

Rationale

There have been conflicting findings for the clinical effectiveness of nebulized antibiotics for the treatment of gram-negative pneumonia in observational studies [508–535]. At least 3 clinical trials investigated the outcomes of patients with gram-negative ventilator-associated pneumonia comparing nebulized antibiotics vs placebo. All 3 trials allowed for the use of systemic antibiotics. In brief, 1 trial compared the outcomes of 100 adults with pneumonia (34% caused by *P. aeruginosa*) treated with nebulized colistin vs placebo [536]; a second trial compared the outcomes of 142 adults with pneumonia (22% caused by *P. aeruginosa*) treated with nebulized amikacin/fosfomycin vs placebo [537]; and the third trial compared the outcomes of 508 adults with pneumonia (32% caused by *P. aeruginosa*) treated with nebulized amikacin vs placebo [538]. None of the 3 clinical trials demonstrated improved clinical outcomes or a survival benefit with nebulized antibiotics compared with placebo for the treatment of ventilator-associated pneumonia, including in a subgroup analyses of patients with drug-resistant pathogens [536–538]. A meta-analysis of 13 trials including 1733 adults with ventilator-associated pneumonia indicated that the addition of nebulized antibiotics was associated with at least partial resolution of clinical symptoms of infection compared to the control group; however, there was significant heterogeneity among the pathogens involved and the definition of clinical response across studies [539]. No survival benefit, reduction in intensive care unit length of stay, or reduction in ventilator days was observed in patients receiving nebulized antibiotics [539].

Reasons for the lack of clinical benefit with nebulized antibiotics in available trials are unclear. In a PK/PD modeling study, aerosolized delivery of the prodrug of colistin to critically ill patients achieved high active drug levels in epithelial lining fluid of the lungs [540]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [541], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [542, 543]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to IV antibiotics [544–546]. The panel suggests against the use of nebulized antibiotics as adjunctive therapy for DTR *P. aeruginosa* pneumonia due to the lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and concerns for respiratory complications such as bronchoconstriction with use of aerosolized antibiotics [547].

SECTION 5: CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections pose significant challenges in healthcare settings [548, 549].

In this guidance document, for simplicity, we will use the term “CRAB” as we recognize that most clinical microbiology laboratories may not be able to accurately separate carbapenem-resistant *A. baumannii* from other species within the *baumannii* and *calcoaceticus* complex [550].

The management of CRAB infections is difficult for several reasons. First, CRAB is most commonly recovered from respiratory specimens or wounds. It is not always clear if a CRAB isolate recovered in a respiratory or wound culture represents a colonizing organism in medically complex patients who are ill due to underlying host factors (eg, patients requiring mechanical ventilation, patients with extensive burns), or a true pathogen, leading to uncertainty about the need for antibiotic therapy. For the same reason, it is challenging to determine if poor clinical outcomes with CRAB infections are attributable to suboptimal antibiotic therapy or to underlying host factors.

Second, once *A. baumannii* exhibits carbapenem resistance, it generally has acquired resistance to most other antibiotics expected to be active against wild-type *A. baumannii* leaving few remaining therapeutic options. The production of OXA carbapenemases (eg, OXA-23, OXA-24/40) mediates resistance to β -lactams including carbapenems and sulbactam [550, 551]. CRAB isolates often produce additional serine β -lactamases (eg, *Acinetobacter baumannii*-derived cephalosporinases [ADCs]), further limiting the utility of common β -lactam agents. Sulbactam resistance is driven primarily by the presence of β -lactamases but also via mutations targeting PBPs (ie, PBP1a/1b, and PBP3) [552–554]. Aminoglycoside modifying enzymes or 16S rRNA methyltransferases generally preclude aminoglycosides as treatment options for CRAB [555–557]. Mutations in the chromosomally encoded quinolone resistance determining regions generally mediate resistance to fluoroquinolones [556].

Finally, despite the number of clinical trials conducted to investigate optimal treatment regimens for CRAB infections, data supporting a prioritization of specific agents with CRAB activity or the additive benefit of commonly used combination regimens for CRAB infections remain incomplete. This guidance document focuses on the treatment of moderate-severe CRAB infections.

Question 5.1: What Is the General Approach for the Treatment of Infections Caused by CRAB?

Suggested approach: The use of an antibiotic regimen which includes a sulbactam-containing agent is suggested for the treatment of CRAB infections. The preferred regimen is sulbactam-durlobactam in combination with a carbapenem (ie, imipenem-cilastatin or meropenem). An alternative regimen is high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) in combination with at least 1 other agent (ie, polymyxin B, minocycline > tigecycline, or cefiderocol), if sulbactam-durlobactam is not available.