Review Article

The next generation of rapid point-of-care testing identification tools for ventilator-associated pneumonia

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Abstract: Ventilator-associated pneumonia (VAP) is a frequent issue in intensive care units (ICU), with a major impact on morbidity, mortality and cost of care. VAP diagnosis remains challenging: traditional culture-based microbiological techniques are still the gold-standard, but are too slow to enable clinicians to improve prognosis with timely antimicrobial therapy adjustment. Prolonged exposure to inappropriate antibiotics has also been shown to increase the incidence of multi-drug-resistant organisms (MDROs). Point-of-care testing (POCT) tools are diagnostic testing methods that can be used at or near the bedside, with delays ranging from a couple minutes to a few hours. The use of POCTs for VAP could allow for faster diagnosis and antimicrobial therapy adjustments. Despite uncertainty regarding their diagnostic value, C-reactive protein (CRP) and procalcitonin (PCT) can be detected using POCTs in few minutes. In VAP, CRP showed a sensitivity of 56% to 88% and specificity of 86% to 91%; PCT showed a sensitivity of 78% to 100% and a specificity between 75% and 97% using non-POCT methods. Automated microscopy could also be used in clinical ICU setting, with reported sensitivity of 100% and specificity of 97%, allowing for antibiotic susceptibility testing (AST) in less than 12 h. Multiplex polymerase chain reaction (MPCR) could allow for identification and AST approximation through the detection of drug-resistance genes in about 6 h, with reported sensitivity of 89.2% and specificity of 97.1%; although use as POCT was shown to result in test failure in about 40% of samples. Despite being at an early development stage, exhalome analysis, which allows for non-invasive fast identification, and chromogenic tests, more suited for the detection of drug-resistance enzymes, are also promising techniques for POCT diagnosis of VAP.

Keywords: Point-of-care; ventilator-associated pneumonia (VAP); intensive care unit (ICU); hospital-acquired pneumonia (HAP)

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Introduction

Despite some advances in the understanding of ventilator-associated pneumonia (VAP) pathophysiology and the causing pathogens, VAP remains a major concern in the critical care setting because of its high incidence (1) and consequences in terms of mortality, morbidity and cost (2,3). VAP represents both a diagnostic and therapeutic challenge.

Clinical and radiologic diagnostic criteria have been shown to be inconsistent with autopsy findings (4) and simple laboratory tests such as C-reactive protein (CRP) and procalcitonin (PCT) are still not recommended, despite some promising results, because of concerns of limited sensitivity and specificity (5). The highest level of certainty for the diagnosis of VAP is thus achieved using "traditional" microbiological data, namely Gram stain examination which is a fast but inaccurate technique (6), and culture-

based identification, obtained through a process that has only been slightly altered since it was first developed at the end of the nineteenth century. The main breakthrough in culture-based clinical microbiology was the recent widespread availability of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) (7) that was shown to decrease the delay to get identification and susceptibility data by more than 10 h. Nevertheless, no significant impact was reported by this before-after study on patient outcomes, except intensive care unit (ICU) length of stay. Several polymerase chain reaction (PCR) kits have been developed or are still under development and could be used in the microbiological diagnosis of VAP, but are still not widely available, probably because of concerns regarding the lack of specificity, and increased cost compared to culture-based techniques (8).

Treating VAP is a difficult task, as initial antimicrobial therapy has to be appropriate and prompt (9,10), and changing the antimicrobial regimen after the first day does not seem to improve outcome (11). However, broad-spectrum antibiotic treatment must be used with caution, as the evidence for a direct association between antibiotics consumption and the emergence of multi-drug-resistant organisms (MDROs) cannot be neglected (12,13). Infections related to these bacteria are associated with high rate of inappropriate antibiotic treatment and worse outcomes (14).

Therefore, the need for nearly-instant diagnostic tools arises, and one of the potential methods to perform quick VAP diagnosis is the use of point-of-care testing (POCT) tools. The term POCT encloses any diagnostic tool performed "at the bedside" or close to it, without relying on central laboratory testing (15). POCT tools are now available in a large variety of settings and are vastly used in ICUs, the most commonly used are the measurement of blood glucose, hemoglobin concentration and arterial blood gas test. They tend to make essential diagnostic tests easily and quickly available, in particular by removing the time needed to package and transport the sample, identify the sample at the laboratory and transmit the result back to the ICU. Timely diagnosis can lead to quickly accurate treatment, which in turn can significantly improve patient outcome, particularly in the ICU setting. POCT tools sometimes also allow lower volumes of blood sample to obtain similar results. Concern remains regarding the reliability of these tools, and their results often need to be taken with caution, sometimes requiring traditional laboratory testing challenge.

Therefore, it seems logical to investigate the accuracy of POCT tools for the diagnosis of VAP. This narrative review aims to discuss the current data on POCT tools in the ICU setting, and its potential impact on near-future improvements and innovations.

Non-specific POCT tools: CRP and PCT

Although biomarkers are not recommended in the diagnosis of VAP (5), some of them are widely used in the clinical setting. Three biomarkers, including soluble triggering receptor expressed on myeloid cells type 1 (sTREM-1), CRP and PCT, were recently investigated for VAP diagnosis (16). However, these markers are not specific and increase in their concentration can be related to both infectious and non-infectious origins. To our knowledge, no POCT is available to this date for sTREM-1.

CRP has a reported sensitivity ranging from 56% to 88% and a specificity ranging from 86% to 91% (17,18), with large uncertainty regarding positivity cut-off (96 to 196 mg/L). CRP could nevertheless be used as a screening tool given its rather high specificity. Some authors also suggest using CRP as a prognostic marker in VAP, as a decrease in CRP during the course of treatment of VAP is associated with patient outcome. In a recent study by Póvoa *et al.* (19), survivors were patients who showed a decrease in CRP levels at day 4 of antimicrobial therapy of more than half the initial value, while patients who did not survive showed nearly no change in CRP level. There was also an association between adequate antibiotic therapy and a decrease in CRP level (P=0.029). POCT CRP has been available for a few years now, and several studies showed that POCT CRP can be useful for community-acquired pneumonia in outpatients (20), as it allows a reduction in antibiotics prescription without worsening outcome. A cost-effectiveness study also showed interesting results, encouraging the use of these tests in this setting (21). There is, however, no data regarding their interest for VAP.

PCT seems to have more interesting diagnostic value, with an estimated sensitivity between 78% to 100% and specificity between 75% and 97% (16). However, other authors reported lower diagnostic accuracy, with sensitivity as low as 41% (22) and specificity as low as 24% (23). PCT could be an interesting tool to discontinue antimicrobial therapy safely in the ICU according to recent studies (24,25), and as such could represent a potential candidate as a POCT tool. POCT to laboratory testing correlation seems to be sufficient (26), but there is no available data regarding its use for VAP, and few results are available for community-acquired pneumonia (27).

Automated microscopy as a POCT tool for VAP

Accelerate Diagnostics™ has been developing automated microscopy tools for many years, based on fluorescent in situ hybridization (FISH), allowing for both rapid pathogen identification and antibiotic susceptibility test (AST). The majority of available data come from positive blood culture, with promising results. Microbiological studies report overall sensitivity of 95.6% and specificity of 99.5% (respectively 95.6% and 99.1% for Gram-positive bacteria, 95.3% and 99.9% for Gram-negative bacteria and 100% and 98.9% for yeasts) (28), with a reported time to identification reduction of 23.5 h and time to AST reduction of 41.9 h compared to conventional microbiological techniques. Data for clinical settings are not yet available in large amount, but preliminary works like that of Kollef *et al.* (29) report a time to identification and AST of 10.2 (range, 8.3–11.5) h for the automated microscopy system *vs.* 51.4 (range, 48.0–54.6) h for conventional methods, with a projected impact on appropriate antibiotics change of 35.8 h and antimicrobial therapy de-escalation of 41.1 h.

Metzger *et al.* reported the use of this method to identify *Staphylococcus aureus* and *Pseudomonas aeruginosa* from broncho-alveolar lavage (BAL) samples taken from patients presenting with VAP (30). Species identification was successful in every sample and unaffected by the presence of a non-targeted specimen (*Klebsiella pneumoniae*). Positive concordance was reported as 13/16 for specimens containing target species above the diagnostic threshold, and 86/90 for specimens containing species under that threshold.

More recently, Douglas *et al.* reported the use of this technology as a microbiological surveillance method for VAP in ICU patients (31). This study used 73 samples collected from 33 patients, with a reported sensitivity of 100% (7/7) and specificity of 97% (64/66) compared to conventional microbiological culture. Interestingly, one of the false positive results for automated microscopy occurred in a patient that was diagnosed with VAP 2 days later on clinical criteria. The projected impact of this innovative technology on antibiotics prescription was a change in antibiotic regimen in 3/7 patients (43%) that would have occurred in about 5 h.

Since this technology uses fully automated sample preparation, FISH and AST, it could thus be easily used inside the ICU, with acceptable encumbrance similar to that of ABG POCT modules, and environment requirements (temperature, humidity) compatible with a clinical setting (32).

Multiplex PCR (MPCR): a promising diagnostic method and a POCT candidate

Over the last years, MPCR has been the subject of a steadily growing interest when it comes to microbiological identification in various clinical situations. The most recent kits not only allow pathogen identification, but can also reveal the presence of the most frequently encountered drug-resistance genes. Prior antimicrobial therapy does not influence PCR diagnostic accuracy. In addition, PCR-based methods allow for detection of non-bacterial pathogens. MPCR has been primarily developed for use with blood samples, and several data regarding this setting are available, including a recent randomized trial published by Banerjee *et al.* showing a significant decrease in broad-spectrum antimicrobial treatment for patients whose positive blood cultures were analyzed using PCR (44 *vs.* 56 h, P=0.01), as well as an increased narrow-spectrum antibiotic use (71 *vs.* 42 h, P=0.04) and a reduction in treatment of contaminants (11% *vs.* 25%, P=0.015) when compared to culture-based identification and AST, without significant difference in mortality, length of stay or cost (33). However, other randomized controlled trials, and meta-analyses reported less encouraging results (34). Several potential explanations could be suggested for this discrepancy, including the fact that blood cultures might not be the gold standard for blood stream infections, and the limited panel of tested bacteria and resistance genes tested in previous studies (35).

Jamal *et al.* studied the accuracy of the Unyvero Pneumonia Application (Curetis AG, Holzgerlingen, Germany) for the microbiological diagnosis of health care-associated pneumonia (36). In this analysis, performed in 49 patients, there was a reported agreement rate between MPCR and conventional culture of 63.3%, mostly due to MPCR detecting more organisms than culture. The Unyvero testing allowed for antimicrobial therapy regimen adjustment for 33 patients, with promising results on outcome, although the lack of a control group does not allow for an estimation of the impact on patient prognosis.

Baudel *et al.* investigated the accuracy of MPCR for the diagnosis of VAP and hospital-acquired pneumonia (HAP) in ICU patients (37). In this pilot study, the authors used the LightCycler 2.0 SeptiFast kit (Roche Diagnostics, Mannheim, Germany) that is only intended for use with blood samples, and PCR was not performed in real time. Among 65 patients with suspected pneumonia and 53 with confirmed pneumonia, MPCR allowed the identification of a pathogen in 66% of samples, *vs.* 23% for direct examination (P<0.001) and 40% for culture

(P=0.01), and the identification rate was taken up to 82% after censoring the specimens containing species for which there was no probe in the MPCR kit. Interestingly, the pathogen identification rate was not influenced by ongoing antimicrobial therapy (66% *vs.* 64%, not significant). This kit does not allow resistance gene detection except for the detection of methicillin-resistant *Staphylococcus aureus*, and thus no data is available regarding this matter. Despite these promising results, this study raises serious concerns regarding colonization-related positive MPCR results, as 42% of the samples gathered from patients for whom the diagnosis of pneumonia was eventually ruled out came back positive.

To address this issue, Clavel *et al.* (38) interestingly chose to correlate the cycle threshold (Ct) obtained in real-time quantitative PCR with colony-forming units (CFU)/mL threshold obtained from conventional culture-based methods analyzed by nephelometry. Using this method, the authors report a sensitivity of 89.2% (range, 83.2–93.6%) and a specificity of 97.1% (range, 96.1–97.9%) using BAL samples, and 71.8% (range, 61.0–81.0%) sensitivity and 96.6% (range, 95.4–97.5%) using endotracheal aspirates (ETA). This work was a proof-of-concept study using various primers independently and thus no data are available regarding time to identification. The method could nevertheless be fully automated according to the authors.

Progress continues to be made on the miniaturization of PCR techniques. In a recent work, Pendleton *et al.* report the use of a palm-sized device weighing less than 100 g: MinION (Oxford Nanopore Technologies, Oxford, UK) (39). Contrary to standard MPCR methods that detect a predefined genetic sequence (e.g., 16S rRNA), this method allows for whole genome sequencing. In a few hours, the authors were able to obtain several thousand base-pair sequences that not only allowed for species identification, but also an accurate prediction of AST. MinION has also been successfully used with urine samples, allowing for identification for all studied samples and AST for 51 out of 55 samples in about 4 h (40). This method would not be bottlenecked by the "taxonomic bet" imposed by primers, although much additional work is needed to be able to automate the use of this tool in ICU setting. In its current state, the high cost of this device is also a serious setback for routine use.

To date, the major report regarding the use of MPCR as a POCT tool is a study by Kunze *et al.* using the Unyvero (Curetis AG, Holzgerlingen, Germany) kit (41). In this study, respiratory samples from 40 patients diagnosed with HAP were analyzed both by conventional culture-based tests and using the Unyvero MPCR. Results were obtained on average in 71 h (min–max: 37.2–217.8 h) using conventional methods *vs.* 6.5 h (min–max: 4.7–18.3 h) for MPCR. In "real-life" conditions, MPCR seem less reliable at the moment, as 10% of the sample analyses resulted in complete failure and another 30% resulted in partial failure. Among the successful or partially successful MPCR analyses, only half of the results were concordant with conventionally obtained results. Discordance was also of a concerning level when it came to predicting antibiotic resistances, probably because of the detection or resistance-related genes from resident species of the airways. This study calls for precaution regarding the use of MPCR inside the ICU, and would position this technique as an add-on to standard care, thus incurring additional cost that would have to be imbalanced with a strong benefit.

There are two major concerns regarding the routine use of MPCR as a POCT tool, contamination and colonization. Firstly, MPCR methods are known to be highly sensitive and require thorough precaution so as not to contaminate samples and produce false positive during manipulation. Laboratory personnel are well trained to this measure, but it would probably be completely otherwise in a clinical setting with partially trained staff working in the hurry of ICU situations. Secondly, thresholds to differentiate between infection and colonization of the airways are still the subject of controversies using conventional methods, and this concern would probably be emphasized by the use of MPCR, with uncertainty regarding the Ct considered as a positive result.

Other emerging methods for bedside VAP diagnosis

Exhalome analysis

One of the POCT tools that have been available for years is used on a daily basis for purposes completely distinct from healthcare, it is the detection of ethanol in exhaled breath. This principle could be used to diagnose VAP in ICU patients. Although research has been steadily active in this field, we still cannot use this easily available sample for microbiological diagnosis, but it could be the case in the near future. Mass spectrometry allows for real-time analysis of exhaled breath or volatile organic compounds (VOC) from various biological samples (including urine to

detect urinary tract infections) (42). It is now possible to obtain a "breathprint" or exhalome in real-time (43), and it is easily conceivable to use fast detection of exhaled breath modifications as a VAP diagnostic tool just like we use modifications of urine composition detected by test strip as a diagnostic tool for urinary tract infections.

Since the first prototype reported in 1954, electronic noses (eNoses) have been the subject of many technological advances (44), allowing for miniaturization. Industry is now capable of offering handheld devices at the size of talkie-walkies like the Cyranose 320 (Sensigent, Baldwin Park, California, USA) that was used in a 2004 study by Hockstein *et al.* to assess the positive diagnosis of pneumonia with a reported prediction rate between 80% and 91.6% (45). These could make solid candidates as POCT tools for VAP.

In 2014, Bos *et al.* reported promising results for the use of eNose in VAP (46), with an area under the curve (AUC) of receiver operating characteristic (ROC) curve of 0.85 [95% confidence interval (CI), 0.69–1.00], not that different from that of the clinical pulmonary infection score (CPIS) (AUC, 0.89; 95% CI, 0.79–0.99) with a significant improvement when combining both diagnostic tools (AUC, 0.94; 95% CI, 0.86–1.00). The same group reported a feasibility study showing acceptable repeatability, no adverse event during the collection procedure and a low consumable cost (47).

In the study performed by Filipiak *et al.* (48), exhalome analysis allowed the authors to successfully detect the presence of pathogen-specific VOCs in samples non-invasively collected from mechanically ventilated patients with suspected VAP in a few hours. They also reported an observed concordance between the variations of the concentration of pathogen-specific VOCs in exhaled breath and the blood CRP level, suggesting a potential interest as a surveillance tool for measuring therapeutic response.

In another recent study, Schnabel *et al.* reported that a subset of 12 VOCs could be used to discriminate patients with VAP from control for whom that diagnosis was ruled out with a sensitivity of 75.8%±13.8% and a specificity of 73.0%±11.8% (ROC AUC, 0.87) in less than an hour (49).

Rapid chromogenic tests

Chromogenic tests have been used for the management of acute pharyngitis for more than a decade now (50), allowing for the selection of patients in need of treatment and thus promoting antibiotic stewardship in outpatients. These tests have a high specificity, and negative predictive value (51). In recent years, similar chromogenic tests have been developed in order to detect the production of extended-spectrum beta-lactamase (ESBL) by *Enterobacteriaceae*. These tests can detect ESBL and/or carbapenemase production in 30 to 120 min, with a sensitivity ranging from 80% to 95% and a specificity between 71% and 100% (52). Some tests designed to specifically detect carbapenemases are also under development, although at an early stage (53).

Recently, Garnier *et al.* reported the use of one of these tests, the β-LACTA™ test (BLT, Bio-Rad, Marnes-la-Coquette, France), in the early escalation or de-escalation of early antibiotic therapy in ICU patients diagnosed with infections caused by *Enterobacteriaceae* species (54). Among the 122 patients included in this analysis, 86 (70%) were diagnosed with pneumonia, and the majority of infections were hospital-acquired in this study (66, 54%). The use of BLT allowed for a more appropriate antibiotic regimen in the BLT-guided group (98% *vs.* 77%, P<0.01) with a significant reduction in time needed for antimicrobial therapy escalation [27 (range, 24–28) *vs.* 50.5 (range, 48–73) h, P<0.01] compared to the standard care control group.

Most of these tests were designed for use with bacterial colonies, but successful detection has been reported using fresh urine samples (55). Detection in respiratory samples appears to be possible according to another work by the same team (56). In this work, the authors report a sensitivity and specificity (and thus positive and negative predictive value) of 100%, using 126 bronchial aspirates containing ESBL producing Gram-negative bacterial strains above the 10^4 CFU/mL threshold. The main limitation regarding the use of this technique as a POCT test is the need for sample preparation—including digestion, haemolysis, centrifugation and incubation—that seem unfit for bedside clinical practice, despite only adding up to about an hour in this study. Automation of this process might be feasible using automated sample preparation instruments.

Conclusions

A long way ahead remains when it comes to moving microbiology from the laboratory to the bedside, but promising techniques are becoming widely available and could represent serious candidates for POCT tools (*Figure 1*). A comprehensive list of those techniques is proposed in *Table 1*, with data regarding time-to-identification, AST study mode and specifications.

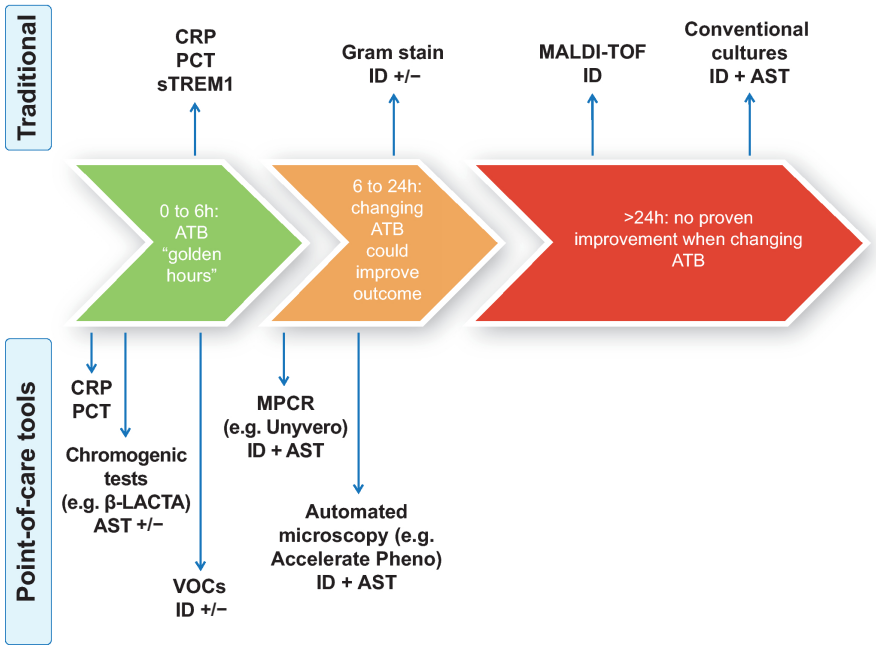

Figure 1 Estimated delays for traditional *vs.* POCT tests in lights of antimicrobial therapy regimen adjustment delays. ATB, antibiotics; CRP, C-reactive protein; PCT, procalcitonin; sTREM1, soluble triggering receptor expressed on myeloid cells type 1; ID, pathogen identification; AST, antibiotics susceptibility test; MPCR, multiplex polymerase chain reaction; VOCs, volatile organic compounds; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight.

Table 1 POCT candidates and their respective characteristics

Names	Samples	ID	AST	Delay	Performances	Comments
CRP/PCT	Blood	No	No	<10 min	CRP: Se, 56–88%; Sp, 86–91% (17,18) PCT: Se, 78–100%; Sp, 75–97% (16)	No clinical data for use in VAP
Accelerate Pheno™	ETA	Yes	Yes	10.2 (range, 8.3–11.5) h (29)	Se, 100%; Sp, 97% (31)	Not officially available for POCT use
LightCycler 2.0 SeptiFast™ (37)	BAL	Yes	No	N/A	82% identification (*vs.* 35% for culture)	Not officially available for POCT use
Clavel *et al.* (custom technique) (38)	BAL, ETA	Yes	No	2.5 h (BAL), 3.25 h (ETA)	BAL: Se, 89.2%; Sp, 97.1% ETA: Se, 71.8%; Sp, 96.6%	Automation could allow POCT use, quantitative analysis available
CuretisUnyvero™ P50	ETA	Yes	Yes	6.5 (range, 4.7–18.3) h (41)	More sensitive than cultures, 45% to 70% agreement (36,41)	40% reported partial or complete test failure in POCT use (41)
MinION™ (39)	Mini-BAL	Yes	Yes	ID, 9 h; AST, 48 h	N/A (100% agreement for n=2)	Not limited by primers, limited available data
VOCs analysis (49)	Exhaled gases	Yes	No	<60 min	Se, 75.8%±13.8%; Sp, 73.0%±11.8%	No invasive sample collection
β-LACTA™	Blood, ETA	No	Yes	30 to 120 min (52,56)	Se, 80–95%; Sp, 71–100%	Using respiratory samples requires preparation and bacterial growth

ID, pathogen identification; AST, antibiotics susceptibility test; CRP, C-reactive protein; PCT, procalcitonin; ETA, endotracheal aspirates; BAL, broncho-alveolar lavage; Se, sensitivity; Sp, specificity; VOCs, volatile organic compounds; N/A, not available.

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Footnote

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