Risk stratification for the development of a subsequent pneumonia after a nondiagnostic bronchoalveolar lavage

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Background. Broncho-alveolar lavage (BAL) is an invasive bedside procedure to define type and concentration of pathologic organisms causing ventilator associated pneumonia (VAP). We evaluated if the absence of pathogens on final results represented a lavage aspect of the BAL as a therapeutic procedure to eliminate organisms.

Methods. BAL results collected from 2008 to 2009 were stratified as positive (POS) \( \geq 100,000 \text{ cfu} \), indeterminate (INT) \( < 100,000 \text{ cfu} \) pathologic organisms, or negative defined as mixed flora (MF) or sterile (STR). The INT, MF, and STR results were assessed by incidence of a subsequent POS sample.

Results. Nine-hundred forty-nine BALs performed on 490 SICU patients were interpreted as POS in 227 patients (46%). 237 non-POS patients needed a subsequent BAL. Any pathogen on the first BAL (INT group) indicates a high likelihood for subsequent BAL which will be POS. Monthly cumulative sum analysis (CUSUM) of yield was unable to identify any specific period in which BAL performance varied from trend.

Conclusion. MF and STR represent adequate sampling of secretions that are clinically benign. Any pathogen, regardless of concentration, should be considered a biomarker for future pneumonia. CUSUM analysis suggest better training in timing and indication may decrease unnecessary procedures yielding negative results. (Surgery 2011;150:703-10.)

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Ventilator associated pneumonia (VAP) is the most common serious complication in the surgery intensive care unit (SICU). It affects up to 27% of mechanically ventilated patients with mortality rates between 20% and 50%, and even as high as 70% in patients infected by multi-resistant pathogens.\(^1\)\(^\text{4}\) Unnecessary antibiotic use is one of the strongest independent predictors for the development of antibiotic resistance.\(^\text{5,6}\) Accurate confirmation of the diagnosis of VAP continues to be a challenge, because no single gold standard clinical manifestation can be used alone to verify the diagnosis, and, in turn, decrease unnecessary antibiotic therapy. Most critical care units follow a VAP diagnosis protocol similar to that proposed by Johanson et al.\(^7\) This includes new or changing consolidation signs on chest radiograph along with two of the following variables: fever greater than 38°C, bandemia, leukocytosis or leukopenia, and purulent secretions.

Clinical suspicion of VAP is confirmed with quantitative culture from a broncho-alveolar lavage (BAL) with acquisition of a bacteriologic sample that will reliably differentiate pneumonia from noninfectious causes of pulmonary inflammation.\(^\text{8-10}\) Because final cultures are not available for 48 to 72 hours, early empiric broad spectrum antibiotics are initiated and have been shown to lower mortality.\(^\text{11-13}\) To minimize antibiotic resistance while allowing full course of antibiotic therapy, VAP guidelines have suggested a strategy for de-escalation.\(^\text{14,15}\) Recent studies have shown that only 40% of quantitative cultures yield microorganism counts considered positive for VAP, resulting in 60% of patients receiving inappropriate antibiotic treatment for a nondiagnostic result, including the presence of the usual flora in the upper respiratory tract, which is termed “mixed flora.” Mixed flora is a unique identification of a BAL specimen. It comprises many different organisms at various different concentrations all
together totaling >100,000, therefore making it extremely difficult to pinpoint the particular organism to treat and thus, antibiotic treatment would be considered an inappropriate manner of treating potential pneumonia especially in critically ill patients who show nonspecific clinical signs suggesting the presence of VAP. In addition, many of the organisms reported in the mixed flora result are part of the upper respiratory tract flora, thereby representing potential colonization rather than true pneumonia. This routinely results in a repeat BAL to reevaluate bacteriologic evidence of a quantitative threshold after a diagnosis of pneumonia.

Hypothesizing that a sample obtained with any form of pathogen, regardless of concentration, should be a marker for an increased risk of future pneumonia, we compared the outcomes of patients with an initial sample containing mixed flora or a sterile sample, against samples with specific pathogens that had not reached a diagnostic threshold and monitored their potential for future pneumonia. Moreover, because unit personnel change on a monthly basis, we used cumulative sum analysis (CUSUM) trend analysis to determine whether periodic appearance of an inappropriately high rate of negative results reflected problems regarding efficacy of technique. This methodology was initially described by Page in 1954 for quality monitoring of industry procedures but statisticians have started using this methodology to detect variances in surgical procedures.

**METHODS**

With the approval of the University of Florida Institutional Review Board, we retrospectively reviewed the microbiology laboratory BAL results of all mechanically ventilated trauma patients admitted to the SICU at our Level 1 trauma center. Study patients consisted of those with clinical suspicion of VAP as defined by the appearance of a new or changing infiltrate on chest radiograph as well as at least 2 of the following: temperature >38°C or <36°C, macroscopically purulent sputum, white blood cell count >10,000 cells/mm³ or the presence of >10% bands. For each BAL performed, culture results were stratified as positive (POS) for pathogenic organisms >10% bands. For each BAL performed, culture results were stratified as positive (POS) for pathogenic organisms >10⁵ CFU/ml, intermediate (INT) containing pathologic organisms <10⁵ CFU/ml, or negative for pathogenic microorganisms. These negative BAL culture results were further defined as either mixed flora (MF) or sterile (STR). All BAL patients were initially treated empirically with broad spectrum antibiotics. Those with confirmed VAP with specific organisms >10⁵ CFU/ml were subsequently de-escalated to treatment with antibiotics tailored to the pathogen.

**BAL technique.** All patients with clinical suspicion of VAP underwent diagnostic fiber optic bronchoscopy with BAL aimed at a site determined by consolidation on chest radiograph. All BALs were attempted to be performed in a uniform manner by surgical residents, fellows, or physician assistants under the supervision of an attending surgeon within 1 hour of temperature >38°C as recommended by Surviving Sepsis guidelines. Compliance with this initiative was not monitored. After the endotracheal tube and upper trachea were suctioned to clear secretions the bronchoscope was introduced into the consolidated lung segment, and the lower airways lavaged with six 20 ml aliquots of sterile saline. The initial 20 ml sterile saline solution instilled into the lung was utilized as a waste sample to avoid culturing normal lung flora. The subsequent five 20 ml aliquots were pooled and sent to the microbiology laboratory for gram stain, and quantitative aerobic culture. After completion of any BAL all patients were placed immediately on broad spectrum empiric antibiotics. Preliminary and final reports of the colony morphology and quality were inspected at 24–72 hours. Gram stain and preliminary cultures were not use for de-escalation of antibiotic therapy as evidence has shown that these are not useful in determining final culture result. Based on the extensive work from Croce et al., a threshold of >10⁵ CFU/ml was considered confirmatory of bacteriologic diagnosis of VAP. When the final pathogen was elucidated, de-escalation of antibiotic therapy was instituted. Cultures with mixed flora >10⁵ CFU/ml were considered VAP and treated according to the preference of the attending surgeon’s assessment of the overall clinical status of the patient during the early part of the study. Review of our data showed that mixed flora >10⁵ showed that this was unnecessary and so approximately after July 2009 antibiotics were stopped if this was found on the final culture. All patients were evaluated for any further need for BAL or subsequent diagnosis of VAP.

**Data analysis.** To assess the clinical relevance of INT, MF, and STR, the incidence of need for subsequent BAL and POS yield of that subsequent BAL were evaluated for each group. Time interval between initial and subsequent BAL was calculated. Intervals less than 7 days, in which the first BAL produced either MF or STR, were analyzed to determine potentially inadequate technique as manifest by the immediate follow-up BAL yielding a POS result. Incidence of subsequent POS was
evaluated by comparing INT to MF and STR using the chi-square test. Alpha was set at .05.

Data was then re-stratified by patient specific sequences of repeated BAL to track the yield of INT through subsequent BAL results. Proportion of distribution of each category for patients’ second, third, and fourth BAL was compared by ANOVA. BAL results for patients with a POS result on third BAL and an initial INT result on the previous 2 BALs were traced back to assess presence of the POS organism in those previous 2 BALs. Finally, CUSUM of monthly positive (POS) yield over time was evaluated to determine whether periodic change in SICU personnel was associated with a definable change in proportion of positive yield, or incidence of repeat BAL within 7 days after an initial negative isolate.

RESULTS

Nine hundred forty-nine BALs performed on 490 SICU patients from 2008–2009 were retrospectively analyzed. All patients evaluated were trauma patients with no concurrent urinary or blood infection identified at the time of bronchoscopy. All BALs were attempted to be performed by a resident physician, fellow, or physician assistant under attending faculty supervision within 1 hour of a patient developing a temperature of 38°C. Initiation of antibiotics after a BAL was based on the clinical status of the patient and the quality of the BAL specimen obtained from the procedure. Decision of antibiotic initiation was carefully considered by the attending physician to prevent any resistance as well as to limit financial waste. Of the 490 patients, 227(46%) were interpreted as POS and confirmatory of VAP. Negative results, as indicated by STR or MF were recorded in 58 (11.9%) and 90 (18.3%) patients, respectively. INT results were identified in 115 patients (23.7%).

Table I illustrates the distribution of the subsequent BAL in patients. The majority of MF patients (58 of 90, 64%) and 27 of 58 (47%) STR patients portended a benign course, and did not require any additional BAL. Only 32 MF patients (36%) required further testing while 31 (53%) STR patients required a subsequent BAL undergoing additional evaluation. Additional BALs in the MF and STR samples were performed at various times. Assessment of the initial inadequacy of the procedure by specifically focusing on the STR and MF results, which was associated with a repeat BAL within 7 days, demonstrated a similar incidence of the need for a subsequent BAL. For the MF group, 19 of 32 (59%) patients and for the STR group 11 of 31(35%) patients required a repeat BAL within 7 days. This collection of samples from the MF and STR groups defines our false negative rate following the initial BAL and represents only 2.8% of all BAL performed during the study period. The fact that almost half of these 2 groups underwent repeat BAL later than 7 days in their SICU stay suggests that clinical assessment for possible VAP stimulated the decision to repeat the BAL, rather than an initial poor quality sample that represented a false negative BAL or inadequate treatment of VAP.

Unlike the MF and STR group, the INT group showed significant difference in its future outcome. A major portion of the patients, 98 of 115 (85%), were associated with ongoing clinical evidence of pneumonia requiring further evaluation with BAL. With resumption of clinical signs of infection, broad spectrum antibiotics were initiated once more after sending blood and urine cultures and performing a bronchoalveolar lavage. In our SICU setting, patients who have been on ventilator support and require a prolonged intubation and repeat bronchialveolar

<table>
<thead>
<tr>
<th>Table I. Proportions of results for 3 subsequent BAL in patient study group and proportion of INT cohort of each BAL</th>
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<td>Patients</td>
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<td>n = 490</td>
</tr>
<tr>
<td>BAL 1</td>
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Surgery Volume 150, Number 4 Qureshi et al 705
lavages are more susceptible of having infectious processes and would benefit from empiric antibiotic treatment. However, our SICU policy strictly follows the threshold that has shown successful results from the critical care team at the University of Tennessee at Memphis for diagnosing ventilator associated pneumonia.

In contradistinction to both the MF and STR groups, presence of subthreshold quantities of any pathogen portended a higher likelihood of a subsequent BAL yielding a POS sample at some point during the SICU stay of the patient (Table I). Again, possibly reflecting clinical suspicion that the INT result reflected inadequate quality of the initial BAL, 48 of the 131 repeat BALs (37%), were conducted within 7 days of the initial study. Table II details progression of first, second, and third BAL results for the study group of 486 patients, which accounts for eight of the original 494 patients who were admitted to SICU twice as individual patient encounters. The proportion of results for the 486 patients who underwent initial BAL, the 237 of this group who received a second BAL, and the 116 who required a third BAL indicate a similar distribution of results for each study. Moreover, sub-cohort analysis of the INT group for outcome of a subsequent BAL also reflects a similar distribution of results (Table II). The majority of yield of these repeated BAL in the INT group cohort were either POS or INT. ANOVA of both the 3 repeat BAL groups and those of the INT cohorts demonstrated no differences and a high correlation among distribution of results categories (R = .94). The incidence of patients who did not require repeat BAL after BAL 2 and BAL 3, as well as in the respective INT groups, emphasizes that the decision to repeat the BAL was based on clinical assessment, rather than collection of an initial poor quality BAL specimen or inadequate treatment of VAP. Since 85% of intermediate specimens required further studies and of which one third were found to actually have a diagnostic specimen, further infections were critical in allowing identification of the most precise organism causing pneumonia. This further elucidation allows appropriate antibiotic utilization and proper treatment of pneumonia in a timely manner.

To assess the potential for quorum sensing or progression of INT category organisms to VAP, patients whose third BAL was POS after 2 preceding INT results were evaluated (Table II). Only 5 patients (1%) followed this specific clinical course. Average time interval between the initial BAL and BAL 2 and 3 was 7.2 and 9.4 days, respectively. Time from original BAL to VAP confirmation via INT ranged from 6 to 28 days, mean = 16.6. Four of these patients developed Pseudomonas aeruginosa VAP, of who only two had the same organism at 85,000 and 20,000 cfu/ml respectively in BAL 2 only. The fifth patient developed H. influenza VAP with no evidence of the organism in the first or second BAL.

Monthly CUSUM analysis of incidence of positive yield demonstrated an inconsistent curve that could not define any reliable relationship with incidence of positive yield and various personnel assigned to the SICU for specific monthly intervals (Fig). This inconsistency may represent an

### Table II. Progression of BAL in specific patient group to trace potential emergence of causative organism in BAL 3. Note similarity of results for initial POS group

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<thead>
<tr>
<th></th>
<th>BAL1 N = 490</th>
<th>BAL2</th>
<th>BAL3</th>
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<tr>
<td><strong>Patients</strong></td>
<td>None 114 51%</td>
<td>POS 33 15%</td>
<td>INT 59 26%</td>
</tr>
<tr>
<td>POS</td>
<td>POS 227 46%</td>
<td>MF 8 4%</td>
<td>MF 5 9%</td>
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<tr>
<td>MF</td>
<td>Str 90 18%</td>
<td>Str 10 5%</td>
<td>Str 2 3%</td>
</tr>
<tr>
<td>Str</td>
<td>INT 58 12%</td>
<td>None 61 53%</td>
<td>POS 24 21%</td>
</tr>
<tr>
<td>INT</td>
<td>INT 115 24%</td>
<td>MF 7 6%</td>
<td>INT 14 24%</td>
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<table>
<thead>
<tr>
<th></th>
<th>None 25 42%</th>
<th>POS 13 22%</th>
<th>INT 5 9%</th>
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<tbody>
<tr>
<td><strong>None</strong></td>
<td>POS 0 0%</td>
<td>MF 0 0%</td>
<td>Str 0 0%</td>
</tr>
<tr>
<td><strong>POS</strong></td>
<td>INT 4 20%</td>
<td><strong>INT</strong> 4 20%</td>
<td><strong>POS</strong> 5 25%</td>
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<tr>
<td><strong>MF</strong></td>
<td><strong>INT</strong> 4 20%</td>
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objective performance metric that will drive better consistency in preventing unnecessary BAL.

DISCUSSION

Evaluation of the incidence of pneumonia in ventilated trauma patients in the surgical intensive care unit has revealed an interesting finding in the course of nondiagnostic specimens we define as intermediate (INT). With diagnosis of VAP being confirmed with >10^5 CFU/ml in our SICU, INT samples represent pathogenic organisms that have not reached the threshold of pneumonia. An overwhelming majority of the INT samples, 85%, required a repeat BAL study with confirmatory studies of pneumonia in up to 30%. Mixed flora, representing a collection of various upper respiratory tract organisms, and sterile samples portended a benign clinical course with 64% and 47% respectively requiring no further clinical management and indicating no future clinical signs of pneumonia. Quality control evaluation with CUSUM analysis revealed no relationship between incidence of positive BAL results and the personnel performing the procedure.

Confirmation of the diagnosis of ventilator associated pneumonia continues to be a challenge for clinicians in the SICU. Multiple cofactors, such as sputum colonization or fluid shifts, can falsly be categorized as infiltrates on radiographic imaging, leading to improper antibiotic utilization. Previous studies have indicated the importance of early diagnosis to avoid morbidity or even mortality.9,10,20,22 Broncho-alveolar lavage has been verified as a useful adjunct in the armamentarium of a clinician to accurately highlight the pathogen causing the infectious process.

The utility of the BAL lies not only in its ability to provide a specific pathogen, or in certain circumstances a variety of pathogens, but also to confirm the diagnosis of VAP. The threshold of >10^5 CFU/ml of specific organisms obtained via BAL can be a guideline for proper antibiotic treatment. Even though many ICUs use this threshold of >10^5 CFU/ml for diagnosing VAP, the appropriate threshold for diagnosis by quantitative BAL methodology has not been established. In human studies, histologic evidence of pneumonia has shown various degrees of bacterial burden associated with increasing severity of histologic lesions; however, no bacterial cutoff could differentiate the histologic presence or absence of pneumonia. Because quantitative BAL has an acceptably low false positive or negative rate, and is cost effective, we have used a threshold of >10^5 CFU/ml to minimize our VAP false negative rate.22 When final cultures do not confirm a positive result, broad spectrum empiric antibiotics initiated immediately after BAL are discontinued, usually at 72 hours after completion of the BAL. Whether this “short burst” of broad spectrum antimicrobial therapy after a bronchial lavage actually avoids progression to more severe pneumonitis and respiratory failure is conjectural.

Mixed flora and sterile samples are 2 results with no clinical relevance to VAP. A previous study by our group evaluating mixed flora showed that antibiotic treatment for this subset of samples provides no clinical benefit.21 Therefore, any form of therapy is counter-productive and the sample should be considered a negative result. Based on the findings from our previous study this investigation further examines INT samples to evaluate the future course of these groups in the ventilated patient. While the MF and STR results represent a sampling of secretions that portend a benign clinical course, analysis of the INT samples indicates quite clearly to be a higher likelihood of later VAP, if clinical symptoms persist. Because many of these patients did not require additional BAL, it is possible that the same “micro burst” of broad spectrum antibiotics after lavage may have been adequate therapy. The INT groups consist of specific pathogens that have not reached a quantitative threshold of >10^5 CFU/ml. As evident by our analysis, an overwhelming majority of INT samples, 85%, required further testing with subsequent POS result at some point during the SICU stay of the patient. It is intriguing to speculate that this higher likelihood of progression to VAP represents proliferation of a specific microorganism to diagnostic levels of 10^5 CFU/ml. In fact, review our POS culture results from BAL 1 and BAL 2 do not confirm this, and actually suggest emergence of a common opportunistic organism in what is obviously an immune stressed host. Although this cohort is far too small to support any inferential conclusion, Pseudomonas is known to have quorum sensing capabilities, which may be reflected by the fact that 2 of the

Fig. CUSUM analysis of BAL yield over monthly time periods during 2 years.
4 VAP did have the organism in the immediately preceding BAL.

Another point of controversy surrounds the appropriate threshold for diagnosing VAP using BAL; we feel the data from Croce et al represents the best data on this topic. Lowering the threshold to $>10^4$ CFU/ml has been shown to result in over-use of broad spectrum antibiotics which can result in resistant organisms, superinfection, and excess charges for patients while not reducing morbidity or mortality. As such, this study was not designed to analyze the different diagnostic thresholds in making the diagnosis of VAP.

An unexpected finding from this analysis is the consistent distribution of result categories, regardless of timing or results of previous BAL. Even the cohort of specific patients who were tracked through their third BAL demonstrated similarity of proportion of results for BALs 1 and 2. In fact, assessment of the patients with an initial POS who underwent repeat BAL demonstrated the same distribution of results. This suggests that the main impetus for determining need for repeat BAL is clinical assessment rather than persistence of an incompletely treated organism. It also suggests that the INT result should not be ignored, even though it has not reached the quantitative value to be labeled as VAP. It should be considered a biomarker of increased VAP risk and possibly lower the clinical threshold for repeat BAL.

Because timely cultures from BAL are a cornerstone of proper pneumonia treatment, proper BAL techniques are paramount to retrieving appropriate samples. CUSUM analysis of our monthly POS rate reflects inconsistencies in our BAL yields. This suggests a need for more standardization of protocols to define indications and timing of BAL. Better understanding of these protocols will most definitely decrease unnecessary BAL procedures, if the performance metrics remains focused only on POS findings. As is suggested by the consistent incidence of patients who do not need subsequent BAL after first, second, or third studies, true “positives” may actually be those in whom VAP is confirmed, and those whose BAL and 3 days of empiric antibiotics produce resolution of the clinical findings that stimulated need for BAL. In other words, true efficacy is related to proper timing of a procedure that provides both appropriate therapy and accurate diagnosis.

The major limitations of this study include its retrospective design and lack of randomization as well as patient limitation to trauma patients. Given the immunologic effects of injury, it is difficult to say whether these results can be extrapolated from trauma patients with critical injury to other types of surgical patients requiring admission to the surgical intensive care unit for mechanical ventilation; therefore, further study of surgical patients seems warranted. Potential selection bias and un-evaluated differences may introduce confounding variables. Moreover, length of follow-up was limited to observation only while the patient was in the intensive care unit. A longer follow-up with regards to infection recurrence or mortality rates may provide more insight into culture results and treatment effectiveness. Finally, we did not examine culture results to determine concurrent infections and antibiotic use for these other nosocomial infections. A prospective study could take this into account.

Nevertheless, what started as a performance assessment to evaluate the incidence of potentially unnecessary BAL has demonstrated that timely BAL based on clinical assessment of need is therapeutic in almost half of cases, confirmatory of VAP (POS) approximately 46% of the time, and indicative of increased risk of emerging VAP in another 23%. When the benign clinical course associated with MF and STR is factored in, the true “yield” of BAL is quite high. Like all things related to critical care of the seriously ill patient, astute clinical assessment remains the major determinant of efficacious timing of BAL.

REFERENCES

DISCUSSION

Dr Jeffrey Claridge (Cleveland, OH): I first would like to applaud you in trying to study a very difficult issue. For those of us who are surgical intensivists and trauma surgeons, we spend a tremendous amount of time trying to diagnose infections, and pneumonia is the hardest of these to diagnose accurately. The system is inefficient and costly.

As you have pointed out in your article, the use of bronchoalveolar lavage (BAL) has a role in diagnosing and directing the treatment of ventilator-associated pneumonia (VAP). Fortunately, I come from the Dr Gross/Fabian VAP training camp. I spent 2 years there. And I believe in the results of BAL, and I recognize 1 of your co-authors, Dr Kerwin, is a prior Fabian/Cross disciple.

In saying that, I do have several questions. First, I am a little concerned about the assumption that you make that if no BAL was done, you had clinical resolution of symptoms. Do you have any clinical data to support that or refute that?

Likewise, you describe the indications for new fever as an indication of BAL. Within 1 hour, you actually talk in your manuscript about obtaining a BAL. Do you really do this all hours of the week and every day? Do you have measurements of your protocol compliance? In other words, if you see what you are concerned about on morning rounds or afternoon rounds for a new pneumonia, do you really get a BAL? And do you measure your compliance rate with that?

You start antibiotics on all patients who get a BAL. Then why do you not use preliminary quantitative cultures, which is recommended by the Fabian and Cross group, to deescalate your treatment much sooner than 3–4 days? The preliminary results typically come back within 24–36 hours.

You discuss the term “MF.” I am curious to know if you consider >100,000 of mixed flora that are obtained distally from a BAL not to be a pneumonia. So MRSA, for example, obtained in a distal bronchial tree is not considered a pneumonia for your group.

Last, you considered everything between 100,000 and 100 to be intermediate or negative. Do you look at the difference of grouping, that is, 10^3 versus 10^4, as we have heard in some of the discussions earlier today? This would actually be very useful in your paper and may actually give you extra ability to say 10^4 are at high risk for developing pneumonia, 10^3 is not.

Dr Irfan Qureshi (Jacksonville, FL): Answering your first question about clinical evidence, we follow patients on whether or not they have a fever. That is the main indication that we use to whether or not they require BAL. Obviously, there is no evidence to show what the exact role is in that, but our most important aspect of whether or not to undergo a BAL is a fever, a temperature.

Do we use empiric antibiotics? We do utilize empiric antibiotics within that time period until we have final results, which take 48–72 hours. We are very aggressive in terms of deescalating the antibiotic therapy when the final results do occur. But sometimes we do use clinical judgment and see whether or not we need further therapy.

To answer your other questions, if we have studied other samples with <10^3, this is a policy that we use from the Memphis group, and that is what has been shown to be the most effective. However, we have not looked at that, and that is something that we can definitely include in our future evaluation.

Dr Timothy Pitts (Cincinnati, OH): As Dr Claridge pointed out, this is a really tough clinical problem and consumes a significant amount of mental, physical, and economic time and resources in the care of intensive care (ICU) patients. And we spend a lot of times on
rounds, probably too much time, trying to figure out simply if the patient has pneumonia or not.

So I applaud the authors in really trying to tackle the intermediate group, that $10^4$ to $10^5$ group, as well as potentially the mixed flora, and even the people who we assume do not have pneumonia based on our early BAL.

Having said that, I have a couple of questions for you. The first is, you limited this study to trauma patients. Unfortunately, as we all know, trauma patients are not the only ones in the surgical ICU who end up with VAP and prolonged ventilator stays. Do you think you can extrapolate your results to a broader patient population? Do you think you can apply this to the nontrauma ICU patient?

Second, you note that 85% of your patients who were in the intermediate group after the initial BAL had ongoing clinical signs and symptoms of pneumonia and required repeat BAL, and sometimes a third BAL as well. And that the majority of these were either positive or intermediate. Were each of these associated with the resumption of empiric antibiotic therapy for your 72-hour window?

And if so, would it be better for us simply to lower our clinical and quantitative threshold down to $10^4$, down to $10,000$ bacteria, and treat all of these? Because, if you are doing 3 BALS, they are all receiving 9 days of antibiotic therapy anyway in this patient population, it may be more efficacious just to treat the pneumonia up front for a short course, say 5–7 days, and be done with it, without requiring repeat BAL.

You also note the Pseudomonas. Of the patients who required ≥2 BAL, Pseudomonas was the most common bug that was cultured, as you noted in the manuscript. Have you had the opportunity to analyze the second BAL group to see whether you should just empirically treat for a given bug based on the first BAL that you do?

And finally, you noted in your conclusion slide that you think that the volume that was used in your lavage may be sufficient to induce a microbiologic or clinical change in this. Do you really think that you are using enough volume to lavage out the “evil humor,” so to speak?

Dr Irfan Qureshi: We limited the study to the trauma patients because the majority of our surgical ICU patients are trauma. However, as you know, trauma patients are very different from general surgery patients, their responses are different.

However, these results, I do not think we can extrapolate to that population. That would necessitate an entirely different study. And at this point, we have not studied those patients. Whether or not the patients with the intermediate sample—and as you have seen, a lot of those patients required subsequent BAL because they continued to show signs of pneumonia. We do not have data to see whether or not they fully responded, but the 2–3 days of antibiotic therapy, if the results were not diagnostic, we did deescalate the therapy. But we would have to look closer whether or not their signs did improve after a few days of therapy.

And as far as the question about the Pseudomonas from the bacteria in the subsequent BALs, we are actually in the process of breaking that data down and looking at it even further to see what the further bacteria on the subsequent BALs are. And hopefully, we will get back with that answer.

And whether or not we send enough volume, I do not have any data on whether or not the amount that we sent is enough to extrapolate the correct organism. We just do not have the data for that right now.

Dr Frederick Luchette (Maywood, IL): A real quick question. As you know, multiply injured patients have multiple reasons to have prophylactic antibiotics on board, like intracranial pressure monitors, open fractures, and so forth. Could that have possibly accounted for the clearance of the BALs on the subsequent BALs? Do you have any information on what type of antibiotics they were on?

Dr Irfan Qureshi: We do have various different patients who are started on broad-spectrum antibiotics. Whether or not that would be enough to clear the organisms that might be potential pathogens, we do not exactly have the answer for that.

However, as you can see from the patients who had mixed flora in sterile sample, 2–3 days of antibiotic therapy and the lavage were enough to not warrant any further therapy. But to see whether or not that few days of antibiotic therapy is enough is something that is very interesting. And we just do not have the answer for that yet.