Published in final edited form as:

Crit Care Med. 2015 June ; 43(6): 1332–1334. doi:10.1097/CCM.0000000000001029.

Combination Therapy for Extreme Drug Resistant (XDR) *Acinetobacter baumannii*: Ready for Prime-Time?

Brad Spellberg, MD¹ and Robert A. Bonomo, MD^{2,3,4}

¹Division of Infectious Diseases, Keck School of Medicine at USC and the Los Angeles County-USC Medical Center, Los Angeles, CA ²Departments of Medicine, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, OH ³Pharmacology, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, OH ⁴Molecular Biology and Microbiology, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, OH

Keywords

Acinetobacter; antibiotics; combination therapy

Acinetobacter baumannii is one of the most antibiotic resistant pathogens encountered in clinical medicine. United States (US) national surveillance data confirm that 50% of *A. baumannii* isolates from US intensive care units are carbapenem-resistant, far higher than for other pathogens, including *Pseudomonas aeruginosa* (20%) or *Klebsiella pneumoniae* (10%) (1). The vast majority of these carbapenem-resistant strains are extreme drug resistant (XDR), defined as resistant to all antibiotics except colistin and tigecycline (2). Bacteremia and ventilator-associated pneumonia caused by XDR *A. baumannii* result in >50% mortality rates (3-7). Multiple retrospective studies establish that it is the carbapenem-resistance that drives remarkably higher mortality (e.g., 3 to 4-fold increased) during *A. baumannii* bacteremia and pneumonia, both by increasing the frequency with which inactive empiric therapy is begun, and by eliminating highly effective definitive therapy, leaving only suboptimal agents available (8-16). Overall, approximately 75,000 cases of XDR *A. baumannii* infections occur annually in world, resulting in 30,000 excess deaths and excess healthcare costs of \$742 million compared to infections caused by susceptible strains (17). Clearly new treatment strategies are needed.

New antibiotics targeting Gram negative bacilli have become available. Unfortunately of the two such antibiotics recently approved by the FDA, ceftolozane-tazobactam has no reliable activity against *A. baumannii*, and ceftazidime-avibactam has activity similar to ceftazidime alone against *A. baumannii*. Eravacycline may soon be approved by the FDA, and does have *in vitro* activity against *A. baumannii*. It is likely that its *in vivo* efficacy will be similar to minocycline or tigecycline for such infections.

In the absence of newly emerging antibacterial agents that are superior to currently available options against XDR *A. baumannii*, one strategy that has been explored is combination therapy to improve outcomes. The therapeutic combination that has been tested most commonly is colistin and rifampin. While earlier, small studies were promising, a recent, multi-center, randomized trial found no mortality benefit of colistin and rifampin versus colistin alone for the treatment of XDR *A. baumannii* infections (18). The other major combination regimens that have been tested include colistin and either tigecycline or carbapenem therapy, the latter based on *in vitro* evidence of synergy even for carbapenem-resistant strains (19). Limited data has suggested the colistin and carbapenem combination therapy may improve outcomes of XDR *A. baumannii* infections (19, 20). However, as the use of colistin and rifampin demonstrates, larger scale validation of these results are required. The execution of these trials is urgent given the outcomes of the infections treated with monotherapy.

In the current issue of Critical Care Medicine, Cheng *et al.* (21) attempt to shed light on this question by providing us with the results of a retrospective evaluation of 55 patients with XDR *A. baumannii* bacteremia treated with either colistin and carbapenem or colistin and tigecycline combination therapy (22). The investigators found a non-significant trend to higher 14-day mortality with colistin and tigecycline compared to colistin and carbapenem therapy (35% vs. 15%, $p = 0.1$), and a strong trend to increased recurrence of bacteremia in the face of ongoing therapy (18% vs. 0%, $p = 0.06$). By multivariate analysis, patients infected with XDR *A. baumannii* strains with tigecycline MICs of $\geq 2 \mu\text{g/ml}$ had a nearly 7-fold higher risk of 14-day mortality if they were treated with colistin and tigecycline than colistin and carbapenem ($p = 0.0009$). These results suggest that the two combination regimens are similar in efficacy if the bacterial strain's tigecycline MIC is $< 2 \mu\text{g/ml}$, but that the colistin and tigecycline combination is inferior in efficacy if the strain's tigecycline MIC is $\geq 2 \mu\text{g/ml}$.

These data are concordant with a recent study by Chuang *et al.* who found that monotherapy with tigecycline resulted in higher mortality in patients with pneumonia caused by *A. baumannii* strains with tigecycline MICs of $\geq 2 \mu\text{g/ml}$ (11). Thus, we have clinical validation that the tigecycline breakpoint of $\geq 2 \mu\text{g/ml}$ indicates resistance for *A. baumannii* in both the blood and the lung. Higher mortality results when bacteremia or pneumonia caused by such strains are treated with tigecycline, whether as monotherapy or part of a combination regimen.

There are limitations of the study by Cheng *et al.* Of primary importance, the study is retrospective, and thus hypothesis-generating rather than hypothesis-confirming. It is also small and underpowered, which likely accounts for the lack of significance in the primary comparison of survival between the two combination regimens. Furthermore, outcomes described for patients treated with monotherapy are not known, and were not compared to either combination regimen. Finally, while the study illuminates the relevance of the tigecycline MIC breakpoint for *A. baumannii*, data are not available for carbapenem MICs. For example, does the current carbapenem breakpoint predict failure with monotherapy carbapenem? And does combination therapy with colistin plus carbapenem result in different outcomes depending on the carbapenem MIC, as was found with tigecycline?

Further study with larger datasets, and ideally with prospective design, is required to clarify these questions.

In the meantime, even though the available data are hypothesis-generating, the outcomes of XDR *A. baumannii* are sufficiently bad and studies are hard enough to conduct that these data are actionable. We can safely conclude that it is imprudent to use tigecycline-based combination regimens to treat patients infected with strains of *A. baumannii* with tigecycline MICs of ≥ 2 $\mu\text{g/ml}$. And monotherapy tigecycline most certainly should not be used to treat such patients. *A. baumannii* is a remarkable foe. The current data underscore ability of *Acinetobacter spp.* to recrudescence even after initial clearance from blood, and its capacity to develop resistance in the middle of the course of therapy. Our therapeutic armamentarium for XDR *A. baumannii* infections is limited, and is likely to remain so for the foreseeable future. These data provide us some guidance as to how to treat such infections. But we have a long way to go, and much to learn, to improve outcomes further. We are still at the beginning of exploring the impact of combination therapy on outcomes from these infections. We have learned what combination regimens not to use. But we do not yet know which ones to use—i.e., which ones result in superior outcomes compared to monotherapy. We need prospective studies to answer this question, and to make combination therapy ready for prime-time.

Acknowledgments

Copyright form disclosures: Dr. Spellberg received support for article research from the National Institutes of Health (NIH). His institution received grant support from the NIH (Dr. Spellberg is a funded investigator who does research on *Acinetobacter*). Dr. Bonomo received support for article research from the NIH.

References

1. Shlaes DM, Sahm D, Opiela C, et al. Commentary: The FDA Reboot of Antibiotic Development. *Antimicrob Agents Chemother*. 2013; 57:4605–4607. [PubMed: 23896479]
2. Infectious Diseases Society of A. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. *Clin Infect Dis*. 2012; 55(8):1031–1046. [PubMed: 22891041]
3. Park YK, Peck KR, Cheong HS, et al. Extreme drug resistance in *Acinetobacter baumannii* infections in intensive care units, South Korea. *Emerg Infect Dis*. 2009; 15(8):1325–1327. [PubMed: 19751609]
4. Tseng YC, Wang JT, Wu FL, et al. Prognosis of adult patients with bacteremia caused by extensively resistant *Acinetobacter baumannii*. *Diagn Microbiol Infect Dis*. 2007; 59(2):181–190. [PubMed: 17662564]
5. Metan G, Sariguzel F, Sumerkan B. Factors influencing survival in patients with multi-drug-resistant *Acinetobacter bacteraemia*. *Eur J Intern Med*. 2009; 20(5):540–544. [PubMed: 19712862]
6. Gordon NC, Wareham DW. A review of clinical and microbiological outcomes following treatment of infections involving multidrug-resistant *Acinetobacter baumannii* with tigecycline. *J Antimicrob Chemother*. 2009; 63(4):775–780. [PubMed: 19158109]
7. Munoz-Price LS, Zembower T, Penugonda S, et al. Clinical Outcomes of Carbapenem-Resistant *Acinetobacter baumannii* Bloodstream Infections: Study of a 2-State Monoclonal Outbreak. *Infect Control Hosp Epidemiol*. 2010
8. Liu C, Shih S, Wang N, et al. Risk factors of mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. *J Microbiol Immunol Infect*. 2014
9. Nutman A, Glick R, Temkin E, et al. A case-control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteremia. *Clin Microbiol Infect*. 2014

10. Kwon SH, Ahn HL, Han OY, et al. Efficacy and Safety Profile Comparison of Colistin and Tigecycline on the Extensively Drug Resistant *Acinetobacter baumannii*. *Biol Pharm Bull.* 2014; 37(3):340–346. [PubMed: 24583855]
11. Chuang YC, Cheng CY, Sheng WH, et al. 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.* 2014; 14(1):102. [PubMed: 24564226]
12. Lee HY, Chen CL, Wu SR, et al. Risk Factors and Outcome Analysis of *Acinetobacter baumannii* Complex Bacteremia in Critical Patients. *Crit Care Med.* 2014
13. Park SY, Choo JW, Kwon SH, et al. Risk Factors for Mortality in Patients with *Acinetobacter baumannii* Bacteremia. *Infect Chemother.* 2013; 45(3):325–330. [PubMed: 24396634]
14. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis. *Clin Microbiol Infect.* 2013
15. Santimaleeworagun W, Wongpoowarak P, Chayakul P, et al. Clinical outcomes of patients infected with carbapenem-resistant *Acinetobacter baumannii* treated with single or combination antibiotic therapy. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet.* 2011; 94(7): 863–870. [PubMed: 21774295]
16. Zheng YL, Wan YF, Zhou LY, et al. Risk factors and mortality of patients with nosocomial carbapenem-resistant *Acinetobacter baumannii* pneumonia. *Am J Infect Control.* 2013
17. Spellberg B, Rex JH. The value of single-pathogen antibacterial agents. *Nat Rev Drug Discov.* 2013; 12(12):963. [PubMed: 24232373]
18. Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial. *Clin Infect Dis.* 2013; 57(3): 349–358. [PubMed: 23616495]
19. Marchand, CL.; Miller, LL.; Halasohoris, JR., et al. ASM Biodefense and Emerging Diseases Research Meeting. Washington D.C.: 2013. E5564 Enhances Prophylactic Antibiotic Efficacy in a Murine Model of Inhalational Anthrax.. 2013
20. Shields RK, Clancy CJ, Gillis LM, et al. Epidemiology, Clinical Characteristics and Outcomes of Extensively Drug-Resistant *Acinetobacter baumannii* Infections among Solid Organ Transplant Recipients. *PLoS One.* 2012; 7(12):e52349. [PubMed: 23285002]
21. Cheng A, Chuang Y-C, Sheng W, et al. Excess Mortality Associated with Colistin-Tigecycline Compared with Colistin-Carbapenem Combination Therapy for Extensively Drug-Resistant *Acinetobacter baumannii* Bacteremia - a Preliminary Multicenter Prospective Study. *Crit Care Med.* 2015 in press.
22. Louie A, Fregeau C, Liu W, et al. Pharmacodynamics of levofloxacin in a murine pneumonia model of *Pseudomonas aeruginosa* infection: determination of epithelial lining fluid targets. *Antimicrob Agents Chemother.* 2009; 53(8):3325–3330. [PubMed: 19364849]