BRIEF REPORT

OPEN

Lower Respiratory Tract Coinfection in the ICU: Prevalence and Clinical Significance of Coinfection Detected via Microbiological Analysis of Bronchoalveolar Lavage Fluid With a Comparison of Invasive Methodologies

Casey S. Zelus, MD[1]
Michael A. Blaha, MD[2]
Kaeli K. Samson, MA[3]
Andre C. Kalil, MD[1]
Trevor C. Van Schooneveld, MD[1]
Jasmine R. Marcelin, MD[1]
Kelly A. Cawcutt, MD, MS[1]

OBJECTIVES: Pneumonia remains a significant cause of morbidity and mortality, with increasing interest in the detection and clinical significance of coinfection. Further investigation into the impact of bronchoalveolar lavage (BAL) sampling methodology and efficient clinical utilization of microbiological analyses is needed to guide the management of lower respiratory tract infection in the ICU.

DESIGN: Retrospective observational study.

SETTING: ICUs at a single center between August 1, 2012, and January 1, 2018.

PATIENTS: Mechanically ventilated adult patients who underwent BAL testing during an ICU admission were included.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: BAL methodology (bronchoscopic vs nonbronchoscopic), microbiological diagnostic testing, and clinical outcomes measures were obtained. Chi-square or Fisher exact tests assessed associations between categorical variables, whereas Kruskal-Wallis tests analyzed differences in distributions of measures. BAL samples from 803 patients met inclusion criteria. Coinfection was detected more frequently via bronchoscopic BAL compared with nonbronchoscopic BAL (26% vs 9%; $p < 0.001$). Viruses were detected more frequently in bronchoscopic (42% vs 13%; $p < 0.001$) and bacteria in nonbronchoscopic (42% vs 33%; $p = 0.011$) BALs. A positive correlation between mortality and the number of organisms isolated was identified, with 43%, 48%, and 58% 30-day mortality among those with 0, 1, and more than 2 organisms, respectively ($p = 0.003$). Viral organism detection was associated with increased 30-day mortality (56% vs 46%; $p = 0.033$).

CONCLUSIONS: Even in the setting of standardized institutional techniques, retrospective evaluation of bronchoscopic and nonbronchoscopic BAL methodologies did not reveal similar microbiologic yield in critically ill patients, though bronchoscopic BAL overall yielded more organisms, and occurrence of multiple organisms in BAL was associated with worse outcome. Prospective data are needed for direct comparison of both methods to develop more standardized approaches for use in different patient groups.

KEY WORDS: bronchoalveolar lavage; coinfection; critical care; diagnostic microbiology; lower respiratory tract infection

Lower respiratory tract infections (LRTIs) were the most common cause of infection-related mortality and the fourth most common cause of death in 2019 according to the World Health Organization (1). Pneumonia due to simultaneous infection by bacterial and viral respiratory pathogens, termed

DOI: 10.1097/CCE.0000000000000708

"co-infection," has emerged as a growing area of interest (2), with reports that coinfection complicates nearly 40% of cases, and is associated with increased rates of mechanical ventilation, morbidity, and mortality (3–5). Noninvasive methods including sputum or endotracheal aspirates remain recommended in the diagnostic evaluation of LRTI due to tolerability, safety, and ease of acquisition (6). Nevertheless, lower contamination rates and fewer false positives have been reported with more invasive methods like bronchoalveolar lavage (BAL) (7–10). Nonbronchoscopic BAL is a unique technique, bridging the divide between noninvasive respiratory sampling techniques and traditional bronchoscopic BAL (11). Microbiologic yield from nonbronchoscopic BALs appears to be comparable with bronchoscopy while being less invasive and more affordable, although a few studies directly compare the two methods (11–16). We aimed to compare the diagnostic utility of bronchoscopic and nonbronchoscopic BALs among ICU patients and evaluate these methods with respect to the isolation of specific pathogen types.

MATERIALS AND METHODS

Study Design, Patient Population, and Procedural Methodology

We performed a single-center retrospective analysis of mechanically ventilated adult ICU patients with a BAL sample per standard organizational techniques (traditional bronchoscopic or nonbronchoscopic, utilizing telescopic catheters. See Supplemental Material, http://links.lww.com/CCX/B4, for further details) and at the clinical discretion of the intensivist between August 1, 2012, and January 1, 2018. Exclusion criteria included age less than or equal to 19 years, no microbiologic testing performed, non-ICU level of care, and documented brain death at the time of BAL. Only the first BAL sample meeting inclusion criteria were used.

Immunocompromised was defined as malignancy-receiving chemotherapy or radiation, history of organ transplant, HIV, or immunosuppressive medication use. BAL-detected organism types were classified into acid-fast bacilli (AFB), bacteria, fungi, and viruses. Bacterial, fungal, and AFB detections were defined by growth on respective media and viral detection by polymerase chain reaction (PCR; plus culture for cytomegalovirus). Infection categories were defined as no infection, monoinfection, and coinfection corresponding to the detection of zero, one, and greater than or equal to two organism types from the BAL sample, respectively. Diagnostic testing for pathogens (described in **Supplemental Table 1**, http://links.lww.com/CCX/B4) was performed at the discretion of the ordering physician. This study was approved by the University of Nebraska Medical Center Institutional Review Board (Protocol 841-18-EP).

Outcome

The primary outcome was the diagnostic yield of bronchoscopic and nonbronchoscopic BAL methodologies to assess for microbiologically detected coinfection among critically ill adults.

Statistical Analysis

Categorical variables were assessed using chi-square tests, Fisher exact tests, or Mantel-Haenszel chi-square tests, as appropriate. *T* tests were used, unless significant skew was present, in which Wilcoxon rank-sum tests were used. Kruskal-Wallis tests were used for categorical examination of differences in distributions of measures of length of stay (LOS). Logistic regression was used to account for confounding with BAL type and immunocompromised status as predictors. All analyses were performed using SAS software Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and BAL Characteristics, and Epidemiology of LRTI

Demographic characteristics of 803 BAL samples meeting inclusion criteria are shown in **Table 1**. Organisms were detected in 62% of BALs, with 19% having coinfection. The most frequently identified organisms of each type were *Staphylococcus aureus* (n = 92), *Mycobacterium arupense* (n = 9), *Candida albicans* (n = 173), and Epstein-Barr virus (n = 73) (**Supplemental Table 2**, http://links.lww.com/CCX/B4).

BAL Sampling Methodology and Microbiologic Yield

Bronchoscopic and nonbronchoscopic methodologies were employed in 58% (n = 461) and 42% (n = 339) of patients, respectively. Organism detection significantly

TABLE 1.
Baseline Characteristics of ICU Patients With Bronchoalveolar Lavage Fluid Obtained for Analysis

Characteristic	All Bronchoalveolar Lavages (*n* = 803)	Bronchoscopic, 57.6% (*n* = 461)	Nonbronchoscopic, 42.4% (*n* = 339)	*p*
Age, yr, mean (SD)	58.3 (15.8)	57.3 (16.3)	59.7 (15.0)	0.04[a]
Sex, *n* (%)				
Female	283 (35.2)	171 (37.1)	111 (32.7)	0.20
Male	520 (64.8)	290 (62.9)	228 (67.3)	
Ethnicity, *n* (%)				
Hispanic	35 (4.4)	26 (5.6)	9 (2.7)	0.04
Non-Hispanic	768 (95.6)	435 (94.4)	330 (97.4)	
Race, *n* (%)				
Asian	14 (1.7)	9 (2.0)	5 (1.5)	0.18[b]
African American/Black	68 (8.5)	33 (7.2)	35 (10.3)	
American Indian/Alaska Native	8 (1.0)	5 (1.1)	3 (0.9)	
White	680 (84.7)	392 (85.0)	285 (84.1)	
Native Hawaiian/Pacific Islander	2 (0.3)	0 (0)	2 (0.6)	
Other/refused/unknown	31 (3.9)	22 (4.8)	9 (2.7)	
Host immune status, *n* (%)				
Immunocompetent	606 (75.5)	319 (69.2)	285 (84.1)	< 0.0001
Immunocompromised	197 (24.5)	142 (30.8)	54 (15.9)	
Infection, *n* (%)				
0	307 (38.2)	147 (32.0)	160 (47.2)	< 0.0001[c]
1	345 (43.0)	193 (41.9)	150 (44.3)	
2+	151 (18.8)	121 (26.3)	29 (8.6)	

[a]Independent samples *t* test.
[b]Fisher exact test.
[c]Mantel-Haenszel χ^2.
Data are presented as *n* (%) and *p* values for comparison between bronchoscopic versus nonbronchoscopic generated from chi-square tests unless otherwise indicated.

differed between the two methodologies ($p < 0.0001$), with a higher proportion of bronchoscopic BALs detecting organisms on microbiological analysis (68% vs 53%), including higher rates of coinfection (26% vs 9%), compared with nonbronchoscopic BALs (**Fig. 1*A***). Bacteria were more frequently isolated from nonbronchoscopic BAL (42% vs 33%; $p = 0.011$), whereas bronchoscopic BALs had higher rates of viruses detected (42% vs 13%; $p = < 0.0001$) (**Fig. 1*B***). There was no difference in rates of isolation for AFB and fungal organisms by BAL methodology. An increased proportion of immunocompromised patients underwent bronchoscopy compared with immunocompetent patients (31% vs 16%; $p < 0.001$), and immunocompromised patients were less likely to have bacteria isolated (21% vs 42%; $p < 0.0001$) and more likely to have viruses isolated (44% vs 27%; $p = 0.0001$). In a subgroup analysis of only immunocompromised patients, those undergoing bronchoscopic BAL had a significantly increased odds of having viruses isolated (2.91 [95% CI, 1.22–6.95]) and a significantly decreased odds of bacterial isolation (0.36 [95% CI 0.17–0.74]), relative to those undergoing nonbronchoscopic BAL.

Clinical Outcomes

There was a significant association between mortality and number of organism types detected by BAL

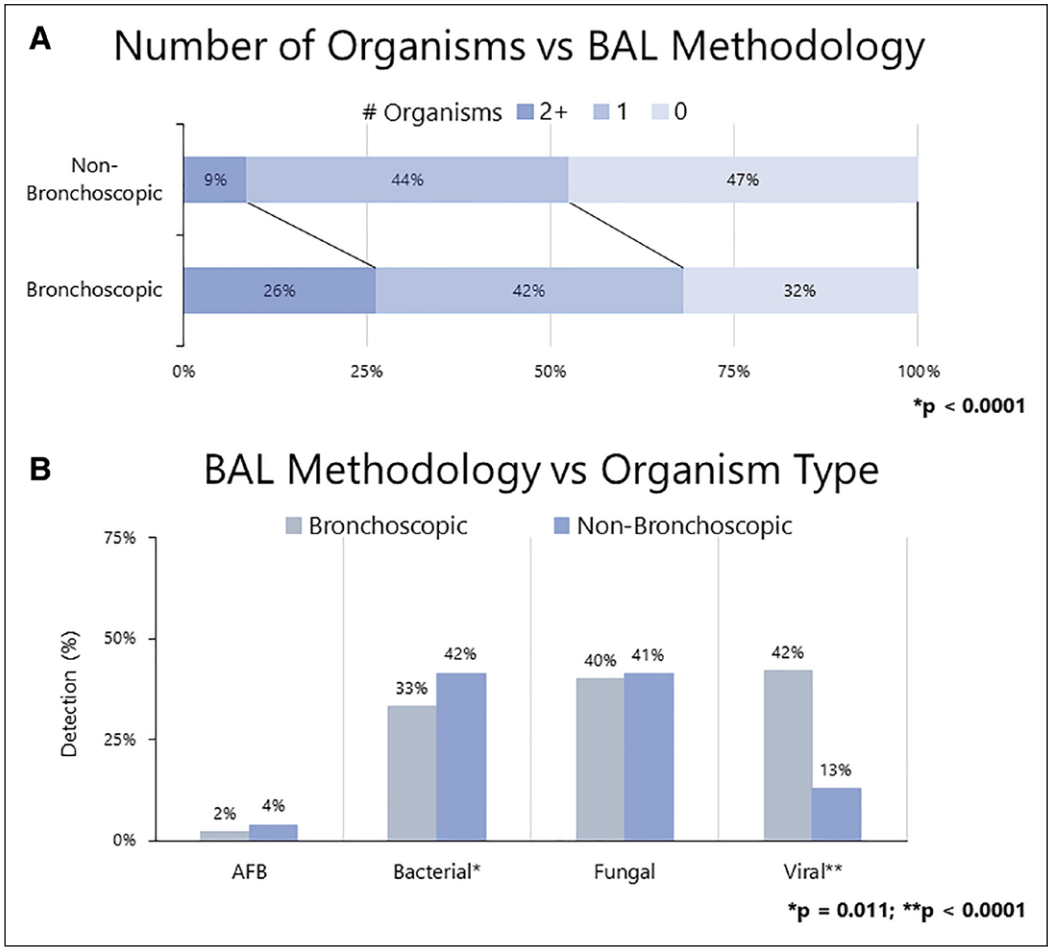

Figure 1. Number (**A**) and type (**B**) of organisms isolated from microbiological analysis of bronchoalveolar lavage fluid with respect to methodology used to obtain the sample.

(**Table 2**), with a 30-day mortality of 48% among patients with BAL sampling, 43% for patients with no organisms detected, to 58% for those with two or more organisms detected on BAL (p = 0.003) (**Fig. 2*A***). Among those tested for viruses, a positive result was associated with 56% mortality within 30 days of BAL compared with 46% among those with a negative result (p = 0.033) (**Fig. 2*B***). Neither the number of organism types detected nor BAL methodology demonstrated a significant association with hospital or ICU LOS (**Table 3**).

DISCUSSION

Among ICU patients, BAL methodology differences may have microbiologic diagnostic implications and resultant prognostic clinical value. Although one trial comparing bronchoscopic sampling to clinical criteria alone in ventilator-associated pneumonia demonstrated decreased mortality and antibiotic use (17), neither method of BAL sampling has been shown to be superior to the other (14, 15, 18, 19). Nonbronchoscopic techniques are purported to be a safer, cheaper, and easily accessible alternative to bronchoscopic BALs (20, 21). However, generalizability is limited among nonbronchoscopic BAL samples due to variation in catheter utilization, lavage fluid volumes, and quantitative analysis thresholds (7, 12, 22–30). Study of diagnostic techniques and optimal methodologies represents an ongoing research priority. The Infectious

TABLE 2.
Impact of Bronchoalveolar Lavage Organism Burden on Clinical Outcomes

	Number of Organism Type(s)			
Outcome	**0**	**1**	**2+**	***p***
30-d mortality, *n* (%)	132 (43.0)	165 (47.8)	88 (58.3)	0.003
Median hospital LOS, d (IQR)	18 (10–29)	19 (10–31)	18 (9–33)	0.93
Median ICU LOS, d (IQR)	10 (5–18)	11 (5–19)	11 (5–21)	0.65

IQR = interquartile range, LOS = length of stay.
Thirty-day mortality calculated as difference between bronchoalveolar lavage and death dates.

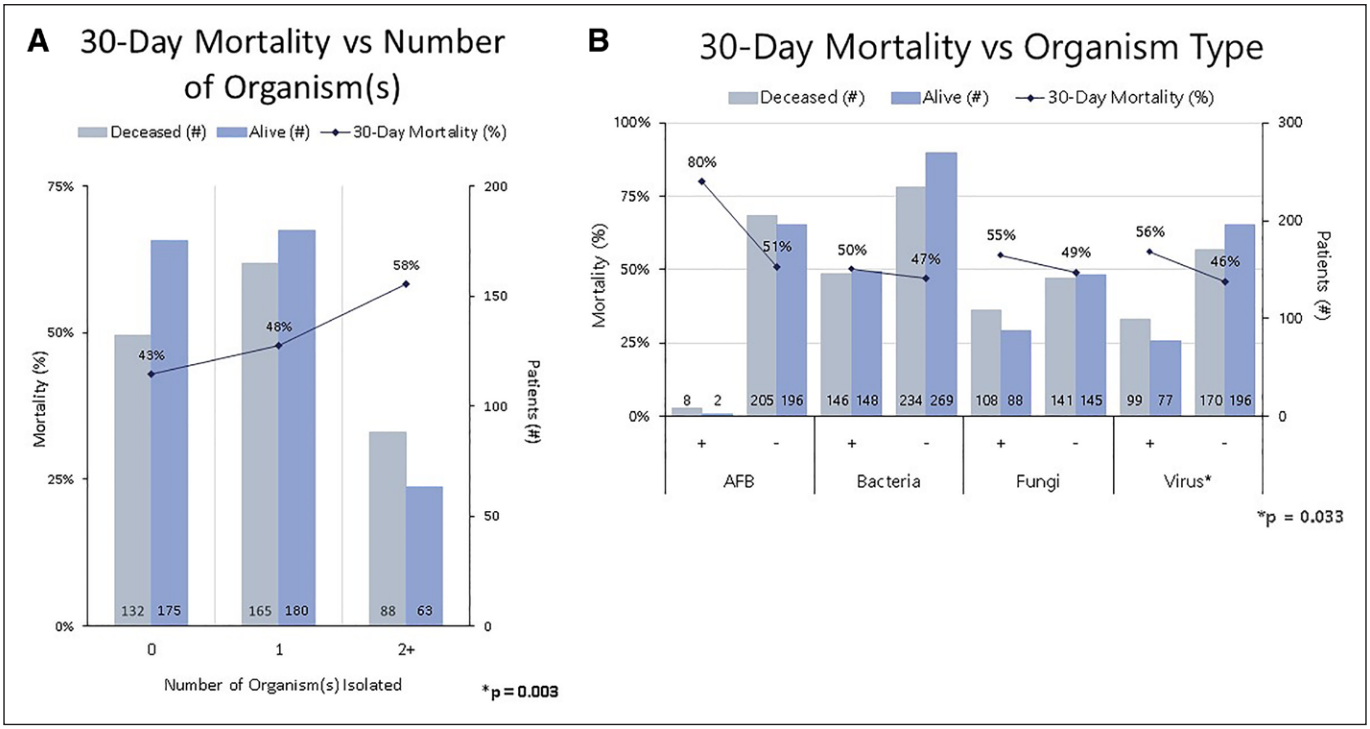

Figure 2. 30-day mortality compared with the number (**A**) and type (**B**) of organism(s) isolated from microbiological analysis of bronchoalveolar lavage fluid.

Diseases Society of America guidelines for nosocomial pneumonia noted insufficient evidence to recommend invasive techniques over noninvasive or to recommend one BAL methodology above the other for diagnosis of nosocomial pneumonia (6).

Our study provides unique, "real-world" data with bronchoscopic BALs, demonstrating high percentages of detected organisms and coinfection compared with nonbronchoscopic BALs, in the setting of standardized organizational techniques for both sampling methods during the study period. Interestingly, in our study, nonbronchoscopic BALs isolated bacteria more frequently, but fewer organisms overall. Bronchoscopic BAL isolated more organisms overall, and specifically more viruses. These differences may be due to sampling technique differences; however, in practice, the patients with a higher severity of illness and immunosuppression may be more likely to undergo bronchoscopy.

The literature on coinfection is confounded by the lack of gold standard definition and diagnostic test strategy. Although coinfection is commonly defined as concurrent bacterial and viral infections (31), we expanded the definition to include two or more of any

TABLE 3.
Impact of Bronchoalveolar Lavage Methodology on Clinical Outcomes

	Bronchoalveolar Lavage Methodology			
Outcome	**Overall**	**Bronchoscopic**	**Nonbronchoscopic**	***p***
30-d mortality, *n* (%)	385 (48.0)	223 (48.4)	160 (47.2)	0.74[a]
Median hospital LOS, d (IQR)	18 (10–31)	18 (9–30)	19 (11–32)	0.11[b]
Median ICU LOS, d (IQR)	10 (5–19)	10 (5–19)	11 (6–20)	0.09[b]

IQR = interquartile range, LOS = length of stay.

Thirty-day mortality calculated as difference between bronchoalveolar lavage and death dates. *p* values for comparison between bronchoscopic versus nonbronchoscopic generated from

[a]χ^2 and

[b]Wilcoxon rank-sum test.

organism types as there are few studies inclusive of fungal pathogens, which may present as a coinfection. The few studies evaluating fungal pathogens almost exclusively included immunocompromised patients and focused on *Pneumocystis jirovecii* pneumonia in HIV (15, 32, 33). Our study demonstrated no difference in fungal detection by methodology in either patient population. *Candida* species was found often among our BAL samples, but these organisms frequently colonize the respiratory tract. The identification of coinfections with any combination of organisms raises questions to the clinical relevance of those detected and whether they are pathogens, contaminants, or colonizers.

This study demonstrates an association between mortality and number of isolated organisms. This finding is intuitive, as higher infectious burdens are more likely to result in worse clinical outcomes. We also note a high overall mortality. BAL sampling may be a marker for severely ill patients, which may have biased the findings, and further investigation of this was beyond the scope of this study. Viruses were associated with higher mortality, and herpesviruses were the most frequently isolated in our study. Nevertheless, it remains unclear if the viruses are a primary pathogen, facilitating the acquisition of other pulmonary infections or merely reflecting the severity of critical illness (31, 34–38). Although herpesviruses can cause pneumonia in immunocompromised patients, critical illness has been associated with increased frequency of viral detection including in acute respiratory distress syndrome in several studies (39). Although the utility of PCR panels in detecting respiratory viruses may have limited management implications, our findings suggest consideration of respiratory viral testing as a prognostic aid. Ultimately, our understanding of the epidemiology of viral LRTI is still evolving, and further studies are needed to better characterize their frequency and implications (40–43).

To our knowledge, our study represents the largest to date examining the impact of sampling methodology on the results of BAL microbiological analyses, with the sample size in our study an order of magnitude larger than that seen in most of the available literature. This is especially significant considering the variability of prior studies that have thwarted attempts at meta-analysis. The "real-world" data on BAL methodology use also reflect the complexities influencing intensivists' choice of sampling techniques and diagnostic testing to evaluate respiratory syndromes. With standardized methodology in place at our institution at the time of our study, the potential for bias in sampling technique is reduced compared with prior studies in the literature. However, interinstitutional variability in sampling methodology and heterogeneous patient populations may limit generalizability to other practices, and ultimately, further characterization and cross-specialty standardization would be essential to reducing the variability of results.

In addition to host immune status, other confounding factors may have been present, which biased clinicians' choice of BAL methodology and subsequently impacted our comparative analysis. This study focused on organisms isolated from BAL samples and did not assess individual clinical diagnoses or treatment decisions based on the BAL findings. Therefore, our analysis is limited by the inability to distinguish whether the organisms isolated reflect true pathogens or merely colonization, which affects how our results would be interpreted and acted upon in a clinical context. Contaminants may be inappropriately treated if not recognized as such; therefore, these limitations highlight the critical need for further study on optimal clinical decision-making, and diagnostic and antimicrobial stewardship among critically ill patients. Furthermore, the indirect method for classifying organism type based on culture media may have resulted in the misclassification of some organisms and introduces the possibility of skewed findings with organisms having a variable capacity for growth on different culture media. This also limits the extent to which the associations described in our study can be extended to specific organisms.

CONCLUSIONS

Even with standardized institutional techniques, retrospective evaluation of bronchoscopic and non-bronchoscopic BAL methodologies did not reveal similar microbiologic yield in critically ill patients. Bronchoscopic BAL overall yielded more organisms, and occurrence of multiple organisms in BAL was associated with worse outcomes. Standardized definitions of coinfection, such as "the simultaneous presence of more than one distinct organism type using AFB, bacterial, fungal, and viral categories," BAL methodologies (categorized into bronchoscopic and non-bronchoscopic), and consistent BAL sampling methodology

nomenclature will enhance future characterization of LRTI diagnostics in the ICU, thereby providing greater opportunities for diagnostic stewardship to augment clinical decision-making. Prospective studies directly comparing BAL methodology are needed and should compare findings with respect to host immune status to inform more standardized approaches for BAL sampling in different patient groups.

ACKNOWLEDGMENTS

Study data were collected and managed using the REDCap electronic data capture tools hosted at the University of Nebraska Medical Center. We thank the Research Information Technology Office, which is funded by the Vice Chancellor for Research, for service and support.

1 *Department of Internal Medicine, Division of Infectious Diseases, College of Public Health, University of Nebraska Medical Center, Omaha, NE.*

2 *Department of Anesthesiology, College of Public Health, University of Nebraska Medical Center, Omaha, NE.*

3 *Department of Biostatistics, College of Public Health, University of Nebraska Medical Center, Omaha, NE.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: kelly.cawcutt@unmc.edu

REFERENCES

1. The World Health Organization: The Top 10 Causes of Death. 2019. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
2. Cawcutt KA, Kalil AC: Viral and bacterial co-infection in pneumonia: Do we know enough to improve clinical care? *Crit Care* 2017; 21:19
3. Karhu J, Ala-Kokko TI, Vuorinen T, et al: Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. *Clin Infect Dis* 2014; 59:62–70
4. Ruuskanen O, Lahti E, Jennings LC, et al: Viral pneumonia. *Lancet* 2011; 377:1264–1275
5. Voiriot G, Visseaux B, Cohen J, et al: Viral-bacterial coinfection affects the presentation and alters the prognosis of severe community-acquired pneumonia. *Crit Care* 2016; 20:375
6. Kalil AC, Metersky ML, Klompas M, et al: Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63:e61–e111
7. Afify MH, Shaheen EA, El-Dahdouh SS, et al: Comparison between bronchoscopic BAL and non-bronchoscopic BAL in patients with VAP. *Egypt J Chest Dis Tuberc* 2016; 65:113–119
8. Afolabi-Brown O, Marcus M, Speciale P, et al: Bronchoscopic and nonbronchoscopic methods of airway culturing in tracheostomized children. *Respir Care* 2014; 59:582–587
9. Garrouste-Orgeas M, Chevret S, Arlet G, et al: Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. *Am J Respir Crit Care Med* 1997; 156:1647–1655
10. Rajasekhar T, Anuradha K, Suhasini T, et al: The role of quantitative cultures of non-bronchoscopic samples in ventilator associated pneumonia. *Indian J Med Microbiol* 2006; 24:107–113
11. Levy H: Comparison of Ballard catheter bronchoalveolar lavage with bronchoscopic bronchoalveolar lavage. *Chest* 1994; 106:1753–1756
12. Ghosh S, Finch CG, Champlin RE, et al: Comparison and cost effectiveness of bronchoscopic and non-bronchoscopic bronchoalveolar lavage in hematological malignancies and stem cell recipients. *Biol Blood Marrow Transpl* 2009; 15:91–92
13. Papazian L, Martin C, Meric B, et al: A reappraisal of blind bronchial sampling in the microbiologic diagnosis of nosocomial bronchopneumonia. A comparative study in ventilated patients. *Chest* 1993; 103:236–242
14. Papazian L, Thomas P, Garbe L, et al: Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1995; 152:1982–1991
15. Tasbakan MS, Gurgun A, Basoglu OK, et al: Comparison of bronchoalveolar lavage and mini-bronchoalveolar lavage in the diagnosis of pneumonia in immunocompromised patients. *Respiration* 2011; 81:229–235
16. Singh N, Rogers P, Atwood CW, et al: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000; 162:505–511
17. Fagon JY, Chastre J, Wolff M, et al: Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 2000; 132:621–630
18. Azadeh N, Sakata KK, Brighton AM, et al: FilmArray respiratory panel assay: Comparison of nasopharyngeal swabs and bronchoalveolar lavage samples. *J Clin Microbiol* 2015; 53:3784–3787
19. Fujitani S, Cohen-Melamed MH, Tuttle RP, et al: Comparison of semi-quantitative endotracheal aspirates to quantitative non-bronchoscopic bronchoalveolar lavage in diagnosing ventilator-associated pneumonia. *Respir Care* 2009; 54:1453–1461
20. Bustamante EA, Levy H: Sputum induction compared with bronchoalveolar lavage by Ballard catheter to diagnose Pneumocystis carinii pneumonia. *Chest* 1994; 105:816–822

21. Kollef MH, Bock KR, Richards RD, et al: The safety and diagnostic accuracy of minibronchoalveolar lavage in patients with suspected ventilator-associated pneumonia. *Ann Intern Med* 1995; 122:743–748
22. Baughman RP, Spencer RE, Kleykamp BO, et al: Ventilator associated pneumonia: Quality of nonbronchoscopic bronchoalveolar lavage sample affects diagnostic yield. *Eur Respir J* 2000; 16:1152–1157
23. Bello S, Tajada A, Chacón E, et al: "Blind" protected specimen brushing versus bronchoscopic techniques in the aetiolological diagnosis of ventilator-associated pneumonia. *Eur Respir J* 1996; 9:1494–1499
24. Brun-Buisson C, Fartoukh M, Lechapt E, et al: Contribution of blinded, protected quantitative specimens to the diagnostic and therapeutic management of ventilator-associated pneumonia. *Chest* 2005; 128:533–544
25. Fujitani S, Yu VL: Quantitative cultures for diagnosing ventilator-associated pneumonia: A critique. *Clin Infect Dis* 2006; 43(Suppl 2):S106–S113
26. Hussain SM, Abubaker J, Ali M, et al: Comparison of quantitative bronchoscopic lavage cultures (B-BAL) with blind NG tube lavage (N-BAL) cultures in the diagnosis of ventilator associated pneumonia (VAP). *J Coll Physicians Surg Pak* 2009; 19:245–248
27. Khilnani GC, Arafath TK, Hadda V, et al: Comparison of bronchoscopic and non-bronchoscopic techniques for diagnosis of ventilator associated pneumonia. *Indian J Crit Care Med* 2011; 15:16–23
28. Meyer P, Rousseau H, Maillet JM, et al: Evaluation of blind nasotracheal suctioning and non-bronchoscopic minibronchoalveolar lavage in critically ill patients with infectious pneumonia: A preliminary study. *Respir Care* 2014; 59:345–352
29. Solé Violán J, Rodríguez de Castro F, Caminero Luna J, et al: Comparative efficacy of bronchoalveolar lavage and telescoping plugged catheter in the diagnosis of pneumonia in mechanically ventilated patients. *Chest* 1993; 103:386–390
30. Wearden PD, Chendrasekhar A, Timberlake GA: Comparison of nonbronchoscopic techniques with bronchoscopic brushing in the diagnosis of ventilator-associated pneumonia. *J Trauma* 1996; 41:703–707
31. Holter JC, Müller F, Bjørang O, et al: Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: A 3-year prospective study in Norway. *BMC Infect Dis* 2015; 15:64
32. Caughey G, Wong H, Gamsu G, et al: Nonbronchoscopic bronchoalveolar lavage for the diagnosis for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Chest* 1985; 88:659–662
33. van Gaalen S, Duff M, Arroyave LF, et al: Characteristics of hospital admissions for pneumonia in HIV-positive individuals in Winnipeg, Manitoba: A cross-sectional retrospective analysis. *Int J STD AIDS* 2018; 29:115–121
34. Chertow DS, Memoli MJ: Bacterial coinfection in influenza: A grand rounds review. *JAMA* 2013; 309:275–282
35. Jain S, Self WH, Wunderink RG, et al; CDC EPIC Study Team: Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015; 373:415–427
36. Jennings LC, Anderson TP, Beynon KA, et al: Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax* 2008; 63:42–48
37. Johnstone J, Majumdar SR, Fox JD, et al: Viral infection in adults hospitalized with community-acquired pneumonia: Prevalence, pathogens, and presentation. *Chest* 2008; 134:1141–1148
38. Self WH, Wunderink RG, Williams DJ, et al: Staphylococcus aureus community-acquired pneumonia: Prevalence, clinical characteristics, and outcomes. *Clin Infect Dis* 2016; 63:300–309
39. Barbier F, Andremont A, Wolff M, et al: Hospital-acquired pneumonia and ventilator-associated pneumonia: Recent advances in epidemiology and management. *Curr Opin Pulm Med* 2013; 19:216–228
40. Choi SH, Hong SB, Ko GB, et al: Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med* 2012; 186:325–332
41. García-García ML, Calvo C, Pozo F, et al: Spectrum of respiratory viruses in children with community-acquired pneumonia. *Pediatr Infect Dis J* 2012; 31:808–813
42. Lieberman D, Shimoni A, Shemer-Avni Y, et al: Respiratory viruses in adults with community-acquired pneumonia. *Chest* 2010; 138:811–816
43. Pretorius MA, Madhi SA, Cohen C, et al: Respiratory viral coinfections identified by a 10-plex real-time reverse-transcription polymerase chain reaction assay in patients hospitalized with severe acute respiratory illness--South Africa, 2009-2010. *J Infect Dis* 2012; 206(Suppl 1):S159–S165