A Review of the Value of Point-of-Care Testing for Community-acquired Pneumonia

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Abstract

Introduction: Community-acquired pneumonia (CAP) is an infectious disease associated with high mortality worldwide. Although *Streptococcus pneumoniae* remains the most frequent pathogen in CAP, data from recent studies using molecular tests have shown that respiratory viruses play a key role in adults with pneumonia. The impact of difficult-to-treat pathogens on the outcomes of pneumonia is also important even though they represent only a small proportion of overall cases. Despite improvements in the microbiological diagnosis of CAP in recent decades, the identification of the causative pathogen is often delayed because of difficulties in obtaining good-quality sputum samples, issues in transporting samples, and slow laboratory processes. Therefore, the initial treatment of CAP is usually empirical. Point-of-care testing (POCT) was introduced to avoid treatment delays and reduce reliance on empirical antibiotics.

Areas covered: This review summarizes the main scientific evidence on the role of POCT in the diagnosis and management of patients with CAP. We searched for articles on POCT in pneumonia on PubMed from inception to January 20th 2024. The references in the identified articles were also searched.

Expert opinion: POCT involves rapid diagnostic assays that can be performed at the bedside. These tests can produce results that could help guide initial therapy and management. The use of POCT is recommended in severe CAP and in patients with known immunosuppression.

Keywords: pneumonia; point-of-care; diagnosis; community-acquired pneumonia; microbiological diagnosis; test

1. Introduction

Pneumonia entails a massive burden of disease, suffering, and economic costs globally [1,2]. Community-acquired pneumonia (CAP) is a life-threatening lung infection that particularly affects high-risk individuals, such as the young, the elderly, those with multiple morbidities, and those with immunosuppression [2,3]. Between 10% and 20% of inpatients with CAP require intensive care unit (ICU) admission [4–6]. While the 30-day mortality is approximately 8%–10% in patients with CAP hospitalized in a general ward [7,8], it can reach 40%–50% in patients admitted to the ICU with severe CAP, especially if they require invasive mechanical ventilation [4,9].

Streptococcus pneumoniae remains the most common pathogen in CAP [2,8]. The incidence of CAP caused by respiratory viruses has increased in adults over time [10,11]. Although identifying the etiology of CAP is important, it is only determined in approximately 30%–40% of cases. The etiology of CAP has undergone significant changes during the last decade. This, together with the difficulties in attaining a rapid etiological diagnosis in a large proportion of patients, hamper the timely initiation of adequate antimicrobial therapy, which is known to be one of the main prognostic factors in severe CAP [10–12].

The implementation of accurate point-of-care testing (POCT) could help to avoid delays in identifying the most common microorganisms that cause CAP as well as the mechanisms of antimicrobial resistance, thus increasing the ability to offer patients an earlier treatment with appropriate antimicrobial therapy based on microbiological confirmation. Indeed, effective POCT will allow microbiological diagnosis at the bedside, thereby immediately informing the attending physician, preventing delays in

sample transport, and decreasing the time to pathogen identification [13]. A limitation is that the wide variety of microorganisms known to cause pneumonia cannot be covered by POCT, which is typically more limited. Compounding this limitation is the fact that only a few studies have evaluated POCT for pneumonia in specific care settings such as general wards and ICUs. The main body of evidence for POCT includes studies that have compared testing with conventional methods to evaluate their sensitivity and specificity. These studies have also been performed in the laboratory and not at the bedside. This review discusses the main scientific evidence on the role of POCT in CAP management.

2. Microbial etiology of pneumonia and current microbiological diagnoses

Knowing the microbial etiology of pneumonia is vital in order to ensure targeted antimicrobial therapy, avoid the overuse of antibiotics, and prevent the emergence of antibiotic resistance by selection pressure [2]. The etiology of CAP differs by infection severity and season [8,14]. Evidence shows that the microbial etiology of CAP remains unknown in approximately 50%–60% of cases despite diagnostic testing [8,15].

Pneumococcus remains the most common pathogen in pneumonia in adults. However, recent studies have reported an increase in the incidence of CAP caused by respiratory viruses, with these accounting for 7%–30% of cases among hospitalized adults with CAP that has defined etiologies [15]. A large study on the severity and outcomes of adults with CAP caused by influenza and non-influenza viruses in China reported that influenza, other respiratory viruses (non-influenza), and mixed viral infections accounted for 63%, 27%, and 10% of CAP cases, respectively [11]. Similar outcomes have been reported for adults with influenza and non-influenza viral pneumonia. Of

note, non-influenza viruses have been associated with a higher incidence of complications [11]. An observational study from Spain reported that viral sepsis was present in 61% of all patients with a diagnosis of viral pneumonia, with viral sepsis accounting for 3% of the adults admitted to the emergency department with a diagnosis of CAP and 19% of those admitted to the ICU [10].

It is also important to note that a minority of pneumonia cases are caused by difficult-to-treat pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and antibiotic-resistant Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. These are associated with a more severe presentation and higher mortality [16]. Between 5% and 6% of CAP cases also present with a co-infection, typically involving a combination of bacteria and respiratory viruses [17] (Figure 1A, 1B).

International guidelines recommend performing a microbiological diagnosis for pneumonia based on disease severity [18,19] (Figure 2). The guidelines also recommend not to perform a sputum Gram stain or culture routinely in outpatients with CAP [18,19]. They do, however, recommend obtaining sputum and blood samples and nasopharyngeal swabs for respiratory viruses (e.g., influenza A virus, influenza B virus, parainfluenza viruses, rhinoviruses, adenoviruses, respiratory syncytial virus [RSV], human metapneumovirus [hMPV], and coronaviruses), as well as performing urinary antigen tests for pneumococcus and *Legionella pneumophila* in patients with severe pneumonia, complications, sepsis or septic shock, immunosuppression, and no adequate response to initial therapy. Hence, determining the etiology in these cases could improve the quality of treatment decisions [18,19]. Respiratory and blood

samples should be collected before starting antibiotic therapy to increase the culture yields. Bronchoalveolar lavage (BAL) or tracheal aspirates (TAs) are recommended in patients admitted to the ICU with severe pneumonia. A pleural fluid culture should be performed in patients with pleural effusion [18,19]. Extensive microbiological testing is advocated in patients with severe CAP, especially in those with immunosuppression and at risk from either MRSA or *P. aeruginosa* given the associated higher risk of treatment failure and death [18,19]. Recent guidelines for severe CAP have recommended rapid diagnostic testing of viruses and bacterial pathogens to inform decisions about escalating or de-escalating empirical therapy. A critical underpinning of this recommendation is that evidence has shown an association between the use of broad-spectrum antibiotics and an increased risk of death in patients with CAP [20–22].

Knowing the microbiology of pneumonia in adults with CAP will contribute to improving the adequacy of antimicrobial therapy, prevent the excessive use of broad-spectrum antibiotics, and decrease the risk of treatment failure. However, there has been little advance in the implementation of new methods for the microbiological diagnosis of pneumonia in clinical practice, especially for bacterial etiologies. Identifying the microbiological cause of pneumonia currently takes between 24 and 48 hours, necessitating the initiation of empirical antimicrobial therapy to avoid disease progression [12]. Although molecular testing provides opportunities to identify multiple pathogens, detect markers of resistance, and help guide appropriate antibiotic therapy, the testing still needs to be validated, especially in severe pneumonia.

3. Fundamentals of point-of-care testing (POCT)

POCT incorporates various technologies to provide a real-time, portable, accurate, and rapid detection at the bedside (i.e., in the emergency department, ward or ICU). It offers the promise of rapid results that could improve patient management and is increasingly playing a vital role in preventing and controlling the spread of infectious diseases.

POCT for CAP can use blood, nasopharyngeal, urine, and BAL samples. However, the most frequent POCT for CAP involves antigen-detection rapid diagnostic tests (Ag-RDTs) and nucleic acid amplification-based techniques (NAATs) (Figure 3).

Ag-RDTs are a single-use lateral flow test based on antigen detection, for which results are available in 15–30 minutes. The highly specific binding affinity of the antigens and antibodies makes this technique a simple, fast, and effective diagnostic tool for detecting respiratory viruses and bacteria such as pneumococcus and *Legionella*. The enzyme-linked immunosorbent assay (ELISA) is the most frequently applied technique, with other techniques including chemiluminescence immunoassays (CLIAs) and lateral flow assays (LFAs). The Ag-RDT sample should be taken in the acute phase of the infection so that the yield of antigens is sufficient for testing.

NAATs amplify a specific region of the nucleic acid sequence of the pathogen and can detect very small amounts of the target sequences. One of the most widely used NAATs is real-time reverse transcription polymerase chain reaction (RT-qPCR). Other techniques include loop-mediated isothermal amplification (LAMP).

A detailed description and a summarized account of the clinical evidence of the POCT techniques by type of microorganism (viruses and bacteria) are provided in the

following two sections (sections 4 and 5, respectively).

4. POCT for respiratory viruses

4.1. Antigen-detection rapid diagnostic tests (Ag-RDTs)

A systematic review and meta-analysis [23] of 143 articles that included data from 69,699 individuals evaluated Ag-RDTs for viruses. It included 118 studies that investigated immunochromatographic assays for the influenza A and B viruses, reporting a sensitivity and specificity of 69% (95% confidence interval [95% CI], 64%–74%) and 97% (95% CI, 96%–98%), respectively. The Ag-RDTs for RSV were evaluated in 35 studies comprising 16,110 individuals (63% were children) and reported a sensitivity of 83% (95% CI, 77%–87%) and a specificity of 97% (95% CI, 95%–98%). In a subgroup analysis, the best performing tests were the Sofia® RSV FIA (sensitivity, 84% [95% CI, 77%–89%]; specificity, 96% [95% CI, 88%–99%]) and BinaxNOW™ RSV (sensitivity, 84% [95% CI, 71%–91%]; specificity, 96% [95% CI, 86%–99%]). The Ag-RDTs for hMPV were evaluated in 5 studies comprising 1,578 individuals, presenting a sensitivity of 59% (95% CI, 36%–78%) and a specificity of 99% (95% CI, 95%–100%).

A recently published article compared four Ag-RDTs (Abbott Panbio COVID-19 Ag Rapid Test, SD Biosensor Standard Q COVID-19 Ag Test, Humasis COVID-19 Ag Test, and SG Medical Acrosis COVID-19 Ag Test) with RT-qPCR for SARS-CoV-2, using 1,503 nasopharyngeal swabs. The Ag-RDTs had a positive predictive value of 99% to 100%, but the sensitivity was 77% for the Acrosis test and 54%–56% for the other three kits. All four Ag-RDTs could detect 10 SARS-CoV-2 variants, including the Pre-Delta, Delta, and Omicron variants. Results indicated that the Acrosis test was the most accurate for

detecting SARS-CoV-2 [24].

A prospective study evaluated the accuracy (sensitivity and specificity relative to real-time RT-PCR) of the LumiraDx™ SARS-CoV-2 Ag Test and the influenza A or B virus assay in 887 patients from 18 UK primary care practices when the Omicron variant was the most prevalent (June to December 2022) [25]. In that study, 17% of the patients tested positive for SARS-CoV-2, 12% for influenza A, and 0.6% for influenza B. The sensitivity and specificity of the test for SARS-CoV-2 were 80.8% and 98.9%, respectively, while those for the influenza A virus assay were 61.5% and 99.4%, respectively. In brief, Ag-RDTs for respiratory viruses show, overall, high specificity with suboptimal sensitivity. Larger studies are required to support the value of Ag-RDTs in patients with pneumonia.

4.2. Nucleic acid amplification-based techniques (NAATs)

Relevant data on NAAT for POCT were obtained from the ResPOC open-label randomized controlled trial (RCT)[26]. This RCT evaluated POCT for 15 respiratory viruses (FilmArray® Respiratory Panel, using nasopharyngeal samples) in patients with acute respiratory infections who had visited UK emergency departments across two winter seasons. Patients were randomized to receive either POCT or routine clinical care. Overall, 83% of the patients from both groups received antibiotics and more than half of the patients in the POCT group received an antibiotic before test results were available. However, 10% of the patients in the POCT group received either a single dose of an antibiotic or a course for less than 48 hours (17%) when compared to the control group (3% received single doses or brief courses of antibiotic in 9%). A neuraminidase inhibitor was prescribed in 91% of the patients with a positive POCT

compared to 65% in the control group. The length of stay (LOS) in hospital was shorter in the POCT group (5.7 days [SD, 6.3]) than in the control group (6.8 days [SD, 7.7]; difference, -1.1; 95% CI, -2.2 to -0.3; p = 0.0443). POCT was associated with an earlier diagnosis of an influenza virus infection and a shorter time to starting antiviral therapy. Although patients in the POCT group received a single dose or a shorter course of antibiotics compared to those in the control group, POCT for respiratory viruses did not reduce the proportion of patients who received antibiotics [26]. Another RCT from Denmark compared the effect of POCT to those of conventional methods on antibiotic prescriptions in hospitalized patients with CAP. No difference was found between the two study groups in the use of narrow-spectrum antibiotics at 4 h after patient admission (63% in POCT vs. 60% in the standard-of-care group; p = 0.134). Antibiotic therapy was more targeted at 4 h (OR, 5.68; 95% CI, 2.49 to 12.94) and 48 h (OR, 4.20; 95% CI, 1.87-9.40) as well as more adequate at 48 h (OR, 2.11; 95% CI, 1.23-3.61) in the POCT group. However, there were no significant differences in the 30-day mortality (OR, 0.90; 95% CI, 0.43-1.86; p = 0.787) or transfer to ICU (OR, 0.54; 95% CI, 0.10-2.91; p = 0.475) [27].

A meta-analysis exploring the diagnostic accuracy of various NAATs for influenza A and B detection in CAP included 89 studies (n = 43,762 individuals) and showed a sensitivity of 94% (95% CI, 90%–96%) and a specificity of 98% (95% CI, 97%–99%). The most frequently reported tests were Cepheid and BioFire. For the detection of RSV, 38 studies (n = 18,833 individuals) evaluated PCR tests, showing a sensitivity of 93% (95% CI, 89%–96%) and a specificity of 99% (95% CI, 98%–99%) [23].

A study on the use of the Xpert® Xpress SARS-CoV-2/Flu/RSV test on nasopharyngeal,

TA, and BAL samples found that this test had 100% positive and negative agreements for all four viruses in the nasopharyngeal samples. For the TA and BAL samples, there was 96% and 100% positive percent agreement, respectively, only for SARS-CoV-2. No positive flu/RSV samples were obtained from the TA or BAL samples. Compared to the reference PCR test, the Xpert® Xpress SARS-CoV-2/Flu/RSV test had a significant impact on the rapid detection of SARS-CoV-2, influenza A, influenza B, and RSV, as well as on the management of the infection [28].

The multicenter open-label FluPOC RCT investigated the clinical impact of POCT (FilmArray Respiratory Panel 2, using nasopharyngeal and sputum samples) in adults admitted to UK hospitals with influenza. The study included 623 patients, of whom 307 were in the POCT group and 306 in the control group. Antivirals were started in 99% of the 100 patients with a positive POCT result and only in 62% of the 102 positive cases in the control group. Of note, the time to antiviral therapy initiation was shorter in the POCT group (1 hour; interquartile range [IQR], 0.0–6.0) compared to the control group (6 hours; IQR, 0.0–12.0). Isolation measures were also more commonly implemented in the POCT group (70%) than in the control group (38%) [29].

Another RCT compared the impact of syndromic molecular POCT to that of conventional diagnostic tests on the detection of respiratory viruses and bacteria in patients admitted to the ICU with pneumonia [30]. The syndromic approach is a symptom-driven method that groups probable pathogens into one rapid molecular test that maximizes the chance of obtaining a clinically relevant answer in a clinically relevant timeframe. This trial included 200 patients with pneumonia, of whom 100 were in the POCT group and 100 in the standard testing control group. CAP, hospital-

acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) were present in 85, 69, and 46 patients, respectively. The median time to obtaining results was 1.7 hours for POCT and 66.7 hours for standard testing (difference, -65.0 hours; 95% CI, -68.0 to -62.0; $p < 0.0001$). Furthermore, 71% of the patients in the POCT group had an identified pathogen compared to 51% in the control group (difference, 20%; 95% CI, 7-33; $p = 0.004$), with the result-directed therapy initiated in 80% and 29%, respectively (difference, 51%; 95% CI, 39–63; $p < 0.0001$). Antibiotics were de-escalated in 42% of the patients in the POCT group compared to 8% in the control group (difference, 34%; 95% CI, 23-45; $p < 0.0001$) [30].

A recent Norwegian RCT investigated POCT (detection of 27 bacterial and viral respiratory pathogens with 7 resistance markers) in pathogen-directed therapy provided within 48 h after randomization in patients with CAP in an emergency department. POCT reduced the median time to pathogen-directed therapy by 9.4 hours compared to the standard-of-care group. The median response time (from patient admission to receiving a respiratory sample test result) was significantly reduced for the POCT group compared to the standard-of-care group (53.8 hours) [31].

In a prospective interrupted “on-off” study of adults admitted to a respiratory unit (December 2018 to April 2019), nasopharyngeal samples were subjected to GeneXpert rapid POCT for influenza and RSV (on-period) [32]. Testing was performed in the respiratory assessment unit or sent to the laboratory for multiplex PCR (to identify 12 respiratory viruses). In total, 755 samples were evaluated by POCT and 390 samples were evaluated by multiplex PCR. A respiratory virus was identified in 22% of the cases by POCT compared with 35% by multiplex PCR. Shorter isolation times (mean

difference, 16.9 hours; $p < 0.001$), LOS (mean difference, 15.5 hours; $p = 0.05$), and turnaround times (mean difference, 28.3 hours; $p < 0.001$) were observed in the POCT group compared to the multiplex PCR group.

Overall, the available evidence from multiple RCTs shows the potential of POCT to enhance the diagnosis and targeted antimicrobial therapy of patients with CAP in various clinical settings.

5. POCT for bacterial pathogens

5.1. Rapid antigen diagnostic tests

The urinary antigen test (UAT) for *S. pneumoniae* detection is widely used worldwide. The test is non-invasive, unaffected by previous antibiotic use, and takes only 15 minutes to produce results [33–35]. The reported specificity is 90%–100% and the reported sensitivity is 65%–100% [35–37]. A prospective study evaluated the time trend of the sensitivity of the pneumococcal UAT (BinaxNOW™) over 15 years, using data from 446 patients [38]. The authors of the study reported a significant gradual decrease in the sensitivity of the BinaxNOW™ test from 81% in 2001 to 49% in 2015. These results may be partly explained by the change in pneumococcal serotypes over time [39,40] and the decrease in the incidence of invasive pneumococcal pneumonia in recent decades [41]. After performing a multivariate analysis, the authors of the abovementioned prospective study reported that the male sex (0.467 [0.296-0.736]; $p = 0.001$), white blood cell count (0.959 [0.930-0.989]; $p = 0.008$), and the time trend per year (0.900 [0.859-0.943]; $p < 0.001$) were predictors of negative BinaxNOW™ results [38]. Hence, given that the sensitivity of this test has decreased over time, it is important to be cautious when interpreting BinaxNOW™ results in daily clinical

practice.

A retrospective study from the USA, which included data from 159,894 patients with pneumonia in 170 hospitals, investigated variations in UAT use and the association between UAT use and antibiotic de-escalation and clinical outcomes. Overall, 16% of the patients (n = 25,932) received a UAT, with 18% admitted to the ICU and 15% not admitted to the ICU. Patients who had a UAT were typically younger, less likely to have aspiration pneumonia (6% vs. 10% without a UAT), and more likely to have either sepsis (38% vs. 33% without a UAT) or require ICU admission (34% vs. 29% without a UAT). The rate of positive UATs was 7.2% and did not vary by center. Patients with a positive UAT result more often had a positive pneumococcus culture (25% vs. 2%; $p < 0.001$) and less often had resistant bacteria (5% vs. 7%; $p < 0.05$). The authors reported that UAT use was associated with antibiotic de-escalation following a positive test, thus concluding that an increased use of UATs and the narrowing of antibiotic therapy after a positive UAT result improved antimicrobial stewardship [42].

A meta-analysis analyzed the use of an *S. pneumoniae* UAT in 12 studies (n = 2,826 individuals) performed in hospital settings, with 11 of these studies evaluating the Alere BinaxNOW™ test. Pooled sensitivity was 70% (95% CI, 60%–79%) and the specificity was 83% (95% CI, 63%–93%) [23]. A prospective study evaluating four UATs (BinaxNOW™, ImmuView® *S. pneumoniae* and *Legionella*, STANDARD™ F *S. pneumoniae* Ag FIA, and Sofia® *S. pneumoniae* FIA) showed sensitivities ranging from 76.9% to 86.5% and specificities from 84.2% to 89.7%. No significant differences were found among the four UATs. The assays had a high level of agreement with one another, with 84.5% of the samples testing consistently across all four tests [43].

According to the annual epidemiological report of Legionnaires' disease from the European Centre for Disease Prevention and Control (ECDC), the *L. pneumophila* UAT was reported to be the most frequently used test in Europe in 2020 (n = 7,284; 87%) [44]. However, it is important to note that this UAT only detects *L. pneumophila* serogroup 1 and that other species of *Legionella* have been reported in recent decades, including *L. longbeachae*, *L. micdadei*, and *L. bozemanii* [45]. In 2022, an outbreak of *L. pneumophila* serotype 2 was reported in Italy, highlighting this limitation [46]. A recent meta-analysis of 21 studies (n = 5,772 patients) reported that the pooled sensitivity and specificity of *Legionella* UATs were 0.79 (95% CI, 0.71–0.85) and 1.00 (95% CI, 0.99–1.00), respectively. In a subgroup analysis, the sensitivity and specificity for *L. pneumophilia* serogroup 1 UATs were 0.86 (95% CI, 0.78–0.91) and 1.00 (95% CI, 0.99–1.00), respectively [47]. There is little information about the use of Ag-RDTs for bacterium detection in specific care settings. However, results from studies evaluating sensitivity and specificity have demonstrated the value of these tests for the rapid identification of common causative pathogens (e.g., pneumococcus and *Legionella spp.*) in severe pneumonia [12].

5.2. NAATs

Pooled evidence from a recent meta-analysis exploring the diagnostic accuracy of various NAATs for bacterial detection in CAP represents the main backbone in this area [23]. For *S. pneumoniae*, six studies (n = 2,221 individuals) were included in the meta-analysis, showing a pooled sensitivity of 96% (95% CI, 93%–98%) and a specificity of 91% (95% CI, 71%–98%) for the NAATs. The study by Gadsby et al. [48] compared the performance of the Unyvero P55 Pneumonia Cartridge with routine bacterial cultures

and in-house bacterial multiplex rt-PCR assays in 74 BAL samples from patients admitted to the ICU in Edinburgh, UK. The sensitivity and specificity of the Unyvero P55 Pneumonia Cartridge were 56.9% and 58.5%, respectively, while the corresponding values for the in-house PCR testing were 63.2% and 54.8%, respectively. Additional organisms were detected by the Unyvero P55 Pneumonia Cartridge and the in-house bacterial PCR panels in 16.2% of the samples. Antibiotics were changed based on the results of the routine testing; however, changes could have been made much earlier based on the results of the molecular method. The main limitation of this POCT was the lower sensitivity and specificity for detecting antibiotic resistance, which were 18.8% and 94.9%, respectively. A multicenter RCT also evaluated the impact of the Unyvero POCT. Among 208 patients hospitalized with pneumonia who were at risk from Gram-negative pathogens and due to undergo a bronchoscopy for a BAL sample, 100 were randomized to undergo POCT and 108 were subjected to conventional methods [49]. The duration of inappropriate antibiotic therapy was significantly shorter in the POCT group compared to the control group (adjusted mean duration, 47.1 hours [34.7–59.5] vs. 85.7 hours [78.8–95.6]; $p < 0.0001$). This translated into a decrease of 45% in the duration of inadequate antibiotic therapy (37.9–52.1). These results showed the impact of POCT in critically ill patients who were at risk from drug-resistant pathogens. Although both studies **[48] [49]** evaluated the same POCT for pneumonia, testing was not implemented in a specific care setting. Nevertheless, the sensitivity and specificity of this POCT are important for understanding its value in diagnosing pneumonia, showing potential value if implemented.

Although drug-resistant bacteria only account for 2%–6% of CAP cases, these pathogens are associated with a more severe presentation and higher mortality

[50,51]. POCT for drug-resistant pathogens has also been investigated, especially in critically ill patients, to improve early detection and avoid broad-spectrum antibiotic overuse. Indeed, empirical broad-spectrum antibiotics are initiated in approximately 30% of patients with CAP, which has been associated with poor outcomes in CAP, including increased mortality [21,22].

A prospective study evaluated the BioFire FilmArray Pneumonia panel for identifying bacteria and their resistance profiles in 187 BAL samples from patients with lower respiratory tract infections (LRTIs) (57 patients had HAP and 130 had CAP) [52]. The samples were also analyzed using conventional methods. In patients with HAP, *Acinetobacter baumannii* and *Klebsiella pneumoniae* were the most frequently identified pathogens, while *CTX-M* and *KPC* were the most prevalent antimicrobial resistance genes. In patients with CAP, *Haemophilus influenzae* and *S. aureus* were the most frequently identified pathogens, while *CTX-M* and *VIM* were the most prevalent antimicrobial genes. Another multicenter study evaluated the Unyvero pneumonia system for the identification of pathogens and resistance patterns in samples from 84 patients with LRTIs admitted to the ICU [53]. BAL samples were collected and analyzed with the Unyvero pneumonia system and compared with conventional methods. Overall, concordance between the two methods was 82.1%, but the Unyvero pneumonia system detected more microorganisms (38.1% vs. 27.4%; $p < 0.05$) and more polymicrobial infections (10.7% vs. 2.4%; $p = 0.01$). The Unyvero pneumonia system also performed well for antibiotic-resistant pathogens, excluding *P. aeruginosa*, showing a concordance of 87.5%–100% for MRSA and carbapenem-resistant isolates, but only 20%–33.3% for *P. aeruginosa.*

A meta-analysis of data from 22 studies including 5,163 patients with pneumonia (CAP, HAP, and VAP) evaluated nasal screening for MRSA and the subsequent development of MRSA pneumonia. It revealed that the incidence of MRSA pneumonia was 10% and that nasal screening had a positive predictive value (PPV) of 44.8% and a negative predictive value (NPV) of 96.5%. The NPV among CAP/HAP and VAP did not differ significantly at 98.1% and 94.8%, respectively. The authors reported that the test did not affect clinical outcomes, although reductions were reported for the length of MRSA therapy, length of monitoring, and health costs [54]. An RCT, assessing the effect of antibiotic management based on the results of POCT compared with routine care (45 patients: 22 patients in the POCT group and 23 in the usual care group) using BAL samples to detect MRSA, reported that the Gene Xpert MRSA/SA SSTI test had a sensitivity of 96%, with a negative likelihood ratio of 0.04 for MRSA. There was a decrease in the duration of vancomycin and linezolid treatment in the intervention group (32 h [IQR, 22–48] vs. 72 h [IQR, 50–113]; $p < 0.001$). In-hospital mortality was 14% in the intervention group and 39% for routine care (95% CI, -3.3 to 50.3; $p = 0.06$) [55].

POCT for the identification and detection of resistance genes could complement the routine conventional diagnosis of pneumonia and improve its management. However, more studies of POCT are needed in specific care settings.

6. Biomarkers and POCT

Biomarkers can be used in the diagnosis of pneumonia to help differentiate between bacterial and viral infections [56,57] and improve antimicrobial stewardship [58–62]. An early diagnosis of pneumonia could lead to more appropriate antimicrobial

treatment, less overuse of broad-spectrum antibiotics, and improved outcomes. C-reactive protein (CRP) and procalcitonin (PCT) remain the most widely used biomarkers in pneumonia [60,63–66].

6.1. C-reactive protein POCT

CRP levels increase after the first three days of infection, with a peak at 36–50 hours from infection, and can be used to identify lung infections from non-infectious causes. CRP increases in response to any inflammation and its level can be modified by corticosteroids and antibiotics. POCT-CRP has been shown to reduce antibiotic prescriptions safely in patients with LRTIs in different settings. A Cochrane meta-analysis of data from 12 trials with 10,218 patients suggested that POCT-CRP safely reduced antibiotic prescriptions among primary care patients with acute LRTIs, with a reduction from 516 antibiotic prescriptions per 1,000 participants in the control group to 397 prescriptions per 1,000 participants in the intervention group [67]. An RCT in 11 Dutch nursing homes that included 241 patients with symptoms of LRTIs showed that antibiotics were prescribed for 54% of the patients in the POCT group and 82% in the control group. Patients in the intervention group had a 4.93-fold higher chance (95% CI, 1.91–12.73) of not being prescribed antibiotics at the initial consultation than those in the control group, irrespective of the attending physician or baseline characteristics [68].

A systematic review and meta-analysis of different POCT for pneumonia performed a sub-analysis for POCT-CRP, aiming to differentiate between bacterial and viral pneumonia using different cut-off values (> 10 mg/L, > 20 mg/L, > 50 mg/L, and > 100 mg/L). Among 10 studies with data from 5,191 individuals, the sensitivity for POCT-CRP

varied between 52% (95% CI, 34%–69%) and 90% (95% CI, 67%–98%), while the specificity varied between 42% (95% CI, 26%–60%) and 91% (95% CI, 82%–96%) [23]. At a cut-off value of > 50 mg/L (6 studies; 4,505 patients), they observed a higher sensitivity (75%) and specificity (75%). However, a CRP of > 10 mg/L had the best performance in terms of sensitivity (90%), albeit with lower specificity (42%). The main limitations to using POCT-CRP in the diagnosis of pneumonia include the following: it has a delayed response to clinical stimuli (starting at 4–6 hours and peaking at 36 hours); CRP levels are elevated in inflammatory diseases, trauma, myocardial infarctions, fungal infections, and malignancy; and CRP levels decrease in the case of liver injury and corticosteroid use [69].

Finally, the accuracy of the FebriDx POCT was investigated in a prospective observational study of patients with suspected LRTIs admitted to the emergency department of an academic hospital in the Netherlands [70]. The FebriDX POCT requires a single drop of blood for the immunoassay to analyze the presence of elevated CRP levels (≥ 20 mg/L) and myxovirus resistance protein A (MxA, ≥ 40 ng/mL), the latter being a protein that is involved in the antiviral response regulated by type-I interferons. According to the manufacturer, the results from this test should be interpreted as follows: a positive CRP line and a negative MxA line indicate a bacterial infection; a positive MxA line and either a positive or negative CRP line indicate a viral infection; and negative CRP and MxA lines and a positive control line indicate negative results. The sensitivity and specificity of the FebriDx POCT for detecting bacterial infections are 87% (95% CI, 72%–96%) and 67% (95% CI, 55%–77%), respectively, while the corresponding values for detecting viral infections are 56% (95% CI, 40%–72%) and 92% (95% CI, 83%–97%), respectively. The test has been used in immunocompetent

patients with symptoms of LRTIs.

6.2. Procalcitonin POCT

PCT levels rise rapidly in response to microbial toxins and host responses, peaking at 12–24 hours after infection. Results from several studies show that PCT levels ≤ 0.1 µg/L indicate a high likelihood of a viral infection, whereas levels ≥ 0.25 µg/L indicate a high likelihood of bacterial pneumonia [71]. However, a multicenter prospective surveillance study of 1,735 adults hospitalized with CAP showed that no PCT threshold perfectly discriminated between viral and bacterial pathogens. Furthermore, it reported that when identifying any bacterial pathogen, a PCT threshold of 0.1 ng/mL had a sensitivity and specificity of 80.9% (95% CI, 75.3%-85.7%) and 51.6% (95% CI, 46.6%-56.5%), respectively [64]. Similarly, results from a meta-analysis of 12 studies including 2,408 patients with CAP reported that PCT had a sensitivity and specificity of 0.55 (95% CI, 0.37–0.71; I^2 = 95.5%) and 0.76 (95% CI, 0.62–0.86; I^2 = 94.1%), respectively [58]. Another systematic review and meta-analysis of different POC tests for pneumonia evaluated the diagnostic performance of PCT at cut-offs of > 0.1 µg/L, > 0.25 µg/L, and > 0.5 µg/L, reporting a sensitivity ranging from 44% (95% CI, 14%–79%) to 74% (95% CI, 38%–93) and a specificity ranging from 74% (95% CI, 36%–94%) to 93% (95% CI, 43%–100%) [23]. A PCT > 0.1 µg/L (four studies; n = 1,092 patients) showed a sensitivity of 74% (95% CI, 38%–93%) and a specificity of 74% (95% CI, 36%–94%) [23].

These data show that PCT levels are unlikely to provide reliable evidence for differentiating between bacterial and viral infections or guide decision-making processes related to initiating antibiotic therapy in patients with CAP. Existing guidelines for CAP do not recommend PCT testing when starting antimicrobial therapy

[18].

PCT has also been explored for guiding the prescribing of antibiotics in cases of COVID-19. Despite the reported lower rate of bacterial co-infections with COVID-19, antibiotics were commonly prescribed during the pandemic, especially in hospitalized patients. In one multicenter study, three patient groups with COVID-19 were compared to investigate the role of PCT in guiding antibiotic prescriptions during the first week of admission (a PCT group and two non-PCT control groups). Antibiotics were prescribed in 27% of the patients in the PCT group, 44% in non-PCT control group 1, and 45% in non-PCT control group 2. The PCT group had a lower probability of receiving antibiotics in the first seven days of admission (odds ratio [OR], 0.33; 95% CI, 0.16–0.66) compared to the two control groups (OR, 0.42; 95% CI, 0.28–0.62) [72].

An interesting study from Spain reported that patients with COVID-19 and PCT values > 0.2, > 0.5, > 1, and > 2 ng/Ml were significantly more likely to have co-infections than those with lower PCT values (p = 0.017, p = 0.031, p < 0.001, and p < 0.001, respectively). The authors recommended that antibiotics should not be initiated in patients with COVID-19 and PCT values < 0.2, especially if they also present high ferritin levels and an oxygen saturation level > 94% [73]. However, a study evaluating the use of PCT in critically ill patients with COVID-19 demonstrated that a PCT level ≥ 0.5 ng/mL within 72 hours of hospital presentation did not predict concomitant bacterial pneumonia in critically ill patients with COVID-19. The sensitivity and specificity of PCT to predict a co-infection with bacterial pneumonia in patients with COVID-19 pneumonia admitted to the ICU were 26.1% and 78.2%, respectively (NPV = 73.2%). The authors suggested that using PCT to rule out a diagnosis of bacterial

pneumonia in critically ill patients with COVID-19 is potentially dangerous and may delay the initiation of antibiotics and increase both morbidity and mortality [74]. Although multivariate modeling did reveal a significant association when combining two biomarkers (PCT and CRP) to detect a bacterial co-infection, it did not demonstrate the necessary sensitivity and specificity for this combination to serve as a reliable tool for ruling out bacterial co-infections. Our multicenter study on the value of PCT and CRP to identify bacterial co-infections among critically ill patients with COVID-19 suggested that PCT and CRP measurements alone, and at a single time-point, are not useful for diagnosing or excluding bacterial co-infections in this population [75].

PCT is an increasingly available biomarker, especially in reference hospitals. However, PCT has some limitations that should be taken into consideration when managing patients with pneumonia. Unfortunately, there are limited studies on POCT for PCT in a specific clinical setting. Biomarkers that are identifiable by POCT have the advantage of offering rapid results that have the potential to help in the management of pneumonia. However, more studies are needed on their cost-effectiveness (equipment, staff training, and maintenance) and impact in specific care settings.

7. POCT and CAP outcomes

An early identification of the CAP etiology allows for appropriate antimicrobial therapy and better outcomes. When using the pneumococcal and *Legionella* UATs, several studies have reported shorter LOS and reductions in both in-hospital and 30-day mortality [42,76–79]. A retrospective study from Spain (n = 1,452 patients) compared the 30-day and long-term mortalities in patients with *Legionella* CAP (n = 260) or

pneumococcal CAP (n = 1,192) diagnosed with UATs. It showed a higher 30-day mortality for *Legionella* CAP than for pneumococcal CAP and a significantly lower long-term survival in patients diagnosed early by UATs. This demonstrates the impact of using UATs at admission to obtain a rapid etiological diagnosis for both types of pneumonia [76].

A retrospective study of more than 6,000 patients with CAP in Japan also investigated the association between the UAT timing and in-hospital mortality associated with *Legionella* CAP. The tested group had lower 30-day and in-hospital mortalities when compared to the control group (5.7 vs. 7.7%; OR, 0.72; 95% CI, 0.55-0.95; p = 0.020). The authors also reported that the tested group showed a significantly shorter LOS and a reduced duration of antibiotic therapy than the control group. Overall, the use of UATs upon admission was suggested to be beneficial for patients with severe CAP [77].

Effective antibiotic therapy based on sensitivities is pivotal for the management of CAP, helping to avoid the overuse of broad-spectrum antibiotics as well as drug resistance and prevent complications such as infections with *Clostridioides difficile* [2]. Existing CAP guidelines strongly recommend a switch from intravenous to oral antibiotics as soon as patients reach clinical stability [18]. The main advantages of an early switch in antibiotic therapy are a decreased risk of infection, a reduced LOS, and lower health costs. An RCT (n = 800 patients) that evaluated the impact of molecular POCT for viral and atypical pathogens in addition to routine real-time PCR showed that the use of molecular POCT could reduce the duration of intravenous antibiotic therapy in patients hospitalized with LRTIs. Overall, the duration of the intravenous therapy was shorter in the POCT group (7 days; IQR, 5–9) compared with the control group (8

days; SD, 6– 1; $p < 0.001$). The LOS was also shorter in the intervention group, at 8.0 days (IQR, 7.0–11.0) versus 9.0 days (IQR, 7.0-12.0; $p < 0.001$) [80].

It is well known that the early use of antiviral therapy is associated with lower mortality in patients with influenza infections [81]. The FluPOC trial showed that routine molecular POCT for the influenza virus was associated with improvements in early diagnosis and appropriate antiviral therapy in adults admitted with acute respiratory illnesses. The importance of this was also demonstrated for early patient isolation in the prevention of in-hospital transmission [29]. Prior to the obtention of these results, the intervention group in the ResPOC trial showed a reduction in LOS of -1.7 days (95% CI, -0.3 to -0.4; $p = 0.0085$) between the positive POCT group (4.7 ± 4.6 days) and the negative POCT group (6.5 ± 7.2 days) [26]. They also reported a reduction in the duration of antibiotic therapy of -1.7 days (95% CI, -2.9 to -0.6; $p = 0.0033$). Patients with a positive POCT received antibiotics over a mean duration of 6.2 days, whereas patients with a negative POCT received antibiotics for 8 ± 5.3 days. Other studies have reported similar results [82–84].

A multicenter RCT evaluated whether the use of multiplex bacterial PCR (Unyvero pneumonia system) with BAL samples supported antimicrobial stewardship in patients with pneumonia. Among 208 patients randomized into the PCR group (n = 100) and the conventional test group (n = 108), the duration of inadequate antibiotic therapy was significantly shorter in the PCR group (adjusted mean duration, 47.1 h [34.7–59.5] vs. 85.7 h [78.8–95.6]; $p < 0.0001$).

8. Impact of the COVID-19 pandemic on POCT development

As of June 2023, the World Health Organization (WHO) reports that there have been

768 million confirmed cases of COVID-19 and 6.9 million deaths [85]. Throughout the pandemic, POCT was increasingly adopted for mass screening with shorter response times. Several POC tests were authorized for emergency use at that time based mainly on the detection of nucleic acids, proteins, viral antigens, and human antibodies [86].

A Cochrane meta-analysis on rapid antigen POCT for SARS-CoV-2 included data from 152 studies (66% from Europe) that had evaluated single-test applications of 49 different commercial antigen assays (n = 100,462 samples). Among the 16,822 cases with confirmed SARS-CoV-2, antigen tests correctly identified a COVID-19 infection in an average of 73% of individuals with symptoms and 55% of individuals without symptoms. The tests were the most precise when used in the first week of symptom onset (on average, 82% of confirmed COVID-19 cases had a positive antigen test). In the cases without symptoms, the tests were the most precise in the individuals who were likely to have been in contact with a person with a COVID-19 infection (on average, 64% of confirmed cases had a positive antigen test). In individuals without a SARS-CoV-2 infection, the antigen tests correctly excluded a COVID-19 infection in 99.6% of those with symptoms and 99.7% without symptoms. These results demonstrated the importance and impact of POCT in the diagnosis of COVID-19 [87].

POCT for SARS-CoV-2 was mainly developed using three technologies: RT-qPCR, LAMP-based assays (RT-LAMP), and clustered regularly interspaced short palindromic repeats (CRISPR). A recently published study reported on the fabrication and clinical validation of the PATHPOD POCT based on the LAMP assay for detecting COVID-19. The test could detect 30 to 50 copies of pure plasmid DNA per reaction within 40 minutes. In the validation study of 398 samples, PATHPOD showed a sensitivity, specificity, and

accuracy of 73.4%, 96.2%, and 89.2%, respectively (samples were prepared with the boiling method). When using purified RNA, the sensitivity, specificity, and accuracy increased to 87%, 98.3%, and 92.5%, respectively [88].

A rapid review and network meta-analysis on the diagnostic test accuracy for COVID-19 analyzed data from 23 rapid molecular tests, involving 10,449 participants. Among the 23 commercial rapid molecular tests analyzed, those with the highest sensitivity and specificity were Xpert Xpress by Cepheid (sensitivity, 0.99 [0.83–1.00]; specificity, 0.97 [0.69–1.00]), GeneSoC by Kyorin Pharmaceutical Co. Ltd. (sensitivity, 0.89 [0.33–1.00]; specificity, 0.88 [0.33–1.00]), and Truenat Beta CoV by Molbio Diagnostics (sensitivity, 0.90 [0.31–1.00]; specificity, 0.86 [0.30–1.00]). The authors reported that 15 rapid molecular tests had a sensitivity of ≥ 0.80 and that 3 rapid molecular tests had a specificity of ≥ 0.97 [89].

9. Cost-effectiveness and POCT

The ability to diagnose pneumonia at the bedside is very important, especially in the cases of severe pneumonia that may require ICU admission. Not only does it remove the need to send patient samples to a central laboratory, but it also optimizes decision-making on therapy and management. POCT is vital for the assessment and management of highly contagious infections, such as those caused by the influenza virus, SARS-CoV-2, and the Middle East respiratory syndrome-related coronavirus, providing an early identification of the causative pathogen. This allows for the necessary isolation measures to be implemented quickly to avoid the spread of infection. Before the COVID-19 pandemic, implementing POCT in clinical practice was far from reality. However, the pandemic emphasized the importance of POCT in

routine clinical practice. During the 3 years of the pandemic, more than 32 POC tests for SARS-CoV-2 received approval from the US Food and Drug Administration (FDA) [86]. The same should be possible for CAP.

In 2014, an RCT investigated the clinical effectiveness and cost-effectiveness of POCT for the influenza virus, RSV, and *S. pneumoniae* versus traditional laboratory cultures when managing the acute admission of elderly patients and those at high-risk aged 18 to 64 years. Results showed that costs and quality-adjusted life years (QALYs) were similar for each diagnostic strategy. The average total costs to the UK National Health Service for the three diagnostic groups were comparable at £2,159 in the near-patient group, £1,978 in the molecular group, and £2,327 in the traditional group. The probability that any one strategy was the least costly did not exceed 79%. Moreover, the total cost of the conventional laboratory culture was the highest and was associated with the lowest gain in terms of QALYs. Incrementally, PCR was the most cost-effective (78% probability at a willingness to pay £20,000/QALY) [90].

A cost-impact study using a simulation model estimated the economic cost and clinical impact of a novel diagnostic test known as LMMBV (LIAISON + MeMed BV). This test was used to differentiate between bacterial and respiratory viral infections in patients with pneumonia admitted to Spanish, Italian, and German emergency departments, comparing against standard-of-care testing [91]. The main outcomes were fewer patients on antibiotics, days saved, fewer hospital admissions, and shorter length of hospital stays. In their analysis, LMMBV was associated with a reduction in antibiotic prescriptions (43%) and days of treatment (1.02 per patient), which translated to a reduction in antibiotic use and a saving of approximately 1,020 antibiotic days per

1,000 patients, lowering the risk of complications. In terms of economic costs, the study showed that implementing the LMMBV test would allow savings of up to €364 and €328 per patient for hospitals and €91 and €59 per patient in Italy and Germany, respectively. In Spain, the average saving per patient could reach €165 [91].

A prospective study in the Netherlands investigated the potential impact of POCT compared to conventional methods in the diagnosis of the influenza virus and RSV for patient management and in-hospital costs between 2016 and 2017. The authors reported that the influenza virus and RSV were detected in 31% and 7% of the patients, respectively. The mean total in-hospital cost per patient with conventional testing was €5,243, which decreased to €4,904 with the implementation of POCT, with the main impact on the time to diagnosis. Additionally, costs fell to €4,206 when the impact of POCT was considered for hospital discharge. The authors concluded that in a single influenza season, a total cost reduction of €95,937 to €293,471 could be achieved at the hospital level by implementing POCT [92].

The economic costs of POCT, especially for microbiological identification, are higher compared to conventional methods. However, there is very little information about the economic impact of implementing POCT for patients with severe pneumonia. A comprehensive economic study is warranted to elucidate the impact of POCT on patients with CAP.

10. Expert opinion

POCT has the potential for a faster identification of the pathogens that cause pneumonia. This means it can help guide adequate antimicrobial therapy, avoiding the overuse of broad-spectrum antibiotics and improving the management of patients

with pneumonia, especially in severe cases where difficult-to-treat pathogens are common [50,51]. Given that we have observed an increase in the incidence of elderly patients admitted to the ICU with pneumonia and since there has also been a rise in the incidence of immunocompromised patients with pneumonia [2,93], POCT can play a key role in the rapid identification of the respiratory viruses related to severe pneumonia in these populations. It can also allow for the early initiation of antiviral therapy and the avoidance of antibiotic overuse, both of which may have important repercussions in these vulnerable populations.

In the case of highly contagious pathogens, such as the influenza virus, RSV, and SARS-CoV-2, the use of POCT may accelerate their identification and help initiate the necessary isolation procedures to prevent nosocomial transmission. Additionally, POCT can relieve pressure on central laboratories, especially during epidemics or pandemics, as observed with COVID-19. The implementation of POCT in strategic care sites, such as primary care, emergency departments, and the ICU, can eliminate sample transportation, reduce turnaround times, and ensure adequate and early antimicrobial therapy. This simple analytical process has the potential to relieve pressure on clinical laboratories in these settings.

Due to the limited information on the economic impact of POCT implementation for both patients with severe pneumonia and particular populations, future studies are needed before testing can be included in routine clinical practice. Further research is also necessary to determine the clinical usefulness and recommendations for specific populations, such as the immunosuppressed, elderly, and people with multiple comorbidities.

11. Current barriers and gaps for POCT implementation

The 'real-life' experience of POCT is limited. POCT has been shown to produce better results than conventional tests when compared under controlled conditions. The implementation of POCT may be advantageous when a rapid result is needed to guide antimicrobial therapy, especially in severe pneumonia. Nevertheless, there are likely to be significant challenges related to the implementation of POCT, including the cost of the equipment and consumables, the training of personnel, and the continued quality control.

In approximately 60% to 70% of the studies that we have included in this review, POCT was not really performed in a specific setting and was performed in the laboratory, especially in the studies that had no controlled situations such as the RCTs. This makes it difficult to interpret the real impact on clinical practice and calls into question its main advantages, such as the lower need for personnel and specific training. Further studies are needed to determine the real value of POCT in a specific setting (e.g., primary care, emergency departments, and the ICU).

Article highlights

- Point-of-care testing (POCT) involves the use of rapid diagnostic tests that can be performed at the bedside. These tests can give a result earlier than standard testing, thereby helping to guide patient management.
- Given that extended microbiological diagnosis is still recommended by international guidelines for the management of severe pneumonia, POCT in the emergency department or the ICU could improve management.
- POCT has potentially important roles in the management of individual patients in community outbreaks, seasonal respiratory illnesses, and the surveillance of respiratory pathogens such as the influenza virus, RSV, and SARS-CoV-2.
- The implementation of POCT could be an important asset in current multistakeholder efforts to reduce the overuse of antibiotics.
- POCT was developed to facilitate the identification of pathogens in a short period without needing a specific infrastructure. It might, therefore, help prevent the collapse of central laboratories in the event of public health emergencies, such as that observed during the COVID-19 pandemic.

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Declaration of interest

The authors have no relevant affiliations or financial involvements with any organization or entity that has a financial interest in, or financial conflict with, the subject matter or materials discussed in this manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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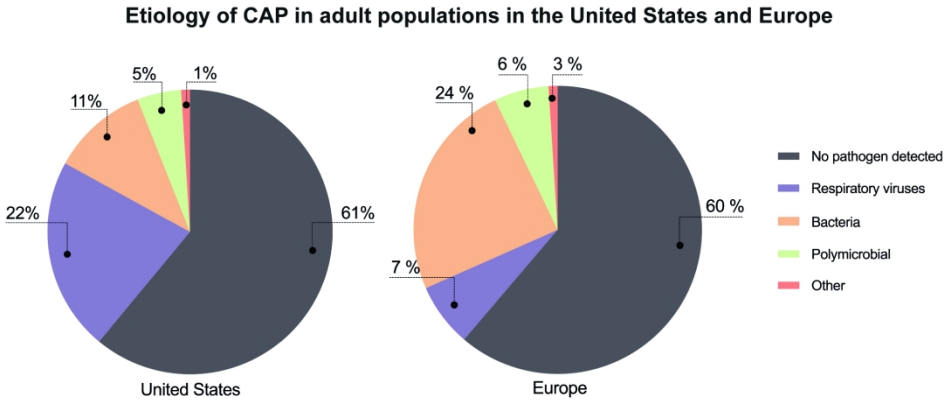

1A

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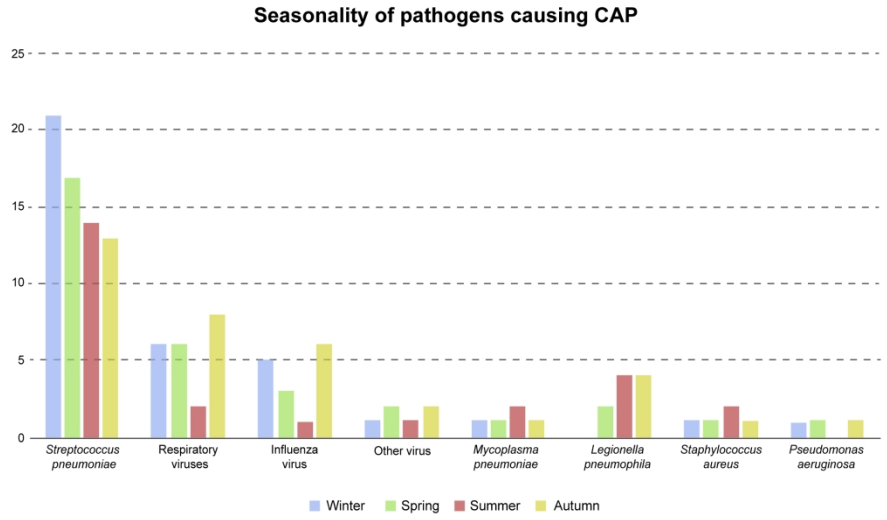

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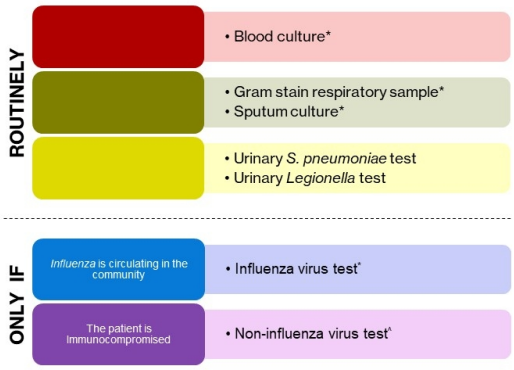

Figure legend: * Blood and respiratory sample cultures are also recommended for patients receiving empirical treatment for MRSA or PA, those with a history of MRSA or PA infection, and patients with prior hospitalization and antibiotic therapy within the past 90 days. Abbreviations: MRSA indicates *Methicillin-resistant Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*.

Figure 2

338x190mm (96 x 96 DPI)

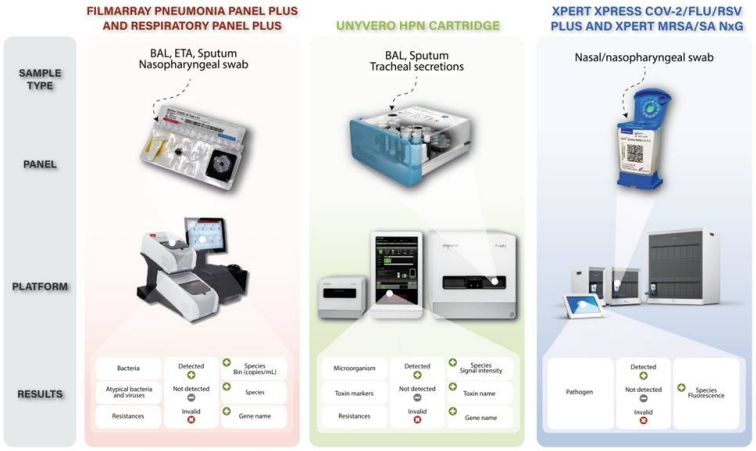

Figure 3.
Abbreviations: BAL indicates bronchoalveolar lavage; ETA, endotracheal aspirate

Figure 3

338x190mm (96 x 96 DPI)

	BioFire Film Array		Sistema Cepheid GeneXpert	Antigen Tests		
Panel	Respiratory panel plus	Pneumonia panel plus	Xpert Xpress CoV-2 /Flu/RSV plus	BinaxNOW Influenza A&B	BinaxNOW RSV	Sofia SARS Antigen FIA
Pathogens	19 viruses[a]	9 viruses[b]	SARS-CoV-2 Influenza A/B RSV	Influenza A/B	RSV	SARS-CoV-2
Resistance	No resistances detected					
Turnaround time	≈ 1 h		25 min	15 min		
Sample type	Nasopharyngeal swab	BAL min-BAL sputum ETA	Nasal or nasopharyngeal swabs	Nasal lavage/aspiration Nasal swab Nasopharyngeal swab	Nasal lavage Nasopharyngeal swab	Nasal swab
Se/Sp %	SARS-CoV-2 PPA 98.4 % NPA 98.9 % ------- Other pathogens Se 97.1 % Sp 99.3 %	BAL Se 96.2 % Sp 98.3 % ------- Sputum/ETA Se 96.3 % Sp 97.2 %	Nasal swab PPA 92.3-100 % NPA 98.2-100 % ------- Nasopharyngeal swab PPA 92.4-100 % NPA 97.1-100 %	Influenza A Se 70-89 % Sp 90-99 % -------- Influenza B Se 50-69 % Sp 94-100 %	Nasal lavage Se 89 % Sp 100 % ------- Nasopharyngeal swab Se 93 % Sp 93 %	PPA 96.7 % NPA 100 %

Abbreviations: CoV: Coronavirus; RSV: Respiratory Syncytial Virus; SARS: Severe Acute Respiratory Syndrome; BAL: Bronchoalveolar Lavage; ETA: Endotracheal Aspirate; Se: Sensibility; Sp: Specificity; PPA: Positive Percent Agreement; NPA: Negative Percent Agreement. All sensitivity and specificity values have been extracted from kits and information provided by each manufacturer. [a] Detectable viruses include Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Middle East respiratory syndrome coronavirus, Severe acute respiratory syndrome coronavirus 2, Human metapneumovirus, Human rhinovirus/enterovirus, Influenza A virus, Influenza A virus A/H1, Influenza A virus A/H3, Influenza A virus A/H1-2009, Influenza B virus, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4 and Respiratory syncytial virus. [b] Detectable viruses include Influenza A, Influenza B, Adenovirus, Coronavirus, Parainfluenza virus, Respiratory Syncytial virus, Human Rhinovirus/Enterovirus, Human Metapneumovirus and Middle East Respiratory Syndrome Coronavirus.

	BioFire Film Array		Curetis Unyvero System	Sistema Cepheid GeneXpert	Antigen Tests	
Panel	Respiratory panel plus	Pneumonia panel plus	Hospitalized Pneumonia Cartridge	Xpert SA Nasal Complete	Alere BinaxNOW S. pneumoniae	Alere BinaxNOW L. pneumophila
Pathogens	4 bacteria[a]	18 bacteria[b]	17 bacteria 4 others/fungi[c]	MRSA/SA	Steptococcus pneumoniae	Legionella pneumophila (serogroup 1)
Resistance	No resistance detected	7 resistance markers[d]	17 resistance markers[e]		No resistance detected	
Turnaround time	≈ 1 h		≈ 4 h	1 h	15 min	
Sample type	Nasopharyngeal swab	BAL min-BAL sputum ETA	Sputum BAL Tracheal secretions	Nasal swab	Urine CSF	Urine
Se/Sp %	Se 97.1 % Sp 99.3 %	BAL Se 96.2 % Sp 98.3 % ------- Sputum/ETA Se 96.3 % Sp 97.2 %	Se 88.8 % Sp 94.9 %	MRSA Se 91.9 % Sp 97.9 % ------- SA Se 93.3 % Sp 90.5 %	Urine Se 86 % Sp 94 % ------- CSF Se 97 % Sp 99 %	Se 95 % Sp 95 %

Abbreviations: SA: *Staphylococcus aureus*; MRSA: Methicillin-resistant *Staphylococcus aureus*; BAL: Bronchoalveolar Lavage; ETA: Endotracheal Aspirate; CSF: Cerebrospinal Fluid; Se: Sensitivity; Sp: Specificity. All sensitivity and specificity values have been extracted from kits and information provided by each manufacturer. [a] Detectable bacteria include *Bordetella parapertussis*, *Bordetella pertussis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. [b] Detectable bacteria include *Acinetobacter calcoaceticus-baumannii complex*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae group*, *Moraxella catarrhalis*, *Proteus spp.*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. [c] Detectable pathogens include *Acinetobacter baumannii complex*, *Chlamydia pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae complex*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Klebsiella variicola*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Morganella morganii*, *Mycoplasma pneumoniae*, *Pneumocystis jirovecii*, *Proteus spp.*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia* and *Streptococcus pneumoniae*. [d] Resistance markers include ESBL (CTX-M), Carbapenemases (KPC, NDM, Oxa48-like, VIM and IMP) and Methicillin resistance genes (*mec*A/*mec*C and MREJ). [e] Resistance markers include Carbapenemases (*bla*KPC, *bla*IMP, *bla*NDM, *bla*OXA-23, *bla*OXA-24/40, *bla*OXA-48, *bla*OXA-58 and *bla*VIM), 3rd-generation Cephalosporinases (*bla*CTX-M), Fluoroquinolones resistance genes (*gyr*A83 and *gyr*A87), Macrolide/Lincosamide resistance genes (*erm*B), Oxacillin resistance genes (*mec*A and *mec*C), Penicillin resistance genes (*bla*TEM and *bla*SHV) and Sulfonamide resistance genes (*sul*1).

A Review of the Value of Point-of-Care Testing for Community-Acquired Pneumonia

Abstract

Introduction: Community-acquired pneumonia (CAP) is an infectious disease associated with high mortality worldwide. Although *Streptococcus pneumoniae* remains the most frequent pathogen in CAP, data from recent studies using molecular tests have shown that respiratory viruses play a key role in adults with pneumonia. The impact of difficult-to-treat pathogens on the outcomes of pneumonia is also important even though they represent only a small proportion of overall cases. Despite improvements in the microbiological diagnosis of CAP in recent decades, the identification of the causative pathogen is often delayed because of difficulties in obtaining good-quality sputum samples, issues in transporting samples, and slow laboratory processes. Therefore, the initial treatment of CAP is usually empirical. Point-of-care testing (POCT) was introduced to avoid treatment delays and reduce reliance on empirical antibiotics.

Areas covered: This review summarizes the main scientific evidence on the role of POCT in the diagnosis and management of patients with CAP. We searched for articles on POCT in pneumonia on PubMed from inception to January 20th 2024. The references in the identified articles were also searched.

Expert opinion: POCT involves rapid diagnostic assays that can be performed at the bedside. These tests can produce results that could help guide initial therapy and management. The use of POCT is recommended in severe CAP and in patients with known immunosuppression.

Keywords: pneumonia; point-of-care; diagnosis; community-acquired pneumonia; microbiological diagnosis; test

1. Introduction

Pneumonia entails a massive burden of disease, suffering, and economic costs globally [1,2]. Community-acquired pneumonia (CAP) is a life-threatening lung infection that particularly affects high-risk individuals, such as the young, the elderly, those with multiple morbidities, and those with immunosuppression [2,3]. Between 10% and 20% of inpatients with CAP require intensive care unit (ICU) admission [4–6]. While the 30-day mortality is approximately 8%–10% in patients with CAP hospitalized in a general ward [7,8], it can reach 40%–50% in patients admitted to the ICU with severe CAP, especially if they require invasive mechanical ventilation [4,9].

Streptococcus pneumoniae remains the most common pathogen in CAP [2,8]. The incidence of CAP caused by respiratory viruses has increased in adults over time [10,11]. Although identifying the etiology of CAP is important, it is only determined in approximately 30%–40% of cases. The etiology of CAP has undergone significant changes during the last decade. This, together with the difficulties in attaining a rapid etiological diagnosis in a large proportion of patients, hamper the timely initiation of adequate antimicrobial therapy, which is known to be one of the main prognostic factors in severe CAP [10–12].

The implementation of accurate point-of-care testing (POCT) could help to avoid delays in identifying the most common microorganisms that cause CAP as well as the mechanisms of antimicrobial resistance, thus increasing the ability to offer patients an earlier treatment with appropriate antimicrobial therapy based on microbiological confirmation. Indeed, effective POCT will allow microbiological diagnosis at the bedside, thereby immediately informing the attending physician, preventing delays in

sample transport, and decreasing the time to pathogen identification [13]. A limitation is that the wide variety of microorganisms known to cause pneumonia cannot be covered by POCT, which is typically more limited. Compounding this limitation is the fact that only a few studies have evaluated POCT for pneumonia in specific care settings such as general wards and ICUs. The main body of evidence for POCT includes studies that have compared testing with conventional methods to evaluate their sensitivity and specificity. These studies have also been performed in the laboratory and not at the bedside. This review discusses the main scientific evidence on the role of POCT in CAP management.

2. Microbial etiology of pneumonia and current microbiological diagnoses

Knowing the microbial etiology of pneumonia is vital in order to ensure targeted antimicrobial therapy, avoid the overuse of antibiotics, and prevent the emergence of antibiotic resistance by selection pressure [2]. The etiology of CAP differs by infection severity and season [8,14]. Evidence shows that the microbial etiology of CAP remains unknown in approximately 50%–60% of cases despite diagnostic testing [8,15].

Pneumococcus remains the most common pathogen in pneumonia in adults. However, recent studies have reported an increase in the incidence of CAP caused by respiratory viruses, with these accounting for 7%–30% of cases among hospitalized adults with CAP that has defined etiologies [15]. A large study on the severity and outcomes of adults with CAP caused by influenza and non-influenza viruses in China reported that influenza, other respiratory viruses (non-influenza), and mixed viral infections accounted for 63%, 27%, and 10% of CAP cases, respectively [11]. Similar outcomes have been reported for adults with influenza and non-influenza viral pneumonia. Of

note, non-influenza viruses have been associated with a higher incidence of complications [11]. An observational study from Spain reported that viral sepsis was present in 61% of all patients with a diagnosis of viral pneumonia, with viral sepsis accounting for 3% of the adults admitted to the emergency department with a diagnosis of CAP and 19% of those admitted to the ICU [10].

It is also important to note that a minority of pneumonia cases are caused by difficult-to-treat pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and antibiotic-resistant Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. These are associated with a more severe presentation and higher mortality [16]. Between 5% and 6% of CAP cases also present with a co-infection, typically involving a combination of bacteria and respiratory viruses [17] (Figure 1A, 1B).

International guidelines recommend performing a microbiological diagnosis for pneumonia based on disease severity [18,19] (Figure 2). The guidelines also recommend not to perform a sputum Gram stain or culture routinely in outpatients with CAP [18,19]. They do, however, recommend obtaining sputum and blood samples and nasopharyngeal swabs for respiratory viruses (e.g., influenza A virus, influenza B virus, parainfluenza viruses, rhinoviruses, adenoviruses, respiratory syncytial virus [RSV], human metapneumovirus [hMPV], and coronaviruses), as well as performing urinary antigen tests for pneumococcus and *Legionella pneumophila* in patients with severe pneumonia, complications, sepsis or septic shock, immunosuppression, and no adequate response to initial therapy. Hence, determining the etiology in these cases could improve the quality of treatment decisions [18,19]. Respiratory and blood

samples should be collected before starting antibiotic therapy to increase the culture yields. Bronchoalveolar lavage (BAL) or tracheal aspirates (TAs) are recommended in patients admitted to the ICU with severe pneumonia. A pleural fluid culture should be performed in patients with pleural effusion [18,19]. Extensive microbiological testing is advocated in patients with severe CAP, especially in those with immunosuppression and at risk from either MRSA or *P. aeruginosa* given the associated higher risk of treatment failure and death [18,19]. Recent guidelines for severe CAP have recommended rapid diagnostic testing of viruses and bacterial pathogens to inform decisions about escalating or de-escalating empirical therapy. A critical underpinning of this recommendation is that evidence has shown an association between the use of broad-spectrum antibiotics and an increased risk of death in patients with CAP [20–22].

Knowing the microbiology of pneumonia in adults with CAP will contribute to improving the adequacy of antimicrobial therapy, prevent the excessive use of broad-spectrum antibiotics, and decrease the risk of treatment failure. However, there has been little advance in the implementation of new methods for the microbiological diagnosis of pneumonia in clinical practice, especially for bacterial etiologies. Identifying the microbiological cause of pneumonia currently takes between 24 and 48 hours, necessitating the initiation of empirical antimicrobial therapy to avoid disease progression [12]. Although molecular testing provides opportunities to identify multiple pathogens, detect markers of resistance, and help guide appropriate antibiotic therapy, the testing still needs to be validated, especially in severe pneumonia.

3. Fundamentals of point-of-care testing (POCT)

POCT incorporates various technologies to provide a real-time, portable, accurate, and rapid detection at the bedside (i.e., in the emergency department, ward or ICU). It offers the promise of rapid results that could improve patient management and is increasingly playing a vital role in preventing and controlling the spread of infectious diseases.

POCT for CAP can use blood, nasopharyngeal, urine, and BAL samples. However, the most frequent POCT for CAP involves antigen-detection rapid diagnostic tests (Ag-RDTs) and nucleic acid amplification-based techniques (NAATs) (Figure 3).

Ag-RDTs are a single-use lateral flow test based on antigen detection, for which results are available in 15–30 minutes. The highly specific binding affinity of the antigens and antibodies makes this technique a simple, fast, and effective diagnostic tool for detecting respiratory viruses and bacteria such as pneumococcus and *Legionella*. The enzyme-linked immunosorbent assay (ELISA) is the most frequently applied technique, with other techniques including chemiluminescence immunoassays (CLIAs) and lateral flow assays (LFAs). The Ag-RDT sample should be taken in the acute phase of the infection so that the yield of antigens is sufficient for testing.

NAATs amplify a specific region of the nucleic acid sequence of the pathogen and can detect very small amounts of the target sequences. One of the most widely used NAATs is real-time reverse transcription polymerase chain reaction (RT-qPCR). Other techniques include loop-mediated isothermal amplification (LAMP).

A detailed description and a summarized account of the clinical evidence of the POCT techniques by type of microorganism (viruses and bacteria) are provided in the

following two sections (sections 4 and 5, respectively).

4. POCT for respiratory viruses

4.1. Antigen-detection rapid diagnostic tests (Ag-RDTs)

A systematic review and meta-analysis [23] of 143 articles that included data from 69,699 individuals evaluated Ag-RDTs for viruses. It included 118 studies that investigated immunochromatographic assays for the influenza A and B viruses, reporting a sensitivity and specificity of 69% (95% confidence interval [95% CI], 64%–74%) and 97% (95% CI, 96%–98%), respectively. The Ag-RDTs for RSV were evaluated in 35 studies comprising 16,110 individuals (63% were children) and reported a sensitivity of 83% (95% CI, 77%–87%) and a specificity of 97% (95% CI, 95%–98%). In a subgroup analysis, the best performing tests were the Sofia® RSV FIA (sensitivity, 84% [95% CI, 77%–89%]; specificity, 96% [95% CI, 88%–99%]) and BinaxNOW™ RSV (sensitivity, 84% [95% CI, 71%–91%]; specificity, 96% [95% CI, 86%–99%]). The Ag-RDTs for hMPV were evaluated in 5 studies comprising 1,578 individuals, presenting a sensitivity of 59% (95% CI, 36%–78%) and a specificity of 99% (95% CI, 95%–100%).

A recently published article compared four Ag-RDTs (Abbott Panbio COVID-19 Ag Rapid Test, SD Biosensor Standard Q COVID-19 Ag Test, Humasis COVID-19 Ag Test, and SG Medical Acrosis COVID-19 Ag Test) with RT-qPCR for SARS-CoV-2, using 1,503 nasopharyngeal swabs. The Ag-RDTs had a positive predictive value of 99% to 100%, but the sensitivity was 77% for the Acrosis test and 54%–56% for the other three kits. All four Ag-RDTs could detect 10 SARS-CoV-2 variants, including the Pre-Delta, Delta, and Omicron variants. Results indicated that the Acrosis test was the most accurate for

detecting SARS-CoV-2 [24].

A prospective study evaluated the accuracy (sensitivity and specificity relative to real-time RT-PCR) of the LumiraDx™ SARS-CoV-2 Ag Test and the influenza A or B virus assay in 887 patients from 18 UK primary care practices when the Omicron variant was the most prevalent (June to December 2022) [25]. In that study, 17% of the patients tested positive for SARS-CoV-2, 12% for influenza A, and 0.6% for influenza B. The sensitivity and specificity of the test for SARS-CoV-2 were 80.8% and 98.9%, respectively, while those for the influenza A virus assay were 61.5% and 99.4%, respectively. In brief, Ag-RDTs for respiratory viruses show, overall, high specificity with suboptimal sensitivity. Larger studies are required to support the value of Ag-RDTs in patients with pneumonia.

4.2. Nucleic acid amplification-based techniques (NAATs)

Relevant data on NAAT for POCT were obtained from the ResPOC open-label randomized controlled trial (RCT)[26]. This RCT evaluated POCT for 15 respiratory viruses (FilmArray® Respiratory Panel, using nasopharyngeal samples) in patients with acute respiratory infections who had visited UK emergency departments across two winter seasons. Patients were randomized to receive either POCT or routine clinical care. Overall, 83% of the patients from both groups received antibiotics and more than half of the patients in the POCT group received an antibiotic before test results were available. However, 10% of the patients in the POCT group received either a single dose of an antibiotic or a course for less than 48 hours (17%) when compared to the control group (3% received single doses or brief courses of antibiotic in 9%). A neuraminidase inhibitor was prescribed in 91% of the patients with a positive POCT

compared to 65% in the control group. The length of stay (LOS) in hospital was shorter in the POCT group (5.7 days [SD, 6.3]) than in the control group (6.8 days [SD, 7.7]; difference, -1.1; 95% CI, -2.2 to -0.3; p = 0.0443). POCT was associated with an earlier diagnosis of an influenza virus infection and a shorter time to starting antiviral therapy. Although patients in the POCT group received a single dose or a shorter course of antibiotics compared to those in the control group, POCT for respiratory viruses did not reduce the proportion of patients who received antibiotics [26]. Another RCT from Denmark compared the effect of POCT to those of conventional methods on antibiotic prescriptions in hospitalized patients with CAP. No difference was found between the two study groups in the use of narrow-spectrum antibiotics at 4 h after patient admission (63% in POCT vs. 60% in the standard-of-care group; p = 0.134). Antibiotic therapy was more targeted at 4 h (OR, 5.68; 95% CI, 2.49 to 12.94) and 48 h (OR, 4.20; 95% CI, 1.87-9.40) as well as more adequate at 48 h (OR, 2.11; 95% CI, 1.23-3.61) in the POCT group. However, there were no significant differences in the 30-day mortality (OR, 0.90; 95% CI, 0.43-1.86; p = 0.787) or transfer to ICU (OR, 0.54; 95% CI, 0.10-2.91; p = 0.475) [27].

A meta-analysis exploring the diagnostic accuracy of various NAATs for influenza A and B detection in CAP included 89 studies (n = 43,762 individuals) and showed a sensitivity of 94% (95% CI, 90%–96%) and a specificity of 98% (95% CI, 97%–99%). The most frequently reported tests were Cepheid and BioFire. For the detection of RSV, 38 studies (n = 18,833 individuals) evaluated PCR tests, showing a sensitivity of 93% (95% CI, 89%–96%) and a specificity of 99% (95% CI, 98%–99%) [23].

A study on the use of the Xpert® Xpress SARS-CoV-2/Flu/RSV test on nasopharyngeal,

TA, and BAL samples found that this test had 100% positive and negative agreements for all four viruses in the nasopharyngeal samples. For the TA and BAL samples, there was 96% and 100% positive percent agreement, respectively, only for SARS-CoV-2. No positive flu/RSV samples were obtained from the TA or BAL samples. Compared to the reference PCR test, the Xpert® Xpress SARS-CoV-2/Flu/RSV test had a significant impact on the rapid detection of SARS-CoV-2, influenza A, influenza B, and RSV, as well as on the management of the infection [28].

The multicenter open-label FluPOC RCT investigated the clinical impact of POCT (FilmArray Respiratory Panel 2, using nasopharyngeal and sputum samples) in adults admitted to UK hospitals with influenza. The study included 623 patients, of whom 307 were in the POCT group and 306 in the control group. Antivirals were started in 99% of the 100 patients with a positive POCT result and only in 62% of the 102 positive cases in the control group. Of note, the time to antiviral therapy initiation was shorter in the POCT group (1 hour; interquartile range [IQR], 0.0–6.0) compared to the control group (6 hours; IQR, 0.0–12.0). Isolation measures were also more commonly implemented in the POCT group (70%) than in the control group (38%) [29].

Another RCT compared the impact of syndromic molecular POCT to that of conventional diagnostic tests on the detection of respiratory viruses and bacteria in patients admitted to the ICU with pneumonia [30]. The syndromic approach is a symptom-driven method that groups probable pathogens into one rapid molecular test that maximizes the chance of obtaining a clinically relevant answer in a clinically relevant timeframe. This trial included 200 patients with pneumonia, of whom 100 were in the POCT group and 100 in the standard testing control group. CAP, hospital-

acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) were present in 85, 69, and 46 patients, respectively. The median time to obtaining results was 1.7 hours for POCT and 66.7 hours for standard testing (difference, -65.0 hours; 95% CI, -68.0 to -62.0; $p < 0.0001$). Furthermore, 71% of the patients in the POCT group had an identified pathogen compared to 51% in the control group (difference, 20%; 95% CI, 7-33; $p = 0.004$), with the result-directed therapy initiated in 80% and 29%, respectively (difference, 51%; 95% CI, 39–63; $p < 0.0001$). Antibiotics were de-escalated in 42% of the patients in the POCT group compared to 8% in the control group (difference, 34%; 95% CI, 23-45; $p < 0.0001$) [30].

A recent Norwegian RCT investigated POCT (detection of 27 bacterial and viral respiratory pathogens with 7 resistance markers) in pathogen-directed therapy provided within 48 h after randomization in patients with CAP in an emergency department. POCT reduced the median time to pathogen-directed therapy by 9.4 hours compared to the standard-of-care group. The median response time (from patient admission to receiving a respiratory sample test result) was significantly reduced for the POCT group compared to the standard-of-care group (53.8 hours) [31].

In a prospective interrupted “on-off” study of adults admitted to a respiratory unit (December 2018 to April 2019), nasopharyngeal samples were subjected to GeneXpert rapid POCT for influenza and RSV (on-period) [32]. Testing was performed in the respiratory assessment unit or sent to the laboratory for multiplex PCR (to identify 12 respiratory viruses). In total, 755 samples were evaluated by POCT and 390 samples were evaluated by multiplex PCR. A respiratory virus was identified in 22% of the cases by POCT compared with 35% by multiplex PCR. Shorter isolation times (mean

difference, 16.9 hours; $p < 0.001$), LOS (mean difference, 15.5 hours; $p = 0.05$), and turnaround times (mean difference, 28.3 hours; $p < 0.001$) were observed in the POCT group compared to the multiplex PCR group.

Overall, the available evidence from multiple RCTs shows the potential of POCT to enhance the diagnosis and targeted antimicrobial therapy of patients with CAP in various clinical settings.

5. POCT for bacterial pathogens

5.1. Rapid antigen diagnostic tests

The urinary antigen test (UAT) for *S. pneumoniae* detection is widely used worldwide. The test is non-invasive, unaffected by previous antibiotic use, and takes only 15 minutes to produce results [33–35]. The reported specificity is 90%–100% and the reported sensitivity is 65%–100% [35–37]. A prospective study evaluated the time trend of the sensitivity of the pneumococcal UAT (BinaxNOW™) over 15 years, using data from 446 patients [38]. The authors of the study reported a significant gradual decrease in the sensitivity of the BinaxNOW™ test from 81% in 2001 to 49% in 2015. These results may be partly explained by the change in pneumococcal serotypes over time [39,40] and the decrease in the incidence of invasive pneumococcal pneumonia in recent decades [41]. After performing a multivariate analysis, the authors of the abovementioned prospective study reported that the male sex (0.467 [0.296-0.736]; $p = 0.001$), white blood cell count (0.959 [0.930-0.989]; $p = 0.008$), and the time trend per year (0.900 [0.859-0.943]; $p < 0.001$) were predictors of negative BinaxNOW™ results [38]. Hence, given that the sensitivity of this test has decreased over time, it is important to be cautious when interpreting BinaxNOW™ results in daily clinical

practice.

A retrospective study from the USA, which included data from 159,894 patients with pneumonia in 170 hospitals, investigated variations in UAT use and the association between UAT use and antibiotic de-escalation and clinical outcomes. Overall, 16% of the patients (n = 25,932) received a UAT, with 18% admitted to the ICU and 15% not admitted to the ICU. Patients who had a UAT were typically younger, less likely to have aspiration pneumonia (6% vs. 10% without a UAT), and more likely to have either sepsis (38% vs. 33% without a UAT) or require ICU admission (34% vs. 29% without a UAT). The rate of positive UATs was 7.2% and did not vary by center. Patients with a positive UAT result more often had a positive pneumococcus culture (25% vs. 2%; $p < 0.001$) and less often had resistant bacteria (5% vs. 7%; $p < 0.05$). The authors reported that UAT use was associated with antibiotic de-escalation following a positive test, thus concluding that an increased use of UATs and the narrowing of antibiotic therapy after a positive UAT result improved antimicrobial stewardship [42].

A meta-analysis analyzed the use of an *S. pneumoniae* UAT in 12 studies (n = 2,826 individuals) performed in hospital settings, with 11 of these studies evaluating the Alere BinaxNOW™ test. Pooled sensitivity was 70% (95% CI, 60%–79%) and the specificity was 83% (95% CI, 63%–93%) [23]. A prospective study evaluating four UATs (BinaxNOW™, ImmuView® *S. pneumoniae* and *Legionella*, STANDARD™ F *S. pneumoniae* Ag FIA, and Sofia® *S. pneumoniae* FIA) showed sensitivities ranging from 76.9% to 86.5% and specificities from 84.2% to 89.7%. No significant differences were found among the four UATs. The assays had a high level of agreement with one another, with 84.5% of the samples testing consistently across all four tests [43].

According to the annual epidemiological report of Legionnaires' disease from the European Centre for Disease Prevention and Control (ECDC), the *L. pneumophila* UAT was reported to be the most frequently used test in Europe in 2020 (n = 7,284; 87%) [44]. However, it is important to note that this UAT only detects *L. pneumophila* serogroup 1 and that other species of *Legionella* have been reported in recent decades, including *L. longbeachae*, *L. micdadei*, and *L. bozemanii* [45]. In 2022, an outbreak of *L. pneumophila* serotype 2 was reported in Italy, highlighting this limitation [46]. A recent meta-analysis of 21 studies (n = 5,772 patients) reported that the pooled sensitivity and specificity of *Legionella* UATs were 0.79 (95% CI, 0.71–0.85) and 1.00 (95% CI, 0.99–1.00), respectively. In a subgroup analysis, the sensitivity and specificity for *L. pneumophilia* serogroup 1 UATs were 0.86 (95% CI, 0.78–0.91) and 1.00 (95% CI, 0.99–1.00), respectively [47]. There is little information about the use of Ag-RDTs for bacterium detection in specific care settings. However, results from studies evaluating sensitivity and specificity have demonstrated the value of these tests for the rapid identification of common causative pathogens (e.g., pneumococcus and *Legionella spp.*) in severe pneumonia [12].

5.2. NAATs

Pooled evidence from a recent meta-analysis exploring the diagnostic accuracy of various NAATs for bacterial detection in CAP represents the main backbone in this area [23]. For *S. pneumoniae*, six studies (n = 2,221 individuals) were included in the meta-analysis, showing a pooled sensitivity of 96% (95% CI, 93%–98%) and a specificity of 91% (95% CI, 71%–98%) for the NAATs. The study by Gadsby et al. [48] compared the performance of the Unyvero P55 Pneumonia Cartridge with routine bacterial cultures

and in-house bacterial multiplex rt-PCR assays in 74 BAL samples from patients admitted to the ICU in Edinburgh, UK. The sensitivity and specificity of the Unyvero P55 Pneumonia Cartridge were 56.9% and 58.5%, respectively, while the corresponding values for the in-house PCR testing were 63.2% and 54.8%, respectively. Additional organisms were detected by the Unyvero P55 Pneumonia Cartridge and the in-house bacterial PCR panels in 16.2% of the samples. Antibiotics were changed based on the results of the routine testing; however, changes could have been made much earlier based on the results of the molecular method. The main limitation of this POCT was the lower sensitivity and specificity for detecting antibiotic resistance, which were 18.8% and 94.9%, respectively. A multicenter RCT also evaluated the impact of the Unyvero POCT. Among 208 patients hospitalized with pneumonia who were at risk from Gram-negative pathogens and due to undergo a bronchoscopy for a BAL sample, 100 were randomized to undergo POCT and 108 were subjected to conventional methods [49]. The duration of inappropriate antibiotic therapy was significantly shorter in the POCT group compared to the control group (adjusted mean duration, 47.1 hours [34.7–59.5] vs. 85.7 hours [78.8–95.6]; $p < 0.0001$). This translated into a decrease of 45% in the duration of inadequate antibiotic therapy (37.9–52.1). These results showed the impact of POCT in critically ill patients who were at risk from drug-resistant pathogens. Although both studies **[48] [49]** evaluated the same POCT for pneumonia, testing was not implemented in a specific care setting. Nevertheless, the sensitivity and specificity of this POCT are important for understanding its value in diagnosing pneumonia, showing potential value if implemented.

Although drug-resistant bacteria only account for 2%–6% of CAP cases, these pathogens are associated with a more severe presentation and higher mortality

[50,51]. POCT for drug-resistant pathogens has also been investigated, especially in critically ill patients, to improve early detection and avoid broad-spectrum antibiotic overuse. Indeed, empirical broad-spectrum antibiotics are initiated in approximately 30% of patients with CAP, which has been associated with poor outcomes in CAP, including increased mortality [21,22].

A prospective study evaluated the BioFire FilmArray Pneumonia panel for identifying bacteria and their resistance profiles in 187 BAL samples from patients with lower respiratory tract infections (LRTIs) (57 patients had HAP and 130 had CAP) [52]. The samples were also analyzed using conventional methods. In patients with HAP, *Acinetobacter baumannii* and *Klebsiella pneumoniae* were the most frequently identified pathogens, while *CTX-M* and *KPC* were the most prevalent antimicrobial resistance genes. In patients with CAP, *Haemophilus influenzae* and *S. aureus* were the most frequently identified pathogens, while *CTX-M* and *VIM* were the most prevalent antimicrobial genes. Another multicenter study evaluated the Unyvero pneumonia system for the identification of pathogens and resistance patterns in samples from 84 patients with LRTIs admitted to the ICU [53]. BAL samples were collected and analyzed with the Unyvero pneumonia system and compared with conventional methods. Overall, concordance between the two methods was 82.1%, but the Unyvero pneumonia system detected more microorganisms (38.1% vs. 27.4%; $p < 0.05$) and more polymicrobial infections (10.7% vs. 2.4%; $p = 0.01$). The Unyvero pneumonia system also performed well for antibiotic-resistant pathogens, excluding *P. aeruginosa*, showing a concordance of 87.5%–100% for MRSA and carbapenem-resistant isolates, but only 20%–33.3% for *P. aeruginosa.*

A meta-analysis of data from 22 studies including 5,163 patients with pneumonia (CAP, HAP, and VAP) evaluated nasal screening for MRSA and the subsequent development of MRSA pneumonia. It revealed that the incidence of MRSA pneumonia was 10% and that nasal screening had a positive predictive value (PPV) of 44.8% and a negative predictive value (NPV) of 96.5%. The NPV among CAP/HAP and VAP did not differ significantly at 98.1% and 94.8%, respectively. The authors reported that the test did not affect clinical outcomes, although reductions were reported for the length of MRSA therapy, length of monitoring, and health costs [54]. An RCT, assessing the effect of antibiotic management based on the results of POCT compared with routine care (45 patients: 22 patients in the POCT group and 23 in the usual care group) using BAL samples to detect MRSA, reported that the Gene Xpert MRSA/SA SSTI test had a sensitivity of 96%, with a negative likelihood ratio of 0.04 for MRSA. There was a decrease in the duration of vancomycin and linezolid treatment in the intervention group (32 h [IQR, 22–48] vs. 72 h [IQR, 50–113]; $p < 0.001$). In-hospital mortality was 14% in the intervention group and 39% for routine care (95% CI, -3.3 to 50.3; $p = 0.06$) [55].

POCT for the identification and detection of resistance genes could complement the routine conventional diagnosis of pneumonia and improve its management. However, more studies of POCT are needed in specific care settings.

6. Biomarkers and POCT

Biomarkers can be used in the diagnosis of pneumonia to help differentiate between bacterial and viral infections [56,57] and improve antimicrobial stewardship [58–62]. An early diagnosis of pneumonia could lead to more appropriate antimicrobial

treatment, less overuse of broad-spectrum antibiotics, and improved outcomes. C-reactive protein (CRP) and procalcitonin (PCT) remain the most widely used biomarkers in pneumonia [60,63–66].

6.1. C-reactive protein POCT

CRP levels increase after the first three days of infection, with a peak at 36–50 hours from infection, and can be used to identify lung infections from non-infectious causes. CRP increases in response to any inflammation and its level can be modified by corticosteroids and antibiotics. POCT-CRP has been shown to reduce antibiotic prescriptions safely in patients with LRTIs in different settings. A Cochrane meta-analysis of data from 12 trials with 10,218 patients suggested that POCT-CRP safely reduced antibiotic prescriptions among primary care patients with acute LRTIs, with a reduction from 516 antibiotic prescriptions per 1,000 participants in the control group to 397 prescriptions per 1,000 participants in the intervention group [67]. An RCT in 11 Dutch nursing homes that included 241 patients with symptoms of LRTIs showed that antibiotics were prescribed for 54% of the patients in the POCT group and 82% in the control group. Patients in the intervention group had a 4.93-fold higher chance (95% CI, 1.91–12.73) of not being prescribed antibiotics at the initial consultation than those in the control group, irrespective of the attending physician or baseline characteristics [68].

A systematic review and meta-analysis of different POCT for pneumonia performed a sub-analysis for POCT-CRP, aiming to differentiate between bacterial and viral pneumonia using different cut-off values (> 10 mg/L, > 20 mg/L, > 50 mg/L, and > 100 mg/L). Among 10 studies with data from 5,191 individuals, the sensitivity for POCT-CRP

varied between 52% (95% CI, 34%–69%) and 90% (95% CI, 67%–98%), while the specificity varied between 42% (95% CI, 26%–60%) and 91% (95% CI, 82%–96%) [23]. At a cut-off value of > 50 mg/L (6 studies; 4,505 patients), they observed a higher sensitivity (75%) and specificity (75%). However, a CRP of > 10 mg/L had the best performance in terms of sensitivity (90%), albeit with lower specificity (42%). The main limitations to using POCT-CRP in the diagnosis of pneumonia include the following: it has a delayed response to clinical stimuli (starting at 4–6 hours and peaking at 36 hours); CRP levels are elevated in inflammatory diseases, trauma, myocardial infarctions, fungal infections, and malignancy; and CRP levels decrease in the case of liver injury and corticosteroid use [69].

Finally, the accuracy of the FebriDx POCT was investigated in a prospective observational study of patients with suspected LRTIs admitted to the emergency department of an academic hospital in the Netherlands [70]. The FebriDX POCT requires a single drop of blood for the immunoassay to analyze the presence of elevated CRP levels (≥ 20 mg/L) and myxovirus resistance protein A (MxA, ≥ 40 ng/mL), the latter being a protein that is involved in the antiviral response regulated by type-I interferons. According to the manufacturer, the results from this test should be interpreted as follows: a positive CRP line and a negative MxA line indicate a bacterial infection; a positive MxA line and either a positive or negative CRP line indicate a viral infection; and negative CRP and MxA lines and a positive control line indicate negative results. The sensitivity and specificity of the FebriDx POCT for detecting bacterial infections are 87% (95% CI, 72%–96%) and 67% (95% CI, 55%–77%), respectively, while the corresponding values for detecting viral infections are 56% (95% CI, 40%–72%) and 92% (95% CI, 83%–97%), respectively. The test has been used in immunocompetent

patients with symptoms of LRTIs.

6.2. Procalcitonin POCT

PCT levels rise rapidly in response to microbial toxins and host responses, peaking at 12–24 hours after infection. Results from several studies show that PCT levels ≤ 0.1 µg/L indicate a high likelihood of a viral infection, whereas levels ≥ 0.25 µg/L indicate a high likelihood of bacterial pneumonia [71]. However, a multicenter prospective surveillance study of 1,735 adults hospitalized with CAP showed that no PCT threshold perfectly discriminated between viral and bacterial pathogens. Furthermore, it reported that when identifying any bacterial pathogen, a PCT threshold of 0.1 ng/mL had a sensitivity and specificity of 80.9% (95% CI, 75.3%-85.7%) and 51.6% (95% CI, 46.6%-56.5%), respectively [64]. Similarly, results from a meta-analysis of 12 studies including 2,408 patients with CAP reported that PCT had a sensitivity and specificity of 0.55 (95% CI, 0.37–0.71; I^2 = 95.5%) and 0.76 (95% CI, 0.62–0.86; I^2 = 94.1%), respectively [58]. Another systematic review and meta-analysis of different POC tests for pneumonia evaluated the diagnostic performance of PCT at cut-offs of > 0.1 µg/L, > 0.25 µg/L, and > 0.5 µg/L, reporting a sensitivity ranging from 44% (95% CI, 14%–79%) to 74% (95% CI, 38%–93) and a specificity ranging from 74% (95% CI, 36%–94%) to 93% (95% CI, 43%–100%) [23]. A PCT > 0.1 µg/L (four studies; n = 1,092 patients) showed a sensitivity of 74% (95% CI, 38%–93%) and a specificity of 74% (95% CI, 36%–94%) [23].

These data show that PCT levels are unlikely to provide reliable evidence for differentiating between bacterial and viral infections or guide decision-making processes related to initiating antibiotic therapy in patients with CAP. Existing guidelines for CAP do not recommend PCT testing when starting antimicrobial therapy

[18].

PCT has also been explored for guiding the prescribing of antibiotics in cases of COVID-19. Despite the reported lower rate of bacterial co-infections with COVID-19, antibiotics were commonly prescribed during the pandemic, especially in hospitalized patients. In one multicenter study, three patient groups with COVID-19 were compared to investigate the role of PCT in guiding antibiotic prescriptions during the first week of admission (a PCT group and two non-PCT control groups). Antibiotics were prescribed in 27% of the patients in the PCT group, 44% in non-PCT control group 1, and 45% in non-PCT control group 2. The PCT group had a lower probability of receiving antibiotics in the first seven days of admission (odds ratio [OR], 0.33; 95% CI, 0.16–0.66) compared to the two control groups (OR, 0.42; 95% CI, 0.28–0.62) [72].

An interesting study from Spain reported that patients with COVID-19 and PCT values > 0.2, > 0.5, > 1, and > 2 ng/Ml were significantly more likely to have co-infections than those with lower PCT values (p = 0.017, p = 0.031, p < 0.001, and p < 0.001, respectively). The authors recommended that antibiotics should not be initiated in patients with COVID-19 and PCT values < 0.2, especially if they also present high ferritin levels and an oxygen saturation level > 94% [73]. However, a study evaluating the use of PCT in critically ill patients with COVID-19 demonstrated that a PCT level ≥ 0.5 ng/mL within 72 hours of hospital presentation did not predict concomitant bacterial pneumonia in critically ill patients with COVID-19. The sensitivity and specificity of PCT to predict a co-infection with bacterial pneumonia in patients with COVID-19 pneumonia admitted to the ICU were 26.1% and 78.2%, respectively (NPV = 73.2%). The authors suggested that using PCT to rule out a diagnosis of bacterial

pneumonia in critically ill patients with COVID-19 is potentially dangerous and may delay the initiation of antibiotics and increase both morbidity and mortality [74]. Although multivariate modeling did reveal a significant association when combining two biomarkers (PCT and CRP) to detect a bacterial co-infection, it did not demonstrate the necessary sensitivity and specificity for this combination to serve as a reliable tool for ruling out bacterial co-infections. Our multicenter study on the value of PCT and CRP to identify bacterial co-infections among critically ill patients with COVID-19 suggested that PCT and CRP measurements alone, and at a single time-point, are not useful for diagnosing or excluding bacterial co-infections in this population [75].

PCT is an increasingly available biomarker, especially in reference hospitals. However, PCT has some limitations that should be taken into consideration when managing patients with pneumonia. Unfortunately, there are limited studies on POCT for PCT in a specific clinical setting. Biomarkers that are identifiable by POCT have the advantage of offering rapid results that have the potential to help in the management of pneumonia. However, more studies are needed on their cost-effectiveness (equipment, staff training, and maintenance) and impact in specific care settings.

7. POCT and CAP outcomes

An early identification of the CAP etiology allows for appropriate antimicrobial therapy and better outcomes. When using the pneumococcal and *Legionella* UATs, several studies have reported shorter LOS and reductions in both in-hospital and 30-day mortality [42,76–79]. A retrospective study from Spain (n = 1,452 patients) compared the 30-day and long-term mortalities in patients with *Legionella* CAP (n = 260) or

pneumococcal CAP (n = 1,192) diagnosed with UATs. It showed a higher 30-day mortality for *Legionella* CAP than for pneumococcal CAP and a significantly lower long-term survival in patients diagnosed early by UATs. This demonstrates the impact of using UATs at admission to obtain a rapid etiological diagnosis for both types of pneumonia [76].

A retrospective study of more than 6,000 patients with CAP in Japan also investigated the association between the UAT timing and in-hospital mortality associated with *Legionella* CAP. The tested group had lower 30-day and in-hospital mortalities when compared to the control group (5.7 vs. 7.7%; OR, 0.72; 95% CI, 0.55-0.95; p = 0.020). The authors also reported that the tested group showed a significantly shorter LOS and a reduced duration of antibiotic therapy than the control group. Overall, the use of UATs upon admission was suggested to be beneficial for patients with severe CAP [77].

Effective antibiotic therapy based on sensitivities is pivotal for the management of CAP, helping to avoid the overuse of broad-spectrum antibiotics as well as drug resistance and prevent complications such as infections with *Clostridioides difficile* [2]. Existing CAP guidelines strongly recommend a switch from intravenous to oral antibiotics as soon as patients reach clinical stability [18]. The main advantages of an early switch in antibiotic therapy are a decreased risk of infection, a reduced LOS, and lower health costs. An RCT (n = 800 patients) that evaluated the impact of molecular POCT for viral and atypical pathogens in addition to routine real-time PCR showed that the use of molecular POCT could reduce the duration of intravenous antibiotic therapy in patients hospitalized with LRTIs. Overall, the duration of the intravenous therapy was shorter in the POCT group (7 days; IQR, 5–9) compared with the control group (8

days; SD, 6– 1; $p < 0.001$). The LOS was also shorter in the intervention group, at 8.0 days (IQR, 7.0–11.0) versus 9.0 days (IQR, 7.0-12.0; $p < 0.001$) [80].

It is well known that the early use of antiviral therapy is associated with lower mortality in patients with influenza infections [81]. The FluPOC trial showed that routine molecular POCT for the influenza virus was associated with improvements in early diagnosis and appropriate antiviral therapy in adults admitted with acute respiratory illnesses. The importance of this was also demonstrated for early patient isolation in the prevention of in-hospital transmission [29]. Prior to the obtention of these results, the intervention group in the ResPOC trial showed a reduction in LOS of -1.7 days (95% CI, -0.3 to -0.4; $p = 0.0085$) between the positive POCT group (4.7 ± 4.6 days) and the negative POCT group (6.5 ± 7.2 days) [26]. They also reported a reduction in the duration of antibiotic therapy of -1.7 days (95% CI, -2.9 to -0.6; $p = 0.0033$). Patients with a positive POCT received antibiotics over a mean duration of 6.2 days, whereas patients with a negative POCT received antibiotics for 8 ± 5.3 days. Other studies have reported similar results [82–84].

A multicenter RCT evaluated whether the use of multiplex bacterial PCR (Unyvero pneumonia system) with BAL samples supported antimicrobial stewardship in patients with pneumonia. Among 208 patients randomized into the PCR group (n = 100) and the conventional test group (n = 108), the duration of inadequate antibiotic therapy was significantly shorter in the PCR group (adjusted mean duration, 47.1 h [34.7–59.5] vs. 85.7 h [78.8–95.6]; $p < 0.0001$).

8. Impact of the COVID-19 pandemic on POCT development

As of June 2023, the World Health Organization (WHO) reports that there have been

768 million confirmed cases of COVID-19 and 6.9 million deaths [85]. Throughout the pandemic, POCT was increasingly adopted for mass screening with shorter response times. Several POC tests were authorized for emergency use at that time based mainly on the detection of nucleic acids, proteins, viral antigens, and human antibodies [86].

A Cochrane meta-analysis on rapid antigen POCT for SARS-CoV-2 included data from 152 studies (66% from Europe) that had evaluated single-test applications of 49 different commercial antigen assays (n = 100,462 samples). Among the 16,822 cases with confirmed SARS-CoV-2, antigen tests correctly identified a COVID-19 infection in an average of 73% of individuals with symptoms and 55% of individuals without symptoms. The tests were the most precise when used in the first week of symptom onset (on average, 82% of confirmed COVID-19 cases had a positive antigen test). In the cases without symptoms, the tests were the most precise in the individuals who were likely to have been in contact with a person with a COVID-19 infection (on average, 64% of confirmed cases had a positive antigen test). In individuals without a SARS-CoV-2 infection, the antigen tests correctly excluded a COVID-19 infection in 99.6% of those with symptoms and 99.7% without symptoms. These results demonstrated the importance and impact of POCT in the diagnosis of COVID-19 [87].

POCT for SARS-CoV-2 was mainly developed using three technologies: RT-qPCR, LAMP-based assays (RT-LAMP), and clustered regularly interspaced short palindromic repeats (CRISPR). A recently published study reported on the fabrication and clinical validation of the PATHPOD POCT based on the LAMP assay for detecting COVID-19. The test could detect 30 to 50 copies of pure plasmid DNA per reaction within 40 minutes. In the validation study of 398 samples, PATHPOD showed a sensitivity, specificity, and

accuracy of 73.4%, 96.2%, and 89.2%, respectively (samples were prepared with the boiling method). When using purified RNA, the sensitivity, specificity, and accuracy increased to 87%, 98.3%, and 92.5%, respectively [88].

A rapid review and network meta-analysis on the diagnostic test accuracy for COVID-19 analyzed data from 23 rapid molecular tests, involving 10,449 participants. Among the 23 commercial rapid molecular tests analyzed, those with the highest sensitivity and specificity were Xpert Xpress by Cepheid (sensitivity, 0.99 [0.83–1.00]; specificity, 0.97 [0.69–1.00]), GeneSoC by Kyorin Pharmaceutical Co. Ltd. (sensitivity, 0.89 [0.33–1.00]; specificity, 0.88 [0.33–1.00]), and Truenat Beta CoV by Molbio Diagnostics (sensitivity, 0.90 [0.31–1.00]; specificity, 0.86 [0.30–1.00]). The authors reported that 15 rapid molecular tests had a sensitivity of ≥ 0.80 and that 3 rapid molecular tests had a specificity of ≥ 0.97 [89].

9. Cost-effectiveness and POCT

The ability to diagnose pneumonia at the bedside is very important, especially in the cases of severe pneumonia that may require ICU admission. Not only does it remove the need to send patient samples to a central laboratory, but it also optimizes decision-making on therapy and management. POCT is vital for the assessment and management of highly contagious infections, such as those caused by the influenza virus, SARS-CoV-2, and the Middle East respiratory syndrome-related coronavirus, providing an early identification of the causative pathogen. This allows for the necessary isolation measures to be implemented quickly to avoid the spread of infection. Before the COVID-19 pandemic, implementing POCT in clinical practice was far from reality. However, the pandemic emphasized the importance of POCT in

routine clinical practice. During the 3 years of the pandemic, more than 32 POC tests for SARS-CoV-2 received approval from the US Food and Drug Administration (FDA) [86]. The same should be possible for CAP.

In 2014, an RCT investigated the clinical effectiveness and cost-effectiveness of POCT for the influenza virus, RSV, and *S. pneumoniae* versus traditional laboratory cultures when managing the acute admission of elderly patients and those at high-risk aged 18 to 64 years. Results showed that costs and quality-adjusted life years (QALYs) were similar for each diagnostic strategy. The average total costs to the UK National Health Service for the three diagnostic groups were comparable at £2,159 in the near-patient group, £1,978 in the molecular group, and £2,327 in the traditional group. The probability that any one strategy was the least costly did not exceed 79%. Moreover, the total cost of the conventional laboratory culture was the highest and was associated with the lowest gain in terms of QALYs. Incrementally, PCR was the most cost-effective (78% probability at a willingness to pay £20,000/QALY) [90].

A cost-impact study using a simulation model estimated the economic cost and clinical impact of a novel diagnostic test known as LMMBV (LIAISON + MeMed BV). This test was used to differentiate between bacterial and respiratory viral infections in patients with pneumonia admitted to Spanish, Italian, and German emergency departments, comparing against standard-of-care testing [91]. The main outcomes were fewer patients on antibiotics, days saved, fewer hospital admissions, and shorter length of hospital stays. In their analysis, LMMBV was associated with a reduction in antibiotic prescriptions (43%) and days of treatment (1.02 per patient), which translated to a reduction in antibiotic use and a saving of approximately 1,020 antibiotic days per

1,000 patients, lowering the risk of complications. In terms of economic costs, the study showed that implementing the LMMBV test would allow savings of up to €364 and €328 per patient for hospitals and €91 and €59 per patient in Italy and Germany, respectively. In Spain, the average saving per patient could reach €165 [91].

A prospective study in the Netherlands investigated the potential impact of POCT compared to conventional methods in the diagnosis of the influenza virus and RSV for patient management and in-hospital costs between 2016 and 2017. The authors reported that the influenza virus and RSV were detected in 31% and 7% of the patients, respectively. The mean total in-hospital cost per patient with conventional testing was €5,243, which decreased to €4,904 with the implementation of POCT, with the main impact on the time to diagnosis. Additionally, costs fell to €4,206 when the impact of POCT was considered for hospital discharge. The authors concluded that in a single influenza season, a total cost reduction of €95,937 to €293,471 could be achieved at the hospital level by implementing POCT [92].

The economic costs of POCT, especially for microbiological identification, are higher compared to conventional methods. However, there is very little information about the economic impact of implementing POCT for patients with severe pneumonia. A comprehensive economic study is warranted to elucidate the impact of POCT on patients with CAP.

10. Expert opinion

POCT has the potential for a faster identification of the pathogens that cause pneumonia. This means it can help guide adequate antimicrobial therapy, avoiding the overuse of broad-spectrum antibiotics and improving the management of patients

with pneumonia, especially in severe cases where difficult-to-treat pathogens are common [50,51]. Given that we have observed an increase in the incidence of elderly patients admitted to the ICU with pneumonia and since there has also been a rise in the incidence of immunocompromised patients with pneumonia [2,93], POCT can play a key role in the rapid identification of the respiratory viruses related to severe pneumonia in these populations. It can also allow for the early initiation of antiviral therapy and the avoidance of antibiotic overuse, both of which may have important repercussions in these vulnerable populations.

In the case of highly contagious pathogens, such as the influenza virus, RSV, and SARS-CoV-2, the use of POCT may accelerate their identification and help initiate the necessary isolation procedures to prevent nosocomial transmission. Additionally, POCT can relieve pressure on central laboratories, especially during epidemics or pandemics, as observed with COVID-19. The implementation of POCT in strategic care sites, such as primary care, emergency departments, and the ICU, can eliminate sample transportation, reduce turnaround times, and ensure adequate and early antimicrobial therapy. This simple analytical process has the potential to relieve pressure on clinical laboratories in these settings.

Due to the limited information on the economic impact of POCT implementation for both patients with severe pneumonia and particular populations, future studies are needed before testing can be included in routine clinical practice. Further research is also necessary to determine the clinical usefulness and recommendations for specific populations, such as the immunosuppressed, elderly, and people with multiple comorbidities.

11. Current barriers and gaps for POCT implementation

The 'real-life' experience of POCT is limited. POCT has been shown to produce better results than conventional tests when compared under controlled conditions. The implementation of POCT may be advantageous when a rapid result is needed to guide antimicrobial therapy, especially in severe pneumonia. Nevertheless, there are likely to be significant challenges related to the implementation of POCT, including the cost of the equipment and consumables, the training of personnel, and the continued quality control.

In approximately 60% to 70% of the studies that we have included in this review, POCT was not really performed in a specific setting and was performed in the laboratory, especially in the studies that had no controlled situations such as the RCTs. This makes it difficult to interpret the real impact on clinical practice and calls into question its main advantages, such as the lower need for personnel and specific training. Further studies are needed to determine the real value of POCT in a specific setting (e.g., primary care, emergency departments, and the ICU).

Article highlights

- Point-of-care testing (POCT) involves the use of rapid diagnostic tests that can be performed at the bedside. These tests can give a result earlier than standard testing, thereby helping to guide patient management.
- Given that extended microbiological diagnosis is still recommended by international guidelines for the management of severe pneumonia, POCT in the emergency department or the ICU could improve management.
- POCT has potentially important roles in the management of individual patients in community outbreaks, seasonal respiratory illnesses, and the surveillance of respiratory pathogens such as the influenza virus, RSV, and SARS-CoV-2.
- The implementation of POCT could be an important asset in current multistakeholder efforts to reduce the overuse of antibiotics.
- POCT was developed to facilitate the identification of pathogens in a short period without needing a specific infrastructure. It might, therefore, help prevent the collapse of central laboratories in the event of public health emergencies, such as that observed during the COVID-19 pandemic.

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Declaration of interest

The authors have no relevant affiliations or financial involvements with any organization or entity that has a financial interest in, or financial conflict with, the subject matter or materials discussed in this manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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