REVIEW ARTICLE

Improving Outcomes of Elderly Patients with Community-Acquired Pneumonia

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Abstract

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality in elderly patients. Therefore, efforts to optimize the healthcare process

for patients with CAP are warranted. An organized approach to management is likely to improve clinical results. Assessing the severity of CAP is crucial to predicting outcome, deciding the site of care, and selecting appropriate empirical therapy. Unfortunately, current prognostic scoring systems for CAP such as CURB-65 (confusion, uraemia, respiratory rate, low blood pressure and 65 years of age) or the Pneumonia Severity Index have not been validated specifically in older adults, in whom assessment of mortality risk alone might not be adequate for predicting outcomes.

Obtaining a microbial diagnosis remains problematic and may be particularly challenging in frail elderly persons, who may have greater difficulties producing sputum. Effective empirical treatment involves selection of a regimen with a spectrum of activity that includes the causative pathogen. Although most cases of CAP are probably caused by a single pathogen, dual and multiple infections are increasingly being reported. *Streptococcus pneumoniae* remains the overriding aetiological agent, particularly in very elderly people. However, respiratory viruses and 'atypical' organisms such as *Chlamydia pneumoniae* are being described with increasing frequency in old patients, and aspiration pneumonia should also be taken into consideration, particularly in very elderly subjects and those with dementia. Age >65 years is a well established risk factor for infection with drug-resistant *S. pneumoniae*. Clinicians should be aware of additional risk factors for acquiring less common pathogens or antibacterial-resistant organisms that may suggest that additions or modifications to the basic empirical regimen are warranted. In addition to administration of antibacterials, appropriate supportive therapy, covering management of severe sepsis and septic shock, respiratory failure, as well as management of any decompensated underlying disease, may be critical to improving outcomes in elderly patients with CAP. Immunization with pneumococcal and influenza vaccines has also been demonstrated to be beneficial in numerous large studies.

There is good evidence that implementation of guidelines leads to improvement in clinical outcomes in elderly patients with CAP, including a reduction in mortality. Protocols should address a comprehensive set of elements in the process of care and should periodically be evaluated to measure their effects on clinically relevant outcomes. Assessment of functional clinical outcome variables, in addition to survival, is strongly recommended for this population.

Community-acquired pneumonia (CAP) is a common acute medical condition worldwide. It remains a major cause of admission to hospital and mortality in developed countries and is a large contributor to healthcare resource consumption and costs.[1-3]

An increasing number of CAP diagnoses involve older patients. In a recent population-based epidemiological study of CAP in adults, half of all cases were in persons aged ≥65 years, and one-quarter were aged ≥75 years.[4] A retrospective cohort study estimated that nearly 915 900 episodes of CAP occur in adults ≥65 years of age each year in the US, and approximately 40% of these require hospitalization.[5] CAP represents the third most frequent hospital diagnosis among patients aged ≥65 years.[6]

Elderly persons are particularly susceptible to CAP. Waning immunity, coupled with age-associated anatomical and physiological changes leading to impaired gag reflex and decreased mucociliary function, set the stage for increased vulnerability to pneumonia. Additional potential risk factors for

pneumonia in the elderly include poor nutrition, swallowing difficulties, bedridden status, use of sedative medications and the presence of various degrees of cardiopulmonary dysfunction.[7-10] Furthermore, many other underlying co-morbid conditions that commonly affect older persons have been identified as risk factors for CAP, and these can affect the aetiology and outcome of pneumonia. Among these, the most prominent factors are alcoholism, immunosuppression, chronic obstructive pulmonary disease (COPD) and other lung diseases, heart disease and institutionalization.[11-13]

The incidence of CAP in old people increases dramatically with age, reaching its highest frequency in patients aged ≥75 years, where rates of up to 342 cases per 10 000 population per year can be found.[4,14] In very elderly patients (aged ≥75 years), the incidence is 9- and 5-fold higher than in those aged 15–44 years and 44–64 years, respectively, and is double the rate found in those aged 65–74 years.[4]

CAP is usually considered a major cause of mortality in the general population. Combined with influenza, CAP remains the seventh highest cause of death in the US.[15] Age is one of the main factors affecting the outcome of CAP, and is independently associated with increased mortality.[16-19] An overall 30-day mortality rate of between 14% and 26% has been reported for patients aged ≥65 years.[20-22] In a study conducted in the US, mortality doubled as age increased from 65–69 years to >90 years.[18] In addition, elderly patients with CAP may be at increased risk for hospital readmissions and long-term mortality after suffering an episode of pneumonia.[23] A mortality rate of 40% within 1 year after hospitalization has been reported, a rate twice that of age-matched, hospitalized control patients,[24] and readmission rates of 59% within 18 months of the hospitalization have been described.[25] Factors independently associated with death in most studies include altered mental status on admission, shock, respiratory failure, renal insufficiency and Gram-negative pneumonia.[20-22,26-29]

In recent years there has been significant progress in many aspects of CAP,[30] and new efforts are warranted to optimize the healthcare process in patients with CAP. Such efforts for improvement in care are most important in the elderly because of the high morbidity and mortality associated with CAP in that setting. Many experts believe that mortality due to CAP can indeed be decreased,[1] and there is growing evidence that implementation of published CAP guidelines can lead to improvement in clinically relevant outcomes,[31-36] including a decrease in mortality.[31,32,34] Recently, a joint committee from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) developed a unified CAP guideline document that contains comprehensive and updated information on several aspects of CAP.[1] This panel emphasized that guidelines should be locally adapted according to unique hosts or epidemiological patterns that may dictate alternative management strategies.

This review focuses on strategies that can improve outcomes in elderly patients with CAP. To include all relevant information on the topic we searched PubMed (1966–2007) for relevant studies using keywords and text terms for CAP in the elderly. Additional data and references were obtained from related articles and a personal archive of references. An organized approach to assessing elderly patients with CAP and an awareness of common pitfalls in the management of the disease in this population are essential to improving outcomes. Some previous reports of CAP in the elderly have considered both patients with pneumonia from the community and nursing home residents. However, it is now well established that pneumonia in patients residing in long-term care facilities and individuals who have recently been hospitalized or who have come into contact with the healthcare environment, the so-called 'healthcare associated pneumonia' (HCAP), is a unique entity that differs from CAP, and in many ways is similar to nosocomial pneumonia.[37-39] HCAP differs from CAP in both its bacteriology and outcomes, and, thus, treatment of HCAP should involve a different approach.[40] Therefore, HCAP is not included in this review.

This article is in accordance with the recent IDSA/ATS guidelines, with emphasis on the clinical characteristics unique to CAP in elderly persons,

and discusses clinical-decision support tools to guide the site-of-care decision, approaches to microbial diagnosis and treatment strategies.

1. Prognostic and Clinical Decision Support Tools to Guide the Site-of-Care Decision

Severity assessment is crucial to predicting outcome and stratifying appropriate therapy. In the last few years, prognostic scoring systems for CAP have been developed to classify patients on the basis of their risk of mortality. The most prominent and validated tools for this purpose are the Pneumonia Severity Index (PSI)[16] and the British Thoracic Society (BTS) criteria.[41] The PSI is a prognostic model that classifies patients according to outcome in five risk classes (class I includes patients with the most favourable prognosis and class V those with the poorest prognosis). The ability of the PSI to predict mortality has been confirmed in multiple studies. On the basis of associated mortality rates, it has been suggested that PSI risk class I and II patients should be treated as outpatients, risk class III patients should be treated in an observation unit or with a short hospitalization, and risk class IV and V patients should be treated as inpatients.[16] The BTS criteria includes five easily measurable factors that have been identified as indicators of increased mortality: confusion, uraemia, respiratory rate, low blood pressure and age ≥65 years, giving rise to the acronym CURB-65[41,42] (table I). The investigators proposed that patients with a CURB-65 score of 0–1 can be treated as outpatients, those with a score of 2 should be admitted to the ward, and patients with a score ≥3 should be considered for intensive care unit (ICU) care.

It is important to acknowledge that although both the PSI and CURB-65 criteria have been rigorously derived and validated in a heterogeneous adult population, they have not been validated specifically in older adults, and mortality was the primary endpoint for both of them. Assessment of clinical outcomes other than survival only (i.e. physical functional ability, cognitive ability, need for nursing home care and overall quality of life) would be desirable in the

Table I. Severity-of-illness score developed by the British Thoracic Society to predict mortality of community-acquired pneumonia (CURB-65)[a][42]

Criteria[b]	Definition
C: confusion	Based on a specific mental test or new-onset disorientation to person, place or time
U: uraemia	Blood urea nitrogen level >7 mmol/L (20 mg/dL)
R: respiratory rate	Respiratory rate >30 breaths/min
B: blood pressure	Low blood pressure (systolic <90 mmHg or diastolic <60 mmHg)
65	Age ≥65 years

a   In the derivation and validation cohorts, the mortality among patients with 0, 1, 2, 3, 4 and 5 criteria was 0.7%, 2.1%, 9.2%, 14.5%, 40% and 57%, respectively.

b   The Infectious Diseases Society of America/American Thoracic Society joint committee recommends hospitalization or, where appropriate and available, intensive in-home healthcare services for patients with ≥2 CURB-65 criteria.[1]

elderly.[42] A few studies have been performed to derive and validate prognostic estimates for clinical outcome in the elderly,[21,26] but unfortunately they have also been limited to mortality endpoints, and have not been as rigorously and widely validated as the PSI and the CURB-65. The largest study, conducted by Conte et al.,[26] analysed data from a cohort of >2500 patients who were hospitalized with CAP. Using hospital mortality as the endpoint, five baseline characteristics were selected to derive and validate a prognostic classification system. In this study, the five features that were independently predictive of hospital mortality were age >85 years, impaired motor response, creatinine level >1.5 mg/dL, presence of coexisting disease and extremely abnormal vital signs.

Use of biomarkers as prognostic and treatment response tools in patients with CAP constitutes an area of growing interest for investigators.[43-48] Both biochemical inflammation and infection markers (e.g. procalcitonin, C-reactive protein or lipopolysaccharide-binding protein) and the so-called 'neurohumoral haemodynamic markers' have been evaluated. Procalcitonin has been found to be a marker of poorer outcome in patients with CAP and to be useful as guidance for antibacterial therapy.[43,46,48] Among neurohumoral haemodynamic markers, B-type natriuretic peptide was shown to be

helpful, when compared with the PSI, for risk stratification of patients with severe CAP in a preliminary study,[49] and pro-adrenomedullin, a peptide with immune-modulating, metabolic and vascular actions, predicted severity and outcome of patients with CAP with a similar prognostic accuracy to the PSI.[50] Recent data have shown that peptide hormones involved in cardiovascular/osmotic homeostasis, such as members of the natriuretic peptide family and vasopressin,[51] could also be helpful as prognostic tools in patients with CAP, suggesting that poor outcomes might be associated with altered cardiovascular/haemodynamic function.

Although these results are very encouraging, the actual utility of biomarkers as prognostic and clinical decision support tools to guide site-of-care decisions is not fully known. Some have been found to add complementary information on disease severity to that provided by established prognostic scores, but further studies are needed before use of biomarkers can be incorporated into clinical practice.

1.1 Deciding on Hospital Admission

As no comparative studies have been conducted to date, it is not known which of the prognostic scoring systems developed is superior in terms of deciding on the need for hospital admission. Several factors are worth noting when using these scores in elderly patients with CAP.

The scoring system of the PSI prognostic model is relatively complex because it involves 20 different variables, thus limiting its practicality. In addition, this model was designed to predict mortality. Therefore, it heavily weights age and co-morbidities that increase the risk of death, and does not directly measure CAP-specific disease severity. Since age is an overwhelming factor in this scoring system, use of the PSI prognostic model may oversimplify admission decisions in elderly patients by placing older subjects in classes with a high risk of mortality, even if they do not have active underlying diseases. With the PSI, most seniors with fever, regardless of their functional status, will reach risk class III, which is the cut-off for hospital admission.

However, some patients who reach high PSI risk classes on the basis of very old age and multiple stable chronic illnesses may be successfully managed as outpatients.[52]

In contrast to the PSI, the CURB-65 criteria were selected to measure severity of illness and to be remembered easily. Unlike the PSI, the CURB-65 score does not directly address underlying diseases. In addition to having an increased risk of death, a high CURB-65 score indicates the need for active medical intervention, warranting hospitalization. However, it should be pointed out that the CURB-65 has not been as extensively validated as the PSI, and has not been specifically studied as a tool for reducing hospital admission rates. Despite these limitations, the IDSA/ATS joint committee preferred the CURB-65 criteria for deciding hospital admission,[1] and recommends hospitalization or, where appropriate and available, intensive in-home healthcare services for patients with CURB-65 scores ≥2. The joint committee felt that the PSI score threshold for patients who would need hospital admission is more difficult to define.

Although prognostic scoring systems are valuable support tools for making clinical decisions regarding hospital admission, relying exclusively on a score when making the hospital admission decision may be unsafe. A number of studies have shown that some patients with low PSI or CURB-65 scores require admission to hospital,[33,53,54] sometimes to intensive care.[55-57]

The IDSA/ATS joint document[1] has emphasized the importance of physician determination of 'subjective' factors that may supersede objective criteria or scores in some patient populations. Among those 'subjective' factors that may not be detected by prognostic and clinical decision support tools, and that should be taken into account when deciding site-of-care in elderly patients with CAP, are the following: (i) ability to safely and reliably take oral medication; (ii) availability of outpatient support resources, including caregivers in the case of dependent patients; (iii) decompensated coexisting illness requiring hospital admission, such as congestive heart failure, diabetes mellitus or ob-

structive lung disease; (iv) other medical or psychosocial needs requiring hospital care, including homelessness, poor overall functional status, vomiting, cognitive dysfunction or psychiatric illness; and (v) lack of response to previous adequate empirical antibacterial therapy.

1.2 Admission to the Intensive Care Unit

The decision regarding whether the patient should be treated in an ICU or in a high-level monitoring unit is also crucial, and may be particularly difficult to make in very elderly patients. According to studies of heterogeneous adult populations, about 10% of hospitalized patients with CAP require ICU admission.[58-69] Most studies show that respiratory failure is the major reason for transfer to the ICU, and the presence of chronic co-morbid conditions is one of the most important determinants of the need for ICU care.[21,58-61]

The indications for ICU admission vary strikingly among patients, physicians, hospitals and countries,[1] underlining the need for accurate and valid criteria to identify patients who are candidates for the ICU. Several sets of objective criteria have been used for this purpose, including the ATS definition of severe CAP,[62] the CURB criteria[41] and PSI severity class V (or IV and V).[16] However, each of these was found to be both overly sensitive and nonspecific in a retrospective evaluation by Angus et al.[57] A set of revised criteria for severe CAP has been recently proposed[1] (table II). Admission to the ICU is indicated for patients with any of the two major criteria (absolute indication) or at least three minor criteria. Age, by itself, was not felt to be an appropriate factor for the ICU admission decision, but the remainder of the CURB-65 criteria are among the set of criteria for the revised definition of severe CAP. Prospective validation of these criteria is needed.

The decision to admit very old patients to ICU deserves special consideration. The prognosis for very elderly patients with CAP receiving mechanical ventilation is disappointing.[63] A recent case series of CAP in patients ≥80 years old showed that patients in this age group were rarely admitted to the

Table II. Revised set of criteria for severe community-acquired pneumonia requiring intensive care unit admission (reproduced from Mandell et al.,[1] with permission from The University of Chicago Press; © 2007 by the Infectious Diseases Society of America. All rights reserved)

Major criteria[a]
Mechanical ventilation with endotracheal intubation
Septic shock requiring vasopressors
Minor criteria[a,b]
Respiratory rate[c] ≥30 breaths/min
PaO_2/FiO_2 ratio[c] ≤250
Multilobar infiltrates
Confusion/disorientation
Uraemia (BUN level ≥20 mg/dL)
Leukopenia[d] (WBC count <4000 cells/mm^3)
Thrombocytopenia (platelet count <100 000 cells/mm^3)
Hypothermia (core temperature <36°C)
Hypotension requiring aggressive fluid resuscitation

a   Admission to the intensive care unit is indicated for patients with any of the two major criteria (absolute indication) or three minor criteria.

b   Other criteria to consider include hypoglycaemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, hyponatraemia, unexplained metabolic acidosis or elevated lactate level, cirrhosis and asplenia.

c   A need for noninvasive ventilation can substitute for a respiratory rate ≥30 breaths/min or a PaO_2/FiO_2 ratio ≤250.

d   As a result of infection alone.

BUN = blood urea nitrogen; **PaO$_2$/FiO$_2$** = arterial oxygen pressure/fraction of inspired oxygen; **WBC** = white blood cell.

ICU and rarely underwent mechanical ventilation.[17] Most experts believe that overall health status, rather than age alone, should be taken into account when deciding whether a very old patient may benefit from intensive care.[17,29,63] The patient's or relatives' wishes regarding the use of aggressive therapeutic procedures should also be respected.

2. Clinical Diagnosis of Pneumonia in the Elderly

The diagnosis of CAP is usually established on the basis of clinical features and physical examination, supported by chest radiography showing an infiltrate. As with other infections in the elderly, the clinical presentation of pneumonia may be somewhat different in older patients. Elderly patients may complain less frequently of pleuritic chest pain,

headache and myalgias, and are more likely to have altered mental status and absence of fever.[17,64]

Occasionally, clinical features are highly suggestive of pneumonia but chest radiography findings are absent or inconclusive. This scenario may be more likely in frail elderly persons, in whom a good-quality image may be difficult to obtain. In such cases it may be wise to treat empirically with antibacterials and repeat the x-ray in 24 hours. Although high-resolution CT might have a role to play when conventional radiography is negative, the clinical significance of CT findings in this setting is unclear.[65]

3. Approaching the Microbial Diagnosis

3.1 General Considerations

Accurate identification of the microorganisms causing CAP remains a challenge for clinicians and microbiologists. Obtaining an aetiological diagnosis may be even more challenging in the setting of frail elderly persons, who may have more difficulties in producing sputum for microbiological testing. Recent epidemiological studies have shown that despite extensive microbiological investigations, the microbial aetiology of CAP remained unidentified in a considerable proportion of cases.[17,19] Given the low yield of most microbial tests and the usual effectiveness of empirical antimicrobial therapy in most cases of CAP, there is much controversy concerning the extent of laboratory testing to achieve aetiological diagnosis in patients with CAP. This has been fuelled by the results of a recent randomized controlled trial that could not demonstrate significant differences in mortality rate or length of hospital stay between patients receiving pathogen-directed therapy and those receiving empirical therapy.[66]

Moreover, in clinical practice, results of microbial testing are rarely available at the time of selection of antimicrobial therapy, and once empirical therapy has been started it is unusual to streamline it on the basis of a diagnostic testing result. Additional concerns over pursuing microbial diagnosis in elderly patients include the risk of complications of invasive diagnostic procedures and undesirable delays in starting antibacterial therapy resulting from the time spent on obtaining the specimens. On the basis of those considerations, a more conservative and focused approach to microbial diagnosis of CAP is now being recommended.[1] This approach should be clinically orientated and the emphasis placed on tests for which results are available within a reasonable window of time, which means they can influence clinical decisions. The recent IDSA/ATS guidelines recommend investigating for specific pathogens that would significantly alter standard (empirical) management decisions when the presence of such pathogens is suspected on the basis of clinical and epidemiological clues.[1]

The results of microbial investigations that are more likely to improve clinical outcome will be those resulting in the need for modification of an initial empirical regimen because of the finding of less common pathogens (e.g. *Staphylococcus aureus*, Gram-negative organisms), unusual pathogens (e.g. *Mycobacterium tuberculosis*, *Nocardia* spp., endemic fungi) or antibacterial-resistant organisms (e.g. drug-resistant *Streptococcus pneumoniae* or meticillin-resistant *S. aureus* [MRSA]). Although narrowing down antibacterial therapy on the basis of diagnostic testing has always been considered a standard of care, the concern about mixed CAP[67,68] and the potential benefit of combination therapy for bacteraemic pneumococcal pneumonia[69,70] have complicated this decision. However, the IDSA/ATS joint committee still recommend it as good medical practice.[1] Narrowing the spectrum of antibacterial therapy may decrease cost, drug adverse effects and antibacterial resistance pressure, although it is unlikely to decrease the individual's risk of death.

3.2 Selecting Microbial Investigations

Basic microbial investigations in sputum (Gram stain and culture), blood (culture) and urine (antigen detection) to make an aetiological diagnosis should be considered in most elderly patients admitted to hospital with CAP. Extensive diagnostic testing should always be performed in patients classified as having severe CAP, those who do not respond to

outpatient antibacterial therapy, patients who have severe underlying diseases or who are immunosuppressed, and in cases complicated by pleural effusion.[1] In patients classified as low severity risk classes and managed as outpatients, microbial investigations are optional.

3.3 Sputum Gram Stain and Culture

The yield from sputum Gram stain and culture is heavily influenced by the quality of the specimen and the absence of prior antibacterial therapy. The best specimens are collected and processed before antibacterials are given. If the patient has received effective antibacterials for more than 6–12 hours, the Gram stain is likely to be nonrevealing for pneumococci; after 12–24 hours the culture will also fail to disclose pneumococci.[71]

Unlike *S. pneumoniae*, many of the other pathogens that cause CAP are unaffected by a single antibacterial dose. The reported yield of sputum Gram stain varies greatly in the literature,[72-74] probably reflecting differences in quality of collecting and processing, use of cytological criteria, prior antibacterial therapy and skill in interpretation. In addition, almost half of all elderly patients are unable to produce any sputum or to produce an adequate sample in a timely manner.[66,75] Such problems are more likely to occur in seriously ill elderly individuals. A meta-analysis has shown that the yield from microscopic examination of the sputum is low because of the relatively small number of patients providing adequate specimens and the lack of definitive results.[76] In a recent analysis, an adequate specimen with a predominant morphotype on Gram stain was found in only 14% of 1669 hospitalized patients with CAP.[75]

Despite the low yield, the sputum Gram stain may provide rapid and meaningful information that can influence therapeutic decisions when a less common or unusual pathogen, such as *S. aureus*, Gram-negative bacilli or *Nocardia* spp., is suspected. A positive Gram stain is highly predictive of a subsequent positive culture result[75] and can help in interpretation of the results of the sputum culture. With a sputum sample of good quality, bacterial culture is expected to reliably reflect material present below the larynx.[77]

A negative result obtained from a good-quality sputum culture may also be of clinical value. For instance, a negative appropriately collected and processed sputum culture that fails to detect *S. aureus* or Gram-negative bacilli provides strong evidence against the presence of these pathogens and should exclude the need for their empirical coverage.[1]

3.4 Antigen Detection

Rapid and simple antigen tests for detection of *S. pneumoniae* and *Legionella pneumophila* serogroup 1 in urine[78-85] and for detection of influenza virus in respiratory tract specimens[86] are available commercially.

The antigen test currently used for detection of *S. pneumoniae* is an immunochromatographic membrane assay that detects C polysaccharide, which is found in the cell wall and is common to all serotypes. This assay has a fairly good specificity for pneumococcal pneumonia in adults, has the potential to detect pneumococcal pneumonia after antibacterial therapy has been started, and increases the overall diagnostic yield for pneumococci in patients with CAP.[78] Studies in adults show a sensitivity of 50–80% and a specificity of >90%.[78,79,81,87] The immunochromatographic membrane assay is a useful test for rapid diagnosis of pneumococcal pneumonia and may be particularly attractive when samples for culture cannot be obtained in a timely fashion or when antibacterial therapy has already been initiated. The main disadvantage is the cost (about $US30 per specimen; 2007 value). False-positive results have been seen in patients with an episode of pneumococcal CAP within the previous 3 months.[79]

Several assays are available for *Legionella* but all detect only *L. pneumophila* serogroup 1. However, this serogroup accounts for 80–95% of community-acquired cases of legionellosis.[82,83] The test has a sensitivity of 70–90% and a specificity of nearly 99% for detection of *L. pneumophila* serogroup 1. False-positive results can also occur in patients with

a previous episode of CAP since the urine continues to be positive for weeks after the episode.[82,83,88]

The main criticism regarding wide use of urinary bacterial antigen detection of *S. pneumoniae* and *L. pneumophila* is that their clinical impact and cost effectiveness in clinical practice remain undetermined. Nonetheless, it is also fair to state that the information provided by these tests could be helpful for individual patients, allowing greater accuracy in directing antibacterial therapy. Also, in the case of the *Legionella* antigen, the test results might have epidemiological implications by facilitating the identification of potential bacterial sources. Therefore, it is reasonable to perform these tests when the presence of such pathogens is suspected on the basis of clinical and epidemiological clues and the results are expected to change management decisions, either from a therapeutic or epidemiological point of view.

When an antigen of either *S. pneumoniae* or *L. pneumophila* is detected, efforts should be made to obtain a sputum specimen for culture. The availability of a culture isolate of *Legionella* increases the likelihood that an environmental source of *Legionella* can be identified and eliminated.[89-91] In the case of a positive pneumococcal urinary antigen, culture should be requested to allow sensitivity testing to be performed. This will provide meaningful information for guiding antibacterial therapy in the individual patient, and important data on antibacterial resistance in the community.

The availability of specific antiviral therapy for influenza and the implications of establishing this diagnosis from the public health point of view make influenza testing an attractive investigation in the appropriate epidemiological setting. Rapid antigen detection tests can provide an aetiological diagnosis of influenza within 15–30 minutes. The assays available have a high specificity, approaching 100%, but a sensitivity of 50–70%.[92,93] However, in patients with typical symptoms during an influenza epidemic, the sensitivity of the assays may not be superior to that of physician judgment.[86,92,93] In addition to low sensitivity, disadvantages include cost (about $US30 per specimen; 2007 value) and

false-positive test results with adenovirus infections. A direct fluorescent antibody test with a higher sensitivity (85–95%) is also available but the turnaround time for the test is approximately 2 hours.

3.5 Blood Cultures

The yield of blood cultures in patients with CAP is low (5–14%) and the influence of this investigation on antibacterial management decisions is weak, due to the fact that the most common bacterial pathogen isolated is *S. pneumoniae*, which is usually covered by empirical antibacterial regimens.[94-96] Therefore, blood cultures may not lead to better outcomes or improvements in antibacterial selection in most elderly patients with CAP[95,97] and should probably be performed selectively.[1] Blood cultures are more likely to be positive and the results more meaningful in patients with severe pneumonia who have a higher likelihood of infection with pathogens that may have not been properly covered by the usual empirical antibacterial therapy, such as *S. aureus*, and *Pseudomonas aeruginosa* and other Gram-negative bacilli.[98-104] Blood cultures are also recommended in immunocompromised patients and in those with significant underlying diseases. The yield for positive blood culture results is reduced by prior antibacterial therapy.[102] Therefore, when performed, blood samples should be obtained before starting antibacterial therapy.

3.6 Other Microbial Investigations

Nucleic acid amplification tests in respiratory samples are increasingly being used for atypical pathogens and *L. pneumophila*[105,106] but most of the assays currently available have not been validated, and extensive published clinical experience is lacking.

Acute- and convalescent-phase serological testing is the standard for diagnosis of infection caused by most atypical pathogens, including *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* species other than *L. pneumophila*. However, these tests have no influence on clinical decisions and are of interest for epidemiological purposes only. A single acute-phase titre is unreliable.[107]

3.7 Invasive Diagnostic Procedures

The yield of microbial investigations is substantially higher when specimens are obtained through invasive procedures, such as bronchoscopic sampling or transthoracic needle aspirates.[75,108-111] However, most invasive procedures have not been prospectively studied for initial management of patients with CAP, their clinical benefit has not been shown, and they may entail risks for the patient. Therefore, they should be considered only in circumstances in which microorganisms other than common bacterial pathogens are being considered, and the results are likely to change individual antibacterial management. The accepted indications for invasive procedures are patients in whom empirical antibacterial therapy has failed and immunocompromised patients.[112,113] For common bacterial pathogens, interpretation is improved with quantitative or semiquantitative cultures.[108,114] As with expectorated sputum, specimens obtained after initiation of antibacterial therapy may be unreliable for common bacterial pathogens and results from such samples must be interpreted with caution.[75,115]

Patients intubated for severe CAP should have endotracheal aspirates obtained soon after intubation. Gram stain and cultures from endotracheal aspirates may be more reliable than expectorated sputum because the sample is clearly from the lower respiratory tract and is less likely to be contaminated by oropharyngeal colonizers. Patients with significant pleural effusions should undergo thoracentesis to obtain pleural fluid for microbial investigation. Although the yield from pleural fluid cultures is low, a positive result indicates the need for pleural drainage.

4. Antimicrobial Therapy

4.1 Principles of Therapy

4.1.1 Role of Empirical Therapy

All clinical practice guidelines agree that once the diagnosis of pneumonia has been made, empirical antimicrobial therapy should be instituted. Prompt administration of appropriate antibacterial therapy is likely to increase the probability of a successful outcome; therefore, therapy should be started as soon as possible after the diagnosis is considered likely.

Two large retrospective studies showed a lower mortality rate among patients with CAP who received antibacterial therapy within the first 4–8 hours.[96,116] The initial study conducted by Meehan et al.[116] evaluated the relationship between processes of care and outcomes in 14 069 hospitalized patients aged ≥65 years. Lower 30-day mortality rates were associated with antibacterial administration within 8 hours after hospital admission. A subsequent analysis found that administration within 4 hours was associated with lower mortality; however, prospective trials of care by protocol have not demonstrated a survival benefit linked to this specific time period.[117,118]

Effective empirical treatment involves selection of an antibacterial regimen with a spectrum of activity that includes the causative pathogen. Appropriate drug selection is dependent on the causative pathogen and its antibacterial susceptibility. Although acute pneumonia in the elderly may be caused by a wide variety of pathogens, a limited number of agents are responsible for most cases. Most cases of CAP are probably caused by a single pathogen, but dual or multiple infections have been reported increasingly in the literature,[67,68,119] and there is growing concern for the concurrent presence of a second pathogen in a significant proportion of cases of CAP previously thought to be monomicrobial.[68]

4.1.2 Impact of Age on Aetiology

A few studies have addressed the impact of age on aetiology of CAP. A prospective study of CAP did not observe any effect of age on the microbial aetiology of CAP, except for a higher incidence of *M. pneumoniae* in patients aged <60 years,[103] and in a review including studies that reported on the aetiology of pneumonia in the elderly compared with studies of pneumonia in younger populations, the proportion of cases due to *Haemophilus influenzae*, *S. aureus* and Gram-negative bacilli was higher among the elderly, while the proportion due

to *Legionella* and other atypical pathogens was higher among younger patients.[120] A recent prospective CAP study[4] found a striking increase in the incidence of pneumococcal pneumonia with aging, particularly amongst people aged ≥75 years, together with a 15-fold higher incidence of influenza virus infection and a 5-fold higher incidence of infections by *Chlamydia* spp. in this age group compared with young adults.

4.1.3 Pathogenic Microorganisms

Table III shows the most common microorganisms causing CAP in elderly persons. The frequency of other aetiological agents, such as *S. pyogenes*, *Neisseria meningitidis*, *Pasteurella multocida*, *H. influenzae* type b, *Chlamydia psittaci* (psittacosis), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularaemia), *M. tuberculosis* and endemic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformans* and *Blastomyces hominis*), varies according to the epidemiological setting, but all are uncommon causes of CAP in the elderly.[19,103,121]

S. pneumoniae remains the overriding aetiological agent for CAP, particularly in very elderly people.[17,19] Although *Chlamydia* or *Mycoplasma* infections are relatively more common in younger populations, such infections do also occur in elderly persons[19,22,122,123] and account for a significant proportion of cases, with the possible exception of the very elderly, in whom they may be less common.[17] A number of studies have shown that *L. pneumophila* may be a significant cause of CAP in elderly patients.[4,19,103] Among the range of pathogens identified by culture of specimens in elderly patients with CAP, most epidemiological studies have in-

Table III. The most common causes of community-acquired pneumonia in elderly persons

Streptococcus pneumoniae, including drug-resistant strains
Haemophilus influenzae
Gram-negative bacilli, including *Pseudomonas aeruginosa*
Staphylococcus aureus
Aspiration pneumonia
Respiratory viruses
Chlamydia pneumoniae
Legionella spp.

cluded *S. aureus* and a number of Gram-negative bacilli typically found in patients with nosocomial pneumonia, in particular *P. aeruginosa*.[17,19,124] These pathogens have been described more commonly in older patients with co-morbidities.[19,103,124] Pneumonia caused by *P. aeruginosa* and other Gram-negative bacilli is of particular concern in patients receiving long-term oral corticosteroids, those with severe underlying bronchopulmonary disease or alcoholism, and patients requiring frequent antibacterial therapy.[19,101,124] Although the exact importance of *S. aureus* as a cause of CAP is uncertain, it has been described more commonly in the setting of active influenza in the community, end-stage renal disease and structural lung disease.[1]

Viruses account for a substantial portion of respiratory illnesses, including pneumonia, in the elderly population. Functional and immunological decline, together with chronic cardiopulmonary diseases associated with old age, predispose patients to pneumonia when viral infection occurs. Viral aetiology has been described in 1–23% of cases of CAP in adults.[17,125,126] Viruses were the second most common causative organisms in adult patients hospitalized with CAP in a recent prospective study, with a trend to more frequent isolation in patients ≥65 years of age,[127] and the third most common aetiological agent among hospitalized patients with CAP aged >80 years.[17] Influenza, of which a much higher incidence was found in very old patients than in younger ones, and respiratory syncytial virus (RSV), are the most commonly identified viral pathogens.[4,17,128] Falsey et al.[129] recently conducted a surveillance study of respiratory illnesses in a cohort of healthy elderly patients and high-risk (those with chronic heart or lung disease) adults, in which RSV and influenza A and B infections were investigated by culture, reverse-transcriptase polymerase chain reaction and serological studies. The annual incidence of RSV infection averaged 5.5% and was nearly twice that of influenza. Both type of viruses accounted for a similar frequency of hospitalizations (11.5% for influenza infections, 10.6% for RSV) and complications, and, although influen-

za resulted in a greater use of healthcare services than RSV in healthy elderly patients, it was similar for the two viruses in patients with chronic heart or lung diseases. Specific antiviral therapy for influenza is currently available, although the best strategy to treat viral infections is probably prevention. The available data support the importance of vaccination as a strategy for CAP management and the appropriateness of developing a vaccine against RSV virus for high-risk and elderly adults.

4.1.4 Aspiration Pneumonia

The relevance of aspiration pneumonia in the elderly remains controversial. Difficulty in swallowing is relatively common among elderly persons, and it has been shown that this age group is more prone to aspiration.[130] In an analysis of CAP in very old patients (≥80 years), aspiration pneumonia was the second most common cause of CAP, accounting for 10% of cases and causing death in 15%.[17] These results are in agreement with those of another recent epidemiological study that found predisposing factors for aspiration pneumonia in 16% of patients aged >75 years.[19] Of interest, in both studies, dementia emerged as a significant comorbid illness in patients with CAP, ranking next after COPD, chronic heart disease and diabetes. Pneumonia is one of the most serious medical conditions seen in late-stage dementia and a common cause of death in these patients.[131] Patients with dementia may be particularly susceptible to pneumonia because of their swallowing difficulties and use of sedative medications, factors that have been found to increase the risk of pneumonia in elderly patients living in long-term facilities.[132,133] The frequency of aspiration pneumonia in other studies has probably been underestimated as a result of the difficulties inherent in making the diagnosis; recognition of the disorder requires careful clinical evaluation when aspiration is not observed.[134] Moreover, microbiological data are often negative because the invasive techniques necessary to obtain a reliable diagnosis are not usually carried out.

Addressing the role of aspiration in the development of CAP in the elderly, several studies have evaluated the impact of ACE inhibitors as a means of preventing pneumonia in old subjects. ACE inhibitors improve upper airway reflexes such as cough and swallowing by inactivating metabolism of the protussive peptides substance P and bradykinin.[135] ACE inhibitors were shown to reduce the risk of pneumonia in two prospective observational studies of elderly Japanese patients,[136,137] but failed to reduce risk in two later studies of old patients without a history of stroke.[138,139] Accordingly, ACE inhibitors seem to prevent pneumonia in selected elderly subjects, mainly in those with swallowing disorders, in whom aspiration or silent aspiration are very common. However, such beneficial effects, which were confirmed in participants of Asian ethnicity in a *post hoc* subanalysis of a large randomized trial of the ACE inhibitor perindopril, were not found among Caucasians.[140]

4.1.5 Effect of Proton Pump Inhibitor Therapy

In contrast to ACE inhibitors, proton pump inhibitors (PPIs) have been associated with an increased risk of pneumonia. In a recent large case-control study,[141] in which more than half of the patients were aged ≥60 years, PPI use was associated with a higher risk of CAP (adjusted odds ratio [OR] 1.5%; 95% CI 1.3, 1.7). The increase in risk was more pronounced in patients who had recently initiated therapy (OR 5.0; 95% CI 2.1, 11.7). A plausible explanation for this is that the profound inhibition of acid secretion caused by PPIs could break the defence barrier of the 'acid wall' for pathogens passing from the gastrointestinal tract to the respiratory tract.[141]

4.1.6 Influence of Aetiology on Severity of Pneumonia

Information on the aetiology of elderly patients with CAP requiring admission to the ICU is lacking. Data from heterogeneous adult populations indicate that a large number of microorganisms must be considered. In a review of nine studies that included 890 patients with CAP admitted to the ICU, the most common pathogens were *S. pneumoniae*, *Legionella* spp., *H. influenzae*, Enterobacteriaceae spp., *S. aureus* and *Pseudomonas* spp.[125] The atypical pathogens responsible for severe CAP may vary over time

but can collectively account for ≥20% of severe pneumonia episodes.[142]

4.1.7 Antibacterial Resistance

Newly emerging patterns of antibacterial resistance among common pathogens causing CAP are of special concern in the elderly. Age >65 years is a well described risk factor for infection with drug-resistant *S. pneumoniae* (DRSP), and this is an important consideration when selecting antimicrobial therapy.[97] Although the incidence of β-lactam-resistant *S. pneumoniae* appears to have stabilized or even decreased in the past few years, resistance to macrolides amongst this pathogen continues to increase.[143,144]

The clinical relevance of DRSP is not clear because only a limited number of well controlled studies have examined the implications of *in vitro* resistance on patient outcomes.[145-147] However, there are data indicating that current levels of β-lactam resistance do not generally result in CAP treatment failures, even in the presence of bacteraemia, as long as appropriate agents (i.e. amoxicillin, ceftriaxone or cefotaxime) and doses are used.[97,148] In contrast, the available information suggests that resistance to macrolides[149-151] and older fluoroquinolones (ciprofloxacin and levofloxacin)[152-154] does result in clinical failure. However, levofloxacin-resistant pneumococcal isolates remain rare in most geographical areas, and no failures have been reported for the newer fluoroquinolones (moxifloxacin and gemifloxacin).

Community-acquired meticillin-resistant *S. aureus* (CA-MRSA) remains rare in most geographical regions but may be an emerging problem for CAP treatment.[155,156] CA-MRSA are epidemiologically, genotypically and phenotypically distinct from hospital-acquired strains.[157,158] Most CA-MRSA strains contain the gene for Panton-Valentine leukocidin,[156,158] a toxin associated with clinical features of necrotizing pneumonia, shock and respiratory failure, as well as formation of abscesses and empyemas. CA-MRSA is a well described cause of skin infections, mainly in children. However, CA-MRSA pneumonia in adults has been reported, often in association with preceding influenza.[159,160]

4.1.8 Indications for Modification of Standard Empirical Antimicrobial Therapy

Risk factors for acquiring CAP by less common pathogens or antibacterial-resistant organisms requiring special consideration and/or modifications to standard empirical treatment are shown in table IV.[1,8,97,101,124,161-171]

4.2 Antimicrobial Treatment Strategies

Because of the limitations of diagnostic testing, almost all patients with CAP are treated empirically. Empirical therapy for CAP is based on prediction of the most likely pathogen(s) and knowledge of local resistance patterns of suspected organisms, and should cover the majority of the common pathogens causing CAP. The importance of epidemiological data in guiding empirical therapeutic decisions in patients with CAP has been recognized by different specialist society guidelines. Thus, patients with CAP have often been classified into several groups, each with a list of likely pathogens and a suggested empirical therapy, based on stratification according to age, place of therapy, co-morbidity and severity. However, it should be acknowledged that there is too much overlap among groups for this information to be used as the sole guide for therapeutic decisions. Clinicians should be aware of risk factors for acquiring less common pathogens or antibacterial-resistant organisms that may suggest additions or modifications to the basic empirical regimen (table IV).

Once the aetiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should ideally be directed at that pathogen – the so-called pathogen-directed therapy. This strategy has long been considered the standard of care, and it is still endorsed by recent guidelines from the IDSA/ATS joint committee.[1] However, careful consideration should be given to cases of severe pneumonia, especially of bacteraemic *S. pneumoniae* CAP, until the implications of the finding that dual therapy was associated with reduced mortality in bacteraemic pneumococcal pneumonia[69,70,172-174] have been clarified. It is important to note that the benefit of combination ther-

Table IV. Risk factors for acquiring community-acquired pneumonia (CAP) by less common pathogens or antibacterial-resistant organisms requiring special considerations and/or additions or modifications to the basic empirical antibacterial regimen

Organism	Risk factors and/or underlying conditions	Suggested additions or modifications to the basic empirical regimen and/or special considerations
DRSP, including β-lactam-resistant *Streptococcus pneumoniae*	Age >65 years, β-lactam therapy within the previous 3 months, alcoholism, medical co-morbidities, immunosuppressive illness or therapy, and exposure to a child in a daycare centre.[97,161] Recent therapy or repeated courses of therapy with β-lactams, macrolides or fluoroquinolones are risk factors for pneumococcal resistance to the same class of antibacterial[165-169]	The standard empirical combination therapy, which includes a β-lactam (i.e. amoxicillin, ceftriaxone or cefotaxime) and sometimes a respiratory fluoroquinolone, should be adequate until susceptibility results are available. Pathogen-directed therapy with a β-lactam or a fluoroquinolone is appropriate for most strains of DRSP
Gram-negative bacilli, including *Pseudomonas aeruginosa*	Severe COPD, alcoholism, chronic oral corticosteroid administration, structural lung diseases (e.g. bronchiectasis), repeated exacerbations of COPD leading to frequent corticosteroid and/or antibacterial use, and prior antibacterial therapy[101,124]	An antipneumococcal, antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem or meropenem) plus either ciprofloxacin or levofloxacin (750 mg) *or* The above β-lactam plus an aminoglycoside and azithromycin *or* The β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for β-lactam)
MSSA	Active influenza in the community, end-stage renal disease, structural lung disease (e.g. bronchiectasis)	The standard empirical combination therapy, which includes a β-lactam and sometimes a fluoroquinolone, should be adequate until susceptibility results are available and specific therapy with an antistaphylococcal penicillin can be initiated. Linezolid and vancomycin are not optimal drugs for MSSA
CA-MRSA	CA-MRSA CAP remains rare in most communities Presentation with cavitary infiltrates without risk factors for anaerobic aspiration pneumonia May be associated with preceding influenza	Diagnosis is usually straightforward, with high yields from sputum and blood cultures Either vancomycin or linezolid should be added to the standard empirical therapy. Daptomycin should never be used, as it is ineffective in the lung because of inhibition by pulmonary surfactant[170]
Anaerobic bacteria	Risk factors for aspiration, including a history of loss of consciousness as a result of alcohol/drug overdose or after seizures in patients with concomitant gingival disease or oesophogeal motility disorders Endobronchial obstruction	Anaerobic bacteria cannot be detected by usual non-invasive diagnostic methods. Anaerobic coverage is clearly indicated only in the classical aspiration pleuropulmonary syndrome. If anaerobic coverage is considered, β-lactam/β-lactamase inhibitor (amoxicillin/clavulanic acid, piperacillin/tazobactam, ticarcillin/clavulanic acid, sulbactam/ampicillin) plus a fluoroquinolone can be used.[1,8] Moxifloxacin alone is active *in vitro* against anaerobes[171]
Legionella pneumophila	Hotel or cruise stay in previous 2 weeks	The standard empirical combination therapy, which includes a macrolide or a fluoroquinolone, should be adequate. Identification of a potential environmental source
Influenza A	Influenza active in the community Typical symptoms during the appropriate season Travel to southern hemisphere or tropics outside influenza season	Early treatment (within 48 hours of the onset of symptoms) with oseltamivir or zanamivir is recommended for influenza A[1,162-164] Infection control measures

CA-MRSA = community-acquired meticillin-resistant *Staphylococcus aureus*; **COPD** = chronic obstructive pulmonary disease; **DRSP** = drug-resistant *Streptococcus pneumoniae*; **MSSA** = meticillin-sensitive *S. aureus*.

apy was particularly pronounced in the more severely ill patients in two studies.[69,70] Therefore, discontinuation of combination therapy after results of cultures are known is most likely safe in patients with non-severe CAP.

The aging process and co-morbidities may lead to impaired renal and hepatic function in old patients, in whom multidrug therapy for coexisting diseases is also a common issue. Accordingly, drug doses and drug interactions must be carefully moni-

tored, as well as the adverse effects of antimicrobials.[8]

4.3 Selecting the Appropriate Empirical Antimicrobial Regimen

Selection of antimicrobial regimens has become complicated by the frequency of DRSP to β-lactams and macrolides, and by increasing concern about mixed infections.[68,97,144,147,149-151] Resistance patterns vary by geography; therefore, antibacterial recommendations must be modified on the basis of local susceptibility patterns. In addition, age >65 years has been identified as a risk factor for β-lactam-resistant pneumococci.[97] This information should be taken into consideration when selecting an empirical regimen.

Recommendations for empirical therapy in elderly patients with CAP according to the site of care/severity are detailed in table V. For outpatients and patients admitted to a general ward, either a respiratory fluoroquinolone or a β-lactam plus a macrolide are recommended. There are several reasons for these recommendations. First, both regimens provide adequate coverage for the overwhelming majority of CAP pathogens in the elderly, including most strains of DRSP and atypical agents. Secondly, a number of observational studies indicate that use of a macrolide with a cephalosporin, as part of an initial empirical regimen for patients with CAP admitted to hospital, may be associated with shorter length of hospital stay and lower mortality rate than treatment with a cephalosporin alone.[175-178] Gleason et al.[179] assessed the effect of specific antimicrobial therapy for hospitalized elderly patients with pneumonia. Initial treatment with a second-generation cephalosporin and a macrolide, a third-generation cephalosporin and a macrolide, or a fluoroquinolone alone, was associated with lower 30-day mortality than treatment with a cephalosporin alone. In addition, recent data suggest an advantage with use of an empirical β-lactam/macrolide combination, rather than a monotherapy regimen, for treatment of CAP that is subsequently determined to be associated with pneumococcal bacteraemia.[69,70,172] Thirdly, there are good data

Table V. Recommendations for empirical antimicrobial therapy in elderly patients with community-acquired pneumonia (CAP)

1. Outpatient treatment[a]

A respiratory fluoroquinolone (moxifloxacin, levofloxacin, gemifloxacin)

or

A β-lactam *plus* a macrolide (preferred β-lactam agents include high-dose amoxicillin 1 g three times daily or amoxicillin/clavulanic acid 2 g twice daily)

2. Inpatient treatment, non-severe CAP (admitted to a general ward)

A respiratory fluoroquinolone (moxifloxacin, levofloxacin gemifloxacin)

or

A β-lactam *plus* a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone and ampicillin; ertapenem for selected patients). Doxycycline may be an alternative to the macrolide. For penicillin-allergic patients, a respiratory fluoroquinolone should be used

3. Inpatient treatment, severe CAP (admitted to intensive care unit)

A β-lactam (cefotaxime, ceftriaxone or sulbactam/ampicillin) *plus* either azithromycin or a fluoroquinolone. For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended

a   In geographic areas with low rates of infection with high-level (≥16 μg/mL) macrolide-resistant *Streptococcus pneumoniae*, selected elderly patients with no co-morbidities and no use of antimicrobials within the previous 3 months might also be treated with a macrolide alone (preferably azithromycin because of its enhanced activity against *Haemophilus* spp.). For patients with either significant risk of drug-resistant *S. pneumoniae* or co-morbidities (chronic heart, lung, liver or renal disease, diabetes mellitus, alcoholism, malignancy, asplenia, immunosuppressing conditions or use of immunosuppressant drugs), monotherapy with a macrolide alone is not recommended.

supporting efficacy and safety for respiratory fluoroquinolones in elderly patients.[180,181] In a recent double-blind, randomized controlled trial to determine the efficacy and safety of moxifloxacin versus those of levofloxacin in the treatment of CAP in hospitalized elderly patients (age ≥65 years), use of both regimens resulted in high cure rates.[180] In this trial, intravenous/oral moxifloxacin achieved ≥90% cure in all severity and age subgroups and was associated with faster clinical recovery than intravenous/oral levofloxacin therapy, with a comparable safety profile. Finally, although macrolides have long been prescribed as monotherapy for outpatients with CAP and no co-morbidity, resistant strains of pneumococci to these drugs are on the rise in many

geographical regions of the world and several studies have demonstrated that clinical failure can occur with a resistant isolate.[150,151] Thus, for elderly patients with either co-morbidities (chronic heart, lung, liver or renal disease, diabetes, alcoholism, malignancy, asplenia, immunosuppressing conditions or use of immunosuppressant drugs) or any significant risk of DRSP infection, monotherapy with a macrolide is no longer recommended, at least in areas where macrolide-resistant *S. pneumoniae* is a concern.

For patients admitted to the ICU, a potent antipneumococcal β-lactam and either a macrolide or a fluoroquinolone is the regimen recommended by the IDSA/ATS joint committee.[1] This recommendation is extrapolated from data obtained in nonsevere cases, and from retrospective analyses of cohorts of patients with severe CAP. Only one randomized controlled trial of treatment for severe CAP is available.[182] In this trial, levofloxacin was compared with cefotaxime combined with ofloxacin. Treatment with the fluoroquinolone alone resulted in a trend toward inferior outcome. Therefore, until more information is available, combination empirical therapy is recommended for severe CAP.

4.4 Additions or Modifications to the Basic Empirical Antimicrobial Regimen

The recommended standard empirical regimen should routinely cover the most common pathogens that cause CAP, all of the atypical pathogens and most of the relevant Enterobacteriaceae species. Table IV shows suggested additions or modifications to the basic empirical regimen when less common pathogens or antibacterial-resistant organisms are suspected. Treatment of *P. aeruginosa* infection or MRSA is the main reason for modifying the standard empirical regimen. Empirical antibacterial therapy for elderly patients with CAP in whom aspiration pneumonia is suspected should include adequate antianaerobic coverage, although the need for such coverage in persons with 'minor' predisposing factors for aspiration (e.g. swallowing difficulties or use of sedative medications) remains controversial.[1,17]

5. Supportive Therapy

In addition to administration of antibacterials, appropriate supportive therapy, covering management of severe sepsis and septic shock, respiratory failure and any decompensated underlying disease, may be critical to improving outcomes in elderly patients with CAP.

Prompt recognition of hypoxaemia may be important. All patients should be screened by pulse oximetry and those with hypoxaemia or respiratory distress should undergo a cautious trial of noninvasive ventilation, unless they require immediate intubation because of severe hypoxaemia (arterial oxygen pressure/fraction of inspired oxygen [PaO_2/FiO_2] ratio <150) and bilateral alveolar infiltrates.[1] In a prospective randomized evaluation of noninvasive ventilation in patients with CAP, patients who received noninvasive ventilation had a 25% absolute risk reduction in the need for intubation.[104] Patients with underlying COPD are most likely to benefit from noninvasive ventilation.[183,184]

The management of severe sepsis and septic shock in patients with CAP is not significantly different from that for patients with other sources of infection. Patients with CAP who have persistent septic shock despite adequate fluid resuscitation should be considered for immunomodulatory treatment with drotrecogin alfa within 24 hours of admission. This drug has been shown to increase short- and long-term survival rates in subjects with sepsis, including patients aged ≥75 years,[185-187] in a trial in which patients with CAP made up a significant fraction of participants.[188] There is no evidence that the main risk of drotrecogin alfa therapy (i.e. serious bleeding) is affected by patient age.[187] Use of drotrecogin alfa should be considered in elderly patients with severe CAP when the following conditions are met: (i) high risk of death as indicated by an Acute Physiologic and Chronic Health Assessment (APACHE) II score ≥25; (ii) the patient, family and healthcare team have chosen aggressive care; and (iii) a favourable benefit-risk profile. The greatest reduction in the mortality rate is expected in patients with *S. pneumoniae* infection.[189] In patients with severe CAP caused by a pathogen other

than *S. pneumoniae* and treated with appropriate antibacterials, there is no evidence that drotrecogin alfa affects mortality.

Hypotensive, fluid-resuscitated patients with severe CAP should be screened for occult adrenal insufficiency, particularly subjects who are taking intermittent corticosteroid treatment, such as those with severe COPD.[1] A multicentre trial has found that stress-dose corticosteroid therapy (200–300 mg of hydrocortisone per day or equivalent) improves outcomes of vasopressor-dependent patients with septic shock who do not have an appropriate cortisol response to stimulation.[190] This trial included many patients with CAP. If corticosteroids are used in elderly patients, close monitoring of plasma glucose is required.

Old patients with CAP constitute a high-risk group for development of deep venous thrombosis (DVT). In a large clinical trial,[191] age >75 years and acute infectious disease were independent risk factors for development of DVT. Additional risk factors were chronic respiratory disease and cancer, both of which are more frequent among elderly subjects. The benefit from DVT pharmacological prophylaxis for acutely ill medical patients who are hospitalized for >1–2 days has been demonstrated in three clinical double-blind, placebo-controlled trials,[192-194] in which the DVT rate was approximately halved compared with placebo, without an increase in the major bleeding complication rate.

Early mobilization has been shown to be a simple and effective therapeutic intervention that improves health outcomes among patients with myocardial infarction and those undergoing total knee replacement.[195,196] In a randomized trial conducted in 458 hospitalized patients with CAP, early mobilization reduced overall hospital length of stay and use of institutional resources without increasing the risk of adverse outcomes, and this effect was higher among PSI category III patients, which includes mainly older subjects.[197]

6. Assessing Clinical Stability

Most patients with CAP receiving appropriate therapy become clinically stable within 3–7 days.

Usually, patients classified within higher-severity PSI classes take longer to reach clinical stability than patients in lower-risk classes.[198] As expected, older patients with multiple co-morbidities recover more slowly.

Patients admitted to hospital should be switched from intravenous to oral therapy when they are haemodynamically stable and improving clinically, are able to ingest medications and have a normally functioning gastrointestinal tract.[1] If they have an appropriate environment for continued care, they should be discharged as soon as they are clinically stable, there is no need to treat any co-morbidity and there are no unmet social needs.[199-201]

The following set of criteria for assessing clinical stability has been proposed and validated:[198,202-204] (i) temperature ≤37.8ºC; (ii) heart rate ≤100 beats/min; (iii) respiratory rate ≤24 breaths/min; (iv) systolic blood pressure >90 mmHg; (v) arterial oxygen saturation ≥90% or PaO_2 ≥60 mmHg on room air; (vi) ability to maintain oral intake; and (vii) normal mental status. When all of these criteria are met, patients can be safely switched to oral therapy and discharged. Whether there is a need to wait for all of these criteria to be present before a patient is discharged is unclear, but elderly patients frequently require hospitalization beyond the time required to achieve physiological stability in order to recover function that has declined during the acute illness.[8] For older patients with multiple co-morbidities, arrangements for follow-up care, including rehabilitation, should be initiated early.

The optimal duration of antimicrobial therapy in the elderly is uncertain because of the scarcity of data from clinical trials for this population. Since old patients tend to be more severely ill and more often require hospitalization, a longer duration of therapy might in theory be beneficial. However, although most patients with CAP have been treated for 7–10 days or longer, the available data suggest that a shorter duration of therapy may be safe and effective in both inpatients and outpatients, including older subjects.[181,205] Recently, Shorr et al.[181] published a subgroup analysis of outcomes in patients aged ≥65 years in a double-blind controlled trial conduct-

ed at 70 US centres involving patients in PSI class I/ II and III/IV randomized to receive levofloxacin 750 mg/day for 5 days or levofloxacin 500 mg/day for 10 days. The analysis included 177 elderly patients, 80 of whom received levofloxacin 750 mg/ day for 5 days and 97 who received levofloxacin 500 mg/day for 10 days. Despite the halved duration of therapy, unadjusted clinical success rates were comparable between the two groups (89.0% and 91.9% in the 750- and 500-mg arms, respectively; 95% CI −7.1, 12.7). Microbiological eradication rates were 90.3% in the 750-mg arm and 87.5% in the 500-mg arm (p-value not significant). The incidence of treatment-emergent adverse events did not differ between the two study treatment arms.

The IDSA/ATS joint committee[1] recommends that patients with CAP should be treated for a minimum of 5 days, be afebrile for 48–72 hours and have no more than one CAP-associated sign of clinical instability before discontinuation of therapy. Patients with persistent clinical instability are often readmitted to the hospital and may not be candidates for short-duration therapy.

The IDSA/ATS joint committee[1] also states that a longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if the pneumonia was complicated by extrapulmonary infection, such as meningitis or endocarditis. Short-duration therapy may also be suboptimal for patients who present cavities or other signs of tissue necrosis and for those with bacteraemic *S. aureus* pneumonia (because of the risk of associated endocarditis and deep-seated infection) or *P. aeruginosa* pneumonia.

7. Prevention

The higher incidence of CAP with advancing age make elderly patients the most likely group to benefit from vaccination, in spite of the reduced efficacy of vaccines in this population.[206] Numerous large studies have convincingly established the efficacy of pneumococcal and influenza vaccines and their limitations.[207-214] In a large retrospective cohort study of adults aged ≥65 years, the 23-valent polysaccharide pneumococcal vaccine (PPV) was shown to significantly reduce the incidence of pneumococcal bacteraemia; however, it had no impact on the risk of CAP, and was even associated with a slight increase in hospitalizations for pneumonia.[207] Although the results of a previous randomized trial had shown similar results with respect to the inability of pneumococcal vaccine to prevent overall or pneumococcal pneumonia,[208] in a recent prospective study of 3 years' duration, the 23-valent PPV effectively prevented pneumococcal pneumonia, with or without bacteraemia, and decreased rates of overall pneumonia and mortality due to pneumonia in older adults.[209] Influenza vaccination has been shown to significantly reduce the risk of influenza infections and mortality in elderly patients in the community setting (relative risk 0.76; 95% CI 0.60, 0.97) in large cohort studies, although this efficacy differs according to co-morbid conditions and demographic factors.[210,211] In addition to a reduction in mortality from all causes, vaccination against influenza was associated with a reduction in the risk of hospitalization for cardiac disease, cerebrovascular disease, pneumonia or influenza in two large cohorts of patients aged ≥65 years.[212] The frequency of lower respiratory tract infection was not reduced after a first influenza vaccination in a population-based study, although annual revaccination reduced the risk of pneumonia or lower respiratory tract infections in community-dwelling elderly individuals without co-morbidities.[213] An interesting prospective study of >250 000 subjects conducted in Sweden disclosed an additive effect of influenza and pneumococcal vaccines on the incidence of hospital admissions for influenza, pneumonia, invasive pneumococcal disease and in-hospital mortality for pneumonia in elderly persons compared with either vaccination alone.[214]

8. Utilization of Guidelines to Improve Process of Care and Clinical Outcomes

There is strong evidence that utilization of specialty society guidelines for CAP leads to improvement in the process of care and clinical relevant outcomes.[31-34,215] A number of studies have reported beneficial effects on clinically relevant para-

meters following the introduction of a protocol that increases adherence to published guidelines.[32-36,52,117,215-218]

A reduction in mortality with the introduction of guideline-based protocols has been found in several studies.[31,32,34] Dean et al.[31] utilized data from the Centers for Medicare and Medicaid for Utah from 1993 to 2003 to determine if pneumonia guideline implementation was associated with improved clinical outcomes in elderly patients (≥66 years). They analyzed data from 17 728 patients (mean age 72 years) admitted to hospital, and observed that an increase in guideline compliance was associated with decreased 30-day mortality and a lower readmission rate. Improved clinical outcomes were also associated with pneumonia guideline utilization.[31]

Protocols using guidelines to decrease hospitalization have also found that the number of less ill patients admitted to hospital is consistently lower. Using admission decision support, Marrie et al.[33] conducted a cluster randomized trial in which hospitals were randomized to manage patients with pneumonia according to a clinical pathway or conventional care. Use of the clinical pathway was associated with an 18% decrease (from 49% to 31%) in admission of low-risk patients to the hospital (PSI classes I–III) without differences in patient satisfaction scores or rate of readmission. Although the trial was not limited to elderly persons, the mean age of patients was 64 years.

Studies assessing duration of hospitalization after implementation of guidelines have also shown that length of hospital stay may be significantly shortened.[33,34,36,117] Some other markers of process of care, such as the time to first antibacterial dose, can also improve with use of CAP protocols.[36,117,218]

The IDSA/ATS consensus document[1] emphasizes that data showing a benefit from implementation of CAP guidelines have arisen from protocols addressing a comprehensive set of elements in the process of care, rather than only specific aspects of CAP. The elements considered important for local CAP guidelines, according to the IDSA/ATS panel, are shown in table VI, and include general recom-

Table VI. Elements important for local community-acquired pneumonia guidelines according to the Infectious Disease Society of America/American Thoracic Society[1] (reproduced from Mandell et al.,[1] with permission from The University of Chicago Press; © 2007 by the Infectious Diseases Society of America. All rights reserved)

All patients
Initiation of antibacterial therapy at site of diagnosis for hospitalized patients
Antibacterial selection
empirical
specific
Admission decision support
Assessment of oxygenation
Intensive care unit admission support
Smoking cessation
Influenza and pneumococcal vaccine administration
Follow-up evaluation
Inpatients only
Diagnostic studies
timing
types of studies
Prophylaxis against thromboembolic disease
Early mobilization
Thoracentesis for patients with significant parapneumonic effusions
Discharge decision support
Patient education

mendations of good medical care for inpatients, such as early mobilization and prophylaxis against thromboembolic disease.

Finally, it is important to emphasize that guidelines should be directed toward improvement in the process of care and most relevant clinical outcomes, and that these parameters should be evaluated to measure effect. Outcome parameters that can be used to measure the effect of CAP guideline implementation in the elderly are listed in table VII. Studying more than one outcome is important. Assessment of clinical outcomes other than survival (i.e. physical functional ability, cognitive ability, need for nursing home care and overall quality of life) is strongly recommended for this population because these outcomes influence the most relevant and practical issues involving the need for home care, placement in extended care facilities and end-of-life decisions.[42]

Table VII. Possible outcome parameters to be measured in elderly patients with community-acquired pneumonia

Mortality
Hospital admission
Intensive care unit admission
Treatment failure
Drug toxicity and adverse effects
Hospital readmission
Unscheduled return to emergency department or primary physician office
Functional decline
physical functional ability
cognitive ability
Need for nursing home care
Quality of life
Return to normal activities
Patient satisfaction
Cost of care

9. Conclusions

CAP is a major cause of morbidity and mortality in elderly patients. An organized approach to optimization of the healthcare process is likely to improve clinical results. Severity assessment is crucial to predicting outcome and selecting appropriate empirical antibacterial therapy, and should be accomplished through a rigorous patient risk-stratification based on objective criteria and prediction tools. Because of the low yield of most microbial tests and the usual effectiveness of empirical antimicrobial therapy, a focused, clinically orientated approach to microbial diagnosis is recommended. Prompt administration of appropriate antibacterial therapy increases the probability of a successful outcome; therefore, therapy should be started as soon as possible. Currently recommended empirical antimicrobial regimens provide adequate coverage for the overwhelming majority of pathogens that cause CAP in the elderly, including most strains of DRSP. Nevertheless, clinicians should be aware of risk factors for acquiring less common pathogens or antibacterial-resistant organisms that may suggest the need for additions or modifications to the basic empirical regimen. In addition to administration of antibacterials, appropriate supportive therapy, covering management of severe sepsis and septic shock, respiratory failure and any decompensated underlying disease, may be critical to improve clinical results.

A growing body of data suggests that implementation of CAP guidelines leads to improvement in clinical outcomes in the elderly population. Protocols should address a comprehensive set of elements in the process of care and should be periodically evaluated to measure their effect on clinically relevant outcomes. Assessment of functional variables, in addition to survival, is recommended.

Acknowledgements

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