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EDITORIAL

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Excessive antimicrobial usage causes measurable harm to patients with suspected ventilator-associated pneumonia

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Controversies regarding the management, optimal use of antibiotic therapy, and diagnostic methodology have spawned an accumulating body of literature attempting to address these issues. Over 300 studies have been published in peer-review journals in the past 8 years dealing with management of ventilator-associated pneumonia. A frustrating dilemma, nevertheless, is that there is no consensus on even the precise definition of ventilator-associated pneumonia. The greatest uncertainty deals with the necessity for invasive diagnostic methods, specifically quantitative cultures from the lung by bronchoalveolar lavage (BAL) or protected specimen brush (PSB). We do not wish to become embroiled in this controversy; however, it must be conceded that despite numerous labor-intensive and rigorous trials by respected investigators, no consensus exists on the necessity of such procedures, and routine use of these procedures have not widely been adopted in intensive care units.

In an editorial dealing with this thorny topic (with the wonderful title of "Is there any gold in these standards?"), Chinsky suggested a nihilistic, but pragmatic solution. Since there is no gold standard approach to even defining this entity, Dr. Chinsky wrote "Pick a definition of VAP for your institution and apply it consistently" [1]. Such is the state of affairs.

Since a consensus "definition" of VAP that can incontrovertibly diagnose pneumonia appears to be an elusive goal, we designed a study that was targeted towards clinically meaningful end-points, e.g., patient outcome, decrease in antimicrobial resistance and resource utilization that did not depend on the definition of VAP. In a randomized comparative trial [2], we limited the number and duration of antibiotics in those patients that were considered unlikely to be harmed by an approach of antibiotic restraint. This was done through the use of a clinical pulmonary infection score (CPIS) designed by Pugin et al. [3]. When the study was performed in which standard therapy (multiple antibiotics for prolonged duration) was used for CPIS >6 and experimental therapy of limiting duration (3 days) and number of antibiotics (monotherapy) was used for CPIS <6, we were gratified to find that none of the patients randomized to the 3-day monotherapy group experienced progressive infection with subsequent morbidity or mortality. Thus, the CPIS score proved cost-effective as an operational criteria in deciding which patients could receive limited antibiotic therapy. Note that no attempt was made to precisely define VAP.

The salutary effects of limiting the number and duration of antibiotics included a significantly lower incidence of infections caused by antimicrobial-resistant organisms and subsequent superinfection ($P = 0.017$), as might have been predicted. Antibiotic costs were 60% lower in the experimental vs therapy group as would be expected.

Somewhat to our surprise, the length of stay also decreased significantly ($P = 0.04$) in the 3-day monotherapy group. Patients were discharged from the ICU a mean of 5 days earlier than the patients who received standard antibiotic therapy, However, the most important finding was not emphasized in our original article; 30-day mortality was also lower for the 3-day monotherapy group. Specifically, patients who had been randomized into the standard therapy of multiple antimicrobial agents

(range 1–4) for prolonged duration (4–20 days, mean = 9.8 days), experienced a 30-day mortality of 31% vs a 30-day mortality of 13% for the 3-day monotherapy group ($P = 0.06$).

We point out that studies showing that appropriate antibiotics are necessary for optimal outcome have been quickly embraced by physicians. So, while clinicians have been successful in ensuring that appropriate antimicrobial therapy is initiated by prescribing multiple broad-spectrum antibiotics so that all possible pathogens could be covered, clinicians are not as successful at restricting antibiotics when the likelihood of infection is low. This is not necessarily the fault of conscientious clinicians who envision their primary responsibility as ensuring immediate survival of their patients; the theoretical risk of the emergence of antimicrobial resistant organisms becomes secondary and remote. To underscore this point, when an investigative group reported that they were unable to show that initial appropriate therapy for VAP was clearly associated with outcome [4], an editorialist rejected this conclusion as "not an issue for debate" [5].

It is under-appreciated that excessive broad-spectrum therapy increases mortality and morbidity. Broad-spectrum antimicrobial use leads to greater emergence of multiply-resistant organisms in patients with VAP [2, 6, 7]. Broad-spectrum empiric antibiotic therapy is initiated for most patients with pulmonary infiltrates, yet only 30–70% will turn out to have pneumonia [8, 9]. In addition, broad-spectrum antimicrobial use once initiated can easily spiral into a vicious circle [10].

In this issue of the Intensive Care Medicine, Luyt et al. present an important simulation study [11] of the utility of CPIS for the management of VAP using data from a widely-cited and rigorous study using invasive methods [12]. They showed that CPIS >6 over-diagnosed pneumonia when bronchoscopic criteria based on PBS and/or BAL was used; 69% of the patients would have been diagnosed as having VAP using a cutoff of >6 vs 44% with bronchoscopy criteria. Increasing the cut-off to >7 yielded the best accuracy for the diagnosis of VAP.

At our institution, during the conduct of the Singh protocol and the ensuing 3 years, it is noteworthy that we have not experienced a single case of a patient with an invasive infection leading to death in a patient with CPIS <6 receiving 3-day monotherapy. Our worst fear was that we might encounter a *Pseudomonas aeruginosa* pneumonia that would be treated unsuccessfully with monotherapy or a gram-negative bacteremia in which the microorganism was resistant to the monotherapy prescribed. That never happened. So, the finding of the Luyt et al. is pertinent; they show that our cutoff of CPIS >6 was overly conservative! Moreover, in a study of VAP defined by invasive methods or blood culture, Luna et al. confirmed that serial measurements of a decreasing CPIS at day 3 was predictive of a favorable outcome [13].

In our study, the most enduring impact came from the fact that physicians using this approach experienced a major behavioral change toward antibiotic usage. At the initiation of the experimental 3-day monotherapy protocol, most clinicians in the ICU were apprehensive. Although the attending physicians readily agreed with initiation of the protocol, the residents and fellows in the intensive care unit were less sanguine, especially when their first patient with pulmonary infiltrates had to be enrolled into the protocol. As one critical care physician asked us, "Would you enroll your mother in this protocol?". The anxiety among physicians gradually dissipated as patient after patient received the 3-day monotherapy with no overt disaster. Patients in the experimental group were not only faring well but were being discharged earlier from the ICU. Complete resolution of infiltrates was seen in 41% of 3-day monotherapy group vs 21% in the standard therapy group; none of the patients experienced progression of pulmonary infiltrates in the 3-day group vs 10% in the standard therapy group. Since our study was not blinded, this favorable outcome did not go unnoticed by the ICU physicians. So, as the study progressed, the physicians began to minimize both the number and duration of antibiotics as part of their standard therapy. Our study was terminated prematurely when an attending surgeon decreed that all of his patients with CPIS <6 were to receive only 3 days of monotherapy.

Based on both the Luyt study [11] and our study [2], we recommend that the Singh protocol be replicated at each individual institution before it is accepted as routine policy. The reasons are the fact that our study was terminated prematurely by the Institutional Review Board, since morbidity was unexpectedly higher in the standard therapy group, and the Luyt study was only a simulation. Moreover, the demographic profile of our patient population and the antibiotic susceptibility profile of our hospital-acquired pathogens would likely be different from other hospitals. However, we believe the most important reason to replicate the study is that the insights gained by the clinician at the bedside and the higher morbidity, and possibly mortality, seen with the current antibiotic practices will be the most powerful deterrent to excess antibiotic prescription.

If our study is replicated in other hospitals, we point out the CPIS as formulated by Pugin is not inviolate. Luyt et al. showed that the cut-off of CPIS can be increased to include more patients who could qualify for the 3-day monotherapy [11]. Fartoukh et al. showed the inclusion of gram-stain results into the CPIS improved its sensitivity [14]. Luna et al. questioned the predictive value of the leukocyte count in calculating the CPIS [13].

The antibiotic chosen as monotherapy can also be flexible based on the in vitro susceptibilities of antibiotics at the individual institution. For example, we now use levofloxacin in place of ciprofloxacin which was admin-

istered in our original study protocol because levofloxacin is pharmacodynamically superior and less expensive. Moreover, the in vitro susceptibility of levofloxacin for *P. aeruginosa* at our hospital now is now identical to that of ciprofloxacin. We selected quinolones because they have excellent activity against *Legionella*, an easily-overlooked cause of hospital-acquired pneumonia. They possess coverage against both gram-positive and gram-negative pathogens. Moreover, quinolones are less likely to induce extended spectrum beta-lactamase production in gram-negative bacteria.

On the other hand, there are some aspects of our original study that we feel should remain intact. One suggested modification of our proposal is to use combination therapy instead of monotherapy, while still limiting therapy to 3 days in patients with low CPIS. We believe this violates the spirit and intent of the study, especially since monotherapy has been shown to be adequate.

Given the results of Luyt et al., we also suggest that physicians who use invasive procedures routinely in management of VAP, should reconsider their approach. The studies by Singh et al. [2] and Luyt et al. [11] provide strong circumstantial evidence that such procedures are unnecessary for most patients with pulmonary infiltrates. After all, no invasive procedures were performed on any of our patients with CPIS <6 and their outcome was uniformly favorable. In our opinion, the simulation data from Luyt et al. suggest that quantitative cultures obtained by invasive procedures need not be routine for patients with low CPIS. We suggest that for those who believe in the superiority of invasive diagnostic methods in limiting antibiotic therapy, should confine these methods only to those patients whose CPIS is >6 (or 7).

The ICUs most likely to benefit from this protocol are those in which antibiotic-resistant *Acinetobacter,* methicillin-resistant *Staphylococcus aureus* (MRSA), and *Candida glabrata* have become endemic pathogens since they emerge under the selection pressure of prolonged broad-spectrum antimicrobial agents. Once these and other resistant organisms become endemic, spiraling empiricism sets in with addition of vancomycin for MRSA, amphotericin for *C. glabrata*, aminoglycosides for double-coverage of *P. aeruginosa*. With the widespread use of these potentially nephrotoxic antibiotic combinations, is it any surprise that renal dysfunction is fast becoming a major problem in the ICU?

The biggest problem facing the routine adoption of the Singh protocol is no longer skepticism by ICU physicians. The ICU physicians, in our hospital, have readily accepted the concept because morbidity and mortality decreased in their patients receiving the 3-day monotherapy. Given the fact that ours is a teaching program with a continual stream of new housestaff and faculty, sustained education is necessary to ensure compliance. The University of Virginia has adopted the Singh protocol as part of their clinical pathway protocol and University of Utah has placed CPIS in the Palm Pilots of their physician staff. At our hospital, this protocol is now monitored using the Toyota Production Method of Quality Control [15]. Automatic alerts occur when antibiotics for pulmonary infiltrates are being prescribed.

Finally, as critical care and pulmonary physicians recognize that excessive antimicrobial agent use causes measurable harm to their ICU patients, the day may come when a new randomized study is proposed: for patients with a low CPIS (or its modification): a) standard therapy of 3-day monotherapy vs b) an experimental approach of no antibiotics with watchful waiting and vigilant monitoring.

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