



# Ventilator-associated pneumonia diagnosis: a prioritization exercise based on multi-criteria decision analysis

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## Abstract

The aim was to provide global experts ranking on priorities in diagnostic tools for VAP in clinical practice. A multiple criteria decision analysis (MCDA) was performed to identify diagnosis tools for VAP diagnosis. Priority factors were identified after literature review. An international, multidisciplinary expert panel reviewed variables and ranked diagnostic tools. Experts from ten European hospitals participated. Regarding bedside clinical practices, seven required chest X-ray use in all patients, whereas six reported the use of blood cultures and endotracheal aspirate in all patients. Invasive techniques were routinely performed in seven sites. CRP, PCT, and Gram stains were performed in all patients by 5, 2, and 8, respectively. Impact on patient outcomes, safety, and impact on the decision to start antibiotic therapy were ranked as the top three relevant concerns (7.7/10, 7/10, and 6.9/10, respectively). Chest X-ray was ranked as the most important imaging technique to diagnose VAP (score 251.7). Apart from blood cultures, endotracheal aspirate culture was identified as the main collection method for the microbiological testing (scores of 274.8 and 246.8, respectively). Mini-BAL was the preferred invasive technique with a score of 208. Top three biomarkers were CRP (score 184.3), PCT (181.3), and WBC (166.4). Gram stain (192.5) was prioritized among laboratory diagnostic techniques. Using MCDA, it is recommended to perform a combination of diagnostic techniques including images (chest X-ray), culture of clinical specimens (blood cultures and endotracheal aspirate), and biomarkers (CRP or PCT) for VAP diagnosis at the bedside. Gram stain was ranked as the preferred laboratory technique.

**Keywords** VAP · Diagnosis · MCDA · Multicriteria decision analysis · Ventilator-associated pneumonia · Microbiology diagnosis · Biomarkers · Imaging

## Introduction

Ventilator-associated pneumonia (VAP) is a chest infection occurring 48 h after the initiation of mechanical ventilation. It is responsible for increasing hospital length of stay and costs [1, 2]. Many efforts are still being performed to reduce their burden, especially using prevention bundles [3, 4], which have been shown to be effective in reducing its rate. VAP is a continuous process presenting with nonspecific clinical features [5], with some limitations regarding its definition and

diagnosis, because gold-standard tests are still lacking. It is also missing clear evidence to prioritize diagnostic tests and how they impact clinical outcomes. As evidence is weak, expert opinion should be taken into account. Multi-criteria decision analysis (MCDA) is widely used in decision-making in various areas in order to rank priorities and is also used in medicine with the same purpose putting together evidence and expert opinion [6, 7].

Our aim is to create a set of priorities of tools for VAP diagnosis in adult patients using a MCDA. Furthermore, we also want to provide data regarding experts' preferences and the use of diagnostic tools in their practice.

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## Methods

An international panel of experts with a background in intensive care medicine and clinical microbiology was directly

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invited by email to participate in this study by filling an electronic survey (Supplementary material 1). Participants were chosen by study coordinator (JR), according to their expertise in clinical practice, participation in clinical studies, and publications. Experts also contributed to article revision and provision of the final version.

A comprehensive list of VAP diagnostic tests and priority criteria included in multi-criteria decision analysis (MCDA, methodology described elsewhere [8]) were chosen by the study coordinator after literature review [9–11]. Seven priority criteria were defined by authors (JFC and JR) and independently weighted by the panel, according to their relative importance to each other. Diagnostic tests were evaluated individually against priority criteria, by each expert. These results were then multiplied by the weight of each priority criterion to obtain individual scores for each diagnostic test. Then, sum score was obtained after addition of all the partial scores previously achieved. Each variable was transformed into a 0–10 scale in order to facilitate their comparison. All responses are categorical variables since they are reported using descriptive statistics (proportions and percentages). Median and interquartile range (IQR) were used to analyze nonparametric variables.

Panel members were also inquired about their perceived relevance of each diagnostic tool and also about their use in clinical practice. For the purpose of this study, VAP is defined as a chest infection that occurs after 48 h of endotracheal tube placement [9, 10]. This study focuses on adult patients. Due to the lack of patients, data in this study, ethical approval, and informed consent were waived.

## Results

A panel of ten European experts with background in intensive care medicine and clinical microbiology accepted to participate in our study.

Seven in 10 experts confirmed the use of chest X-ray in all patients with VAP, while 5/10 and 4/10 admitted the use of chest CT and lung ultrasound in more than 50% of patients, respectively. The whole group used at least one imaging technique for VAP diagnosis. Blood cultures and endotracheal aspirate were declared to be the most used methods to obtain microbiological specimens for culture. All group members reported their use in more than 60% and 50% of cases, respectively. Any invasive technique is used in more than 50% of VAP patients by 7 experts, while bronchoalveolar lavage is the most commonly used technique (5/10 reported its use in more than 50% of patients). Transbronchial biopsy was reported as the least used bronchoscopy technique. All declined the use of IL6 and IL10, as well as pro-adrenomedulin in VAP diagnosis in their practice. White blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT) are used in all patients by 7/10, 5/10, and 2/10 members of the panel, respectively.

Two (2/10) reported the absence of the use of biomarkers in 10–20% of patients, while 3/10 reported no use of CRP and PCT. Gram stain and MALDI-TOF (matrix assisted laser desorption ionization-time of flight) were reported as the most used among microbiological techniques, performed in all patients by 8/10 and 6/10 physicians, respectively.

After an MCDA, impact in patient outcomes (7.7/10), risk to the patient (7.0/10), and impact on decision to start antibiotic therapy (6.9/10) were ranked as the major concerns for VAP diagnosis, followed by time to clinical relevant result (6.0/10), test availability (5.7/10), need for professional experience (4.0/10), and cost (2.7/10).

Chest X-ray was ranked as the most important imaging technique (score 251.7). “None imaging technique use” strategy obtained the least score (143.6). Blood cultures and endotracheal aspirate culture were scored as the most important microbiological cultures (scores 274.8 and 246.8). Among invasive techniques, mini-bronchoalveolar lavage (mini-BAL) was ranked first (208.0), followed by bronchoalveolar lavage (BAL; 204.9), the telescopic catheter (176.7), and transbronchial biopsy (78.7). Among these techniques, mini-BAL was intended as the safest (score 46.7) and BAL the riskier (after transbronchial biopsy, that is rarely used). Meanwhile, the same distribution appeared in need of professionals’ experience, where mini-BAL was ranked as the one that needs less experience (Table 1).

CRP (score 184.3), PCT (score 171.3), and WBC (score 166.4) were ordered as the most important biomarkers in VAP diagnosis. Gram stain had the most favorable score in microbiological techniques (score 192.5), followed by MALDI-TOF (score 180.0), PCR tests (score 177.5), and Gene Expert® for ESBL (score 162.9). Regarding time to clinical relevant result, Gram stain, PCR tests, and MALDI-TOF were top scored. Table 1 shows the overall results of the MCDA analysis. According to panel members ranking, chest CT is the imaging technique that impacts the strongest on patient outcomes. Blood cultures, MALDI-TOF, and PCR are the more important in test microbiology cultures and techniques, and PCT is intended as the biomarker with most impacting on patient outcomes. Gram stain, MALDI-TOF, and PCR tests were scored first in “Time to clinical relevant result”. Bronchoscopy techniques (included transbronchial biopsy) were considered as the unsafest for VAP diagnosis (Table 1).

In this study survey, the panel was also asked to show their own relevance for each test (Table 2 shows, in a 10 value scale, expert preference in VAP diagnosis). Chest X-ray was the preferred imaging technique (score 8.5/10), bronchoalveolar lavage culture the preferred away to assess lung pathogens (score 8.0/10). Procalcitonin (score 8.4/10) and CRP (score 8.0/10) were classified as the most relevant biomarkers. Gram stain (8.3/10) was the preferred microbiological technique.

**Table 1** MCDA results

|                                     | Impact on patient outcomes | Risk to the patient | Impact on decision to start antibiotic therapy | Time to clinical relevant result | Test availability | Need of professionals experience | Cost | Sum score |
|-------------------------------------|----------------------------|---------------------|--|----------------------------------|-------------------|----------------------------------|------|-----------|
| Weight                              | 7.7                        | 7                   | 6.9  | 6                                | 5.7               | 4                                | 2.7  |           |
| Imaging techniques                  |                            |                     |  |                                  |                   |                                  |      |           |
| X-ray                               | 55.8                       | 49                  | 53.5   |                                  | 54.2              | 23                               | 16.2 | 251.7     |
| Chest CT                            | 69.3                       | 47.3                | 55.2   |                                  | 32.8              | 20                               | 6.8  | 231.4     |
| Lung ultrasound                     | 48.1                       | 56                  | 46.6   |                                  | 37                | 17                               | 18.2 | 222.9     |
| None                                | 18.8                       | 22.8                | 17.2   |                                  | 18.5              | 40                               | 26.3 | 143.6     |
| Microbiological tests               |                            |                     |  |                                  |                   |                                  |      |           |
| Blood cultures                      | 57.8                       | 67.7                | 50.6   |                                  | 49.4              | 30                               | 19.3 | 274.8     |
| Endotracheal aspirate culture       | 33.4                       | 59.5                | 42.6   |                                  | 53.2              | 33.3                             | 24.8 | 246.8     |
| Mini-bronchoalveolar lavage culture | 47.5                       | 46.7                | 40.3   |                                  | 30.4              | 26                               | 17.1 | 208       |
| Bronchoalveolar lavage culture      | 53.9                       | 28                  | 54.1   |                                  | 31.4              | 22.6                             | 14.9 | 204.9     |
| Telescopic catheter                 | 51.3                       | 31                  | 35.7   |                                  | 25.7              | 20                               | 13   | 176.7     |
| Transbronchial biopsy               | 25.7                       | 11.7                | 18.4   |                                  | 9.5               | 8                                | 5.4  | 78.7      |
| Biomarkers                          |                            |                     |  |                                  |                   |                                  |      |           |
| CRP                                 | 63.8                       |                     | 53.2   |                                  | 48                |                                  | 19.3 | 184.3     |
| PCT                                 | 66                         |                     | 57.2   |                                  | 41.5              |                                  | 16.6 | 181.3     |
| WBC                                 | 40.7                       |                     | 53.2   |                                  | 52.1              |                                  | 20.4 | 166.4     |
| Pro-adrenomedullin                  | 47.3                       |                     | 27.6   |                                  | 21.2              |                                  | 10   | 106.1     |
| None                                | 17.6                       |                     | 33.5   |                                  | 27.7              |                                  | 23.9 | 102.7     |
| IL6                                 | 39.6                       |                     | 28.6   |                                  | 18.7              |                                  | 9.6  | 96.5      |
| IL10                                | 33                         |                     | 22.7   |                                  | 18.7              |                                  | 8.1  | 82.5      |
| DIAGNOSTIC techniques               |                            |                     |  |                                  |                   |                                  |      |           |
| Gram stain                          | 52.9                       |                     |  | 51                               | 49.2              | 17.5                             | 21.9 | 192.5     |
| MALDI-TOF                           | 59.7                       |                     |  | 42.7                             | 46.3              | 18.5                             | 12.8 | 180       |
| PCR tests                           | 59.7                       |                     |  | 45.8                             | 39.2              | 23                               | 9.8  | 177.5     |
| Gene Expert® for ESBL               | 56.8                       |                     |  | 39.8                             | 32.8              | 24                               | 9.5  | 162.9     |
| Multiplex PCR                       | 52                         |                     |  | 34.5                             | 28.5              | 22                               | 9.8  | 146.8     |
| Serological tests                   | 25                         |                     |  | 21.7                             | 29.9              | 25                               | 16.5 | 118.1     |
| Rapid automated microscopy          | 29.8                       |                     |  | 27                               | 15.7              | 19                               | 15.5 | 107       |
| None                                | 2.9                        |                     |  | 7.5                              | 15                | 31                               | 25.6 | 82        |

## Discussion

This study represents the first comprehensive recommendations for VAP diagnosis, enclosing image, microbiologic specimens, biomarkers, and lab tests using a formal decision support tool. According to this, VAP diagnosis should be based on chest X-ray, blood cultures, endotracheal aspirate, CRP (or PCT), and Gram stain.

The clinical diagnostic criteria for VAP are subjective, lack specificity. For that, the use of diagnostic tools is widely variable according to local practices and different beliefs of its importance [12]. We evaluated some priority factors that can affect the diagnostic approach. Impact on patient outcomes and risk were the characteristics of major concern to experts,

revealing concerns with final patient results and also the importance of risk evaluation before diagnostic tools use. Time to clinical relevant result is also a key decision factor, which had only been tested for microbiological techniques, in order to rank these techniques as they are critical to assess rapidly deteriorating patients. Surprisingly, in an era dominated by health economics and healthcare resource limitation, experts stated the cost as the least important characteristic, in spite of being an important limitation in tool availability.

Chest X-ray is the preferred imaging method for VAP diagnosis in this study. No expert stated to bypass an imaging method to diagnose VAP in clinical practice, in contrast to the CDC approach [13, 14], which excludes any imaging method for ventilator-associated events (VAE) surveillance. Our results

**Table 2** Experts panel preference in VAP diagnosis (in proportion 0–10)

| Imaging techniques |     | Microbiological tests |     | Biomarkers |     | Other laboratory techniques |     |
|--------------------|-----|-----------------------|-----|------------|-----|-----------------------------|-----|
| Chest X-ray        | 8.5 | BAL culture           | 8.0 | PCT        | 8.4 | Gram stain                  | 8.3 |
| Chest CT           | 7.8 | Mini-BAL culture      | 7.0 | CRP        | 8.0 | MALDI-TOF                   | 7.5 |
| Lung ultrasound    | 6.3 | ET aspirate           | 5.8 | WBC        | 6.3 | Gene Expert®                | 6.8 |
| None               | 2.5 | Blood cultures        | 5.3 | Pro-ADM    | 5.0 | Multiplex PCR               | 6.5 |
|                    |     | Telescopic catheter   | 6.3 | None       | 4.7 | PCR tests                   | 6.1 |
|                    |     | Transbronchial biopsy | 2.5 | IL6        | 3.9 | Rapid automated microscopy  | 4.8 |
|                    |     |                       |     | IL 10      | 3.7 | Serological tests           | 3.9 |
|                    |     |                       |     |            |     | None                        | 1.3 |

BAL bronchoalveolar lavage, ET aspirate endotracheal aspirate, Pro-ADM pro-adrenomedullin

are in line with the ECDC strategy [15], which preserves chest imaging as a key for VAP surveillance and also with studies showing different prognosis of VAP and ventilator-associated tracheobronchitis [16]. In spite of this controversy, it is pertinent to keep in mind that VAP surveillance and diagnosis or clinical management are different approaches. Important to note that, despite lung ultrasound (LUS) use is increasing [17], in our study experts ranked as the least important imaging technique. This could be explained by the lack of training and access in LUS, which can limit its use.

In IDSA/ATS 2016 [10] and ERS/ESICM/ESCMID/ALAT 2017 [9] guidelines, biomarkers used are not supported in VAP diagnosis as well as in decision for antibiotic withdrawal (except in specific circumstances). Meanwhile, biomarkers are abundantly used worldwide in VAP diagnosis, despite clear evidence proving that their positive impact on outcomes had never been published [18]. Most of our panel declared the use of WBC, CRP, and PCT in clinical practice, in spite of MCDA showed a preference by CRP and PCT. This could be explained by their low cost, and also, their use is generally intended as a good clinical practice (as some behaviors in medicine that are not supported by high-quality evidence). Differently, IL6, IL10, and Pro-adrenomedullin remain usefulness tools beyond investigational purposes.

Microbiological cultures and tests remain one of the most divergent issues in different guidelines [9–11]. Blood cultures, despite infrequently positive, were previously recognized as important tools in VAP [19], since bacteremic VAP is associated with higher mortality [20]. Although, in our MCDA experts ranked blood cultures as the most important culture specimen, when asked about their preferences in VAP diagnosis, blood cultures were only the fourth preferred. Between the other methods of specimens' collection for culture, endotracheal aspirate score first in MCDA, at the same time as BAL and mini-BAL were the preferred (by this order) invasive techniques. This can be related to the controversy about this issue in international guidelines. While American guidelines [10] recommend noninvasive and semi-quantitative sampling, European guidelines [9] recommend invasive and quantitative

sampling. Interestingly, both are qualified as “Weak recommendation” and “Low-quality evidence”, exposing that this concerning issue recommendation is more associated with divergent interpretation than different recognized evidence.

On the other hand, in the MCDA, mini-BAL scored slightly better than BAL, mainly driven by risk profile (safer) and less necessity for professionals' experience. This represents an important field, as in some places professionals lack experience in bronchoscopic BAL or if experienced operators are not always present. Besides cost and availability were out of the highest experts priorities, very specific tests as PCR tests and multiplex PCR were not in the top priorities regarding microbiological techniques. Timely results are of the highest importance in critically ill patient outcomes [21, 22] and also in reducing antibiotic pressure; therefore, the need for timely results is a relevant issue. In this subject, Gram stain, PCR tests, and Multiplex PCR that are able to produce results within 1–2 h can have a special role. Notwithstanding, it is also important to take into account local microbiology because tools like Gene Expert® for ESBL can be prioritized in some places.

This study has several limitations. First, the experts panel a limited European panel that can impair study generalization for other areas. Second, derived recommendations and data from patients did not take into account nor the number of patients treated in physicians ICUs, neither the physicians' experience. Third, specific patients admitted to each ICU (cardiac, burns, trauma, etc) were not addressed. Fourth, the availability of diagnostic tools in each hospital was not addressed, which could limit physicians' experience with some diagnostic techniques, influencing their beliefs.

The strengths include the study methodology (MCDA) and the possible generalization of this data, as previously reported [23], and the possibility to update this information in the future if new diagnostic tools becomes available in clinical practice.

Through MCDA analysis, this experts panel recommends for VAP diagnosis a set of chest X-ray, blood cultures, endotracheal aspirate, CRP (and PCT), and Gram stain.

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