EDITORIAL COMMENTARY

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Which Patients Would Benefit From Antibiotic Prophylaxis: A "Burning" Question?

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(See the Major Article by Tagami et al on pages 60–6.)

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Antibiotic therapy is a double-edged sword. Since its discovery, it has saved the lives of billions of patients worldwide, but the overzealous and very often unjustified use of antibiotics has led to the appearance of several multidrug-resistant bacteria and the increasingly frequent appearance of invasive fungal infections in critically ill patients [1, 2]. Furthermore, beyond these indirect effects, antibiotics, like any drugs, have undesired side effects as well. Due to this rationale, which is also supported by large surveys, the current guidelines in several fields of medicine support antibiotic prophylaxis for a smaller group of patients than previous versions. This change was based on a review of scientific evidence, which showed that the risk of adverse reactions to antibiotics outweighs the benefits of prophylaxis for most patients, and this concept has widely been accepted and articulated in guidelines released by several societies [3, 4].

In critical care medicine, antibiotic prophylaxis has also been questioned in several fields such as perioperative care [5] and acute pancreatitis [4], as well as in patients with severe burn injuries [6]. Regarding the latter instances, there is a common feature in that there are many fewer of these patients compared with the numbers of those who undergo surgery. Therefore, to undertake large-scale prospective randomized trials in this population is extremely difficult. This is reflected by the fact that there are only a few clinical trials on burn patients, which were mainly performed in single centers with a limited number of patients; hence, robust conclusions are difficult to draw. To overcome this problem, large multicenter studies should be designed, but multicenter studies also have their serious limitations, especially in intensive care medicine [7]. Therefore, in intensive care medicine, we may have to put more effort and emphasis on large observational studies and registries on both the national and international levels.

In this issue of *Clinical Infectious Diseases*, Tagami et al report on their results extracted from the Japanese Diagnosis Procedure Combination database. They identified 2893 patients with severe burns over an almost 3-year period. Patients were divided into subgroups of those who received mechanical ventilation within 2 days after admission (n = 692) and those who did not (n = 2201). From these 2 groups they generated 2 additional propensity score–matched subgroups: 232 mechanically ventilated patients in the control (no prophylaxis) group were compared to 232 ventilated patients who received antibiotic prophylaxis. Similarly, in the nonventilated group, an additional 2 subgroups were created with 526 in each arm. There was a huge difference in 28-day in-hospital mortality between the ventilated and nonventilated patients (42.5% vs 6.7%, respectively), indicating that dividing patients into groups as defined by the need of mechanical ventilation clearly separated the whole cohort by severity. This is also underlined by the Charlson comorbidity index, indicating that approximately 55% of patients requiring mechanical ventilation had a high (≥2) comorbidity index compared with <10% in the nonventilated group.

The most interesting finding of this report is that the authors only found a significant association between antibiotic prophylaxis and 28-day mortality in mechanically ventilated patients. There was an approximate 10% difference in mortality between controls and those receiving prophylaxis both in the unmatched (48.6% vs 38.3%) and matched groups (47.0% vs 36.6%, respectively), and logistic regression and Cox regression analyses showed a significant association between the use of prophylactic antibiotics and the lower mortality. In patients without mechanical ventilation, 28-day in-hospital mortality showed no significant difference between any of the subgroups.

Most current guidelines on burn injury management and antibiotic therapy/prophylaxis either "stay put" or suggest "no antibiotics without proven infections" [6, 8]. Not giving antibiotic prophylaxis to patients with burn injuries, in general, may be beneficial for the majority of patients. Indeed, in this study by Tagami

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et al, antibiotic prophylaxis had no effect on outcome in 76% of patients. However, these were the less ill patients and, most important, did not require mechanical ventilation. On the contrary, in the sicker, mechanically ventilated subgroup, antibiotic prophylaxis might have caused a significant reduction in mortality.

As with any retrospective analysis, the study by Tagami et al has several limitations. However, as mentioned by the authors, performing large multicenter prospective randomized trials to overcome these shortcomings may not be that easy and would, in fact, be extremely difficult in patients with burn injuries. The participating centers should follow very similar approaches in all details of care, including sedation, fluid therapy, ventilation strategy, hemodynamic support, nurse to patient ratio, and so on, as all of these have a proven effect on outcome. Unfortunately, it seems naive to believe that these conditions could be fulfilled; simply recruiting more patients from more centers may dilute the data, and increase the noise-to-signal ratio, and we may end up with yet another multicenter prospective randomized trial with nonsignificant differences between the study and the control arms, reported in >70% of large trials in intensive care, especially where mortality was the primary endpoint [9]. Therefore, we agree with the authors that the data extracted from this large Japanese national database provide the best attainable evidence on this issue at present.

However, several very interesting and important questions are yet to be answered. Although mechanical ventilation served as a good indicator in dividing this cohort by severity, it may not be a sufficient (and definitely not the only) indicator of administering antibiotic prophylaxis to patients with burns. Using other tools, such as biomarkers of inflammation and organ dysfunction scores, in addition and in combination may lead us to more sophisticated care, which can lead us toward individualized patient management, when patients get what they need and not what the protocols dictate they have. It is also important to note that regarding future studies, mortality may not be the best outcome measure as it is confounded by so many factors in critically ill patients. Due to the limitations of the database in the current study, we do not know the cause of death for these patients. Finding the appropriate endpoints and designing high-quality prospective studies should be the task of future research.

Nevertheless, what we know at present should be enough to tilt the scale toward refraining from antibiotic prophylaxis in the severely burned patients in general, but considering it in those requiring mechanical ventilation. Finally, because critically ill patients are not admitted to intensive care units in large numbers, studies are difficult to design and take a long time to complete. Therefore, the Japanese Diagnosis Procedure Combination database and the message of the current analysis serves as an excellent example that registries are invaluable for clinicians. The results of the extracted data can reveal important information and facts, which can and should change our everyday practice and may improve patient outcomes.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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