Editorial Commentary

Antibiotic stewardship in critically ill patients with suspected ventilator-associated pneumonia

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The rapid spread of antimicrobial resistance is a worldwide problem. A multicenter international prevalence survey revealed that 70% of patients received some kind of antibiotics during their stay in the intensive care unit (ICU) (1). Because antibiotic exposure accelerates the emergence of antimicrobial resistance (2), antimicrobial stewardship is being increasingly emphasized. The key actions of antimicrobial stewardship in ICUs are optimizing antibiotic choice and minimizing the unnecessary administration of antibiotics.

Antimicrobial de-escalation is one part of an established strategy to optimize antibiotics. Numerous observational studies have elucidated the efficacy of antimicrobial de-escalation over the past decade. Recently, several systematic reviews showed that antimicrobial de-escalation reduced the use of broad-spectrum antibiotics without compromising patients' outcomes in critically ill settings (3-5). Minimizing unnecessary antibiotic administration is another essential element of antimicrobial stewardship in ICUs. For confirmed infections, limiting the duration of antibiotic administration may be an effective strategy. Recent studies suggested that the duration of therapy for most infections in critically ill patients can be reduced to 7 days or less (6). To determine the timing of antibiotic cessation, biomarkers such as procalcitonin or C-reactive protein can be used. Several randomized studies clarified that a procalcitonin-guided algorithm could reduce the duration of therapy for confirmed sepsis without worsening mortality (7). Another strategy for minimizing unnecessary antibiotic administration may be early discontinuation of antibiotics in patients in whom infection cannot be confirmed. As it is often difficult to distinguish sepsis from other noninfectious inflammatory conditions, antibiotics are frequently used for patients with presumed—but not confirmed—sepsis. A previous study reported that about 40% of patients diagnosed with sepsis who were admitted to ICUs did not actually have infections (8). To avoid unnecessary antibiotic exposure to patients without infections, it is important to confirm whether patients with presumed sepsis truly have infections. So far, however, there are few studies trying to rule out infections for presumed sepsis in the early phase of treatment.

To conquer these clinical questions mentioned above, Hellyer *et al.* (9) conducted a randomized controlled trial to evaluate whether the measurement of IL-1β and IL-8 in bronchoalveolar lavage fluid (BALF) could be used to improve antibiotic stewardship in patients with suspected ventilator-associated pneumonia (VAP). They enrolled 209 patients with suspected VAP who were assigned to a biomarker-guided recommendation group (n=103) or routine use of antibiotics group (n=106) in the intention-to-treat analysis. A protocolized bronchoscopy and bronchoalveolar lavage (BAL) were performed in all randomly assigned patients. In the biomarker-guided recommendation group, physicians were advised to consider discontinuation of antibiotics if the results were below the cut-off values for the biomarkers. In the routine use of antibiotics group, each patient received routine use of

antibiotics. Although a previous study revealed that the negative predictive value of the test for microbiologically confirmed VAP was estimated at 1.0 (10), the biomarker-guided recommendation on antibiotics did not achieve significant improvement of antibiotic-free days as a primary outcome, either in the intention-to-treat (P=0.58) or per-protocol analyses (P=0.28). The authors also found no differences for any of the secondary outcomes, including antibiotic-associated infections and 28-day mortality, between the groups.

The reported trial was unique and challenged clinical research to restrict the overuse of antibiotic agents. Evaluating IL-1β and IL-8 concentrations in BALF was a novel method to exclude microbiologically confirmed VAP with high negative predictive value on the day of the examination. However, the reduction in antibiotics was not achieved due to several assumed factors. First, the BAL assays in this trial were frequently of low quality, and thus there were more unsuccessful assays in the present study than in the previous study [22/103 (21.4%) *vs.* 7/157 (4.5%)]. Differences in the physicians' proficiency with bronchoscopic technique could also influence the rates of unsuccessful assays. The physicians managing the patients with VAP could not be well-trained in bronchoscopic techniques. A nationwide survey of the diagnosis and management of VAP revealed that 24.5% of respondents described inadequate training in bronchoscopy, and 9.5% had no training at all (11). In fact, 7 institutions in the present study reported very infrequent or no use of BAL in the usual diagnosis of suspected VAP. Second, there were fewer patients with low IL-1β and IL-8 concentrations in BALF than those in the previous study [17/103 (16.5%) *vs.* 43/150 (28.7%)]. Due to the small population with values below the cut-off, the study did not have enough power to detect the superiority of the intervention. Finally, and most importantly in our view, the biomarker-guided recommendation on antibiotics was obeyed in only 4 of 17 cases (24%), even though every physician was educated on the high negative predictive value of the test for confirming VAP. Moreover, the physicians in the present study referred not only to the protocolized suggestion based on the biomarkers (intervention), but also to the BALF culture (standard reference of VAP diagnosis). These physicians' preferences for antibiotic choice may have diluted the positive impact of interventions on the outcomes. A similar tendency was observed in another randomized control trial evaluating the efficacy of procalcitonin-guided antibiotic treatment in critically ill patients with VAP. Discouragement of the start of antibiotics and recommendations to complete antibiotics were often rejected by physicians if their patients were clinically unstable (12). The fact that recommendations to discontinue antibiotics in this trial were refused indicates difficulty in the management of suspected hospital-acquired infection in critically ill settings. Various invasions against patients make it difficult to diagnose infection correctly. Moreover, delayed or inappropriate antibiotic therapy in severely ill patients may be crucial (13,14). Inherent concern about potential infection affects the physician's decision to prescribe antibiotics. Therefore, to overcome physicians' concern and change their behavior, a validation study is needed to assess whether a biomarker-guided discontinuation strategy has no detrimental effects on patient outcomes.

Optimizing antibiotic choice and minimizing the unnecessary administration of antibiotics are two of the most important fundamental actions of antimicrobial stewardship in ICUs. Further clinical trials of both actions must be continued to confront this potentially catastrophic world health problem. Currently, we are conducting a randomized controlled trial to evaluate whether Gram stain-guided antibiotic therapy restricts the overuse of broad-spectrum antibiotics without impairing patient outcomes in patients with VAP (15). Antibiotic choice based on estimation of causative pathogens is thought to be an essential strategy to optimize antibiotics. Gram staining is a traditional method, but we have demonstrated the efficacy of Gram staining on guiding appropriate antibiotic choice (16,17). Clinical trials that improve antimicrobial stewardship will be the driving force to overcome the rapid pandemic spread of antimicrobial resistance throughout the world.

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