Nosocomial pneumonia: de-escalation is what matters

The American Thoracic Society guideline\(^1\) for management of hospital-acquired, ventilator-associated, and health-care associated pneumonia in adults is probably one of the most authoritative document for clinicians caring for patients with nosocomial pneumonia worldwide. This authority stems from the interpretation of available data for a complex issue provided by an experienced group of clinical scientists, resulting in a seemingly very differentiated and balanced set of useful recommendations. Nevertheless, the conceptual framework and recommended treatment regimens are chiefly an expert-based rather than an evidence-based statement. In *The Lancet Infectious Diseases* today, the guideline faces its worst-case scenario: adherence for treatment of patients with risk factors for multidrug-resistant (MDR) pathogens is associated with increased mortality.\(^2\) Moreover, the investigators recommend stopping of guideline implementation until a randomised trial is done.

According to the guideline,\(^1\) patients with risk factors for MDR pathogens should receive a triple regimen, with dual coverage of Gram-negative pathogens and meticillin-resistant *Staphylococcus aureus* (MRSA). The present study\(^2\) reports that, in patients in whom pathogens were subsequently identified, adherence to this recommendation resulted in a 28-day mortality of 35% in patients receiving compliant treatment and 21% in those receiving non-compliant therapy, even after adjustment for severity of illness. What reasons could account for this counterintuitive finding?

First, because triple coverage aims to include at least one drug active against an MDR pathogen to avoid excess mortality of initially inadequate treatment, comparison of the proportion of treatment regimens active against underlying MDR pathogens in both groups was crucial. However, in the study,\(^2\) initial empirical treatment was active in 81% of patients receiving compliant treatment and 21% in those receiving non-compliant therapy, even after adjustment for severity of illness. What reasons could account for this counterintuitive finding?

Second, differences between groups might be explained by timing of antimicrobial therapy. In patients with septic shock, initiation within 1 h of diagnosis is crucial for survival. Timeliness of treatment initiation was not assessed in this study.

Third, excess mortality might be related to treatment toxicity of triple coverage. Renal toxic effects are the main issue in this regard because they are the main acute toxic effect of aminoglycosides, colistin, MRSA-active drugs, and quinolones. Moreover, renal failure is an independent determinant of mortality in intensive-care units, with an increment of serum creatinine of 0.3 mg per dL or more in 48 h predicting clinical outcome.\(^3\) In today’s study,\(^2\) use of aminoglycosides and colistin was associated with an increased risk of deterioration of renal function. Furthermore, survival decreased with increasing risk-injury-failure-loss-end stage (RIFLE) score severity of renal insult. However, the number of patients with renal injury and failure on aminoglycosides and colistin was low, not consistently different from the group not receiving these drugs, and seemingly not high enough to affect outcomes.

So with detailed review, the available data might explain equivalence, but not excess mortality. Therefore, concerns about the study methods need to be addressed. A crucial issue is whether adjustment for risk of death was truly achieved. In particular, severity of illness was assessed by acute physiology and chronic health evaluation (APACHE) II score, which is of questionable validity as a stratification technique. The decision to
include only cancer and end-stage lung, heart, renal, and liver disease as comorbidities accounts for the high prognostic effect of these conditions but might not identify important differences between advanced but not end-stage conditions. Moreover, septic shock and functional status, both crucial in terms of prognosis, were not systematically assessed.

Another concern is the failure to follow a standard of microbial investigation, which might have biased the analysis of adequacy of antimicrobial treatment.

The disregard of treatment de-escalation in classification of compliance is perhaps the most serious argument against Kett and colleagues’ analysis. The authors state that in patients receiving secondary Gram-negative coverage but without pseudomonas or acinetobacter infection, the secondary agent was discontinued by day 3 in more than 50% of patients and by day 5 in 75% of patients. Similarly, MRSA coverage was discontinued by day 3 in 48% of patients without MRSA. Nevertheless, this means that around 25–50% of patients classified as compliant were actually non-compliant to guidelines in a strict sense. This misclassification is important to note because the triple-coverage approach for patients at risk of MDR is invariably linked to the notion of de-escalation of antimicrobial treatment according to microbial results.

Taken together, the validity of today’s analysis is subject to controversy. In my view, it does not provide a convincing link between pathogens (particularly MDRs), applied antimicrobial treatments, the rate of appropriate and inappropriate treatments according to pathogens isolated, the effect of treatment adequacy on clinical outcome (adjusted for severity and comorbidity), and the effect of treatment-related toxic effects on outcomes.

However, the recommended triple approach is not necessarily correct: initial dual coverage might be better in patients with septic shock and those with P aeruginosa bacteraemia and ventilator-associated pneumonia. In these patients, de-escalation (ie, monotherapy) according to culture and susceptibility results is adequate. Additionally, combination therapy can improve the appropriateness of empirical therapy in episodes attributed to extended-spectrum β-lactamase-producing or AmpC-producing Enterobacteriaceae and P aeruginosa. Conversely, superiority of dual coverage of Gram-negative enteric bacteria in haemodynamically stable patients is unresolved.

aminoglycoside combinations have been associated with a worse outcome, but the studies used dosage schedules now recognised as inadequate. The rationale for regular empirical MRSA coverage remains questionable, at least in patients who are haemodynamically stable. Overall, the triple-coverage approach in patients at risk of MDR seems insensitive to local variations of MDR prevalence and does not account for considerations about treatment restrictions in elderly and severely disabled patients. In particular, the notion of health-care-associated pneumonia is poorly supported by available data, and implies overtreatment in many patients.

All patients with septic shock, and probably severe sepsis, should receive dual coverage or triple coverage if MRSA is a concern. Whether all haemodynamically stable patients with nosocomial pneumonia need such a wide coverage is questionable; at least, de-escalation treatment is mandatory, since it reduces selection pressure, organ toxic effects, and saves money. After all, de-escalation is what matters. The definition of non-adherence to American Thoracic Society guidelines should not read “less than triple therapy” but rather “less than long-term prognosis and risk-adjusted broad coverage and de-escalation according to culture and susceptibility results”.

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I declare that I have no conflicts of interest.

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