Diagnostic Strategies for Healthcare-Associated Pneumonia

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ABSTRACT

The first point of a good diagnostic strategy for healthcare-associated pneumonia (HCAP) is correct classification of patients with specific criteria, as suggested by the last American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines. However, clinical practice and recent literature have suggested new risk factors for multidrug-resistant infection (MRI): the presence of permanent indwelling devices, prior antibiotic use in the last 3 months, chronic and advanced pulmonary diseases (chronic obstructive pulmonary disease, bronchiectasis, etc.), history of alcoholism, and immunosuppression. The clinical presentation in HCAP patients is often unusual (mild respiratory symptoms and frequent extrapulmonary manifestations) due to different factors: advanced age, neurological disorders, and multiple chronic comorbidities. Moreover, HCAP commonly presents a worse clinical course than community-acquired pneumonia, a prolonged length of stay, and a mortality rate close to hospital-acquired pneumonia. Chest radiography and routine laboratory markers (including C-reactive protein) are always needed for clinical evaluation and severity assessment. The clinical use of new biomarkers of infection and sepsis (procalcitonin, etc.) is currently being investigated. Extensive microbiological testing to overcome the high prevalence of MRI in HCAP, including urinary antigens for Legionella and Streptococcus pneumoniae; blood cultures; Gram staining and low respiratory tract secretions (sputum, tracheobronchial aspirate, fibrobronchial aspirate, protected specimen brush, bronchoalveolar lavage); and cultures for aerobic, anaerobic, mycobacterial, and fungal pathogens are recommended, whereas the indication for serology tests for respiratory viruses and atypical pathogens is low. By contrast, the new polymerase chain reaction–based techniques for the rapid identification (2 to 4 hours) of microbial pathogens in respiratory samples (nasopharyngeal swab, bronchoalveolar lavage) seem to be the most innovative future perspective in the diagnostics of HCAP.

KEYWORDS: HCAP, diagnostic tests, etiology in HCAP

DEFINITION OF HEALTHCARE-ASSOCIATED PNEUMONIA

In the last 2 decades the literature has described a group of patients commonly residing in long-term care facilities (LTCFs) (nursing homes, hemodialysis centers, etc.) or with some contact with the healthcare environment, whose pneumonia usually shows a worse clinical course and outcomes [mortality, length of stay (LOS)1–3, etc.] than that of patients with community-acquired pneumonia (CAP). These findings have led to the development
of the new concept of healthcare-associated pneumonia (HCAP).

Nonetheless, it is uncertain whether the previous clinical conditions (older age, impaired functional status, high number of comorbidities, etc.) or a different microbiological etiology than CAP can be considered as the main cause of these findings.

Although the definition criteria for HCAP have not been clearly established, it is evident that more attention is needed on this issue because the number of patients attending outpatient health care settings (LTCFs, domiciliary care programs, etc.) is increasing worldwide.4,5

The first point of a good diagnostic strategy, in the context of the initial evaluation (medical history collection and physical examination), is the correct classification of patients with HCAP.

The last American Thoracic Society/Infectious Diseases Society of North America (ATS/IDSA) guidelines for the management of hospital-acquired pneumonia (HAP) define specific criteria (Table 1) to identify HCAP patients and recommend antimicrobial therapy similar to that administered in cases of HAP.6

However, clinical practice and recent literature have suggested that all patients with permanent indwelling devices (e.g., permanent urinary and other permanent catheters, gastrostomy, nasogastric tube, etc.) are at risk of multidrug-resistant infections (MRIs).7 Therefore, it is likely that this additional criterion should be considered to identify HCAP patients because it represents a strong risk factor for MRI and could consistently influence the diagnostic and therapeutic approach.

Accordingly, to detect HCAP patients with tangible risk factors for MRI, it is strongly recommended to consider, alongside the ATS/IDSA criteria, the factors shown in Table 2.

Table 1 Risk Factors for Multidrug-Resistant Pathogens Causing Hospital-Acquired Pneumonia, Healthcare-Associated Pneumonia, and Ventilator-Associated Pneumonia

<table>
<thead>
<tr>
<th>Antimicrobial therapy in preceding 90 days</th>
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<tr>
<td>Current hospitalization of 5 days or more</td>
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<tr>
<td>High frequency of antibiotic resistance in the community or in the specific hospital unit</td>
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<tr>
<td>Presence of risk factors for HCAP:</td>
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<td>Hospitalization for 2 or more days in the preceding 90 days</td>
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<tr>
<td>Residence in a nursing home or extended care facility</td>
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<td>Home infusion therapy (including antibiotics)</td>
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<td>Chronic dialysis within 30 days</td>
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<tr>
<td>Home wound care</td>
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<tr>
<td>Family member with multidrug-resistant pathogen</td>
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<tr>
<td>Immunosuppressive disease and/or therapy</td>
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From Reference 6, with permission.

Actually, due to the lack of information, awareness about HCAP seems inadequate and does not facilitate the recognition of MRI risk factors among patients fulfilling the ATS/IDSA criteria for HCAP. Indeed, despite the bad prognosis of pneumonia in this set of patients, not all HCAPs really have to be empirically treated for nosocomial microorganisms because this could lead to the overuse of antibiotics, with the resulting possibility of emergent resistances and inadequate antibiotic coverage of some community pathogens such as Legionella spp.8 and Chlamydia pneumoniae.9

Consequently, wide diagnostic testing is recommended to optimize the initiation and downscaling of antibiotic therapy, despite the frequent practical difficulties, such as the fact that many patients are not able to provide a good sputum specimen for analysis, and it is often impossible to distinguish between chronic airway colonization and a new infection causing pneumonia.

**CLINICAL PRESENTATION**

The clinical presentation of HCAP patients is frequently unusual and nonclassical as a consequence of different conditioning factors, including advanced age, the presence of neurological disorders, and/or multiple chronic comorbidities.

In regard to pneumonia in elderly patients, Osler described it as “a painless and often lethal event”10; indeed, the classic respiratory symptoms of pneumonia, such as cough, expectoration, dyspnea, and pleuritic chest pain, are commonly mild11,12 and less frequent than in younger patients. On the other hand, extrapulmonary manifestations, including mental confusion and gastrointestinal disorders (anorexia, nausea, vomiting, abdominal pain, etc.), are very frequent and often predominate over respiratory symptoms.13 It has also been observed that in older CAP patients many symptoms (cough, sputum, fatigue, anorexia, myalgias, etc.) are longer lasting than in younger patients.14 Riquelme et al reported dyspnea to be the most frequent symptom in older patients with CAP, whereas 19% of the patients did not present cough, sputum, or pleuritic pain, and altered mental status was present in almost 45% of this group.15
In addition, it is known that fever is less commonly present in older compared with younger CAP patients, likely as a result of an altered thermoregulatory capacity to produce and respond to endogenous pyrogens. In their recent review Niederman and Brito provide a very good description of the clinical features of pneumonia in the elderly.

A variable proportion of HCAP patients have neurologological and cerebrovascular disorders with frequent impairment in swallowing or cough reflexes that implies an elevated incidence of bronchoaspiration. The reported incidence of dysphagia, particularly in nursing homes, is between 50 and 75%. The definition of bronchoaspiration implies the aspiration of a considerable inoculum of pathogens from a previous colonized oropharynx or of a little inoculum in the presence of predisposing conditions that make the clearance of the aspirated secretions difficult, such as a high virulent bacterial burden, forceless coughing, insufficient ciliary transport, or altered immunoresponse. Indeed, Vergis et al. identified witnessed aspiration and sedative medication as the most important risk factors for pneumonia in LTCFs, and Kikuchi and colleagues demonstrated the occurrence of aspiration in 71% of elderly patients with CAP compared with 10% in healthy age-matched control subjects.

Moreover, dysphasia can significantly hinder the interpretation of signs and symptoms during medical evaluation.

The clinical presentation of pneumonia in patients with multiple chronic comorbidities (chronic obstructive pulmonary disease, congestive heart failure, renal failure, etc.) may suggest an acute exacerbation of a comorbidity rather than pneumonia.

In conclusion, in patients with recent contact with the healthcare environment and with suspicion of pneumonia, prompt and well-oriented diagnostic testing is fundamental because an unusual clinical presentation (older age, neurological disorders, comorbid illnesses) and the frequent predominance of the symptoms of comorbidities can cause a considerable delay in the first dose of antibiotic, the administration of which is generally considered a predictor of outcome in pneumonia.

**CLINICAL COURSE**

Despite the great differences among the studies published on the microbial etiology of HCAP, it has been unanimously described that, compared with CAP, HCAP patients have a more severe clinical presentation (hypoxemia, need for mechanical ventilation support, multilobar infiltration) but not a different incidence of complications (pleural effusion, myocardial infarction, etc.). In addition, a prolonged LOS and a mortality rate close to HAP are also reported.

**DIAGNOSTIC TESTS**

**Radiology**

Along with a correct history and an extensive clinical evaluation, chest radiography (preferably posteroanterior and lateral positions) is always needed to define the presence of a new pulmonary infiltrate, the severity of the disease, and the presence of complications. It is important to be aware of the existence of different pathological conditions, such as the presence of atelectasis, pulmonary edema (cardiogenic and noncardiogenic), pleural effusion, hemorrhage, neoplastic lesions, infectious and malformative cysts, pulmonary infarction (i.e., pulmonary thromboembolism), drug-induced pulmonary lesions (oxygen, chemotherapy agents, amiodarone, etc.), diffuse alveolar damage [adult respiratory distress syndrome (ARDS)], organizing pneumonia [bronchiolitis obliterans organizing pneumonia (BOOP)], that can erroneously be interpreted as pneumonia. In case of doubt or relevant disagreement between the clinical presentation and the radiological findings, it is recommended to perform a computed tomographic (CT) scan.

**Laboratory Tests**

Routine laboratory markers are a fundamental part of the clinical evaluation for deciding the site of care and severity assessment. Recommended assessments include blood cell count, electrolytes, hepatic and renal function, arterial blood gases, C-reactive protein (CRP) and procalcitonin (PCT) levels.

CRP is an acute inflammatory mediator that is released from the liver by interleukin-6 (IL-6) stimulation, after tissue damage as part of systemic inflammatory response. It is a useful marker of sepsis, infection, and response to treatment. Unfortunately, there are some limitations to its use: serum CRP levels slowly increase (at least 24 hours after the onset of infection) and do not reliably correlate with the severity of the disease. In addition, CRP levels also increase in non-infectious inflammatory processes such as coronary syndrome or postoperative periods. No specific evaluations have been made in HCAP patients but it has been demonstrated that high serum levels of CRP in elderly patients with pneumonia are a useful prognostic marker of disease severity.

PCT is a new marker of bacterial infection that has been widely investigated in the last decade since the first description in 1996 of elevated serum levels of PCT, the prohormone of calcitonin, in inhalational burn injury, in several sepsis syndromes, and in endotoxemia. It is a peptide synthesized in monocytes undergoing adhesion processes but not in circulating polymorphonuclear cells. Tissue cells produce PCT only when interacting with activated monocytes. Different studies
have demonstrated that PCT is helpful to differentiate bacterial infections from other inflammatory (i.e., ARDS, autoimmune diseases) or infectious (i.e., viral) diseases for its cytokine-like role in host defense versus bacterial infections. PCT monitoring, therefore, cannot only limit the overuse of antibiotics but can also contribute to an early evaluation of disease severity.

Furthermore, high levels of PCT at admission and at day 3 are a good predictor of treatment failure. Indeed, in an attempt to improve current sepsis definitions, the PIRO (predisposition, insult infection, response, organ dysfunction) concept recommends the use of readily measurable circulating biomarkers as an additional tool for the timely assessment and severity classification of septic patients and the prediction of mortality.

No specific studies on the utility of PCT measurements in HCAP patients are available in the literature, but it is likely that in patients with an atypical clinical presentation [mild and unusual symptoms of lower respiratory tract infection (LRTI)], biological markers may have a greater role in achieving the diagnosis of pneumonia.

However, for the diagnosis of infections, the diagnostic accuracy of PCT has a primary importance: whereas PCT levels lower than 0.1 ng/dL suggest the absence of bacterial infection and interruption of antibiotic therapy (when previously initiated) and levels of PCT ≥ 0.5 ng/dL are clearly associated with bacterial infection, PCT levels between 0.26 and 0.5 ng/dL can still indicate a possible bacterial infection and can be of diagnostic value in conditions other than sepsis.

Kruger and colleagues indicate a cutoff level of 0.228 ng/mL to predict patients at low risk of death from CAP in all severity score classes. As a consequence, very sensitive assays (with a functional detection limit less than 0.5 ng/mL) are recommended. Nonetheless, despite the evidence-based recommendation to monitor PCT levels in critically ill patients with sepsis, it remains unclear whether an altered immuneresponse secondary to diseases, drugs, or aging can affect the expression of PCT in respiratory bacterial infections. Therefore, more information is needed on the pathophysiology of PCT and, consequently, on its diagnostic value in specific categories of patients, such as the very elderly and immunosuppressed individuals (chemotherapy, corticosteroids, hematopoietic disorders, etc.) who may be highly represented among HCAP.

Other new inflammatory biomarkers, including Pro-adrenomedullin, pro-atrial natriuretic peptide (ANP), carbamoyl phosphate sinthase-1 (CPS-1), pro-endothelin-1 (pro-ET-1), and copeptine (pro-vasoressine), are currently being investigated as possible helpful biomarkers for individual risk assessment and outcome prediction in sepsis and severe infection and to detect cardiovascular abnormalities in pneumonia patients.

**Etiologic Diagnosis**

A variety of microbiological tests, with various indications and limitations, are commonly available to investigate the microbial etiology of pneumonia. Nevertheless, the diagnostic value of many specimens obtained routinely, as well as those achieved through more invasive procedures (fiber-bronchoscopy, etc.) is controversial even in critically ill patients.

Blood cultures are usually recommended for more severe patients and for those who have not previously received antibiotics. Metersky and colleagues demonstrated that in these patients false-positive results were less likely than in patients with mild illness and in those who had previously been administered antibiotics. Different studies have evaluated the contribution of blood culture to clinical management of hospitalized patients with CAP and have found blood cultures to be of poor utility in directing antibiotic therapy, rarely cost saving, and weak from an epidemiological point of view. By contrast, we should consider that HCAP patients are more similar to HAP patients in whom blood cultures are strongly recommended. Indeed, the microbial pattern can considerably differ from CAP (unusual antimicrobial resistance, presence of atypical/uncommon pathogens), and, as a consequence, the empirical antibiotic therapy is more likely to be inadequate. Thus a greater effort to achieve the etiological diagnosis is justified in HCAP, despite the possible increase in costs.

Sputum is the most common specimen obtained in LRTI, but it is also the most problematic. First, many patients do not have productive cough or are too weak to provide a deep respiratory sample. Second, very strict screening criteria for microscopic examination of sputum must be followed to ensure the quality of the microbiological determination (proportion of epithelial and polymorphonuclear (PMN) cells, etc.). A variety of suggestions to improve sputum quality include no ingestion of food for 1 to 2 hours, rinsing the mouth with water or saline solution, rapid transport of specimens to the laboratory, and prompt inoculation of culture media. However, there is no clear evidence that any of these procedures improve the utility of the sputum specimen. Sputum induction with a 3% NaCl solution, suggested in the past to obtain specimens less contaminated from the upper respiratory tract, is currently not recommended because no benefits have been demonstrated for the etiological investigation and because of the risk of provoking bronchial obstruction.

Nonetheless, the visualization of a predominant bacterial morphology in Gram staining of lower respiratory tract (LRT) secretions may be useful in predicting
the etiologic agent, especially in intensive care settings where the promptness in achieving an etiological diagnosis and in directing the antibiotic therapy toward gram-positive or -negative microorganisms is fundamental and may be life-saving in some circumstances.

Although the sensitivity and specificity of Gram staining of LRT secretions ranges widely between 57 and 95% and between 48 and 87%, respectively, according to the type and quality of specimens, negative Gram stains and cultures in patients who have not previously received antibiotics have a high negative predictive value (94%), suggesting that other noninfectious causes of pulmonary infiltrates should be investigated (pulmonary edema, neoplasia, etc.)

Whereas the importance of Gram staining and sputum culture in the evaluation of pneumonia in hospitalized patients is clear, their role in patients with pneumonia not severe enough to require hospitalization is debated because the overall yield is low and because the impact on clinical care is infrequent.

Although previous antibiotic use, good specimen quality, and rapid transport to the laboratory improve the sensitivity and specificity of Gram staining and sputum culture, their role in patients with CAP, the microbial etiology was obtained in 59% of cases by sputum examination and in 41% by other techniques.

However, it is important to remember that HCAP patients, particularly those residing in LTCFs, have a high prevalence of colonization of the upper respiratory tract from pathogen microorganisms, and this finding can seriously hinder the etiological diagnosis and mislead antibiotic therapy.

The collection of TBAS is the simplest and least invasive technique to obtain respiratory samples in intubated patients at a relatively low cost. Qualitative culture has a limited value because, despite having acceptable sensitivity (90 to 100%), its specificity for infection is very poor (14 to 47%). However, quantitative cultures of TBAS, with a cutoff point of 10^3 CFU/mL have shown an accuracy similar to that of bronchoscopic sampling methods and with the advantage of a high negative predictive value in case of patients who have not previously received antibiotics. The study by El Solh and colleagues analyzed the diagnostic value of TBAS cultures in comparison with PSB and BAL in 75 patients with severe nursing home–acquired pneumonia admitted to the intensive care unit (ICU). They obtained an etiological diagnosis in 49 patients (65%), either with BAL or with PSB, with an absolute concordance in 33 cases (67%) between the two techniques. In comparison, the accuracy of TBAS was favorable at a cutoff point of 10^3 CFU/mL (sensitivity of 90% and specificity of 77%), with the results coinciding with PSB and BAL in 30 cases (61%).

Quantitative FBAS also seems to obtain results similar to invasive sampling methods in terms of diagnostic yield and clinical outcome. The PSB technique allows LRT sampling by advancing a catheter containing a sealed sampling brush through the working channel of the bronchoscope allowing 0.01 mL of secretions to be collected for microbial investigation. The selected threshold to discriminate colonization and infections is 10^3 CFU/mL, and PSB has shown a high sensitivity (above 70%) and specificity (80 to 90%) for infection. It should be pointed out that the diagnostic yield decreases markedly if the sample is obtained under antibiotic treatment. This technique is simple and the sampling fast, minimizing side effects of the procedure.

BAL is performed through the insertion of the bronchoscope and can collect samples from both distal bronchi and a large alveolar area. After blocking the tip of the bronchoscope in a segmental or subsegmental bronchus, 100 to 150 mL of saline are instilled and aspirated consecutively. Quantitative culture of BAL, with a cutoff point at 10^4 CFU/mL, has very good sensitivity and specificity (approaching 100%). The utility of BAL in immunosuppressed patients with pulmonary infiltrates has been clearly demonstrated, with the
early use of the information provided by this method in this specific population being related to a better outcome. In CAP there is no firm information supporting its use and possible side effects, and contraindications are weighted individually in each patient.

Alternatively, there are “blind” techniques to obtain LRT secretions through the insertion of a catheter in a distal bronchus without the help of fibrobronchoscopy. In this case, the sensitivity and specificity are 74 to 97% and 74 to 100%, respectively, for BAS, and 63 to 100% and 66 to 96% for BAL.

El Solh and colleagues studied the microbial etiology in older patients (≥ 75 years) with severe pneumonia admitted to the ICU: 57 individuals were residing in the community and 47 in nursing homes. A similar diagnostic yield (BAL, PSB performed blindly or via bronchoscopic guide) was described in both groups of CAP and nursing home–acquired pneumonia, suggesting that the accuracy and diagnostic value of the invasive techniques to obtain LRT secretions are comparable in both groups. In addition, invasive bronchial sampling in this series led to a change in microbial therapy in 40% of cases and discontinuation of antibiotics in 10% of definite pneumonia, with no differences in mortality or in the incidence of complications between patients who underwent a bronchoscopy and those who did not.

However, due to the severity of underlying medical illnesses, the risks of invasive diagnostic approaches (bronchoscopy or needle aspiration) make their application in the practice more infrequent. Nevertheless, an LRT sample should always be collected in intubated or tracheostomized patients.

It is recommended to test all the respiratory samples for mycobacterial (Ziehl-Nielsen and auramine stains; mycobacterial culture) as well as fungal pathogens, particularly in patients with bronchiectasis or suspected immunosuppression because the number of immunosuppressed patients among HCAP patients can be considerably higher than in CAP cases, as shown in the large HCAP series from the group in St. Louis, Missouri, where immunosuppressed patients ranged between 23 and 39% of all HCAP patients with positive cultures.

A diagnostic thoracentesis should always be performed in patients with large pleural effusion to investigate parapneumonic effusion and empyema, complications that can make the treatment considerably difficult and delay the achievement of clinical stability. Gram staining and culture for aerobic and anaerobic bacteria and pneumococcal antigen tests should be performed in the pleural liquid. A retrospective comparative study of empyema in 114 community–residing and 55 nursing home–residing patients described that the latter patients had a delayed clinical presentation and a higher yield of anaerobic organisms compared with individuals from the community. These findings suggest that particular attention is necessary with HCAP patients because the clinical presentation is often misleading in defining the severity and etiology of the disease, and more extensive diagnostic procedures are needed in these patients.

Tests for the determination of urinary antigens for Legionella pneumophila and Streptococcus pneumoniae are usually available in emergency departments (EDs) at a low cost and with good feasibility. Pneumococcal testing (all serotypes) has a good sensitivity (≥70%) and specificity (≥90%), but it has some limitations: false-positive results have been reported in individuals who had received specific vaccination or with bronchial colonization. In addition, a positive result can be observed up to 25 weeks after the infection, therefore making more difficult to differentiate acute infection from S. pneumoniae. On the other hand, notwithstanding its high sensitivity (70 to 90%) and specificity (>90%), the urinary antigen test for Legionella, which is positive from the third day of infection, is able to detect only serotype 1, accounting for 75 to 90% of all infections for Legionella, and not serotypes 4 and 6, which also cause infections in humans.

Alternative diagnostic tests for Legionella are LRT culture, direct fluorescent antibody (DFA) staining in respiratory secretions and tissue samples (rapid but technically demanding), seroconversion (titers ≥ 1:128), or nucleic acid amplification.

Large epidemiological studies have clearly demonstrated that older adults living in LTCFs are at a higher risk for invasive pneumococcal disease and death than community–living older adults, and outbreaks of multidrug-resistant (MDR) pneumococci and of Legionella among nursing home residents have been widely described. These data confirm the relevance of low-cost and easy-to-perform determinations for pneumococcal and Legionella infections in this population.

Nasopharyngeal swab is an additional easy-to-perform and low-cost test, useful for the determination of respiratory virus (influenza viruses A and B, parainfluenza virus, respiratory syncytial virus, adenovirus, coronavirus, and rhinovirus). Viral diagnostic methods include culture, rapid antigen detection, real time polymerase chain reaction (RT-PCR), and serologic testing, with availability and sensitivity varying on the basis of the specific virus. Respiratory secretions appropriate for testing include nasal swab or wash specimens, sputum specimens, and BAL fluid samples.

Studies on CAP in adults indicate a viral etiology in 1 to 23% of cases, with the influenza virus being the most common, whereas the information about viruses in HCAP is reduced, with the frequency of viral detection ranging between 0 and 14% of all cases with a known etiological diagnosis. Today, pure viral pneumonia is uncommon, perhaps because prior infection and vaccination have induced immunity among older
persons. The true incidence of secondary bacterial pneumonia during influenza is unknown, but it is clear that dual viral–bacterial infections are more severe than viral infections alone, as evidenced by higher rates of intensive care use and morbidity.73 An observational 3-year study in LTCFs investigated serology for viral infections in 382 patients. A total of 204 viral infections were identified in 157 subjects; the human metapneumovirus (13%) and coronavirus (11%) were the most frequently isolated viruses.78 The presence of bronchitis, pneumonia, and any LRTIs was strongly associated with the presence of a viral infection. This work undoubtedly demonstrates that a wide range of respiratory viruses circulate among LTCFs, contributing to the morbidity of respiratory illnesses.

A specific nasopharyngeal swab is indicated for methicillin-resistant Staphylococcus aureus (MRSA) detection when suspected. Nonetheless, it may be difficult to distinguish between MRSA colonization (healthy carriers), which is relatively frequent in weakened patients, and new MRSA infections. Indeed, different authors have described that S. aureus infections as relatively common in the nursing home population, especially in individuals with indwelling devices, and these findings have reinforced the idea of new outbreaks of community-acquired MRSA. In our experience community MRSA infections are anecdotal, and contact with the healthcare environment should be investigated because it seems to be the most frequent source of such infections.

The suspicion of “atypical pneumonia” should be taken into account when dealing with older and nursing home patients because epidemic episodes have been described in these populations.8,5,81 Serology testing is available for Chlamydia pneumoniae and Mycoplasma pneumoniae, accounting for a variable number of pneumonia cases (up to 21% of CAP,83 2 to 27% of HCAP statistics12,30), but also for virus (see before). The utility of serology in routine testing is poor due to the delay in obtaining results, although it has an important role in populational studies and for epidemiological purposes.84,85 However, the empirical antibiotic treatment of HCAP should always cover atypical pathogens (macrolides, quinolones, etc.).33 Nasopharyngeal swab has also recently been used, when available, for PCR determination of an increasing number of microorganisms.86

In view of such a wide panel of microbiological tests the decision of the physician is guided by specific clinical indications, procedural risks, the clinical conditions of patients, time to results, and so forth.

Indicators for more extensive diagnostic tests should be considered, including (1) early failure, (2) pleural effusion, (3) cavitation, (4) recent travel to exotic places, and (5) history of immunosuppression (urgent fiberbronchoscopy [FBS]).

### Table 3 Main Causes of Recurrent Pneumonia

<table>
<thead>
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<th>Sources of aspiration</th>
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<tr>
<td>Dysphagia and cough reflex disorders19,89</td>
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<tr>
<td>Hiatal hernia as a cause of repetitive nocturnal bronchoaspiration (gastric regurgitation)90,91</td>
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<tr>
<td>Dental plaque and pharyngeal colonization by pathogenic microorganisms19,92,93</td>
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<td>Sleep apnea-related bronco-aspirations94,95</td>
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<td>Bronchiectasis: idiopathic and secondary96</td>
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<td>Humoral immunity disorders (i.e., common variable immunodeficiency57).</td>
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<td>Middle lobe syndrome56</td>
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<td>Obstructive pneumonia and cancer59</td>
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### FUTURE PERSPECTIVES

In the last decade, the rapid and successful growth of molecular diagnostics has led to great interest in the development and dissemination of devices (microarray expression platforms and RT-PCR87,88 based on techniques of nucleic acid amplification for the rapid identification (2 to 4 hours) of pathogenic microorganisms on respiratory samples (from nasopharyngeal swab to BAL). Possible limitations related to the use of these techniques include the relatively high cost and technical difficulty. On the other hand, a timely etiological diagnosis along with the knowledge of antibiotic resistance can drastically reduce the number of hospitalizations and improve clinical outcome at any site of care.

Among HCAP patients it is quite frequent to observe cases of recurring pneumonia due to the peculiar underlying pathophysiology (comorbidities, aging, aspiration, poor oral hygiene, etc.). In these cases a wider diagnostic investigation is suggested to rule out the documented causes of recurring respiratory infections listed in Table 3.19,89–99

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