Influence of Bronchoscopy on the Diagnosis of and Outcomes from Ventilator-Associated Pneumonia

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Abstract

Background: Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection affecting as many as 27% of mechanically ventilated patients. Ventilator-associated pneumonia is an important source of morbidity and mortality in the surgical intensive care unit (SICU). The optimal diagnostic method for VAP has remained controversial and the role of therapeutic bronchoscopy in the clearance of pulmonary secretions with VAP, in essence source control, remains unknown. Our unit utilizes bronchoscopy inconsistently for these purposes and we chose to evaluate its effectiveness in our patient population with the hypothesis that bronchoscopic diagnosis and therapy results in lower mortality rates and faster clinical resolution.

Methods: We analyzed retrospectively all patients treated for VAP in a single SICU between September 2003 and December 2011. Patients were divided into groups based upon diagnostic method and receipt of therapeutic bronchoscopy, and were analyzed for differences in time to clinical resolution and mortality.

Results: A total of 360 patients were included in the study, including 493 episodes of VAP. The diagnostic bronchoscopy group had statistically higher APACHE II scores ($p=0.02$) and fewer days in hospital prior to diagnosis ($p=0.02$) when compared with the non-invasive diagnosis group. Diagnostic bronchoscopy was associated with shorter length of stay and shorter duration of antibiotics whereas receipt of a therapeutic bronchoscopy was associated with the opposite effects by multivariable analysis.

Conclusion: Our hypothesis was disproved and our findings are similar to those found in recent publications. This study supports no definitive conclusions, but further consideration of the role of bronchoscopy is urged in both the diagnosis and treatment of VAP. In our population, bronchoscopy for diagnostic or therapeutic purposes in VAP was not associated with better outcomes. However, differences in baseline characteristics suggest a randomized trial may be needed to answer more completely this question.

HEALTHCARE-ASSOCIATED PNEUMONIA represents up to 27% of all intensive care unit (ICU) infections. Of these, 90% occur in mechanically ventilated patients with each episode costing approximately \$40,000 [1]. Ventilator-associated pneumonia (VAP) is caused by colonization of the lower respiratory tract by potentially pathogenic oropharyngeal flora. Near-ubiquitous leakage of oropharyngeal secretions around the endotracheal tube (ETT) coupled with biofilm formation on the tube itself provide a direct pathway for pathogenic organisms to colonize and infect the lower respiratory tract [1,2]. Overall, VAP is estimated to affect between 8% to 30% of mechanically ventilated patients with higher rates at trauma centers [1,3,4]. The reported associated

mortality for VAP is 18%–30% [3, 5, 6]. On the other hand, VAP-attributable mortality, ranges from 69% in surgical ICU patients to 0% in the trauma population [7].

There is little agreement in the literature about the best method for obtaining an appropriate culture in the setting of VAP. A recent Cochrane review found no evidence to support quantitative more than qualitative cultures [6]. However, there is some evidence that diagnostic bronchoscopy may improve VAP related outcomes, although this is also disputed in the literature [8,9]. On the other hand, bronchoscopy may be able to direct clinical attention away from the lungs toward other sites because as few as 42% of patients with clinically suspected VAP have pneumonia [10,11].

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It is unclear whether the mechanical and physical aspects of bronchoscopy alter the outcome of VAP. Trauma to the airway, the dispersion of pathogens with saline during bronchoalveolar lavage (BAL), or simply the presence of an additional foreign body in the airway may delay the clinical resolution and lead to worse outcomes. Conversely, better source control through the removal of mucus plugs from the endotracheal tube and airway could improve outcomes. On the basis of previous reports, our institution has, over several years, used aggressive bronchoscopic diagnosis and serial bronchoscopy for pulmonary toilet increasingly in VAP patients. We have developed an informal, clinician-driven protocol involving bronchoscopic diagnosis with BAL, and serial therapeutic bronchoscopies for patients believed to be at high risk. The number of serial bronchoscopies is based upon the appearance of the airway and volume of purulent secretions on the previous evaluation. Patients that are believed by the treatment team to be at high risk for respiratory decline from VAP, have thick secretions, or may have difficulty clearing their airways were generally treated in this manner. Based upon our experience with this practice, we hypothesized that repeated bronchoscopy would lead to lower mortality and hasten clinical resolution of VAP.

Patients and Methods

The University of Virginia IRB granted approval for this protocol. We analyzed all patients on the general surgery, trauma, and transplantation services diagnosed with culture-confirmed, VAP from September 2003 through June 2011. In accordance with the U.S. Centers for Disease Control and Prevention (CDC) definition, all patients were mechanically ventilated for at least 48 hours prior to the onset of VAP [12]. Information regarding bronchoscopic diagnosis was obtained by evaluating the origin of the specimen for culture. We defined a diagnostic bronchoscopy as one performed within 24 h of the initiation of antibiotics for VAP. Cases not meeting this definition were diagnosed via endotracheal suction, generally with quantitative cultures of specimens. Therapeutic bronchoscopies were defined as those occurring more than 24 h but within eight days of the initiation of antibiotics. The number of therapeutic bronchoscopies occurring during this eight-day period was recorded, although patients were dichotomized ultimately as having or not having a therapeutic bronchoscopy, regardless of the total number performed. Our primary outcome was all-cause, inpatient mortality. Secondary outcomes included days to resolution of fever (less than 38.5°C and 38°C), days to resolution of white blood cell (WBC) count (to less than $15,000 \times 10^9$ cells/L and $11,000 \times 10^9$ cells/L), hospital length of stay, and duration of antibiotic therapy.

The cohort was divided initially into two groups based upon initial diagnostic method. Those that received a non-invasive diagnostic method were placed in one group whereas those who received a diagnostic bronchoscopy were placed in the second. Baseline differences between groups were evaluated using univariate methods. Chi-square analysis, Wilcoxon ranked sum, and Fisher exact test were used where appropriate. The time from initiation of antibiotics to resolution of fever or WBC count was used to establish time to clinical resolution. A similar analysis was performed on the same patient population segregated based upon receipt of

therapeutic bronchoscopy, regardless of the diagnostic technique. Finally, the same analysis was repeated on a smaller cohort of patients, comparing patients who received a diagnostic bronchoscopy to a group that received a diagnostic bronchoscopy and therapeutic bronchoscopy. Subgroup analysis of trauma patients was also completed.

Multi-variable linear regression for continuous outcomes and logistic regression for mortality were performed using *a priori* predictor variables, including age, gender, diagnostic bronchoscopy, therapeutic bronchoscopy, Acute Physiology and Chronic Health Evaluation (APACHE) II score, trauma, transfusion, and days in hospital prior to diagnosis of VAP. All data analysis was performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

A total of 360 patients had 493 episodes of VAP during the study period. We found no differences between study groups with regards to age, race, transplant or rates of trauma (Table 1). Fewer females underwent bronchoscopy for diagnosis. Patients who received a diagnostic bronchoscopy had higher APACHE II scores, lower rates of transfusion, and had fewer days of hospitalization prior to developing VAP. Patients who received a diagnostic bronchoscopy were also more likely to receive a therapeutic bronchoscopy. Similar trends were noted when divided according to receipt of a therapeutic bronchoscopy (Table 2). When comparing those patients who received only a diagnostic bronchoscopy, those who also received a therapeutic bronchoscopy were younger statistically than those who received a diagnostic bronchoscopy alone (Table 3). There was no difference in mortality regardless of categorization by diagnostic method or receipt of therapeutic bronchoscopy. Our overall mortality for surgical patients was 37.9% compared with 7.7% for trauma patients ($p < 0.0001$). The organisms isolated most commonly are listed in Table 4.

A subgroup analysis of trauma patients echoed the findings above. We found no difference between trauma patients and others in terms of time to clinical resolution, length of stay, or mortality based upon receipt of a therapeutic bronchoscopy. The same was true when only analyzing patients that received an initial diagnostic bronchoscopy. Trauma patients who received a therapeutic bronchoscopy, irrespective of diagnostic procedure, had significantly more days of antibiotic therapy (median: 12; interquartile range (IQR): 9–17; $p = 0.009$) compared with those that only underwent a diagnostic procedure (median: 10; IQR: 8–14). When only considering patients who received an initial diagnostic bronchoscopy, those who also received a therapeutic bronchoscopy also had a longer duration of antibiotic therapy (median: 11; IQR: 9–17 vs. median: 9; IQR: 8–13; $p = 0.01$).

After controlling for age, gender, APACHE II score, trauma, transfusions, and time in hospital prior to the diagnosis of VAP with our linear regression models, we identified no relationship between either diagnostic or therapeutic bronchoscopy and time to clinical resolution. Diagnostic bronchoscopy was associated with a shorter median length of stay (median: 0.88 days; 95% CI: 0.78–0.99; $p = 0.03$) than therapeutic bronchoscopy (median: 1.15 d; 95% CI: 1.01–1.31; $p = 0.04$) when holding all other predictors constant. Similarly, diagnostic bronchoscopy was associated with a

TABLE 1. PNEUMONIAS CLASSIFIED BY MODE OF DIAGNOSIS

	<i>Non-Invasive Culture</i>		<i>Diagnostic Bronch.</i>		p
	n/Median	IQR/%	n/Median	IQR/%	
Total	334		159		
Age	54	(38, 66)	53	(41, 66)	1.0
Female	96	28.7%	29	18.2%	0.01
Race: Caucasian	264	79.0%	125	78.6%	0.2
African American	55	16.5%	21	13.2%	
Hispanic	9	2.7%	10	6.3%	
Other	6	1.8%	3	1.9%	
Trauma	219	65.6%	105	66.0%	0.9
Transfusion	279	83.5%	119	74.8%	0.02
Transplant	25	7.5%	8	5.0%	0.3
Therapeutic bronchoscopy	53	15.9%	62	39.0%	<0.0001
APACHE II	20	(16, 23)	20	(17, 26)	0.02
Hospital days prior to VAP	10	(5, 21)	8	(4, 14)	0.001
Days to temp <38.5°C×24 h	2	(1, 2)	2	(1, 3)	0.8
Days to temp <38°C×24 h	2	(1, 3)	2	(1, 3)	0.5
Days to WBC <15,000×10 ⁹ cells/L	2	(1, 5)	2	(1, 5)	0.5
Days to WBC <11,000×10 ⁹ cells/L	4	(1, 10)	5	(2, 11)	0.5
Total length of stay	39	(25, 73)	33	(21, 53)	0.003
Total days of antibiotics	11	(8, 15)	10	(8, 14)	0.2
Deaths/mortality rate	59	17.7%	30	18.9%	0.7

*IQR=25% to 75% interquartile range.

APACHE=Acute Physiology and Chronic Health Evaluation; VAP=ventilator-associated pneumonia; WBC=white blood cell.

shorter median duration of antibiotics (median: 0.88 days; 95% CI: 0.78–0.98; p value=0.02) than therapeutic bronchoscopy (median: 1.28 d; 95% CI: 1.13–1.44; p<0.0001) when other predictors were held constant. We found no association between either diagnostic or therapeutic bronchoscopy with mortality by multi-variable analysis (c-statistic: 0.86). Odds ratios for mortality are given in Table 5.

Discussion

Despite being a common healthcare-associated infection, there is little agreement on whether to use invasive or non-invasive strategies to diagnose VAP. A position paper published in 2010 by the Infectious Diseases Society of America (IDSA) recommends quantitative lower respiratory

TABLE 2. PNEUMONIAS CLASSIFIED BY UTILIZATION OF THERAPEUTIC BRONCHOSCOPY

	<i>No Therapeutic Bronch.</i>		<i>Therapeutic Bronch.</i>		P-value
	n/Median	IQR/%	n/Median	IQR/%	
Total	378		115		
Age	54	(39, 67)	50	(38, 62)	0.06
Female	107	28.3%	18	15.7%	0.006
Race: Caucasian	298	78.8%	91	79.1%	0.5
African American	61	16.1%	15	13.0%	
Hispanic	12	3.2%	7	6.1%	
Other	7	1.9%	2	1.7%	
Trauma	248	65.6%	76	66.1%	0.9
Transfusion	313	82.8%	85	73.9%	0.03
Transplant	27	5.5%	6	5.2%	0.5
Diagnostic bronchoscopy	53	15.9%	62	39.0%	<0.0001
APACHE II	20	(15, 23)	21	(18, 25)	0.003
Hospital days prior to VAP	10	(5, 21)	7	(4, 14)	0.01
Days to temp <38.5°C×24 h	1	(1, 2)	2	(1, 3)	0.07
Days to temp <38°C×24 h	2	(1, 3)	2	(1, 4)	0.5
Days to WBC <15,000×10 ⁹ cells/L	2	(1, 5)	2	(1, 6)	0.1
Days to WBC <11,000×10 ⁹ cells/L	4	(1.5, 10)	7	(2, 11)	0.1
Total length of stay	38	(23, 65)	36	(24, 68)	0.9
Total days of antibiotics	10	(8, 15)	13	(8, 18)	0.0008
Deaths/mortality rate	69	18.3%	20	17.4%	0.8

*IQR=25% to 75% interquartile range.

APACHE=Acute Physiology and Chronic Health Evaluation; VAP=ventilator-associated pneumonia; WBC=white blood cell.

TABLE 3. COMPARISON OF DIAGNOSTIC BRONCHOSCOPY ALONE VERSUS DIAGNOSTIC BRONCHOSCOPY PLUS THERAPEUTIC BRONCHOSCOPY

	Diagnostic Bronchoscopy Only		Therapeutic Bronchoscopy		p
	n/Median	IQR/%	n/Median	IQR/%	
Total	97		62		
Age	55	(43, 72)	48	(33, 68)	0.002
Female	22	22.7%	7	11.3%	0.07
Race: Caucasian	79	81.4%	46	74.2%	0.2
African American	13	13.4%	8	12.9%	
Hispanic	3	3.1%	7	11.3%	
Other	2	2.1%	1	1.6%	
Trauma	64	66.0%	41	66.1%	1
Transfusion	74	76.3%	45	72.6%	0.6
Transplant	6	6.2%	2	3.2%	0.5
APACHE II	20	(15, 27)	21	(18, 26)	0.5
Hospital days prior to VAP	9	(4, 17)	6	(3, 12)	0.1
Days to temp < 38.5°C × 24 h	1	(1, 2)	2	(1, 3)	0.01
Days to temp < 38°C × 24 h	2	(1, 3)	2	(1, 4)	0.09
Days to WBC < 15,000 × 10 ⁹ cells/L	2	(1, 5)	2	(1, 4)	0.8
Days to WBC < 11,000 × 10 ⁹ cells/L	4	(2, 10)	6	(2, 11)	0.2
Total length of stay	34	(20, 51)	32	(22, 55)	0.7
Total days of antibiotics	9	(7, 13)	12	(8, 18)	0.003
Deaths/mortality rate	20	20.6%	10	16.1%	0.5

*IQR=25% to 75% interquartile range.

APACHE= Acute Physiology and Chronic Health Evaluation; VAP= ventilator-associated pneumonia; WBC= white blood cell.

tract culture as the standard for diagnosis but the exact method of procurement is not well-defined [13]. Bronchoalveolar lavage, especially when combined with quantitative culture, has been shown to be a highly accurate method of diagnosis, particularly in the trauma setting [14,15]. En-

dotracheal aspirate has been demonstrated to achieve similar diagnostic accuracy to either BAL or protected specimen brush [16]. Guidelines published by the American Thoracic Society do not endorse any specific method, and even when available, clinical practice often does not reflect these guidelines [1,17].

Five randomized controlled trials have been published in an attempt to answer this question, with mixed results [3,6,9,16,18]. Two meta-analyses (including a Cochrane review) found no difference between invasive and non-invasive diagnostic methods [5,8]. However, these meta-analyses, varied in their inclusion of threshold concentrations of bacterial growth, inclusion of non-quantitative methods, and interpretation of mortality data.

Of the individual randomized trials mentioned above, several demonstrated no difference in outcomes based upon diagnostic method, however, each study contained fewer than 100 patients and may have been underpowered [3,6,18]. The

TABLE 4. MOST COMMON ISOLATED ORGANISMS

Organism	Gram-stain characteristic	Number
<i>Pseudomonas aeruginosa</i>	Gram-negative	112
<i>Staphylococcus aureus</i>	Gram-positive	65
<i>Enterobacter cloacae</i>	Gram-negative	46
<i>Haemophilus influenzae</i>	Gram-negative	40
<i>Klebsiella pneumoniae</i>	Gram-negative	37
Methicillin-resistant <i>S. aureus</i> (MRSA)	Gram-positive	30
<i>Stenotrophomonas maltophilia</i>	Gram-negative	30
<i>Escherichia coli</i>	Gram-negative	29
Mixed flora	Not fully specified	28
<i>Serratia</i> spp.	Gram-negative	27
<i>Acinetobacter</i> spp.	Gram-negative	24
<i>Enterobacter aerogenes</i>	Gram-negative	23
Gram-negative bacillus	Not fully specified	22
<i>Streptococcus</i> spp.	Gram-positive	20
<i>Klebsiella oxytoca</i>	Gram-negative	19
<i>Streptococcus pneumoniae</i>	Gram-positive	19
<i>Proteus mirabilis</i>	Gram-negative	15
<i>Citrobacter</i> spp.	Gram-negative	14
Vancomycin-resistant <i>Enterococcus faecium</i> (VRE)	Gram-positive	10
<i>Moraxella catarrhalis</i>	Gram-negative	5

TABLE 5. ODDS RATIOS FOR MORTALITY

Parameter	Odds ratio (95% CI)	p
Age	1.03 (1.01–1.05)	0.002
Gender: Female	1.05 (0.56–1.96)	0.9
Diagnostic bronchoscopy	1.12 (0.60–2.10)	0.7
Therapeutic bronchoscopy	1.14 (0.57–2.27)	0.7
APACHE II	1.13 (1.07–1.19)	<0.0001
Trauma	0.30 (0.17–0.54)	<0.0001
Transfusion	1.10 (0.45–2.67)	0.8
Hospital days prior to VAP	2.00 (1.49–2.70)	<0.0001

APACHE= Acute Physiology and Chronic Health Evaluation; VAP= Ventilator-associated pneumonia.

trial published by the Canadian Critical Care Trials Group did not report short-term outcome data in terms of mortality or organ-dysfunction scores (other than on day one) that could be used to evaluate the effects of bronchoscopy itself as a therapeutic intervention [6]. On the other hand, Fagon et al. demonstrated lower short-term mortality and decreased Sequential Organ Failure Assessment Scores at three days (6.1 ± 4.0 vs. 7.0 ± 4.3 points; $p=0.33$) and seven days (4.9 ± 4.1 vs. 5.8 ± 4.4 points; $p=0.04$) for their group that had a diagnosis via BAL versus a non-invasive technique. This finding suggests that bronchoscopy has some short-term therapeutic benefit beyond its diagnostic utility [9].

Patients in our study who received diagnostic bronchoscopy, as well as those who received a therapeutic bronchoscopy, had higher APACHE II scores and lower duration of hospitalization prior to VAP versus their respective comparison groups. These differences are probably attributable to our pattern of bronchoscopy use in our surgical and trauma ICU, where we use therapeutic bronchoscopy aggressively in patients who are at risk for or demonstrate a rapid decline in respiratory status. Although both APACHE II and duration of hospitalization prior to the diagnosis of VAP were included in our multi-variable analyses, it is possible that patients who underwent bronchoscopy were different fundamentally from those who did not in ways that were not included in our analysis.

We found no difference in mortality by bronchoscopic categorization by either univariate or multi-variable analysis, which is consistent with previous work confirming that the diagnostic method has little influence on the long-term outcome of VAP [3,5,6,9,16]. However, many of these studies did demonstrate a trend toward lower long-term mortality rates in the invasive diagnosis groups [3,9,16]. Only one study has demonstrated improved mortality on the basis of short-term analysis, and a second describes a protocol that included both diagnostic BAL and endotracheal suction for each patient and demonstrated lower mortality compared with “non-protocol” diagnosed VAP [9,19]. Our overall mortality rate of 18.1%, although not different between bronchoscopy and non-bronchoscopy-diagnosed groups, is similar to that observed in other national studies [6]. Our mortality rates for our trauma patients were also similar across study groups, and lower than those observed for non-trauma patients, consistent with several recent publications [20,21].

Our study has several important limitations. First, this study is an attempt to quantify the effects of a treatment practice that does not currently have a formalized protocol, has only partial adherence, and has variability among providers. The multi-variable analysis represents an attempt to control for confounders that may have influenced outcome measures but probably cannot correct for differences in practices. Second, many of our patients in this study were already on antibiotics at the time of their bronchoscopy. The delay in bronchoscopy for up to 24 h after the initiation of antibiotics may have concealed any potential benefit of the bronchoscopy [11]. Third, given that the effect size of therapeutic bronchoscopy is likely small, our study may be underpowered which increases the likelihood of a type II error. Finally, the utilization of toilet bronchoscopy was large enough to make conclusions from this observational data unreliable to draw.

Conclusion

Our data do not suggest that diagnostic bronchoscopy and BAL are associated with better outcomes than the non-invasive diagnosis of VAP. The role of toilet bronchoscopy to achieve better source control is unclear and probably can only be answered in a randomized study, because its use is variable in practice. Nonetheless, bronchoscopy is still probably justified in patients with VAP complicated by as lobar collapse and hypoxemia, potentially associated with mucus plugging.

Author Disclosure Statement

No competing financial interests exist.

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