Original Article

The role of lung ultrasound in procalcitonin-guided antibiotic discontinuation in ventilator-associated pneumonia

Address for correspondence:
Mona A. Ammar,
Department of Anaesthesia,
Intensive Care and Pain
management, Faculty
of Medicine, Ain Shams
University, Fifth Settlement,
Postal address: 11865, Cairo,
Egypt.
E-mail: Mona.ammar@med.
asu.edu.eg

Mona A. Ammar, Amr Hilal, Waleed Abdalla
Assistant Professor of Anesthesia, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Background and Aims: Starting antibiotic therapy at the proper time is the cornerstone of the management of ventilator-associated pneumonia (VAP). However, using antibiotics for a long duration of therapy in intensive care leads to increased bacterial resistance, financial burden and adverse drug reactions. We hypothesised that lung ultrasound may have a role in guiding antibiotic discontinuation in patients with VAP that will help to reduce the antibiotic duration and decrease the resistance. **Methods:** This was a prospective blinded cohort study from October 2020 to September 2021 in which 62 VAP patients were recruited. Antibiotics were started, procalcitonin (PCT) level and clinical pulmonary infection score were estimated and lung ultrasound (US) was performed on day 1 and repeated on day 7. On day 7, discontinuation of antibiotics was recommended if the PCT level was <0.25 μg/L. A lung reaeration score was recorded. **Results**: Based on the PCT levels, antibiotics were discontinued in 40 patients. The computed tomography findings of VAP had improved in all. The ultrasound reaeration score showed a highly significant negative correlation with the PCT on day 7 (-0.718, $P < 0.001$). A cut-off of 5 for the US score showed a sensitivity of 92.5%, specificity of 95.5%, positive predictive value of 97.4% and negative predictive value of 87.5% in detecting a low PCT score on day 7. **Conclusion**: Lung US is a non-invasive and safe method that can be used to guide antibiotic therapy in VAP.

Key words: Antibiotic, lung, procalcitonin, ultrasound. ventilator-associated pneumonia

INTRODUCTION

Prolonged mechanical ventilation, intensive care unit (ICU) stay and increased antimicrobials usage usually lead to ventilator-associated pneumonia (VAP), and hence healthcare cost and mortality.[1] Acute respiratory infections (ARIs) in critically ill patients comprise a group of heterogeneous infections including bacterial, viral and fungal infections. Starting antibiotic therapy at the proper time is the cornerstone of the management of VAP secondary to bacterial infection. However, a longer duration of antibiotic therapy increases the incidence of bacterial resistance, financial burden and adverse drug reactions.[2]

Procalcitonin (PCT) is a precursor of calcitonin. Cytokines and endotoxin elaborated during infections

with bacteria inhibit the final step in the synthesis of calcitonin; therefore, the level of PCT is elevated, which acts as a specific biomarker for the diagnosis of bacterial infections.[3] PCT could be of benefit in the decision of starting and discontinuation of antibiotic therapy.[4]

Few studies have proved the role and effectiveness of lung ultrasound (US) for the diagnosis and follow-up

of ICU-admitted pneumonia patients.[5] It could be a highly sensitive and specific tool when compared to computed tomography (CT) of the chest for the diagnosis of community-acquired pneumonia (CAP).[6]

We hypothesised that lung US may have a beneficial role in guiding the discontinuation of antibiotics among VAP patients.

METHODS

This prospective blinded cohort study was performed after approval from the university ethics committee (R49/2020) and registered at clinical trials. gov with the number NCT045631004. The study was performed at a university ICU between October 2020 and September 2021. It was conducted as per the principles of the Declaration of Helsinki.

A total of 62 patients of both genders aged 18 years and older with a confirmed diagnosis of VAP by positive sputum culture were enroled for the study. VAP was considered if manifestations occurred following intubation for 48 h and the infection was absent before ventilation.[7] The diagnosis of pneumonia was based on the finding of new and progressive pulmonary infiltrates in chest images together with two of the following clinical criteria: core temperature >38°C or <35.5°C; white blood cell count >12,000 cells/mm³ or <4000 cells/mm³; and clinical evidence of pneumonia as purulent secretions and hypoxaemia.[8] Patients who had a history of a coexisting infection other than VAP, pregnancy, immunosuppressive agents usage other than steroids, neutropenia (white blood cell count ≤1000 cells/mm³) and patients diagnosed with CAP were excluded from the study. As regards the current pandemic, coronavirus disease (COVID)-19 was ruled out by CT scan and polymerase chain reaction (PCR) test.

Once VAP was diagnosed and antibiotics started, it was considered as day 1 and, measurements of PCT level, clinical pulmonary infection score (CPIS) and lung US were done. The operator who performed the US was blinded to the study. After 7 days of antibiotic therapy, clinical, biological and microbiological variables were measured. Lung US and PCT levels were evaluated. Lung reaeration score was assessed through comparison of the extension or resolution of the alveolar-interstitial syndrome and consolidation on day 1 and day 7. Discontinuation of antibiotics was recommended if the PCT level was <0.25 µg/L.

Lung US was performed using Siemens Healthineers-Germany probe 3.6–13 MHz and phased array probe 1–4.8 MHz, all intercostal spaces of the right and left hemithorax were examined, and videos were stored for blind analysis. Regions of interest were carefully examined, and the worst detected finding was considered characteristic for the examined region. Four ultrasound patterns were defined: 1) Normal aeration (no findings suggesting pneumonia): the presence of pleural sliding with A-lines +/- occasional or isolated B-line (N) [Figure 1a], 2) Loss of lung aeration associated with interstitial pneumonia or scattered foci of bronchopneumonia: presence of many well-defined, irregularly spaced B-lines arising from the pleural line or a small subpleural consolidation. (B1) [Figure 1b], 3) Loss of lung aeration associated with confluent bronchopneumonia: multiple abutting B-lines arising from the pleural line or a small subpleural consolidation. (B2) [Figure 1c], 4) Lung consolidation which is characteristic of extensive bronchopneumonia: the presence of tissue patterns containing hyperechoic images and air bronchograms (C) [Figure 1d]. A reaeration score was calculated from changes in the lung US findings [Table 1]. The primary outcome was to assess the correlation between lung US reaeration score and PCT levels in order to discontinue antibiotics therapy in VAP patients.
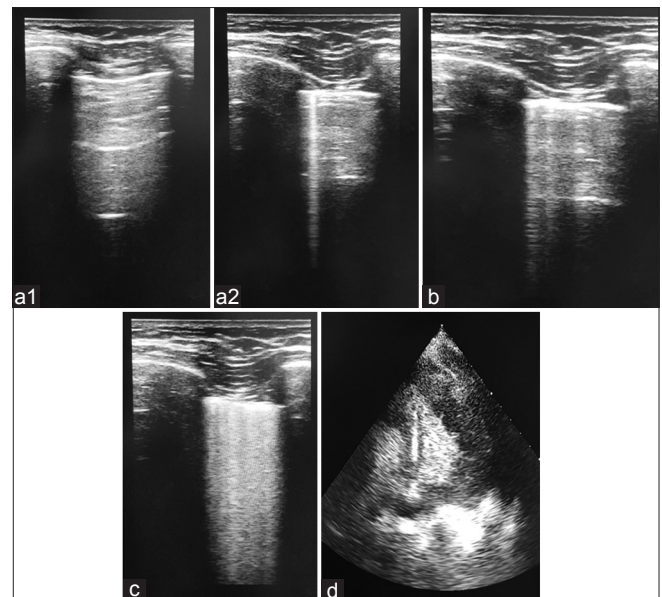

Figure 1: (a1) Normal lung aeration with the presence of pleural sliding and A-line. (a2) Normal lung aeration with the presence of pleural sliding, A-line, and single B- line. (b) Loss of lung aeration associated with interstitial pneumonia. (c) Loss of lung aeration associated with confluent pneumonia. (d) Lung consolidation

Assuming a correlation coefficient between lung US and procalcitonin of 0.50, a sample size of 62 VAP patients would be enough to detect correlation, with an alpha error of 0.01 and 0.95% power of the test. The data were collected, revised, coded, and entered into the International Business Machines Statistical Package for Social Science (IBM SPSS Released 2015, Version 23.0. Armonk, New York). The quantitative data were presented as mean, standard deviations, and ranges when parametric and median with inter-quartile range (IQR) when non-parametric, whereas qualitative variables were presented as numbers and percentages. The comparison between two groups with qualitative data was done using the Chi-square test and the agreement between PCT and lung US using Kappa-agreement. The comparison between the two groups regarding quantitative data was done using an independent t-test when parametric, and Mann–Whitney test when non-parametric. Also, the comparison between two paired readings was done using the Wilcoxon rank test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The receiver operating characteristic (ROC) curve was used in the form of a quantitative model to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC). The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the P value was considered significant at the level of <0.05.

RESULTS

Sixty-two consecutive patients were included in the study; out of these, 39 (62. 6%) were males and 23 (37.1%) were females, and the mean age was 55.13 ± 14.90 years. Initial causes of admission to ICU were poly-trauma patients (n = 12), traumatic brain injury (n = 8), major abdominal surgery (n = 14), post-craniotomy (n = 9), and medical conditions (n = 19). At inclusion in the study (Day 1), the median acute physiology and chronic health evaluation (APACHE) median score was 12 (IQR, 10–14), and the median CPIS was 8.0 (IQR, 8.0–9.0), which decreased to 5 (IQR, 4.0–6.0) on day 7.

Median procalcitonin level was 0.8 (range: 0.2–1.5; IQR, 0.56–0.91) µg/L on day 1, which decreased to 0.2 (range: 0.01–1; IQR, 0.1–0.5) µg/L on day 7 (*P*-value < 0.001).

On day 7, antibiotics were discontinued based on a PCT level of <0.25 µg/L in 40 patients, and all of

them showed improvement in VAP according to CT findings. Antibiotics were continued in 22 patients. In comparison of the two groups, there was no statistical difference with regard to age, gender, and APACHE score, but there was a significant statistical difference in lung reaeration score (median -4 range: from -15 to 8; IQR, from -10 to 5) in whom the antibiotics were continued as compared to those in whom the antibiotics were discontinued (median 6; range: from -5 to 15; IQR, from 6 to 10; *P* value < 0.001).

There was a highly significant negative correlation on day 7 (r = -0.718, *P* < 0.001) between US reaeration score and PCT level and a highly significant positive correlation between reaeration by lung US and CT (r = 0.747**, *P* < 0.001) [Table 2, Figure 2]. ROC curve of US reaeration score and PCT level as regards the decision to stop or to continue antibiotic therapy showed that with a cut-off point of 5 for US score, sensitivity was 92.5%, specificity was 95.5%, PPV was 97.4%, and NPV was 87.5% [Table 3, Figure 3].

DISCUSSION

The findings of the present study show that lung US is a valid non-invasive method for the discontinuation

Table 1: The effects of antibiotics on lung aeration[14]

Quantification of reaeration			Quantification of loss of aeration		
1 point	3 points	5 points	-5 points	-3 points	-1 point
B1→N	B2→N	C→N	N→C	N→B2	N→B1
B2→B1	C→B1			B1→C	B1→B2
C→B2					B2→C

N: Normal aeration (no findings suggesting pneumonia), B1: Loss of lung aeration associated with interstitial pneumonia, B2: Loss of lung aeration associated with confluent bronchopneumonia, C: Lung consolidation which is characteristic of extensive bronchopneumonia

Table 2: Correlation between PCT level, lung ultrasound reaeration score, and CT on day 7

Parameter	PCT		LUS reaeration score		CT reaeration	
	r	P	r	P	r	P
PCT (µg/L)	-	-	-0.718**	≤0.001	-0.552**	≤0.001
LUS reaeration score	-0.718**	≤0.001	-	-	0.747**	≤0.001
CT reaeration	-0.552**	≤0.001	0.747**	≤0.001	-	-

PCT: Procalcitonin, LUS: Lung ultrasound, CT: Computed tomography, *r*–correlation coefficient

Table 3: Agreement for lung ultrasound score and procalcitonin (PCT) level on day 7

Parameter	AUC	Cut-off Point	Sensitivity	Specificity	PPV	NPV
LUS score	0.957	>5	92.5	95.5	97.4	87.5

AUC: Area under the curve, PPV positive predictive value, NPV: negative predictive value, LUS: Lung ultrasound
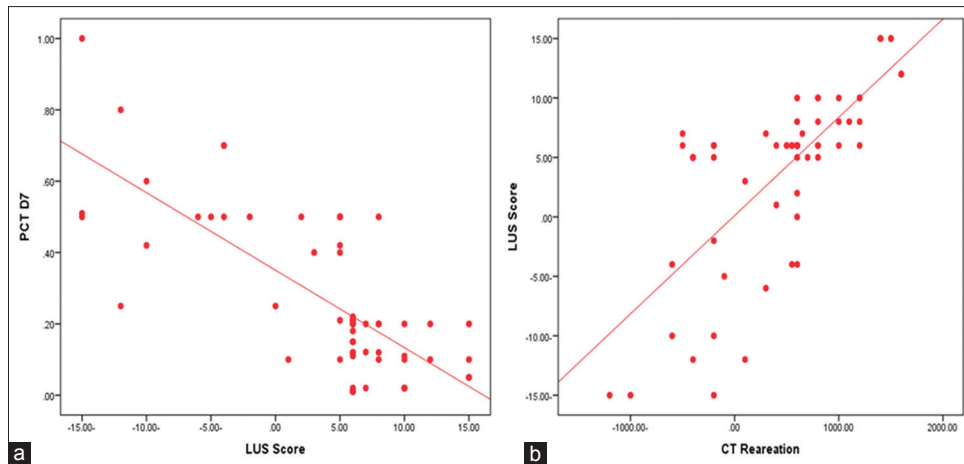
Figure 2: (a) Correlation between lung ultrasound (LUS) reaeration score and procalcitonin (PCT) level on day 7. (b) Correlation between lung ultrasound (LUS) reaeration score and computed tomography (CT) chest on day 7
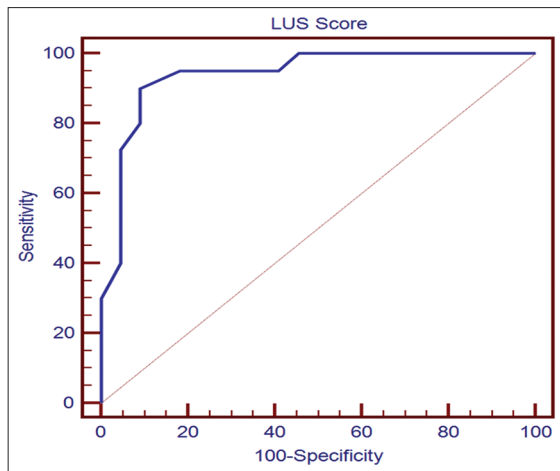

Figure 3: Receiver operating characteristic (ROC) curve for lung ultrasound

of antibiotic therapy in VAP patients. This decision is very critical, requiring precise timing and clear milestones. A shorter course of antibiotic treatment and early discontinuation of antibiotics can help reduce unnecessary costs and decrease antibiotic exposure and antibiotic resistance.[9,10] In addition, clinical practice guidelines for the management of VAP and hospital-acquired pneumonia (HAP) 2016 by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) have mentioned that 7 days of antibiotic therapy instead of a longer duration is recommended for patients with VAP.[11]

In a meta-analysis of 13 trials with 5136 patients using PCT as a guide for antibiotic discontinuation, it was found that it reduced antibiotic exposure and short-term mortality.[12] In another meta-analysis of critically ill adults (5158 randomised; 5,000 analysed), antibiotic

discontinuation guided by PCT was associated with reduced mortality [16 randomised controlled trials, risk ratio (RR) of 0.89, 95% confidence interval of 0.83-0.97, I ^{2} = 0%, low certainty].[13] These findings did not match our results. Scoring systems of lung US based on A and B lines and lung consolidation have been applied for monitoring and quantitative assessment of pulmonary aeration and changes in aeration.[14-17] All these scoring systems divide lung aeration into four patterns that are used to evaluate the aeration and reaeration seen in lung US.[18]

It has been shown in a study that the combination of lung US and PCT is better in the diagnosis of subjects who are ventilated and have signs and symptoms of pneumonia, compared with the use of lung US, PCT, CPIS, and other inflammatory biomarkers alone.[19] In the current study, when US was correlated with PCT levels, there was a statistically significant correlation on day 7 (0.718, $P = 0.000$).

US scores > 5 have been associated with reaeration in CT of > 400 mL and successful antimicrobial treatment. Bouhemad *et al.* showed a highly significant correlation between CT and lung US reaeration (ρ 0.85, $P < 0.0001$).[14] This study supports our results regarding the correlation between lung US and CT results of VAP patients. The chest radiograph is not accurate in predicting lung ventilation. It has been already reported that US has 93.4% sensitivity and 97.7% specificity for the diagnosis of VAP,[20] and this supports our study on the validity of lung US for the assessment of VAP patients. The strength of our study is the simultaneous measurements of lung US, PCT, and CT results during the ICU stay of VAP patients.

Lung US is an operator-dependent technology and this could be a limitation of the current study. Supervised training is needed for operators for correct interpretation of the sonographic findings. Although US is an easy technique, it may be difficult in obese patients, those with pleural calcifications, and patients with dressings on the chest wall; about 20% of the lung surface cannot be visualised by US due to the shielding of anatomic structures (clavicle and scapula).[21] Additionally, the size and location of consolidation may be difficult to detect. Small consolidations located away from pleura and smaller than 20 mm may not be detected by lung US.[22]

CONCLUSION

To conclude, antibiotic discontinuation is a critical decision; lung US is a non-invasive and safe method that can be used to guide antibiotic therapy in VAP patients.

Conflicts of interest
There are no conflicts of interest.

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