POINT:
Should Inhaled Antibiotic Therapy Be Used Routinely for the Treatment of Bacterial Lower Respiratory Tract Infections in the ICU Setting? Yes

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ABBREVIATIONS: BLRTI = bacterial lower respiratory tract infection; DRO = Drug Reference Online; EIB = exercise-induced bronchoconstriction; EIVCD = exercise-induced vocal cord dysfunction; FDA = Food and Drug Administration; GERD = gastroesophageal reflux disease; GNB = gram-negative bacteria; HAP = hospital-acquired pneumonia; MDR = multidrug resistant; MIC = minimal inhibitory concentration; MMAD = mass median aerodynamic diameter; MPC = mutation prevention concentration; PK/PD = pharmacokinetic/pharmacodynamic; RCT = randomized controlled trial; RTI = respiratory tract infection; UACS = upper airway cough syndrome; VAP = ventilator-associated pneumonia; VAT = ventilator-associated tracheobronchitis; WADA = World Anti-Doping Agency; XDR = extremely drug-resistant

Routine use of aerosolized antibiotics is the most rational approach to the current treatment dilemma for severe hospital-acquired pneumonia (HAP) requiring endotracheal intubation and for ventilator-associated pneumonia (VAP). The two main issues for HAP/VAP are inappropriate initial therapy and ineffective therapy for multidrug resistant (MDR) pathogens, particularly gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter* species. The emergence of extended-spectrum β-lactamases and carbapenem resistance in Enterobacteriaceae have made even common pathogens such as *Escherichia coli* difficult to treat.

The most common justification for combination antibiotic therapy for MDR gram-negative pathogens has been avoidance of inappropriate initial therapy. Such therapy has consistently been associated with worse outcomes. Increasing resistance to the β-lactam core antibiotic treatment makes any single β-lactam unreliable as monotherapy. Resistance rates as high as 40% for each of the three main β-lactam classes—penicillins, cephalosporins, and carbapenems—make combination empirical therapy mandatory in most ICUs of large teaching institutions. The most reliable second agent in institutions with high rates of MDR pathogens is an aminoglycoside. Fluoroquinolone overuse has resulted in significant resistance rates and unclear benefit for its use as combination therapy.

What that means in practical terms is that a large proportion of patients with serious HAP/VAP are being treated with the equivalent of IV aminoglycoside monotherapy. The failure rate of IV aminoglycoside monotherapy is so high that all HAP/VAP guidelines recommend against it. Unfortunately, this equivalent of aminoglycoside monotherapy is also being given during the first 3 days of therapy while awaiting culture results. This period may be critical for control of infection. Salvage therapy started after 3 days for completely inappropriate initial therapy is often ineffective. Whether this failure to rescue is true for aminoglycoside monotherapy in MDR-pathogen HAP/VAP is unknown.

The bigger concern addressed by routine aerosolized antibiotics is ineffective IV antibiotic therapy for MDR pathogens. Many clinicians are unaware of the high failure and recurrence rates of standard IV therapy for HAP/VAP. A registration trial of prolonged infusion doripenem compared with imipenem/cilastatin was stopped early for excess mortality and higher clinical failure rates in the doripenem group. Although the differences between treatments were significant, the more important point is the high failure rate in both groups. As seen in Figure 1, clinical success rates for most of the pertinent gram-negative pathogens were distressingly low. These results are likely the best-case scenario, since this and similar trials exclude patients with neutropenia, solid organ and bone marrow...
Various manipulations have been tried to improve the outcome of IV antibiotic treatment in patients with HAP/VAP. By far the most common has been combination therapy with either an aminoglycoside or a fluoroquinolone in addition to a β-lactam. Repeatedly and consistently, meta-analyses of combination therapy compared with monotherapy for HAP/VAP do not find a benefit to combination therapy; both are associated with low clinical success rates.4

Longer duration of therapy has also been suggested as a strategy to improve the outcome of antibiotic treatment of HAP/VAP.3 A large multicenter randomized controlled trial (RCT) clearly demonstrated no survival benefit to continuing therapy for 14 to 15 days compared with 7 to 8 days.5 A higher recurrence rate within 28 days of starting therapy for patients infected with P. aeruginosa and other nonfermenters in the 8-day-treatment group led some to call for longer treatment despite no difference in overall mortality (and in fact, lower mortality specifically in the nonfermenter group who underwent 8 days of therapy). However, the need for > 8 days of therapy essentially represents a failure of the original therapy, and rather than continuing a failing therapy, a switch to alternative treatment regimens is needed. Continuing therapy for 15 days significantly increases the risk of superinfection with antibiotic-resistant pathogens.

Pharmacokinetic and pharmacodynamic (PK/PD) optimization is the third strategy to address the high failure rate of current antibiotic therapy for HAP/VAP. An RCT of doripenem vs imipenem attempts to prove this strategy.3 Doripenem has a lower minimal inhibitory concentration (MIC) than imipenem for most pathogens and was given as a prolonged 3-hour infusion, both of which would result in a much longer time at greater than the MIC, the key PK/PD predictor of successful treatment with β-lactams, compared with imipenem. As seen in Figure 1, despite this apparently unfair PK/PD advantage for doripenem, excess mortality and clinical failure with doripenem forced early stoppage of the trial. Another large RCT6 and a recent meta-analysis7 confirmed that prolonged infusion does not clearly lead to better outcomes despite better PK/PD parameters.

Advantages of routine use of aerosolized antibiotics address each of the problems with current IV treatment of HAP/VAP. The greatest advantage is that levels achieved in the lung are logs greater than can be achieved by IV dosing: levels in the 5,000 µg/mL range have been achieved in BAL.8 Very few pathogens have an MIC to aminoglycosides that cannot be easily achieved locally by aerosolization. Only absolute resistance, such as Stenotrophomonas maltophilia or Proteus species for polymyxin B, would make aerosolized antibiotics ineffective.

Based on these considerations, adding aerosolized antibiotics as initial empirical therapy for patients with HAP/VAP is likely to lead to substantial bacterial killing even if β-lactam resistance is present. The risk of nephrotoxicity with combinations of other nephrotoxins will also be minimized compared with IV aminoglycosides or polymyxins. Therefore, initial empirical aerosol combination therapy is likely to achieve all the benefits demonstrated for empirical IV combination therapy.9

Use of aerosolized antibiotics also addresses the ineffectiveness of typical IV antibiotic therapy. The most likely explanation for the failure of doripenem (and imipenem) monotherapy9 is the presence of a highly carbapenem-resistant clone in the original pneumonia. Given that 10^9 to 10^10 bacteria/mL may be present in the alveolar spaces in some cases of HAP/VAP, the presence of a mutant with β-lactam resistance is highly likely. Alternatively, presence of an inducible β-lactamase may lead to a false laboratory determination of susceptibility if the sample is taken prior to exposure to a β-lactam.

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Figure 1 – Clinical outcome of selected pathogens treated with either pharmacokinetically optimized doripenem or standard-dose imipenem.
These two reasons may explain the development of carbapenem resistance during therapy in up to 50% of Pseudomonas pneumonia cases. In many circumstances, normal host defenses can control this subpopulation once the majority of bacteria are killed with antibiotics. Unfortunately, both overt immunocompromise and the immunoparalysis that is seen in many patients in the ICU, specifically those who experience nosocomial infections, may make this unreliable. Concomitant use of a different antibiotic with nonoverlapping resistance will usually address this subgroup. However, the benefit of IV combination therapy discussed earlier limit its contribution to control of these resistant subpopulations. The same limitations are not true for aerosol therapy.

The greatest hesitancy for routine use of aerosolized antibiotics is limited clinical experience. However, available data suggest that the theoretical benefits of aerosolized antibiotics can be achieved. The first RCT was limited by unclear criteria for VAP and end points, and a study population limited to patients who underwent trauma was likely to have good host immunity. However, despite no difference in their criteria for clinical cure, bacteria eradication occurred in a much higher proportion of patients receiving aerosolized aminoglycosides (68% vs 31%). A more current and pertinent study demonstrated that aerosolized ceftazidime and tobramycin were equivalent to IV therapy with the same agents, with trends toward more successful treatment and decreased antibiotic resistance developing with therapy. Two additional pilot studies demonstrated greater sterilization of airway secretions and, importantly, a lower dose of total antibiotics and fewer new antibiotic prescriptions, suggesting more effective therapy and fewer recurrences. In addition, use of aerosolized antibiotics for carbapenem resistance in Enterobacteriaceae and MDR HAP/VAP appears to have better outcomes than combination IV therapy.

Given the consistently high failure rates with even optimized IV antibiotic therapy and the increasing incidence of MDR pathogens, aerosolized antibiotics should be used routinely in patients at risk for infection with MDR pathogens. Significant further work is needed on optimization of delivery and appropriate formulations for aerosol delivery. However, given that the proportion of suspected patients with HAP/VAP without risk factors for MDR pathogen infection in some ICUs is only 10%, the need for treatment better than current IV therapy is desperately needed.

References