cases in adults, there is increasing recognition that this virus can cause not only complications in utero but neurological complications in adults [2]. Cao-Lormeau et al. conducted a matched case control study to quantify the risk of Guillan–Barré syndrome (GBS) associated with Zika virus infection during a large outbreak in French Polynesia [3]. This study included 42 cases with GBS. The most common Zika virus symptoms were rash, arthralgia, and fever and these preceded GBS onset by a median of 6 days. No patients died and the majority (57%) of patients were able to walk after 3 months. The authors calculated the Zika-associated risk of GBS at 24 per 100,000; that compares to the approximate 1–4 per 100,000 population incidence for GBS worldwide. Of note, they did not find evidence to support dengue as a cause of GBS. Long-term neurological sequelae and post-viral fatigue affecting quality of life are therefore frequently reported.

The Ebola virus caused a large and devastating outbreak of severe infection in West Africa in 2013 and resulted in a mobilization of the international medical and critical care community [4]. Bordes et al. evaluated the use of SOFA to describe organ failures among 22 patients with Ebola virus disease managed at the French Military Ebola Virus Disease Treatment Centre in Conakry, Guinea [5]. They found that the mean ($\pm$ standard deviation) SOFA score was 2.6 ($\pm$ 1.7) on admission and was significantly higher among the six (27%) patients that died (4.8 ± 1.7 versus 1.7 ± 1). They observed that while respiratory, cardiovascular, and neurological dysfunctions were infrequent at admission, coagulation and renal dysfunctions were more prevalent, with an emphasis on the latter among non-survivors. The importance of renal failure as a marker of severity and adverse outcome is consistent with another cohort of patients with Ebola virus disease managed in Europe and the USA where an overall 28-day case fatality rate of 19% (5/27) was observed [6].

*Correspondence: Jean-francois.timsit@aphp.fr

⁴ APHP, Bichat University Hospital Medical and Infectious Diseases ICU, 75018 Paris, France

Full author information is available at the end of the article

Rapid microbiological tests for early diagnosis and effective targeted antimicrobial therapy

A major challenge for intensivists is to initiate adequate antimicrobials promptly for patients with severe infections while at the same time minimizing the overall risk of development of antimicrobial resistant organisms within ICUs through prudent antibiotic use. Classical microbiological tests require at least 24–48 h for microorganism identification and 48–72 h for antibiotic susceptibility profile determination. Furthermore, the early detection of microorganisms may lack sensitivity, especially in the setting of prior receipt of antimicrobial therapy. Use of novel rapid diagnostic tests, including nucleic acid amplification and mass spectrometry-based techniques that reduce the time to definitive etiologic diagnosis, have been increasingly recognized as key components of strategies to reduce the time to effective targeted therapy [7].

Real-time PCR assays that target ribosomal sequences of a panel of selected bacteria and fungi have extensively been studied in patients with suspected sepsis. Warhurst et al. provided results of a study on 1006 episodes of suspected bloodstream infections (BSIs) [8]. Of 77 BSIs diagnosed with traditional methods, only 44 had the same pathogens identified with RT-PCR. In 133 other cases, only the PCR was positive and may reflect alternately a true BSI missed by blood culture or false positive results. This result was confirmed by a systematic review [9]. From 41 phase III diagnostic accuracy studies, summary sensitivity and specificity for SeptiFast™ compared with blood cultures were 0.68 (95% CI 0.63–0.73) and 0.86 (95% CI 0.84–0.89), respectively.

Use of combined nucleic acid amplification testing (NAAT), mass spectrometry, and fluorescence in situ hybridization (FISH) identification techniques has shown similar results to PCR-based rapid diagnostic assays. This testing strategy can potentially identify all pathogens in blood culture or respiratory secretion and selected antibiotic resistance genes within 6 h (vancomycin: VanA/VanB, methicillin: MecA, and carbapenem: carbapenemase-resistant *Enterobacteriaceae*). Many other systems are under development with encouraging preliminary results (Fig. 1). For all these new systems, the interpretation of discordant result and therapeutic implications will need many research efforts and interventional studies.

A two-step multiplex PCR/hybridization assay has also been shown to detect a large panel of respiratory pathogens and genes of ESBL such as CTX-M, SHV, and TEM in a turnaround time of 4–5 h [10]. Preliminary results in nosocomial pneumonia are encouraging but require further confirmation.

FISH-based microscopy identification and antibiotic susceptibility test (ID/AST) systems can evaluate

antibiotic susceptibility from blood cultures or respiratory secretions on the basis of a previously defined panel of phenotypic growth pattern analysis. One recent pilot study reported data from a new accelerated ID/AST automated microscopy system and was able to detect multiresistant bacteria in bronchoalveolar lavage after 5 ± 7 h of culture and 5 h of analysis with a 100% sensitivity and a 97% specificity [11].

The MALDI-TOF MS method is based on ionization with a laser source of bacterial biomolecules containing proteins embedded in a matrix. Once they are sublimated into the gas phase they are projected into a detector. Time of flight after ionization and mass/charge ratio then allow a very accurate recognition of organisms. It can also detect the products of hydrolysis of the antibiotics generated by enzymes such as ESBL. Use of MALDI-TOF can potentially give accurate identification and antibiotic susceptibility results within 1 day of sampling [12]. Rapid detection of enzymes such as ESBL, AmpC, and carbapenemases (KPC, Oxa-48 like, and class B carbapenemases with a lower efficacy) is also possible within 15 min to 2 h using biochemical techniques in isolated colonies but can also be conducted directly in clinical specimens such as urine and blood cultures with more than 90% sensitivity and specificity [7].

New tools and strategies to improve the adequacy of anti-infective therapy

There are a number of considerations within the context of a quality improvement framework for optimizing anti-infective therapy in the ICU in order to optimize efficacy with the least possible collateral damage and these have been highlighted in recent publications.

A first consideration is that optimal selection of first-line empirical antibiotics be based on an adequate risk assessment of resistant pathogens using the example of ESBL-producing *Enterobacteriaceae* infections. Gutierrez-Gutierrez et al. provided data suggesting the efficacy of beta-lactam/beta-lactamase inhibitor combinations in the case of ESBL-producing *Enterobacteriaceae* infections regardless of the source, severity at presentation, or species [13]. A useful algorithm for clinical decision-making for suspected ESBL infections in ICU patients has been proposed, using one of two ESBL predictive scores, both with high sensitivity but poor specificity [14]. Further studies in the critically ill population are needed.

A second area involves the use of pharmacokinetics and pharmacodynamics (PK/PD) for the selection of antibiotic dose and dose interval. Beta-lactam antibiotics have time-dependent activity as bacterial killing and treatment efficacy correlate with the time that free plasma concentrations remain above the minimum inhibitory concentration (MIC) of the pathogen. In the

Fig. 1 Various rapid tests available or under development for identification or antimicrobial resistance. *Top* techniques available for identification. *Bottom* techniques available for antimicrobial resistance. *Blue* molecular methods, *green* phenotypic methods. *AB* antimicrobials, *AST* antimicrobial susceptibility testing, *PCR* polymerase chain reaction, *MecA* methicillin resistance cassette of *Staphylococcus* sp., *Van A, B* detection of resistance genes of *Enterococci* sp., *CTX-M* the most frequently recovered family of extended-spectrum beta-lactamases, *FISH* fluorescent in situ hybridization, *MALDI-TOF* matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry; *T2MR* is a diagnostic detection method utilizing miniaturized magnetic resonance technology (nanoparticles coated with target-specific binding agents are added to a sample containing the target, and the nanoparticles bind to and cluster around that target. This clustering changes the sample water's microscopic environment, which in turn alters the measured magnetic resonance or T2 relaxation signal, thereby indicating the presence of the target)

acute critically ill, increased volume of distribution makes loading doses essential to rapidly achieve therapeutic concentrations and potential glomerular hyperfiltration makes measurement of creatinine clearance mandatory for the decision of adequate maintenance doses [15]. A recent randomized clinical trial showed that beta-lactam infusion demonstrated higher clinical cure rates and better PK/PD target attainment compared to intermittent dosing in critically ill patients with severe sepsis not on extracorporeal renal support [16]. Greater benefits are expected in patients with high illness severity and without renal dysfunction and who are infected with less susceptible microorganisms. In this case, MICs should be requested from the microbiological lab.

The use of adjuvant antibiotics in the appropriate setting may improve outcomes: In cases of toxic shock syndrome (TSS), it is widely accepted that the pivotal regimen should be combined with an agent that suppresses toxin production. Clindamycin or linezolid reduce superantigen production in both staphylococcal and streptococcal

TSS [17]. Similarly, the benefits of adding a macrolide, to the beta-lactam, in severe community-acquired pneumonia may be linked to anti-pneumolysin or to immunomodulatory/anti-inflammatory activities [18]. Further clinical outcome studies are needed in these and other sepsis syndromes.

Tools and strategies to improve infection therapeutics through antimicrobial stewardship programs (ASP): For maximized benefit, all therapeutic strategies should be used with an ASP, which is associated with improved antimicrobial utilization in the ICU, with corresponding improvements in antimicrobial resistance and adverse events. Implementing an ASP requires identification of barriers and facilitators, use of accepted guidelines, use of restrictive and persuasive interventions, role modeling by key opinion leaders, and performance of audit and feedback of prescribing behavior. Tools such as early diagnostic tests and procalcitonin (PCT) are helpful to increase the appropriateness of antimicrobial therapy used in ICU [19].

Author details

¹ Intensive Care Unit, Royal Inland Hospital, Kamloops, BC, Canada. ² Intensive Care Department, Faculty of Medicine, Centro Hospitalar Sao Joao, University of Porto, Porto, Portugal. ³ Grupo de Infecção e Sepsis, Porto, Portugal. ⁴ APHP, Bichat University Hospital Medical and Infectious Diseases ICU, 75018 Paris, France. ⁵ IAME, UMR 1137 Inserm, Université Sorbonne Paris Cité, 75018 Paris, France.

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