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Diagnostic Value of Bronchoscopy in Critically Ill Ventilated Patients with the Lower Respiratory Tract Infections: Role in Detecting Bronchial Microbial Patterns

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Abstract

BACKGROUND: Flexible bronchoscopy is an essential tool in critical care medicine. It provides direct access to the lower airways for sampling bronchial and parenchymal tissues directly at the site of lung lesion.

AIM: The aim of the study was to study the value of Broncho-Alveolar Lavage (BAL) using bronchoscopy in detecting the bronchial microbial patterns in patients with pneumonia and also, to study the effect of antibiotic upgrading according to BAL results on patients' outcome.

PATIENTS AND METHODS: Sixty patients who were admitted to critical care department and developed pneumonia and put on mechanical ventilator were included in the study consecutively. Clinical and laboratory data were recorded on admission. Clinical and laboratory data, CPIS, PSI, PIRO and IBMP-10 scores were recorded on admission. All patients had bronchoalveolar lavage after diagnosis of pneumonia was established. The BALF was sent for culture and sensitivity.

RESULTS: From a total of 60 patients with VAP, 51.7% were males, the age was 59.6 ± 17.5 years, mortality rate was 86.7%. In the non-survival group, the PSI was 133.4 ± 29.4 (p = 0.836). The APACHE II was 18.8 ± 6.6 (p = 0.432), PIRO 1.5 ± 1.1 (p = 0.014), and IBMP – 10 2.3 ± 1.1 (p = 0.021); all were higher in the non-survival group. BAL can detect up to 90% of pathogens responsible for the infection in the lower respiratory tract, while sputum can detect only 55% with accuracy of 65% (p = 0.006). Our results suggest that BAL culture and sensitivity was superior to sputum culture and sensitivity in detecting microorganisms with none of them had statistically significant relation to survival. High PIRO and IBMP-10 scores were good predictors for high mortality unlike PSI or APACHE II.

CONCLUSION: Broncho-Alveolar Lavage (BAL) using bronchoscopy can detect the bronchial microbial patterns and superior to sputum culture but has no impact on mortality.

Introduction

International guidelines recommend obtaining a respiratory tract specimen from all hospitalized CAP, and especially severe CAP patients before antimicrobial therapy to guide antimicrobial treatment whenever good quality purulent samples are available [1].

Respiratory specimens can be collected as deep cough-produced or induced sputum samples, endotracheal suction aspirates, transtracheal or transpulmonary needle punctures, or bronchoscopically assisted aspirates, BAL or protected specimen brushes (PSB) [2], [3].

Several scoring systems have been developed, firstly, to recognize the severity of illness, secondly, to reduce the expensive hospital costs of patients with low risk of mortality, and thirdly, to predict the likelihood of death and complicated disease course. The estimated direct cost of a single CAP hospitalization is very high [4].

Performing bronchoscopy through an endotracheal tube (ETT) in the ICU is a common procedure. The endotracheal tube should be placed before the procedure if the patient's respiratory status is felt to be fragile and the information from bronchoscopy is critical to patient care [5].

Flexible bronchoscopy is an essential tool in critical care medicine. It provides direct access to the lower airways for sampling bronchial and parenchymal tissues directly at the site of lung lesion [5].

Aim of study

To study the value of Broncho-Alveolar Lavage (BAL) using bronchoscopy in detecting the bronchial microbial patterns in patients with pneumonia and also, to study the effect of antibiotic upgrading according to BAL results on patients' outcome.

The ease, safety, and portability of flexible bronchoscopy make it one of the most commonly requested invasive procedure in the intensive care unit (ICU) settings [6].

Methods

Design

This is a prospective, observational, and cohort study to study the value of Broncho-Alveolar Lavage (BAL) using bronchoscopy in detecting the bronchial microbial patterns in patients with pneumonia and also to study the effect of antibiotic escalation according to BAL results on patients outcome.

Population

Over 18 months (between April 2018 and October 2019), 60 patients diagnosed as having lower respiratory tract infection were admitted to the critical care department and put on mechanical ventilation. Flexible bronchoscopy and BAL were done to all these patients.

Inclusion criteria

Patients with unresolved pneumonia (clinical, laboratory, and radiological) despite broad spectrum antibiotic coverage were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

- Patients at extreme ages (Lower than 16 years old and Over 70 years),
- Tracheostomy,
- Known terminal malignancy,
- Severe immunosuppression,
- Coagulopathies,
- Refractory hypoxemia on MV (hypoxemia despite FIO_2 100%) (high risk patients).

Ethical aspects

The study was approved by the Ethical Committee of Cairo University and informed consents obtained from the first degree relative of all enrolled patients.

Procedures\measurements

All patients were subjected to the following

1. Detailed medical history including age, gender, smoking habits, comorbidity, previous glucocorticoid therapy, number of hospitalizations during the past 12 months, antimicrobial pretreatment during the past 24 h and exclusion criteria according to methodology.
2. Detailed physical examination.
3. Laboratory and clinical infection parameters.
4. Clinical scoring systems for pneumonia: Acute Physiology and Chronic Health Evaluation II (APACHE II) score, IBMP-10 score, PIRO score, the pneumonia severity index (PSI) or PORT Score, Clinical Pulmonary Infection Score (CPIS) Calculator,
5. Sputum culture and bronchoalveolar lavage (BAL): Sputum culture withdrawn just after intubation and put in a sterile cup then sent to microbiology laboratory for culture and sensitivity. The site for BAL was chosen according to chest X-ray appearance. BAL was performed in an area of localized pulmonary infiltration if present. When a diffuse infiltrate or no infiltrate, was seen on X-ray, BAL was performed in the most inflamed or purulent pulmonary segment determined by visual inspection. If no inflammation or purulent secretions were seen, BAL was performed in the right lower or middle lobe. The used bronchoscope is Pentax FB-18V fiber-optic bronchoscope having the following criteria: Channel Diameter (mm) 2.8, Distal Tip Diameter (mm) 5.9, Working Length (mm) 600, Angulation (Up/Down) 180/130, Angle of View 120.
6. Follow up clinical, radiological, and laboratory-wise after modification of antibiotics until: Improvement and weaning of mechanical ventilation up to discharge out of ICU or worsening and failure of weaning, up to tracheostomy or death.

Statistical analysis

Data were coded and entered using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test (Chan, 2003a). For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is <5 (Chan, 2003b) for categorical data. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy were calculated as described by (Galen, 1980). p-values < 0.05 were considered as statistically significant.

Results

A total of 60 patients were enrolled in our study. They included 31 males (51.7%) and 29 females (48.3%). The mean age of our patients was 59.63 ± 17.52 years.

All 60 patients of our study population were put on mechanical ventilated, about 55% of them were put on mechanical ventilation due to respiratory causes (mainly respiratory tract infection) and 45% were put on MV related to other causes initially like shock state, bulbar symptoms, and disturbed consciousness level and later they developed severe lower respiratory tract infection.

Sputum sample was withdrawn from all patients in our study just after intubation. Moreover, BAL for culture and sensitivity also sent for all patients (Table 1) and showed the following results (Figure 1):

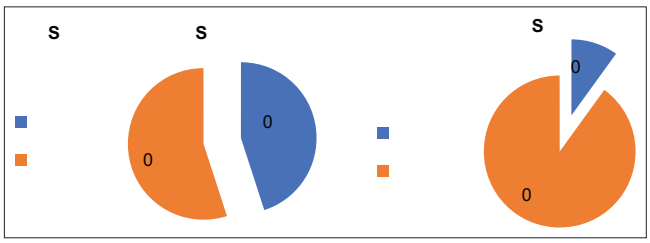

Figure 1: Sputum sample and BAL for all patients after intubation

All of the population of the study had received broad spectrum beta-lactam antibiotic. Around two-thirds of them received dual anti-pseudomonal. About 70% received anti-MRSA. About 25% received polymixins. About 40% received anti-fungal. Around 3% received antiviral therapy as shown in Table 2.

Newly anti-fungal drugs used in our study were: Ecalta (anidulafungin), Vfend (voriconazole), Cancidas (caspofungin), and mycamin (Micafungin).

Relations with survival (Figure 2 and Tables 3-12)

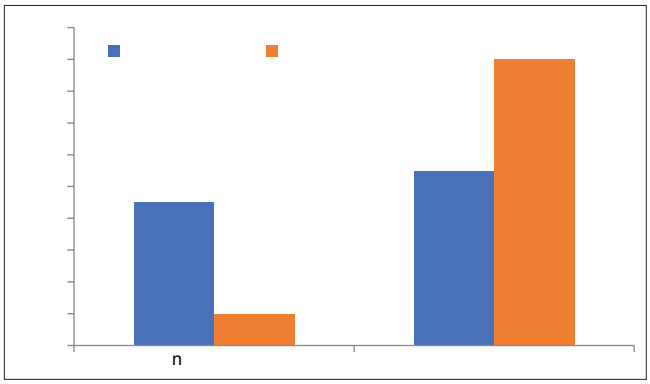

Figure 2: Sputum c\s Vs BAL c\s in detection of organisms

ROC curve for mortality against clinical scoring systems

In our study, the APACHE II and PSI scores have no statistically significant value regarding mortality. PIRO VAP score has the highest statistically significant p-value; however, low sensitivity. The IBMP-10 score has a statistically significant p-value regarding mortality. However, low specificity is shown in Table 13 and diagram (Figure 3).

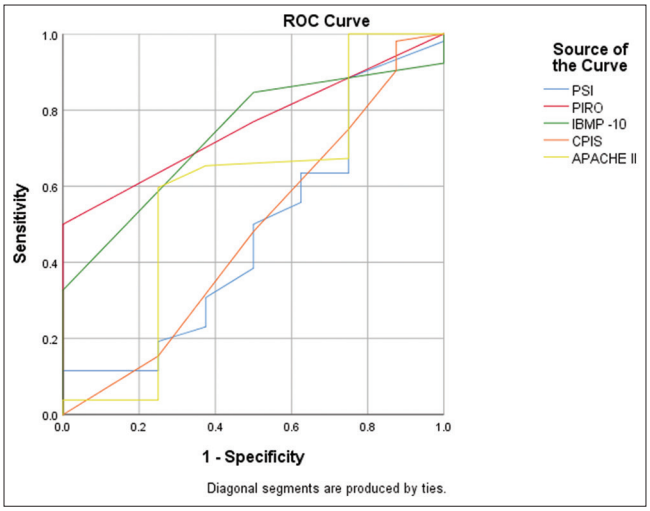

Figure 3: ROC curve for Mortality against clinical scoring systems

Discussion

The role of bronchoscopy with BAL in diagnosing pneumonia and in directing therapy in ventilated patients has been reviewed recently [7], [8], [9]. To appreciate the potential value of BAL in diagnosing bacterial pneumonia, a comparison between traditional sputum culture and BAL has been done to understand the advantages and disadvantages of each technique [8], [9].

Table 1: Microbiological analysis

Culture and sensitivity	n (%)
Sputum culture and sensitivity	
Gram negative organisms	28 (46.7)
Gram negative ± fungal	1 (1.7)
Fungal	4 (6.7)
BAL culture and sensitivity	
Gram-negative organisms	52 (86.7)
Both Gram-negative and positive	2 (3.3)

BAL: Bronchoalveolar lavage.

It is known that acute respiratory failure (ARF) is one of the commonest causes of admission to the intensive care unit (ICU) and occurs secondary to several reasons, including pneumonia, neuromuscular disease, shock, and the need for airway protection. Mechanical ventilation (MV) is the cornerstone of management [10], [11]. This is in concordance with our descriptive data for the need of MV and that of Failkow *et al*. (2016) [12]. In our study, we found that most of the cultured organisms were Gram-negative whether obtained through sputum culture (85%) or BAL culture (96%).

These results are in concordance with Mc Gown (2003) and Bajpai *et al*. (2013). They concluded that CAP is usually caused by Gram-positive and hospital acquired pneumonia by Gram-negative bacteria [13], [14]. Bajpai *et al*. (2013) who studied

Table 2: Antimicrobials used

Antibiotics	Used	n (%)
Broad spectrum (beta-lactams and pipracillin)	Used	60 (100.0)
Anti-Gram-negative (quinolones)	Used	36 (60.0)
Aminoglycosides	Used	7 (11.7)
Polymixins (colistin)	Used	15 (25.0)
Anti-Gram-positive (vancomycin, linezolid, and ticloplanin)	Used	42 (70.0)
Anti-fungal (diflocan and new antifungals)	Used	24 (40.0)
Anti-viral (zovirax and tamiflu)	Used	2 (3.3)
Other antibiotics (anti-anaerobes as flagyl) and tygacil	Used	2 (3.3)

230 patients with the lower respiratory tract infection, about 198 (86.08%) were culture positive. A total of 254 pathogens were recovered with a predominance of Gram-negative isolates (n = 243; 96.05%) Pseudomonas aeruginosa was the most dominant pathogen followed by Klebsiella pneumoniae. Extended spectrum beta-lactamase and methicillin resistant Staphylococcus aureus also isolated [14]. In our study, all of the population had received initially broad spectrum beta-lactam antibiotics. Around two-thirds received double anti-pseudomonal drugs (quinolones were added to beta lactams). About 70%received anti MRSA. About 25% received polymixins. About 40% received anti-fungal. Around 3% received antiviral therapy.

Table 3: Survival according to age

Age ICU, mean ± SD		p
Nonsurvival	Survival	
60.8 ± 17.5	52.4 ± 16.7	0.184

ICU: Intensive care unit, SD: Standard deviation.

We used these protocols initially according to the degree of sepsis and clinical suspicion, after that antibiotics escalated depending on the results of the cultures and sensitivity of BAL and sputum. In concordance to our study, most of the guidelines recommend a combination therapy of a beta-lactam and macrolide or fluoroquinolone in those patients requiring ICU admission, and additional options are for possible pseudomonal infection [15], [16], [17], [18].

Table 4: Relations of gender to survival

Gender	ICU, count (%)		p
	Nonsurvival	Survival	
Male	25 (48.1)	6 (75.0)	0.257
Female	27 (51.9)	2 (25.0)	

ICU: Intensive care unit.

In our study, we found that BAL can detect up to 90% of pathogens responsible for the infection in the lower respiratory tract, while sputum can detect only 55% of organisms by culture. That means while sputum culture showed growth in only 33 patients, BAL showed growth in 54 patients and the whole negative cultures in BAL were negative in sputum culture and statistically we found that sputum culture and sensitivity has accuracy of 65% in comparison with accuracy of BAL in detection of organisms causing lower respiratory tract infection. (With P value 0.006)

Table 5: Relations of mechanical ventilation causes to survival

MV Cause	ICU, count (%)		p
	Nonsurvival	Survival	
Nonrespiratory causes	23 (44.2)	4 (50.0)	1
Respiratory causes	29 (55.8)	4 (50.0)	

ICU: Intensive care unit.

In concordance with our study, Carlos *et al*. (2000) studied BAL fluid in 62 patients with the lower respiratory tract infection, 58 of them were on antibiotic therapy. They found that 45 patients were positive for organisms. This suggests that BAL may be a sensitive diagnostic method even if performed under antibiotic therapy and in treatment failures in clinically diagnosed pneumonias. The main isolates were Gram-negative organisms and MRSA. BAL culture results directed a change of therapy in 75.6% of all positive episodes. In spite of this, he found that there was no difference in mortality among patients who changed therapy guided by BAL culture [19].

Table 6: Survival according to mechanical ventilation duration and intensive care unit stay

ICU stay and MV duration	ICU, mean ± SD		p
	Nonsurvival	Survival	
MV duration	19.5 ± 15.1	14.4 ± 5.9	0.322
ICU Stay	26.4 ± 20.7	17.1 ± 5.9	0.118

ICU: Intensive care unit, SD: Standard deviation.

In our study, the mortality rate was relatively high. The overall outcome was 86.7% (52/60 patients died) mostly because of septic shock and ARDS. Possible explanations may be attributed to the initial severity of illness (multiple comorbidities) or due to multiple organisms' colonization to the lower respiratory tract, of which about 25% were MDR. The late introduction of bronchoscopy and BAL for these severe cases may have a role in our results' high mortality. Fialkow *et al*. (2016) found, in contrast to our study, that the overall outcome regarding mortality was lower than us (51%). The causes of mortality in their study were sepsis and ARDS [12]. In contrast to our study, Chastre *et al*. compared 92 patients suspected of having pneumonia who underwent early bronchoscopy and 49 patients who did not. Mortality among patients who underwent bronchoscopy was 19%, compared with 35% for control patients (P value:03). Antibiotic modification according to BAL results actually changed the outcomes [20].

Table 7: Relation of microbiological data with survival

Microbiological Data	ICU, count (%)		p
	Nonsurvival	Survival	
Sputum culture and sensitivity (yes/no)			
Positive for growth	29 (55.8)	4 (50.0)	1
BAL culture and sensitivity (yes/no)			
Positive for growth	47 (90.4)	7 (87.5)	1
Sputum culture and sensitivity			
Gram-negative	24 (46.2)	4 (50.0)	1
Gram-negative ± fungi	1 (1.9)	0	
Fungi	4 (7.7)	0	
BAL culture and sensitivity			
Gram-negative	45 (86.5)	7 (87.5)	1
Gram-negative and positive	2 (3.8)	0	
BAL culture and sensitivity (MDR pathogen)			
MDR	13 (25.0)	2 (25.0)	1

ICU: Intensive care unit, BAL: Bronchoalveolar lavage, MDR: Multidrug-resistant.

In our study, we found that escalating antibiotics according to sputum and BAL culture and sensitivity results had no statistically significant value regarding mortality and weaning from mechanical ventilator. In concordance with our study, Carlos *et al*. (2000) concluded that there was no difference in mortality among patients who changed therapy guided

by BAL culture [19]. Another study, in concordance with our study, which was done by Shariatzadeh and Marrie (2009) resulted in that positive sputum culture was demonstrated in only a small number of patients with CAP and that did not affect antimicrobial therapy or mortality [21]. Chastre *et al*. (2006) founded, in contrast to our study that an 8-day regimen of antibiotic escalation after early bronchoscopy can probably be standard for patients with VAP and can be statistically significant regarding decreasing mortality and hospital stay [20].

Table 8: Accuracy of sputum culture in detection of organism

Sputum C and S	BAL culture and sensitivity (yes/no), count (%)		p
	Growth	No growth	
Growth	33 (61.1)	0	0.006
No growth	21 (38.9)	6 (100.0)	

BAL: Bronchoalveolar lavage.

In our study, we found that pneumonia severity index (PSI) did not have a statistically significant relation with mortality (P=0.836). However, in contrast to our study, pneumonia severity index was derived and validated as part of the pneumonia patient outcomes research team (PORT) prospective and cohort study for the purpose of identifying patients with CAP at low risk for mortality [22].

Table 9: Accuracy of sputum culture in detection of organism

Statistic	Value (%)	95% CI
Sensitivity	61.11	46.88–74.08
Specificity	100.00	54.07–100.00
PPV	100.00	
NPV	22.22	16.98–28.53
Accuracy	65.00	51.60–76.87

PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval.

Several studies used PSI to assess its capability of predicting mortality in non-CAP pneumonia as Carraba *et al*. (2012) when they used PSI to predict 30-day mortality in health-care associated pneumonia (HCAP) in immunocompetent versus immune suppressed patients. They concluded, in contrast to our study, that PSI would be the best scoring system to predict 30-day mortality in patients without immunosuppression [23]. Similarly, in our study, we found that the APACHE II score did not have a relation with survival (p = 0.432).

Table 10: Sputum culture and sensitivity versus bronchoalveolar lavage culture and sensitivity in detection of organisms

Sputum C and S	BAL culture and sensitivity		p
	No growth	Gram negative	
No growth	6 (100.0)	19 (36.5)	0.040
Gram negative	0	28 (53.8)	

BAL: Bronchoalveolar lavage.

Several studies, in contrast to our study, suggested that APACHE II score should be determined at the time of VAP diagnosis not ICU admission, known as VAP APACHE II score, as described by Furtado *et al*. (2012) [24]. The possible cause of our study results regarding PSI and APACHE II scoring systems may be due to the relatively small number of cases in our study. In the contrary, our study found that the PIRO score and the IBMP-10 score had a statistically significant relation with mortality (P=0.019 and 0.033, respectively).

Table 11: Relation of different response markers with survival

Response markers	Results	ICU, count (%)		p
		Nonsurvival	Survival	
Clinical improvement	Positive	7 (13.5)	2 (25.0)	0.593
Biomarker-wise response (mainly crp)	Positive	11 (21.2)	6 (75.0)	0.005

PIRO score had specificity of 100% but 50% sensitivity. While, IBMP-10 had sensitivity of 84.6% and specificity of 50%. In concordance with our study, Rello *et al*. were the first researchers to publish their results about using PIRO scoring system for CAP severity in 2009, and he mentioned that the PIRO scoring system is feasible for stratification of severity and improved prediction of 28-day mortality when compared with the APACHE II score and the 2007 ATS/IDSA criteria for CAP severity. Furthermore, it was useful to predict health-care utilization (length of stay in the ICU and requirement of mechanical ventilation) [25]. Five hundred twenty-nine patients were enrolled in this useful study in Spain.

Table 12: Survival according to clinical scoring systems

Scoring Systems	ICU, mean ± SD		p
	Non-survival	Survival	
CPIS	6.2 ± 1.4	6.1 ± 2.0	0.849
PSI	133.4 ± 29.4	132.1 ± 27.4	0.836
APACHE II	18.8 ± 6.6	15.6 ± 11.4	0.432
PIRO	1.5 ± 1.1	0.5 ± 0.5	0.014
IBMP-10	2.3 ± 1.1	1.5 ± 0.5	0.021

CPIS: Clinical pulmonary infection score, PSI: Pneumonia severity index, PIRO: Predisposition, insult, response, and organ dysfunction score, IBMP-10: Immunodeficiency, blood pressure, multilobar infiltrates, platelet count, and 10-day hospitalization, SD: Standard deviation, ICU: Intensive care unit.

Furtado, *et al*. (2012) found, in contrast to our study, that APACHE II was the sole score that independently predicted mortality for an independent population of culture positive VAP patients. VAP PIRO score was not a good predictor of ICU- and 28-day mortality. Its low sensitivity and specificity of VAP PIRO score preclude its use clinically as a predictor of ICU mortality. This study was performed on 168 patients [24]. Naeini, *et al*. (2015) in concordance to our study founded that IBMP10, compared to APACHE II, has greater sensitivity, specificity, and AUC to predict mortality in VAP patients. Sixty patients with VAP participated in their study [26]. Against our results, Wiskirchen *et al*. (2011) founded that the IBMP-10 score was not able to predict accurately 14-day mortality in critically ill patients. Conversely, the APACHE II was a valid predictor of both 14- and 28-day mortality when calculated on the day of VAP diagnosis. (Sample size was 168 VAP patients) [27].

Table 13: ROC curve for mortality against clinical scoring systems

Scoring Systems	AUC	p	95% CI		Cut off	Sensitivity %	Specificity %
			Lower bound	Upper bound			
PSI	0.477	0.836	0.245	0.709	-	-	-
PIRO	0.760	0.019	0.626	0.894	1.5	50	100
IBMP-10	0.736	0.033	0.581	0.890	1.5	84.6	50
APACHE II	0.587	0.434	0.336	0.837	-	-	-

AUC: Area under the curve, CI: Confidence interval, PSI: Pneumonia severity index, PIRO: Predisposition, insult, response, and organ dysfunction score, IBMP-10: Immunodeficiency, blood pressure, multilobar infiltrates, platelet count and 10-day hospitalization, APACHE II: Acute Physiology and Chronic Health Evaluation II.

Limitations of the study

Severity of the patients that may prevent us from doing bronchoscopy due to refractory hypoxemia,

hemodynamically unstable patients with severe lower respiratory tract infection could not be assessed by bronchoscopy for fear of deterioration, long time of fungal culture result give the chance for unexpected loss of the result, the presence of coagulopathy that could not be corrected easily due to severity of the patients such as DIC and severe liver cell failure patients, and disapproval of close relatives of the patients to do any invasive procedure.

Conclusion

Statistically, sputum culture and sensitivity has accuracy of 65% in comparison with accuracy of BAL in detection of organisms causing lower respiratory tract infection. (With P value 0.006). We found also that none of bacterial growth in sputum or BAL cultures even MDR pathogens had statistically significant relation to survival. We found also that escalation of antibiotics according to BAL culture and sensitivity results had no statistically significant value regarding mortality and weaning from mechanical ventilator. In our study, regarding scoring systems for pneumonia, we found that the high PIRO and IBMP-10 scores were good predictors for high mortality in patients with the lower respiratory tract infections more than the other scores such as pneumonia severity index and APACHE II scores.

Recommendation

1. We recommend early bronchoscopy and BAL for all patients with deteriorating pneumonia who needed to be mechanically ventilated to early detect the organism and guide the antibiotic therapy.
2. We recommend the use of the new technology (BIOFIRE PCR- the pneumonia panel) early from the BAL fluid soon after intubation and mechanical ventilation so as to early identify and modify the treatment strategy.
3. We recommend the use of multiple scoring systems to assess mortality due to chest conditions in hospitals and research studies.
4. We recommend further studies to use larger number of patients with severe chest infection to assess early BAL on the overall outcome.

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