Michael S. Niederman
Marin H. Kollef

The road forward in the management of *Acinetobacter* infections in the ICU

Received: 13 October 2015
Accepted: 14 October 2015
Published online: 23 October 2015
© Springer-Verlag Berlin Heidelberg and ESICM 2015

M. S. Niederman (✉)
Weill Cornell Medical Center, 425 E. 61st St, New York,
NY 10065, USA
e-mail: msn9004@med.cornell.edu

M. H. Kollef
Washington University, St Louis, MO, USA

Acinetobacter spp. infection is a global problem in ICUs, causing a variety of infections and presenting a challenge to effective therapy, because it is often a multidrug-resistant organism, that can lead to adverse patient outcomes. In the EPIC II point prevalence study of ICU infection, *Acinetobacter* spp. accounted for 8.8 % of all ICU organisms, with rates as high as 19 % in Asia and 17 % in Eastern Europe [1]. In one study of Asian ICUs, in patients with nosocomial pneumonia, *Acinetobacter* spp. infection was the most common cause of VAP, accounting for 36.5 % of all episodes overall, and nearly half of all episodes in Thailand [2]. Most of the clinically relevant ICU infections with this organism come from the *Acinetobacter baumannii* group of organisms. As the frequency of this infection has been rising, our therapeutic options have remained limited, and carbapenems (excluding ertapenem, which is not active against this organism) have been the drug of choice for these organisms, but are less effective than in the past, as resistance to these agents rises. Consequently, we have been forced to resort to therapies with polymyxins, and combinations of other agents (including sulbactam and tigecycline).

It is against this backdrop that we welcome the recent publication in *Intensive Care Medicine* of a multinational, multispecialty consensus statement on the management and prevention of *A. baumannii* infection in the ICU [3]. The document is well organized and offers evidence-graded recommendations on the laboratory diagnosis of infection, the approach to therapy for established infection, and the methods for infection control that can lead to prevention and mitigation of outbreaks with this organism.

Much of the confusion in managing *Acinetobacter* spp. infection comes from the limited therapeutic options, and the consensus statement provides useful information. The authors propose that empiric therapy for this organism be provided when an infection develops in an ICU with a high prevalence of this pathogen, or if a patient has been previously colonized. This is consistent with several recent studies. For example, Nseir and colleagues found that occupying an ICU room that previously housed a patient with *Acinetobacter* infection or colonization raised the likelihood of the subsequent patient in that room acquiring *Acinetobacter* by an odds ratio of 4.2 [4]. ICU ecology also had an impact on the bacteriology of VAP in another study [5]. In that study, 152 patients had early onset VAP with no classic risk factors for resistance, yet 50.7 % harbored multidrug-resistant pathogens, including 15.8 % with *A. baumannii*. The authors identified that one risk factor for acquiring these organisms was hospitalization in an ICU with more than a 25 % incidence of multidrug-resistant pathogens. The impact of environmental exposure and environmental contamination is an important consideration in determining the bacteriology of infection and in choosing empiric therapy in the ICU, and the topic of environmental cleaning to prevent *Acinetobacter* infection is also discussed in the consensus statement.

The statement does suggest that if *Acinetobacter* is being treated in an ICU with a low rate of resistance, then

a carbapenem should be used, generally as a single agent. If however, *Acinetobacter* resistance is common, then they recommend using a multidrug regimen that includes a polymyxin, and maybe also a carbapenem, sulbactam, and/or tigecycline. The role of combination therapy in *Acinetobacter* infection is complex, and the authors do not recommend its use in directed therapy, but do acknowledge the benefit of combination regimens for empiric therapy when high rates of resistance are present, or when agents like sulbactam or tigecycline are used. The authors pay particular attention to dosing and pharmacokinetics in recommending specific therapies and the potential benefit of prolonged infusions of carbapenems, sulbactam, and polymyxins. They also consider the potential benefit of adjunctive aerosolized polymyxin in the therapy of highly resistant pathogens, and in patients with a poor response to systemic therapy, but do not consider if this adjunctive therapy should be used routinely. The role of tigecycline in *Acinetobacter* infection is evolving, and it may be necessary to use higher doses than in the past. The consensus statement recommends a loading dose of 200 mg and a daily dose of 100 mg twice daily for the therapy of nosocomial pneumonia, although this is an unapproved dose. However, the prior failures of tigecycline monotherapy in VAP did involve lower doses, and a recent proof of concept study showed that higher doses are feasible and reasonably well tolerated [6, 7]. However, with multidrug-resistant *Acinetobacter*, and tigecycline MIC values greater than 2 µg/ml, tigecycline-based regimens are less effective than colistin-based regimens [8]. Several new therapies for this pathogen are in development, but are not discussed in the consensus statement. One important therapeutic decision that is also unresolved is duration of therapy, and the consensus statement recommends 2 weeks for severe infections such as VAP and severe sepsis, acknowledging that more data are needed in this area.

Prevention of infection and infection control are also an important focus in the consensus statement. The

Table 1 Research agenda for *Acinetobacter* infection

Define the role of new diagnostic methods in optimizing early therapy of infection and control of epidemics
Determine the clinical relevance of heteroresistance
Define the best empiric therapy regimens when multidrug resistance is likely
Define the optimal duration of therapy for sensitive and resistant pathogens
Determine if routine adjunctive aerosol therapy is valuable
Determine the optimal dosing and infusion methods for <i>Acinetobacter</i> therapy, especially pneumonia
Better identify the role of combination therapy in empiric and definitive management strategies
Optimize methods of environmental decontamination

authors recommend contact precautions whenever a patient harbors this organism, and also they recommend activating a high level of alert and awareness whenever a patient has this organism, focusing on cohort isolation, hand hygiene, and environmental decontamination. In the setting of an outbreak, they also recommend the use of surveillance cultures, using weekly rectal and pharyngeal swabs, and tracheal aspirates from intubated patients. The authors point out that in a true epidemic situation, “it takes a village”, and there must be full cooperation throughout the hospital, from the doctors and nurses, all the way up to the hospital administration.

The current consensus statement is a good step forward. It organizes what we know and provides practical recommendations for current management. Like all good statements of this type, it is evidence graded, so that we know the strength of the current knowledge base and, most importantly, the agenda for future research (Table 1).

Compliance with ethical standards

Conflicts of interest None.

References

1. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K, EPIC II Group of Investigators (2009) International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 302(21):2323–2329
2. Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H et al (2011) High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am J Respir Crit Care Med* 184(12):1409–1417
3. Garnacho-Montero J, Dimopoulos G, Poulakou G, Akova M, Cisneros-Herreros JM, DeWaele J et al (2015) Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU. *Intensive Care Med*. doi:10.1007/s00134-015-4079-4
4. Nseir S, Blazejewski C, Lubret R, Wallet F, Courcol R, Durocher A (2011) Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit. *Clin Microbiol Infect* 17(8):1201–1208
5. Martin-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, Niederman MS, Rello J, EU-VAP Study Investigators (2013) Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. *Intensive Care Med* 39(4):672–681

-
6. Freire AT, Melnyk V, Kim MJ, Datsenko O, Dzyublik O, Glumcher F et al (2010) Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis* 68(2):140–151
 7. Ramirez J, Dartois N, Gandjini H, Yan JL, Korth-Bradley J, McGovern PC (2013) Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother* 57(4):1756–1762
 8. Chuang YC, Cheng CY, Sheng WH, Sun HY, Wang JT, Chen YC, Chang SC (2014) Effectiveness of tigecycline-based versus colistin-based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis. *BMC Infect Dis* 14:102