Point-of-care testing for community-acquired pneumonia: do we have all the answers?

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ABSTRACT

- Point-of-care tests (POCTs) are available for rapid, "bedside" diagnosis of some causes of community-acquired pneumonia.
- POCTs complement other laboratory investigations for pneumonia. Although their sensitivity and specificity are improving, they are generally less sensitive than nucleic acid amplification and culture techniques.
- Questions remain as to the most cost-effective use of POCTs in clinical practice.
- To ensure their maximum value for both individual patients and the public health system, POCTs are probably best used as part of laboratory-designed algorithms for investigating pneumonia.
- POCTs are a valuable tool for surveillance, for rapid investigation of outbreaks, and for use in laboratories with limited diagnostic facilities.

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Point-of-care tests (POCTs) are rapid diagnostic assays that can be performed at the bedside by non-technical personnel. The most important features of an ideal POCT (Box 1) are high sensitivity, high specificity, and the ability to produce a result that guides immediate patient management.[1]

The microbial causes of community-acquired pneumonia (CAP) are hard to differentiate by clinical and radiological findings. The aetiology of pneumonia varies significantly with geographic location (eg, remote northern Australia versus large cities in the southern states), seasonality, whether the pneumonia is community- or hospital-acquired, and the age and underlying health of the patient.

Infections detectable by POCTs may present typically as pneumonia (eg, *Streptococcus pneumoniae* and *Legionella pneumophila* infections) or as influenza-like illnesses or upper respiratory tract infections (eg, influenza and respiratory syncytial virus infections). Although the sensitivity and specificity of POCTs have significantly improved, their sensitivity is still inferior to that of nucleic acid amplification and other laboratory tests.[2-4] Nevertheless, the rapidity of POCTs (producing a result in about 15 minutes) and ease of use offer certain advantages.

However, several questions need to be answered to guide clinicians as to the appropriate use of POCTs in practice: Who should perform POCTs? How should they be used? How reliable are they? What lessons have we learnt so far about their value?

Who should perform POCTs?

One can argue that POCTs are best used in laboratories as part of a laboratory-designed algorithm for diagnosing the multiple causes of pneumonia. This allows the laboratory to interpret the result and generate other useful data such as antimicrobial sensitivity, organism subtyping and molecular epidemiology. For example, the *Legionella* urinary antigen assays have high sensitivity for *Legionella pneumophila* serogroup 1, but lower sensitivity for other serogroups of *L. pneumophila* or non-pneumophila species.[5] The optimal diagnostic sensitivity for this relatively rare disease is achieved with a combination of culture, nucleic acid amplification and serology, along with urinary antigen detection.[5,6] Both serology and culture (which allows comparison of clinical and environmental isolates by molecular fingerprinting) are important, especially for public health purposes. Diagnostic efficiency is probably best achieved by using the POCT alongside these assays in the laboratory. Influenza and legionellosis are notifiable by laboratories to public health authorities. General practitioners performing POCTs will need to do this to avoid the loss of valuable surveillance data.

As with any technology (even if simple to use), experience in performing a test is invaluable: one would have to run a number of specimens to feel confident with the process. In our experience, POCTs for respiratory pathogens work better when performed by laboratory scientists than by people who rarely perform the assays. Laboratories require accreditation by the National Association of Testing Authorities, which imposes regulation on staff skills and training, reporting of results, and quality assurance of assays. This process does not apply to bedside testing. Also, the expense and limited shelf-life of POCT kits mean that stocking large numbers in the surgery or emergency department could be problematic. Some POCTs require laboratory equipment, including pipettes, tubes and heating blocks. It is important to ensure that POCTs are rigorously evaluated independently of testing by the manufacturers.

In contrast to the situation in laboratories and in some overseas practices, GPs in Australia would have to bear the cost of purchasing and performing POCTs, as, at this stage, they cannot directly bill the patient or Medicare for this service. A GP also needs to ask whether the 15 minutes or so needed to perform the POCT dovetails with current consultation times, although this may matter less in large practices or emergency departments where other staff can be deployed to perform the assays. Could other health professionals carry out POCTs — for example, nurses in aged-care facilities during outbreaks, or pharmacists (if neuraminidase inhibitors were to be listed as Schedule 3 drugs for seasonal influenza)? To take an extreme example, given that home-use assays to detect HIV antibodies are available overseas, could patients even self-collect (as reported in cases of severe acute respiratory syndrome [SARS][7]) and test respiratory samples?

How should POCTs be used?

A difficulty for clinicians is developing a rational algorithm for using POCTs in suspected cases of CAP, given the clinical uncertainty in determining the causative organism. Do POCTs separate influenza-like illness from pneumonia? If an influenza POCT is negative, is the clinician then obliged to perform more POCTs to

1 Features of an ideal point-of-care test

An ideal point-of-care test:

- Is highly sensitive and specific;
- Gives a result that improves treatment (and reduces costs) by reducing inappropriate antimicrobial treatment and hospitalisation;
- Can be done rapidly (15–30 minutes);
- Is simple to perform and interpret by non-laboratory personnel;
- Contains internal controls to help assure validity of results;
- Does not require expensive or elaborate equipment;
- Has temperature-stable components that allow easy and prolonged storage; and
- Is relatively inexpensive. ◆

exclude other pathogens? It would quickly become expensive to perform a succession of POCTs, and the doctor may still need to undertake further testing. If a respiratory tract swab is collected to perform one POCT, repeat swabbing may be needed for other tests (eg, viral culture, or even another POCT). This is particularly important for influenza, where isolates are needed to determine whether circulating strains match the current vaccine and to monitor antiviral resistance or the emergence of a pandemic strain.[2] Another problem is the type of clinical sample collected — in pneumonia the viral load is highest in the lower respiratory tract, so sampling only the upper respiratory tract may lead to false-negative results. On the other hand, urine is easier to collect than lower respiratory tract samples in suspected legionellosis or pneumococcal pneumonia.

As with any diagnostic tool, the positive and negative predictive values and the post-test probability of disease depend on disease prevalence in the population being tested. For example, as widespread vaccination reduces the frequency of pneumococcal disease, false-positive test results will increase and the positive predictive value will decrease. The proportion of false-positive results produced by POCTs for influenza and respiratory syncytial virus may increase if the tests are performed outside winter.

How reliable are POCTs?

The reliability of POCTs is crucial to their role in managing CAP. Important lessons were learnt in clinical trials of POCTs for pneumococcal disease, where the purpose of urinary antigen tests was to narrow the spectrum of antibiotics used to treat pneumonia. It was found that the tests may remain positive for at least 1–2 months after infection, and that patients with a low pneumococcal load undetectable by nasopharyngeal culture may have a positive pneumococcal urinary antigen test. There was a high positivity rate among children with pneumococcal colonisation but without invasive disease (colonisation decreases with age). Nasopharyngeal carriage rates in developed countries vary from 9% to 21%, and 50% of children who are carriers can show up as positive in POCTs.[8] In children with nasal colonisation, there is an increased likelihood of pneumococcal antigens reaching the urinary tract, especially in the setting of a concurrent viral upper respiratory tract infection. For example, in one study, 15% of febrile children without identified invasive pneumococcal disease tested positive for pneumococcal antigens.[9]

The relatively low sensitivity and specificity of pneumococcal POCTs can also be explained by the different immunogenicity and variation in antigenaemia of different pneumococcal serotypes. One study showed that POCTs detected 83.8%–100% of slow-clearance serotypes (3, 9N, 18) but only 25%–50% of rapid-clearance serotypes (7, 11, 14).[10]

A moderate-to-high sensitivity (56%–99%) for urinary antigen POCTs for *L. pneumophila* serogroup 1 infections has been demonstrated, with variation explained by differences in test and patient characteristics, the serogroup, the timing of sample collection during the illness, and whether the urine was concentrated (or frozen) before testing.[5,6] Furthermore, test sensitivity was affected by the clinical severity of disease in outbreaks, with 40%–53% of urinary antigen tests positive in mild Legionnaires' disease compared with 88%–100% in severe disease.[11] Sensitivity also varies according to whether the disease is travel-associated, community-acquired or nosocomial (reflecting the heterogeneity of bacterial populations): sensitivities in these groups have been reported as 94%, 76%–87% and 44%–46%, respectively.[12]

What lessons have we learnt so far about the value of POCTs?

POCTs for CAP may be useful in a number of situations (Box 2). This includes environments in which laboratory support is limited — for example, in rural areas, local or "stat" laboratories could perform POCTs, provide immediate results to the clinician, and refer samples for further testing through normal laboratory systems.

POCTs have a valuable role in influenza, where onsite testing may provide rapid information during outbreaks in nursing homes and other "closed" environments.[13] In such situations, test sensitivity is less important, as only a few positive results are needed to identify the outbreak while awaiting more detailed laboratory testing. Point-of-care testing for *Legionella* allows screening of a large number of samples that may arrive after notification of an outbreak. Early diagnosis of Legionnaires' disease is associated with lower mortality after timely antibiotic administration.

A potentially exciting role for POCTs is in community respiratory disease surveillance, where they can be used to enhance clinical reporting of influenza-like illness, determine which viruses are circulating, and guide empirical antiviral therapy.[14] For surveillance (compared with individual patient care), the lower sensitivity of POCTs is less significant.

2 Indications for point-of-care testing in community-acquired pneumonia (CAP)

- For individual patient management (accepting the limitations of the assay, and in conjunction with other laboratory tests, as required);
- For community outbreaks of influenza, respiratory syncytial virus (RSV) infection and legionellosis;
- During peak seasonal activity of influenza and RSV;
- During outbreaks in nursing homes, boarding schools or other "closed" environments;
- As a surveillance tool for respiratory pathogens;
- In laboratories with limited facilities for diagnosing CAP;
- In non-laboratory environments where trained staff are available to perform the assays (eg, large general practices, hospital emergency departments); and
- During periods when laboratory facilities are stretched (eg, in winter, or during an influenza pandemic). ◆

POCTs for influenza have been discussed in the context of an influenza pandemic — for example, in screening returning travellers or at "fever" clinics. However, current POCTs do not distinguish between seasonal human or pandemic (eg, influenza A H5N1) strains, meaning that more specific and sensitive testing is needed in the early phase of a pandemic.[15]

Within our region there are countries in which diseases such as SARS and influenza A H5N1 have emerged and where information on annual respiratory virus activity is limited. These countries may lack sophisticated laboratory facilities, and cost issues are significant. In these environments we should talk more of "point-of-need" testing (making pathology tests available in hospitals where they are needed). In countries with limited facilities, enhancement of existing laboratory infrastructure may be more cost-effective than widespread promotion of point-of-care testing.

New easy-to-perform assays that require minimal amounts of reagent are being applied to infectious disease diagnostics. These so-called "lab in a tube" or "lab on a chip" devices are rapid integrated enclosed systems that handle sample preparation, analysis and detection, although they currently require expensive instrumentation.

Unanswered questions about POCTs

POCTs have a role in the management of CAP, but whether they should be part of the clinician's or laboratory's diagnostic algorithm is debatable. Is the cost and time taken at the bedside in performing three or four POCTs practical? Do they replace standard laboratory tests that are normally performed in this clinical situation? Do they alter management (especially if the result is negative) and allow therapy to be more correctly targeted? Does this lead to better patient outcomes or a financial saving?

It is entirely reasonable for laboratories to determine strategies that incorporate POCTs to provide timely laboratory results, but more questions need to be answered before they can be recommended for widespread use in private practice.

Competing interests

Dominic Dwyer has undertaken clinical trials of various POCTs for respiratory viruses on behalf of the manufacturers. He has presented trial data at national and international meetings.

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