



Natural enemy or friend? Pneumonia in the very elderly critically ill patient

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Pneumonia is a common problem in the elderly with higher short- and long-term mortality than younger patients and similar age patients with other illnesses. Aggressive care may not be justified and broad-spectrum antibiotics may create antibiotic resistant pathogens that harm others. http://bit.ly/2P8LUNp

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Pneumonia has been a serious cause of morbidity and mortality for many years and, more than 100 years ago, Sir William Osler referred to it as "the natural enemy of the old man" [1]. Many studies have documented that elderly individuals have a higher frequency of illness, increased mortality and more subtle clinical features compared to younger populations. This too was known by Osler who commented that "it is not improbable that debility lowers the vitality and renders the individual susceptible" and when the illness occurs, it can be "without chill; the cough and expectoration are slight" and the physical findings non-specific [1]. He noted that while fever was not usually prominent, patients often had altered mental status and that pneumonia could precipitate congestive heart failure [1].

In much of the literature on this topic, elderly has been defined as >65 years of age, and the identification of subgroups, based on age, in this population has not always been part of large series. In the current issue of the *European Respiratory Review*, CILLÓNIZ *et al.* [2] have focused on the problem of pneumonia in the "very elderly", a specific subgroup defined as those aged >85 years, and have specifically discussed those with critical illness. This is a very important and controversial topic, raising issues about whether age itself is important in defining the risk and prognosis of pneumonia, and which very elderly patients with severe illness should be managed in an intensive care unit (ICU), and in which patients the focus should be on comfort, not heroic life support.

Many studies have suggested that in the elderly, pneumonia can start a cascade of events that results in mortality, even after the patient has left the hospital. KAPLAN *et al.* [3] studied 158 960 hospitalised patients with community-acquired pneumonia (CAP) aged ≥ 65 years and compared them to 794 333 matched control patients in the same age range, but admitted to hospital for other diseases. The in-hospital mortality rate for CAP was 11%, but those who were discharged had an additional mortality in the next year of 33.6%. Thus, for many patients, pneumonia is the start of an inexorable decline. The short term and 1-year mortality rate for patients admitted with other diagnoses was not as high as with pneumonia.

The very elderly have a higher mortality from pneumonia than other age groups. LUNA *et al.* [4] observed that age >80 years was a risk factor for mortality (OR 2.0) and that in this group, mortality for those with

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>1 comorbidity was higher than for those with ≤ 1 comorbidities. These data suggest that above 80 years of age there is not "healthy aging", since in this group pneumonia mortality is greater, even in those with one comorbidity than in younger populations with multiple comorbidities. In contrast, LE BORGNE *et al.* [5] observed that patients aged >90 years who were admitted to the ICU with all diagnoses (including 52% with respiratory failure) had a mortality rate of 42.6%, although age was not a predictor of death, but rather other factors such as mechanical ventilation, need for dialysis and the withholding or withdrawing of life support were most predictive.

The worse outcomes of pneumonia that are seen in the very elderly are likely the result of multiple factors. These include immune function decline, a high rate of serious comorbidity, high rates of frailty, impaired functional status, and delays in pneumonia diagnosis. Delays in recognising pneumonia can be the result of non-classical or subtle symptoms that do not lead to a consideration of a pneumonia diagnosis. Chest radiographs can be negative early in the course of pneumonia, especially in older patients, and this also adds to diagnostic delay which in turn can lead to therapy later in the course of illness, adding to mortality [6]. In one study of 96 elderly patients with CAP (mean age 83 years), the chest radiograph on presentation was positive in only 47%, and was a particularly unreliable tool in patients with advanced degrees of frailty [7]. The chest radiograph had a negative predictive value of 73% in those with low degrees of frailty but only 53% in those with advanced levels of frailty.

The site of care decision for CAP patients is important but one that is immeasurably harder in the elderly. In many settings, prognostic scoring indices are used to guide this decision, but in the elderly, prognostic scoring is less accurate than in younger populations, and for any given score the very elderly have a higher mortality [4]. However, most prognostic scoring tools heavily weight age as a risk factor, and thus for similar severity of illness the elderly get a higher score, a predicted higher mortality, and an apparent higher need for advanced care such as ICU [8]. Thus, the elderly have higher predicted mortality than younger patients for the same degree of illness, and higher observed mortality than younger populations in any given prognostic scoring category. Thus, it is hard to decide which of these patients should be considered for ICU admission, and to what extent the ICU can be beneficial for the very elderly, compared to younger patients.

The review by CILLONIZ *et al.* [2] raises an additional question in the site of care decision, and that is whether the very elderly with critical illness should always be admitted to an ICU, or if for some this would not be appropriate, given the patients' wishes, their short- and long-term prognosis, and the likelihood of benefit from ICU admission. As an alternative, they present the use of intermediate care units which have been reported to reduce overall hospital mortality, compared to hospitals without these units. This may be because these units provide an appropriate level of care for many patients, and do not force a dichotomous choice between ICU or no ICU care, the latter offering little chance of recovery for some patients. Decisions about care at the end of life in the elderly are complex, but should be influenced by a realistic view of whether for each patient we are prolonging life or suffering. For some patients, ICU admission offers little chance of recovery or long-term survival. As discussed above, pneumonia may be the "beginning of the end" for some patients, with both high short- and long-term mortality, and ICU care may not be appropriate for them. Osler understood this when he changed his view about pneumonia to an illness that was the "friend of the aged" [1]. Of course, the irony of this description is that at age 70, Osler developed pneumonia with a *Haemophilus influenzae* empyema and died.

One other important issue in pneumonia treatment is the use of antibiotics. The elderly often have more drug resistant bacteria than younger patients, particularly those who have multiple comorbidities, live in chronic care facilities and have received multiple courses of antibiotics. In this population, empiric therapy is usually with a broad-spectrum agent. Antibiotics are among the most used therapies in dying patients, in and out of the ICU, and doctors often use them even when they will not provide CPR. In one study, 45% of patients got antibiotics in the last 24 h of life, independent of a do not resuscitate order, and antibiotics were the most common intervention after hydration [9]. In another study of 95 ICU patients with no planned escalation of care, antibiotics were discontinued less often than dialysis and pressors [10]. Among 423 ICU patients in Toronto (Canada) and Jerusalem (Israel), the absence of a limitation of care order was the only independent predictor of the emergence of antibiotic resistance [11]. However, one needs to consider that the use of our best antibiotics may have limited benefit to patients who develop repeated infections and are not likely to recover because of the severity of their chronic and acute illnesses. When patients receive antibiotics, with little likelihood of benefit, but at the same time therapy induces the emergence of even more antibiotic resistant pathogens (which can occur in up to 25% of these patients), it may result in harm to other patients in the hospital and ICU [12]. Highly resistant pathogens can spread in the ICU to other, more healthy individuals and infect them with organisms that cannot be effectively treated, and can result in the death of these other patients. If this happens, one could question whether the use of broad-spectrum antibiotics in the very elderly critically ill patient, with a low chance of benefitting, created more harm than good. For this population, we may need to consider Osler's view that pneumonia can be the friend of the elderly, and focus our efforts on patient comfort and relief of suffering, rather than treatment with a limited chance of individual patient benefit and a risk of harm to others in the ICU.

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References

- 1 Berk SL. Bacterial pneumonia in the elderly: the observations of Sir William Osler in retrospect. J Am Geriatr Soc 1984; 32: 683–685.
- 2 Cillóniz C, Dominedò C, Pericàs JM, *et al.* Community-acquired pneumonia in critically ill very old patients: a growing problem. *Eur Respir Rev* 2020; 29: 190126.
- 3 Kaplan V, Clermont G, Griffin MF, et al. Pneumonia: still the old man's friend? Arch Intern Med 2003; 163: 317-323.
- 4 Luna CM, Palma I, Niederman MS, et al. The impact of age and comorbidities on the mortality of patients of different age groups admitted with community-acquired pneumonia. Ann Am Thorac Soc 2016; 13: 1519–1526.
- 5 Le Borgne P, Maestraggi Q, Couraud S, et al. Critically ill elderly patients (≥90 years): clinical characteristics, outcome and financial implications. PLoS One 2018; 13: e0198360.
- 6 Niederman MS. Imaging for the management of community-acquired pneumonia: what to do if the chest radiograph is clear. *Chest* 2018; 153: 583–585.
- 7 Ticinesi A, Lauretani F, Nouvenne A, *et al.* Lung ultrasound and chest x-ray for detecting pneumonia in an acute geriatric ward. *Medicine* 2016; 95: e4153.
- 8 Brito V, Niederman MS. Predicting mortality in the elderly with community-acquired pneumonia: should we design a new car or set a new 'speed limit'? *Thorax* 2010; 65: 944–945.
- 9 Phua J, Kee AC, Tan A, et al. End-of-life care in the general wards of a Singaporean hospital: an Asian perspective. J Palliat Med 2011; 14: 1296–1230.
- 10 Morgan CK, Varas GM, Pedroza C, et al. Defining the practice of "no escalation of care" in the ICU. Crit Care Med 2014; 42: 357-361.
- 11 Levin PD, Simor AE, Moses AE, et al. End-of-life treatment and bacterial antibiotic resistance: a potential association. Chest 2010; 138: 588–594.
- 12 Niederman MS, Berger JT. The delivery of futile care is harmful to other patients. *Crit Care Med* 2010; 38: Suppl. 10, S518–S522.





Community-acquired pneumonia in critically ill very old patients: a growing problem

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There is currently no international recommendation for the management of critically ill older patients over 80 years of age with CAP. We report and discuss recent literature in order to help physicians in the decision-making process of these patients. http://bit.ly/2ql0mIz

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ABSTRACT Very old (aged \geq 80 years) adults constitute an increasing proportion of the global population. Currently, this subgroup of patients represents an important percentage of patients admitted to the intensive care unit. Community-acquired pneumonia (CAP) frequently affects very old adults. However, there are no specific recommendations for the management of critically ill very old CAP patients. Multiple morbidities, polypharmacy, immunosenescence and frailty contribute to an increased risk of pneumonia in this population. CAP in critically ill very old patients is associated with higher short-and long-term mortality; however, because of its uncommon presentation, diagnosis can be very difficult. Management of critically ill very old CAP patients should be guided by their baseline characteristics, clinical presentation and risk factors for multidrug-resistant pathogens. Hospitalisation in intermediate care may be a good option for critical ill very old CAP patients who do not require invasive procedures and for whom intensive care is questionable in terms of benefit.

What is the role of community-acquired pneumonia in critically ill very old patients?

Community-acquired pneumonia (CAP) is a major public health problem with high morbidity, mortality and short- and long-term sequelae [1–4]. Very old (aged ≥ 80 years) patients are at increased risk of complications and death by most causes [5]. The incidence of CAP in very old patients continues to rise [6]. The immunosenescence [7], multicomorbidities [8] and frailty [9] of these patients increases their susceptibility to infectious diseases [10, 11]. Moreover, it is reported that CAP is associated with a 16%

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reduction in quality of life during the post-discharge year among elderly patients (mean age 76 years in cases and controls) who survive to hospitalisation for CAP, compared to non-diseased persons [12].

Currently, due to their increased life expectation, over the past two decades the proportion of very old patients admitted to intensive care units (ICUs) has grown significantly worldwide [6, 13, 14], increasing healthcare costs [15–17]. The percentage of very old patients admitted to ICUs ranges from 9–20% in several countries [13, 18–24]. A recent French study reported the 10-year (2006 to 2015) trends in ICU admissions for respiratory infections in the elderly population. The authors found that the absolute number and the percentage of elderly patients admitted to ICUs increased, with the greatest rise in patients aged \geq 85 years (11% in 2006 *versus* 16% in 2015) [6]. Moreover, a recent Spanish study [25] investigated risk factors for mortality in critically ill elderly and very old patients with sepsis in 77 ICUs. Pneumonia was the main cause of sepsis, affecting 62% of very old patients; mortality for sepsis in very old patients was 54%. Similarly, the study by CILLONIZ *et al.* [26] on the topic of sepsis secondary to CAP in very old patients reported that 11% of these patients required ICU admission and 14% developed sepsis with an ICU mortality of 17%.

In this review, we discuss important findings and gaps in knowledge concerning the management of critically ill very old patients with CAP, and propose a series of recommendations to guide basic principles of CAP management in these patients while further evidence is gathered (figure 1).

Clinical presentation of pneumonia in very old patients

Immunosenescence reduces the ability of very old patients to respond to an infection [27]. Some specific symptoms of lower respiratory infection such as cough, fever and chest pain may be atypical in very old patients with pneumonia [28], thus increasing the risk of misdiagnosis and delaying the initiation of the empiric antimicrobial therapy [29, 30]. For these reasons, pneumonia may be associated with high morbidity and mortality and poor long-term outcomes in this subgroup of patients [29, 31]. Falls, altered mental status (*e.g.* delirium), fatigue, lethargy, anorexia, tachypnoea and tachycardia are the most frequent symptoms associated with pneumonia in very old patients [32, 33]. Pneumonia may also be associated with an exacerbation or decompensation of previous chronic comorbidities (diabetes mellitus, cardiac disease, chronic pulmonary disease). Radiographic findings are inconclusive or difficult to interpret in approximately 30% of cases [34]. The inadequate inflammatory response to an infection due to immunosenescence [35, 36] may also lead to an underestimation of pneumonia severity. However, data



FIGURE 1 General recommendations for the management of critically ill very old community-acquired pneumonia (CAP) patients. PSI: pneumonia severity index; ATS: American Thoracic Society; ICU: intensive care unit. [#]: in addition to the antibiotics recommended in guidelines, ceftaroline+macrolide/ceftobiprole +macrolide could be a good option for this population.

regarding the role of biomarkers (leukocyte count, C-reactive protein, procalcitonin) in the early diagnosis and prognosis of pneumonia in critically ill very old patients are limited [37].

What parameters might help guide the management of CAP in critically ill very old patients?

Since the short- and long-term prognosis of critically ill very old patients with CAP mostly depends on previous functional status rather than on the severity of pneumonia at ICU admission, improved tools for patient prognosis in this particular subgroup would be extremely helpful [31, 38].

Age-related changes: immunosenescence and sarcopenia

It is expected that in 2080, the current proportion of people aged ≥ 80 years will have more than doubled, from 6% to 13% of the European population [39].

Immunological age-related changes (immunosenescence) gradually reduce the efficiency of the innate and adaptive immune systems [7]. Few naïve cells, increased dysfunctional memory cells and primary lymphoid organ involution may explain the susceptibility of very old patients to infectious diseases, especially those caused by *Streptococcus pneumoniae* and respiratory viruses [35]. Important barriers to infection, such as the cough reflex and fever, are also affected by immunosenescence. Figure 2 shows age-related changes in the innate and adaptive immune systems.

Sarcopenia is a geriatric syndrome characterised by a loss of skeletal muscle mass and a decrease of muscle strength or physical performance. Some studies have reported that sarcopenia is an independent risk factor for CAP and for some adverse outcomes (length of hospital stay, readmission or death) [40–43]. MARTINEZ *et al.* [41] studied the frequency of sarcopenia in 110 hospitalised elderly patients. The prevalence of sarcopenia in very old patients was 12%. Recently, a study from Peru [43] determined the incidence and risk factors of CAP in older adults with sarcopenia. CAP affected 15% of sarcopenic patients, with a mean age of 82 years. The authors reported that sarcopenia and smoking habits were risk factors for CAP. Unfortunately, data regarding the prevalence and impact of sarcopenia in critically ill very old patients with CAP are limited.

Comorbidities

Very old patients suffer from a variety of chronic diseases that affect the integrity of resistance to an infection. Chronic respiratory diseases, diabetes mellitus, chronic heart disease, COPD and chronic neurological diseases are the most frequent comorbidities reported in critically ill very old patients with CAP [6, 11, 44]. They are associated with longer hospital stays, ICU admission, sepsis [45–47], hospital readmission [48, 49] and mortality [11]. In a Spanish study assessing the impact of age and comorbidities



FIGURE 2 Changes in the adaptive and innate immune system. INF: interferon; IL: interleukin; TNF: tumour necrosis factor; Ig: immunoglobulin.

on the aetiology of pneumonia, 80% of CAP patients had at least one comorbidity (chronic respiratory disease, diabetes mellitus, chronic cardiovascular disease, neurological disease, chronic liver disease or chronic renal disease) with rates varying according to age group, being 81% in patients aged >75 years. The most frequent comorbidity in all the age groups was chronic pulmonary disease (54%). COPD was the most frequent respiratory comorbidity, decreasing in frequency with age. The percentage of comorbidities in critically ill very old patients and very old patients hospitalised on a general ward was similar (81% *versus* 78%, p=0.26). However, diabetes mellitus was more frequent in critically ill very old patients hospitalised on general wards (22% *versus* 31%, p=0.012), whereas neurological diseases were less frequent in critically ill very old patients than in very old patients hospitalised on general wards (30% *versus* 17%, p=0.001) (data not published) [44].

Similarly, Luna *et al.* [11] investigated the effect of age and comorbidities on CAP mortality in 6205 patients, reporting mortality rates of 14% in very old patients. Moreover, in patients with no or only one comorbidity, age ≥ 80 years was associated with increased mortality.

Recently, chronic renal disease and diabetes mellitus have been described as independent risk factors for sepsis secondary to CAP in very old patients, while antibiotic therapy before admission was independently associated with a lower risk of sepsis [26]. Chronic renal disease and neurological disease were reported as independent risk factors for 30-day mortality in very old patients with sepsis secondary to CAP.

Malnutrition

Malnutrition is strongly related to the ageing of the immune system. In 2008, RIQUELME *et al.* [32] studied the clinical and nutritional features of 109 elderly patients with CAP. They reported that 77% of patients presented with malnutrition. In their multivariate analysis, malnutrition (OR 2.7), an albumin level $\leq 3.4 \text{ g} \cdot \text{dL}^{-1}$ (OR 2.7) and brachial muscle perimeter $\leq 24 \text{ cm}$ (OR 4.0) were related to an increased risk of in-hospital mortality.

Two recent papers confirmed the important role of malnutrition in the outcomes of CAP patients. The first study evaluated risk factors associated with hospitalisation in 199 home-healthcare patients with CAP from Taiwan; the mean age of the study population was 82 ± 11 years [50]. The authors reported that 83% of patients presented with anaemia and 34% with hypoalbuminaemia. In their multivariate analysis, anaemia (OR 2.37) and hypoalbuminaemia (OR 1.57) significantly increased the risk of hospitalisation for CAP. The second study evaluated the prevalence and prognostic value of malnutrition in two groups of CAP patients (aged ≥ 65 and <65 years) from Korea [51]. The authors found that the prevalence of malnutrition in the entire cohort was 39%, and it was higher in the elderly group (53% *versus* 12%, p=0.001). Malnutrition (OR 2.52) and Charlson comorbidity index score (OR 1.30) were associated with 2-year mortality.

There are no data about malnutrition and critically ill very old patients with CAP. Since malnutrition is associated with worse short- and long-term outcomes in very old patients with CAP, continual assessment of patient nutritional status is recommended in order not to underestimate, underdiagnose or undertreat it.

Frailty

Frailty is associated with adverse clinical outcomes in older hospitalised patients. It is characterised by a loss of biological reserves, a failure of homeostatic mechanisms and an increased vulnerability to adversities such as falls, disability, hospitalisation, cognitive decline and loss of independence. The prevalence of frailty rises steadily with age: from 4% in the 65–69-year-old group to 7% at 70–74 years, 9% at 75–79 years, 16% at 80–84 years and 26% in the those aged \geq 85 years [52, 53]. A transnational prospective study set up by the European Society of Intensive Care Medicine, with the participation of 311 ICUs from 21 European countries, investigated the impact of frailty on the outcomes of 5021 critically ill very old patients. Frailty (values \geq 5 in the Clinical Frailty Scale (CFS)) was present in 43% of patients and was independently related to 30-day survival [54].

Frailty should be measured in routine clinical practice in order to improve the management of elderly patients with CAP. However, there is no international standard for its assessment. The CFS derived from the Frailty Index (FI) proposed by ROCKWOOD *et al.* [55] is the most frequently used: FI=number of deficits in an individual/total number of deficits measured. It includes variables that represent a range of states, conditions and physiological systems such as mobility, disability, self-rated general health, eyesight, hearing and chronic diseases. The CFS established nine categories for older people: 1) very fit; 2) well, 3) managing well; 4) vulnerable; 5) mildly frail; 6) moderately frail; 7) severely frail; 8) very severely frail; and 9) terminally ill (figure 3).

In 2018, GILBERT *et al.* [56] proposed the Hospital Frailty Risk Score, which is based on 109 diagnostic field codes from the National Health Service Hospital Episode Statistics database. The score was developed and validated in three UK populations, with high prognostic performance. The score is divided into three

1 Very Fit-People who are robust, active energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well-People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, *e.g.* seasonally.

3 Managing Well-People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable-While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail-These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.



6 Moderately Frail-People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.



7 Severely Frail-Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within 6 months).



8 Very Severely Frail-Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.



9 Terminally Ill-Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

FIGURE 3 Clinical Frailty Scale. IADLs: instrumental activities of daily living.

categories: low frailty risk (score <5); intermediate frailty risk (5–15); and high frailty risk (>15). The score was further validated in a tertiary care hospital in Switzerland [57]. The study population comprised 4957 patients: 64% were classified as low frailty risk, 34% as intermediate and 3% as high frailty risk. Patients at intermediate and high frailty risk showed an increased risk of 30-day mortality (OR 2.53 and OR 4.40, respectively, p<0.001) compared with patients in the low frailty risk group. The authors also found that patients with higher frailty risk have longer hospital stay, more severe functional impairment and a lower quality of life. The study confirmed the prognostic value of the Hospital Frailty Risk Score.

Polypharmacy

Because of their chronic conditions, older patients are at increased risk of polypharmacy [58], side-effects and drug-drug interactions [59, 60].

In a study from Canada [61], including 2105 older CAP patients, 45% of patients used four or five medications at baseline. Cardiovascular (63%), alimentary tract and metabolism (49%), nervous system (47%), respiratory (38%), blood and blood-forming and general anti-infective for systemic use (21%) drugs were the most frequently used. The authors also observed that in the 90-day period following a CAP episode, the rate of patients with polypharmacy increased from 45% to 74%.

Because of their multiple comorbidities and polypharmacy, choosing empiric antimicrobial therapy may be challenging in very old patients with infections such as pneumonia [60].

ICU benefit in very old patients: role of severity scores

Currently, 10–20% of all ICU admissions involve very old patients [18, 20–23, 44]. However, the effectiveness of ICU management in this subgroup of patients remains controversial. Since not all very old patients are fragile, advanced age *per se* should not be a limitation to receive critical care therapy.

Disease severity in CAP is used to assess the prognosis and to guide patient management [4]. In critically ill very old patients with pneumonia, the lack of validated criteria and severity scores that accurately identify those patients that would benefit from ICU admission represents a major issue [62]. The most frequently used severity scores in CAP (pneumonia severity index (PSI) [63], CURB65 (confusion, (urea >7 mmol·L⁻¹), respiratory rate \geq 30 breaths·min⁻¹, blood pressure <90mmHg (systolic) \leq 60 mmHg (diastolic), age \geq 65 years) and CRB65 [64]) have some limitations for elderly patients: in the PSI, age and comorbidities score more highly, whereas in CRB65 and CURB65, the low number of variables affects the inclusion of all patients with severe CAP.

The Eldicus study [65] investigated the effect of ICU triage decisions on mortality. Refusal benefited overall mortality according to increasing age, where the group of patients aged >84 years had the highest rate of mortality (36%).

More recently, in a Norwegian multicentre observational study [66], 30% of very old patients were refused ICU treatment. Factors increasing the likelihood of ICU refusal in patients considered too ill/old were advanced age, male sex, university hospital admission, comorbidity and low functional status.

Recently, a US study on pneumonia hospitalisation in adults [67] including 119537 patients, found that approximately 19% required ICU admission and 13% required mechanical ventilation. The rate of pneumonia hospitalisation with ICU admission was 76 per 100000 persons per year in the overall population. In adults aged ≥ 85 years, the rates of hospitalisation and ICU admission were 53 times higher (4368 per 100000) and 46 times higher (695 per 100000) than in the younger group (18–49 years; 83 per 100000 persons per year for hospitalisation and 15 per 100000 persons per year for ICU admission).

A European study [6] of ICU admission due to respiratory infections in the elderly population (<75, 75–79, 80–84, 85–89 and \geq 90 years) over 10 years (2006 to 2015) was also published. The authors reported that 3% of all hospitalisations (n=3 856 785 cases) were due to an acute respiratory infection (n=98 381 cases) and that 15% of those cases required ICU admission (n=15 267 cases). The authors found that there was an overall increase in the number of ICU admissions for all age groups, but with the greatest increases in patients aged 85–89 years (3.3-fold) and \geq 90 years (5.8-fold). Interestingly, the authors also reported that the higher rate of ICU admission was not associated with significant changes in ICU mortality for patients with an acute respiratory infection; rates were 19.7% \pm 3.0%, 24.0% \pm 3.6% and 25.0% \pm 4.0% for the 75–79, 80–84 and 85–89 age groups, respectively. Indeed, the authors reported a significant drop in ICU mortality from 41% in 2006 to 22% in 2015 (p=0.03) for patients aged \geq 90 years. Hospitalisations for CAP and acute exacerbations of COPD increased significantly for all age groups over the 10-year study period.

Meanwhile, a multicentre, prospective study from Canada [68] including 1671 critically ill very old patients who were admitted to 22 ICUs, reported that ICU mortality was 22%, with a median time from ICU admission to death of 10 days. 49% of patients who died were still receiving mechanical ventilation, vasopressors or dialysis.

A retrospective cohort analysis including 328404 elderly (>64 years) patients with pneumonia admitted to ICUs in the USA [69] found potential benefit provided by ICU admission for older patients with low-risk pneumonia. Compared to patients admitted to a general hospital ward, patients admitted to an ICU had significantly lower adjusted 30-day mortality (15% *versus* 21, p=0.02) with no significant differences in health costs associated with ICU admission.

A study by CHEN *et al.* [70] evaluated the performance of two scores (PSI and CURB65) in three groups of CAP patients according to age: 18–64 years, 65–84 years and \geq 85 years. The authors found the worst scores, mainly the PSI, in the group of patients aged 65–84 years and \geq 85 years. This may be due to an overestimated weight of age. The authors therefore proposed a modified score excluding age for this specific population.

Recently, SANZ *et al.* [71] proposed a composite score to predict mortality by combining PSI score and Barthel index. In a study that included 1919 patients aged \geq 65 years, 61% had severe pneumonia (PSI IV–V) and 40% had Barthel index \leq 90. The combination of PSI IV–V and Barthel index \leq 90 constituted the greatest risk factor for mortality (OR 4.17).

Among the scores that predict ICU admission, the need for vasoactive drugs, or the need for mechanical ventilation, the most commonly used are the SMART-COP tool [72], and the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) severity criteria score [73]. Age or comorbidities are not included in the ATS/IDSA criteria since patient selection is based on acute physiologic parameters. In the SMART-COP, the cut-off for age is 50 years.

Recently, DE LANGE et al. [74] proposed a Cumulative Prognostic Score (CPS) to predict 30-day mortality in very old patients admitted to an ICU. Overall, 306 ICUs from 24 European countries participated in the

study; 3730 very old patients with a median age of 84 years were included. The 30-day mortality rate was 42% (1562 deaths), with age, sex, ICU admission diagnosis, CFS, Sequential Organ Failure Assessment, invasive mechanical ventilation and renal replacement therapy being predictors for mortality. The area under the curve for a CPS of \geq 10 points was 0.80. The model predicted 30-day mortality in 91% of all patients who died at a cut-off point of \geq 10 (75% of all patients). Although CPS seems to be a useful tool to guide physicians, several factors relevant to very old patient populations (*e.g.* nutritional status, functional status, dementia and comorbidities) have not been incorporated into the score.

In conclusion, clinical evaluation is the cornerstone when considering ICU admission of very old patients. Age should not be the only factor guiding ICU admission. Delayed ICU admission is associated with a higher risk of death. Patients who may benefit from ICU admission are those who have failed to benefit from therapy during general hospitalisation, and patients requiring organ support or specific monitoring [75, 76].

What is the importance of intermediate care in critically ill very old patients?

In a study from 2014 including data from 167 ICUs in 17 European countries, CAPUZZO *et al.* [77] evaluated whether adults admitted to hospitals with both ICUs and intermediate care units (IMCUs) had lower in-hospital mortality than patients with no IMCU option. The study included 5834 patients: 1397 (24%) died in the hospital and 19% in the ICU. Overall, 5031 (86%) patients were admitted to hospitals with IMCUs and 803 (14%) to those without IMCUs. After adjustments for patient characteristics (illness severity, ICU) and hospital characteristics (number of hospital beds, ICU beds, teaching hospital, for-profit hospital, possibility of extra beds in the ICU, patient ratio in daytime for ICU nurses), the authors reported that the presence of an IMCU in the hospital significantly reduced mortality for adult patients (OR 0.63 (95% CI 0.45–0.88); p=0.007) compared to centres without IMCUs.

Few prospective studies compared mortality in IMCUs and ICUs in very old patients with CAP. IMCUs require less human and technical resources, thus potentially providing a practical alternative for critically ill very old patients who do not require invasive procedures and whose ICU admission is questionable in terms of benefit. IMCUs offer the option of stepping up to ICU care or stepping down to general hospitalisation [78]. Notwithstanding this, evidence supporting the use of IMCUs in critically ill very old patients is scanty and further studies are needed in order to provide specific recommendations for the use of intermediate care in these patients.

Is microbial aetiology in very old patients different from that of the general population?

Overall, CAP causative agents in the elderly differ from those of other age groups because of a higher rate of pneumococcal and influenza infections as well as a lower rate of atypical microorganisms [79].

In 2003, the study by FERNANDEZ-SABE *et al.* [80] that investigated the aetiology and outcomes of CAP in very old patients, reported that *S. pneumoniae* was the main pathogen that caused CAP in very old patients. Legionella and atypical microorganism were very rarely found in very old patients with CAP.

In 2013, a study by our research group, investigated the effect of age and comorbidities on the microbial aetiology of CAP [44]. Our results showed that microbiological diagnosis in CAP decreased with each increasing age group (65–74 years: 43.7%; 75–84 years: 40.7%; and \geq 85 years: 31.4% (p<0.001)), and age did not influence microbial aetiology by itself. *S. pneumoniae* was the pathogen most frequently reported in all age groups (40.7%, 39.4% and 48.9%, respectively), followed by mixed aetiology (16.0%, 13.1% and 10.6%, respectively), atypical pathogens (16.0%, 13.1% and 9.9%, respectively) and respiratory viruses (8.4%, 14.6% and 11.3%, respectively). In patients with at least one comorbidity *Haemophilus influenzae* was the most common pathogen; multidrug-resistant (MDR) pathogens were frequent in patients with one or more comorbidities. GROSS *et al.* [81] found that independent predictors of MDR pathogens in CAP were similar to those identified for other infections (*i.e. Pseudomonas aeruginosa*) colonisation/infection in the previous year, antimicrobial use in the previous 90 days, admission from a nursing home and duration of hospitalisation in the previous 90 or 180 days.

In 2015, another Spanish study [82] proposed the acronym PES for a group of pathogens (*P. aeruginosa, Enterobacteriaceae* extended-spectrum β -lactamase positive (ESBL⁺) and methicillin-resistant *Staphylococcus aureus* (MRSA)) that cause CAP in approximately 6% of cases with a microbiological diagnosis. The authors proposed the "PES score" to identify patients at higher risk of CAP caused by PES. However, the PES score (table 1) lacks a specific age threshold for very old patients and this and other scores need further validation before being systematically recommended in the assessment of MDR microorganisms in CAP occurring in very old patients.

More recently, a study from China [83] evaluated the impact of adherence to current antimicrobial guidelines on the mortality of 3131 hospitalised elderly CAP patients. The authors reported that the rate of

PES score	Points
Age years	
<40	0
40-65	1
>65	2
Male	1
Previous antibiotic use in the past month	
Chronic respiratory disorder	2
Chronic renal failure	3
At emergency room	
Consciousness impairment or aspiration evidence	2
Fever or shivers	-1

TABLE 1 *Pseudomonas aeruginosa*, extended-spectrum β-lactamase-positive Enterobacteriaceae and methicillin-resistant *Staphylococcus aureus* (PES) score

 $\leqslant 1$ point: low-risk multidrug-resistant score; 2–4 points: medium-risk multidrug-resistant score; $\geqslant 5$ points: high-risk multidrug-resistant score.

patients admitted to ICUs increased by age group: 6% in the age group 65–74 years; 9% in the age group 75–84 years; and 14% in the age group >85 years. Microbial aetiology was defined in 14% of patients. *P. aeruginosa* was the most common pathogen (20%), followed by *Klebsiella pneumoniae* (15%), respiratory viruses (14%), *Escherichia coli* (10%), *Acinetobacter spp.*, (8%), *S. aureus* (7%), *S. pneumoniae* (3%) and atypical pathogens (0.6%).

FERRER *et al.* [84] analysed prognostic factors for severe CAP in 664 immunocompetent patients, 154 (23%) of whom were ventilated and 510 (77%) who were non-ventilated; the mean age was 72 years in the nonventilated group and 66 in the ventilated group. Microbial aetiology was established in 51% of patients. *S. pneumoniae* was the main pathogen in both groups, polymicrobial aetiology was more frequent in patients invasively ventilated and *Legionella pneumophila* was less frequent.

In a recent study about sepsis in very old patients with CAP, we observed that an aetiologic diagnosis was achieved more often in very old patients with sepsis compared to very old patients without sepsis (34% *versus* 27%; p=0.01) [26]. Although these data were not published, we found that the microbial aetiology was similar in very old patients admitted to general wards and those admitted to ICU. *S. pneumoniae* was the most frequent pathogen detected in both groups (43% *versus* 53%, p=0.094). Interestingly, polymicrobial aetiology was the second most frequent aetiology in very old patients admitted to ICU (10% *versus* 12%, p=0.44), whereas respiratory viruses were the second more frequent aetiology in very old patients hospitalised in general wards (18% *versus* 9%, p=0.0043).

An international study [85] recently found that risk factors independently associated with CAP due to Enterobacteriaceae were male sex, severe CAP, underweight (body mass index <18.5 kg·m⁻²) and previous ESBL infection. In addition, previous ESBL infection, being underweight, cardiovascular diseases and hospitalisation in the last 12 months were independently associated with MDR Enterobacteriaceae CAP.

In addition to MDR pathogens, microorganisms associated with aspiration pneumonia should be taken into account when approaching microbiologic diagnosis of CAP in very old patients. Aspiration pneumonia, frailty and dementia are tightly intertwined. Findings of pathogens potentially associated with aspiration in CAP occurring in the elderly widely vary and are probably underestimated overall [86].

In brief, CAP in very old patients is caused by the same microorganisms than other age groups. However, increasing age is a risk factor for Enterobacteriaceae and MDR pathogens. Other risk factors for MDR CAP, such as residence in nursing homes, previous colonisation or use of antibiotics, as well as the risk of aspiration pneumonia due to swallowing difficulties should be carefully assessed before instauration of empirical treatment and for deciding preventive contact isolation at admission among other measures. Risk scores, such as PES score, might be of utility but are not adapted to the very old patient population.

Principles for guiding empiric antimicrobial therapy of CAP in very old patients Antibiotic therapy in critically ill very old patients should take into account age-related changes in the tolerance, metabolism and excretion of antimicrobials, as well as drug-drug interactions [87].

Current international guidelines for the management of CAP patients [4, 88] do not provide a specific recommendation for critically ill very old patients. Table 2 summarises the antibiotic therapy recommended in patients with CAP requiring ICU admission.

Pneumonia severity	Moderate severity	High severity	
BTS guidelines	1. CURB65 score 2	1. CURB65 score 3-5	
	Treat with oral <i>/i.v.</i> amoxicillin +clarithromycin or doxycycline, moxifloxacin or levofloxacin	Treat with co-amoxiclav plus clarithromycin/ benzylpenicillin plus levofloxacin or ciprofloxacin/cephalosporine plus clarithromycin	
ATS/IDSA guidelines	 Direct admission to intensive care u and/or respiratory failur 	Direct admission to intensive care unit: septic shock requiring vasopressor support and/or respiratory failure requiring intubation and ventilation β-lactam plus a macrolide or fluoroquinolone	
	β-lactam plus a m		
BTS: British Th	noracic Society; ATS: American Thoraci	c Society; IDSA: Infectious Disease Society of	

TABLE 2 Guidelines for the management and treatment for community-acquired pneumonia

BTS: British Thoracic Society; ATS: American Thoracic Society; IDSA: Infectious Disease Society of America; CURB65: confusion, urea >7 mmol·L⁻¹, respiratory rate \geq 30 breaths·min⁻¹, blood pressure <90mmHg (systolic) \leq 60 mmHg (diastolic), age \geq 65 years.

As stated, the risk of aspiration should be assessed to decide whether an anaerobicidal agent might be included and risk factors for MRSA, *P. aeruginosa* and other Gram-negative bacilli should also be assessed when selecting antibiotic treatment. Furthermore, apart from the recommendations included in current guidelines, there are other options that might be advantageous for treating CAP in critically ill very old patients. For instance, new generation cephalosporines might play an important role in this setting. Ceftaroline is a fifth-generation cephalosporine. Compared to ceftriaxone, it provides better coverage against *S. pneumoniae* and *S. aureus* (both MRSA and methicillin-sensitive *Staphylococcus aureus*) in patients with CAP. Results from the Focus studies [89, 90] and the CAPTURE study [91] demonstrated its efficacy in older patients with CAP caused by one of these microorganisms. Ceftobiprole is also a new cephalosporin active against *S. pneumoniae*, *S. aureus* (MRSA and methicillin-sensitive *Staphylococcus aureus*) and a substantial proportion of *P. aeruginosa*. It is indicated in CAP [92] and hospital-acquired pneumonia but not ventilator-associated pneumonia. Ceftobiprole may be a reasonable option to cover *P. aeruginosa* in addition to *S. pneumoniae* and *S. aureus*. None of these cephalosporines is effective against ESBL Enterobacteriaceae.

There are other new antibiotics in the pipeline that due to their pharmacokinetic/pharmacodynamic properties, spectrum or tolerability might end up being added to the armamentarium for treating CAP in very old patients. AMALAKUHAN *et al.* [93] analysed solithromycin, pristinamycin, nemonoxacin, lefamulin, omadacycline, ceftobiprole and delafloxacin by applying to them the San Antonio NIPS Model (N: novelty of mechanism; I: avoidance of interactions and intolerance; P: favourable pharmacokinetic/pharmacodynamic profile; S: simplicity of dosing). Nemonoxacin and delafloxacin both had a high NIPS index.

Corticosteroids as adjunctive therapy

A randomised study that investigated the effect of corticosteroids on treatment failure among patients with severe CAP (according to ATS/IDSA criteria) with high inflammatory response (initial levels of CRP>15 mg·dL⁻¹) reported that treatment failure was less frequent in patients in the corticosteroid group (13%) compared to patients in the placebo group (31%; p=0.02) and in-hospital mortality was similar between groups (10% *versus* 15%; p=0.37) [94].

Several studies and meta-analyses have shown a reduction in the risk of progression to respiratory distress, a shorter time to clinical stability and a shorter duration of hospital stay in patients with severe CAP receiving adjunctive therapy with corticosteroids [95–97]. The latest ATS/IDSA guidelines do not routinely recommend the use of corticosteroids in adults with severe CAP (conditional recommendation, moderate quality of evidence). However, corticosteroids are suggested in CAP patients with refractory septic shock [4]. Nonetheless, there is no specific evidence available on the use of adjunctive corticosteroids in very old patients with CAP.

Sepsis as a complication in critically ill very old patients with CAP

A 2012 study assessing the impact on outcome of severe sepsis in which the most frequent site of infection was the lung (46%) showed large differences in ICU mortality by age group (46%, 61% and 79% for

<60 years, 60-80 years and very old patients, respectively). Moreover, age was the only variable independently associated with ICU mortality in the multivariate analysis (OR 1.038) [98].

A recent prospective multicentre study including 1490 patients from 77 ICUs in Spain investigated mortality risk factors in critically ill elderly (65–79 years) and very old patients with sepsis. The overall hospital mortality was 49% (n=727) and was significantly higher in very old patients compared to elderly patients (54% *versus* 47%; p=0.02). Predictors of hospital mortality in very old patients with sepsis were age, APACHE II score and prompt adherence to the resuscitation bundles. In 2016, MONTULL *et al.* [46] identified severe sepsis in 37% of 4070 CAP patients. The authors reported that severe sepsis CAP was independently associated with older age, alcohol abuse, COPD and renal disease, whereas previous antibiotic therapy was a protective factor. In another Spanish cohort study [26] that included 1238 very old patients with CAP, 71% presented with sepsis according to the Sepsis-3 definition. Male sex, chronic renal disease and diabetes mellitus were independent sepsis risk factors, while antibiotic therapy before admission was independently associated with a lower risk of sepsis. The authors also reported that in-hospital mortality was significantly higher in very old patients with sepsis than in nonseptic patients (15% *versus* 9%, p=0.006).

More recently, CILLÓNIZ *et al.* [99] investigated pure viral sepsis in CAP patients and reported that viral sepsis, defined according to the Sepsis-3 criteria, affected 19% of patients with a diagnosis of viral pneumonia admitted to ICUs. Interestingly, male sex and age \geq 65years were risk factors for pure viral sepsis; however, pure viral sepsis was not a risk factor for in-hospital mortality. In this study 9% of patients were critically ill very old patients and viral sepsis was present in 11% (data not published).

Critically ill very old patients presenting with CAP and sepsis must be quickly identified: the atypical presentation of pneumonia and sepsis in this subgroup of patients may alert physicians in order to reduce the complications associated with a delay in the start of the empiric antimicrobial therapy.

What is the relationship between hospital discharge and readmission?

The rate of 30-day readmission in very old patients varies from 8–27% [48, 100–102]. Unfortunately, there is limited information about readmission rates in critically ill very old patients with CAP. Readmission is related to preventable and nonpreventable factors. Two studies reported data on preventable factors, although were not specific for critically ill very old patients. In 2017, Dong *et al.* [100] investigated 2892 CAP patients, 15% of whom were readmitted; 40% were \geq 65 years and 33% of them were readmitted. In this group of patients, the distribution of discharge was as follows: home without services (43%); home with healthcare (26%); skilled nursing or subacute rehabilitation facility (16%); and acute rehabilitation or long-term acute care facility (15%). 20% of patients discharged with healthcare and 12% of patients discharged without home services were readmitted. Surprisingly, being discharged with healthcare was associated with a markedly greater risk of readmission in the multivariate regression model (OR 1.58, 95% CI 1.21–2.07). Interestingly, in 2015, FLAATTEN *et al.* [68] reported that among 1671 critically ill very old patients, 20% were discharged to a long-term care facility, 46% went home and 3% went to a rehabilitation facility. Unfortunately, the authors did not report the rate of readmission.

TOLEDO *et al.* [48] included 1756 patients with CAP, whose readmission rates were 28%, 49% and 23%, for age groups 65–74 years, 75–84 years and >84 years, respectively. The overall rate of readmission among ICU patients was 6%; however, percentages by age group were not reported. In the multivariate analysis of factors related to readmission, the only preventable factor was discharge with home healthcare (OR 5.61, 95% CI 1.70–18.50). The authors suggested an inadequate evaluation of patient stability at the time of hospital discharge as a possible explanation.

Overall, these data reflect the importance of discharge disposition as a factor related to readmission in critically ill very old patients with CAP, as well as the need to systematically report these variables in clinical studies.

Long-term outcomes in critically ill very old patients with CAP

During the past decade, several studies reported data about long-term consequences of CAP [103–111]. Major adverse cardiac events have been described during pneumonia hospitalisation and up to 10 years after an episode of CAP, with a prevalence ranging between 10% and 30%, especially in case of pneumococcal pneumonia, elderly patients and severe pneumonia [109, 112–117]. New-onset or worsening heart failure, arrhythmias, stroke and acute coronary syndrome can be an expression of major adverse cardiac events in CAP patients. In a non-human primate model of severe pneumococcal pneumonia, REYES *et al.* [112] showed that *Pneumococcus* invaded the myocardium and induced cardiac injury with necroptosis and apoptosis, followed by cardiac scarring after antibiotic therapy. CORRALES-MEDINA *et al.* [114] investigated the risk of heart failure after hospitalisation for CAP in elderly

patients (median age 77 years). The authors reported that the rate of new-onset heart failure increased following hospital discharge: 30–90 days: 3%; 91 days to 6 months: 6%; 6 months to 1 year: 9%; 1–5 years: 20%; and >5 years from hospital discharge: 31%.

HEYLAND *et al.* [118] evaluated 12-month outcomes in critically ill very old patients after ICU discharge. The study included 610 critically ill very old patients admitted to ICU for at least 24 h. ICU, hospital and 12 months after ICU admission mortality were 14%, 26% and 44%, respectively. 75% of critically ill very old patients admitted to ICU survived and returned to their basic levels of physical function at 1 year.

The study by FERRANTE *et al.* [119] evaluated the relationship between frailty and post-ICU disability in 266 elderly and very old patients (mean age 84 years) admitted to ICU. The authors reported that frailty, prefrailty and nonfrailty were present in 45%, 43% and 12% of patients, respectively. In the multivariable analysis, frailty was associated with 41% greater disability over the 6 months following a critical illness compared to nonfrailty, whereas prefrailty conferred a 28% greater risk of post-ICU disability compared to nonfrailty. Mortality 6 months after ICU admission was twice as high among participants with frailty (55%) compared to those who were prefrail (25%) or nonfrail (26%).

Advanced age is known to be associated with high-risk of long-term mortality. In 2011, ROCH *et al.* [20] evaluated factors influencing short- and long-term outcomes in 299 critically ill very old patients following ICU admission. The authors reported 46% of ICU mortality and 55% of hospital mortality. A higher SAPS II score at ICU admission, the existence of a fatal disease (as reflected by the McCabe score), and a cardiac diagnosis at admission were associated with hospital mortality. 1- and 2-year mortality rates were 72% and 79%, respectively.

A French study of 317 critically ill very old patients reported that 6-month and 1-year mortality after discharge were 56% and 70%, respectively [17]. Another study from Germany, including 372 critically ill very old patients [120], reported that in the overall population 3 months and 1 year after discharge survival was 53% and 35%, respectively. In patients aged \geq 65 years with CAP, mortality at 6 months was reported to be 19% and mortality at 1 year was 41% [107, 121]. In a study published by our research group [26] we reported 22% of 1-year mortality in very old patients with sepsis secondary to CAP.

Vaccination and other prevention measures for CAP in very old patients Current international guidelines recommend specific measures for preventing CAP [4, 73, 88, 122]. The use of pneumococcal vaccines (polysaccharide and conjugate) and influenza vaccines are the most important of these. Intervention in the lifestyle for modifiable risk factors for CAP will also help to reduce the risk of pneumonia in very old patients [123]. Figure 4 summarises the main prevention measures for CAP.



Pneumococal vaccines: two vaccines are currently available: the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococal polysaccharide vaccine (PPSV23).

Influenza vaccine: annual vaccination is recommended.

Lifestyle interventions: stopping smoking, reducing alcohol consumption, having regular dental checks and maintaining good nutritional status, try to minimise contact with children who have acute viral respiratory infections.

FIGURE 4 Prevention of community-acquired pneumonia.

Conclusion

The burden of CAP among critically ill very old patients is high, encompassing significant morbidity, mortality and health costs worldwide. The presence of multiple comorbidities, polypharmacy and frailty characterises these patients and increases the risk of infectious diseases, such as pneumonia. Early recognition and diagnosis of CAP and its complications, such as sepsis, allows for the prompt initiation of the antibiotic therapy. However, due to its atypical presentation in very old patients, the diagnosis of pneumonia may be difficult in some cases. Preventive interventions are of pivotal importance to improve outcomes and reduce the occurrence of adverse consequences.

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References

- 1 Cillóniz C, Liapikou A, Martin-Loeches I, *et al.* Twenty-year trend in mortality among hospitalized patients with pneumococcal community-acquired pneumonia. *PLoS One* 2018; 13: e0200504.
- 2 Arnold FW, Wiemken TL, Peyrani P, *et al.* Mortality differences among hospitalized patients with community-acquired pneumonia in three world regions: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study. *Respir Med* 2013; 107: 1101–1111.
- 3 Restrepo MI, Faverio P, Anzueto A. Long-term prognosis in community-acquired pneumonia. *Curr Opin Infect Dis* 2013; 26: 151–158.
- 4 Metlay JP, Waterer GW, Long AC, *et al.* Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; 200: e45–e67.
- 5 World Health Organization. Men Ageing and Health. Achieving Health Across the Life Span. Geneva, WHO, 1999.
- 6 Laporte L, Hermetet C, Jouan Y, *et al.* Ten-year trends in intensive care admissions for respiratory infections in the elderly. *Ann Intensive Care* 2018; 8: 84.
- 7 Krone CL, van de Groep K, Trzciński K, *et al.* Immunosenescence and pneumococcal disease: an imbalance in host-pathogen interactions. *Lancet Respir Med* 2014; 2: 141–153.
- 8 Weir DL, Majumdar SR, McAlister FA, *et al.* The impact of multimorbidity on short-term events in patients with community-acquired pneumonia: prospective cohort study. *Clin Microbiol Infect* 2015; 21: 264.e7–264.e13.
- 9 Xue Q-L. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011; 27: 1–15.
- 10 Cillóniz C, Rodríguez-Hurtado D, Torres A. Characteristics and management of community-acquired pneumonia in the era of global aging. *Med Sci (Basel)* 2018; 6: E35.
- 11 Luna CM, Palma I, Niederman MS, et al. The impact of age and comorbidities on the mortality of patients of different age groups admitted with community-acquired pneumonia. Ann Am Thorac Soc 2016; 13: 1519–1526.
- 12 Mangen M-JJ, Huijts SM, Bonten MJM, *et al.* The impact of community-acquired pneumonia on the health-related quality-of-life in elderly. *BMC Infect Dis* 2017; 17: 208.
- 13 Nielsson MS, Christiansen CF, Johansen MB, et al. Mortality in elderly ICU patients: a cohort study. Acta Anaesthesiol Scand 2014; 58: 19–26.
- 14 Fuchs L, Chronaki CE, Park S, et al. ICU admission characteristics and mortality rates among elderly and very elderly patients. Intensive Care Med 2012; 38: 1654–1661.
- 15 Rozenbaum MH, Mangen M-JJ, Huijts SM, *et al.* Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: a nationwide retrospective claims database analysis. *Vaccine* 2015; 33: 3193–3199.
- 16 McLaughlin JM, Johnson MH, Kagan SA, et al. Clinical and economic burden of community-acquired pneumonia in the Veterans Health Administration, 2011: a retrospective cohort study. Infection 2015; 43: 671–680.
- 17 Le Borgne P, Maestraggi Q, Couraud S, *et al.* Critically ill elderly patients (≥90 years): Clinical characteristics, outcome and financial implications. *PLoS One* 2018; 13: e0198360.
- 18 Bagshaw SM, Webb SAR, Delaney A, *et al.* Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Crit Care* 2009; 13: R45.
- 19 Reinikainen M, Uusaro A, Niskanen M, *et al.* Intensive care of the elderly in Finland. *Acta Anaesthesiol Scand* 2007; 51: 522–529.
- 20 Roch A, Wiramus S, Pauly V, *et al.* Long-term outcome in medical patients aged 80 or over following admission to an intensive care unit. *Crit Care* 2011; 15: R36.
- 21 Tabah A, Philippart F, Timsit JF, *et al.* Quality of life in patients aged 80 or over after ICU discharge. *Crit Care* 2010; 14: R2.
- 22 Pavoni V, Gianesello L, Paparella L, *et al.* Outcome and quality of life of elderly critically ill patients: an Italian prospective observational study. *Arch Gerontol Geriatr* 2012; 54: e193–e198.
- 23 Andersen FH, Kvåle R. Do elderly intensive care unit patients receive less intensive care treatment and have higher mortality? Acta Anaesthesiol Scand 2012; 56: 1298–1305.

- 24 Flaatten H, de Lange DW, Artigas A, *et al.* The status of intensive care medicine research and a future agenda for very old patients in the ICU. *Intensive Care Med* 2017; 43: 1319–1328.
- 25 Martin-Loeches I, Guia MC, Vallecoccia MS, *et al.* Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicenter cohort study. *Ann Intensive Care* 2019; 9: 26.
- 26 Cilloniz C, Dominedò C, Ielpo A, *et al.* Risk and prognostic factors in very old patients with sepsis secondary to community-acquired pneumonia. *J Clin Med* 2019; 8: E961.
- 27 Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. *Transpl Int* 2009; 22: 1041–1050.
- 28 Gutiérrez F, Masiá M. Improving outcomes of elderly patients with community-acquired pneumonia. Drugs Aging 2008; 25: 585-610.
- 29 Cilloniz C, Ceccato A, San Jose A, et al. Clinical management of community acquired pneumonia in the elderly patient. Expert Rev Respir Med 2016; 10: 1211–1220.
- 30 Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest* 2006; 130: 11–15.
- 31 Zhang ZX, Yong Y, Tan WC, *et al.* Prognostic factors for mortality due to pneumonia among adults from different age groups in Singapore and mortality predictions based on PSI and CURB-65. *Singapore Med J* 2018; 59: 190–198.
- 32 Riquelme R, Riquelme M, Rioseco ML, et al. [Community-acquired pneumonia in the elderly: clinical and nutritional aspects]. Rev Med Chil 2008; 136: 587–593.
- 33 Saldías Peñafiel F, O'Brien Solar A, Gederlini Gollerino A, et al. [Community-acquired pneumonia requiring hospitalization in immunocompetent elderly patients: clinical features, prognostic factors and treatment]. Arch Bronconeumol 2003; 39: 333–340.
- 34 González Del Castillo J, Martín-Sánchez FJ, Llinares P, *et al.* [Consensus guidelines for the management of community acquired pneumonia in the elderly patient]. *Rev Esp Geriatr Gerontol* 2014; 49: 279–291.
- 35 Murray MA, Chotirmall SH. The impact of immunosenescence on pulmonary disease. *Mediators Inflamm* 2015; 2015: 692546.
- 36 Solana R, Tarazona R, Gayoso I, *et al.* Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. *Semin Immunol* 2012; 24: 331–341.
- 37 Nouvenne A, Ticinesi A, Folesani G, et al. The association of serum procalcitonin and high-sensitivity C-reactive protein with pneumonia in elderly multimorbid patients with respiratory symptoms: retrospective cohort study. BMC Geriatr 2016; 16: 16.
- 38 Azoulay E, Vincent J-L, Angus DC, et al. Recovery after critical illness: putting the puzzle together a consensus of 29. Crit Care 2017; 21: 296.
- 39 World Health Organization. Ageing and Health. www.who.int/news-room/fact-sheets/detail/ageing-and-health Date last accessed: 12 March 2019. Date last updated: 05 May 2018.
- Cruz-Jentoft AJ, Kiesswetter E, Drey M, et al. Nutrition, frailty, and sarcopenia. Aging Clin Exp Res 2017; 29: 43–48.
 Martinez BP, Batista AKMS, Gomes IB, et al. Frequency of sarcopenia and associated factors among hospitalized elderly patients. BMC Musculoskelet Disord 2015; 16: 108.
- 42 Tanimoto Y, Watanabe M, Sun W, *et al.* Association between sarcopenia and higher-level functional capacity in daily living in community-dwelling elderly subjects in Japan. *Arch Gerontol Geriatr* 2012; 55: e9–e13.
- 43 Altuna-Venegas S, Aliaga-Vega R, Maguiña JL, *et al.* Risk of community-acquired pneumonia in older adults with sarcopenia of a hospital from Callao, Peru 2010–2015. *Arch Gerontol Geriatr* 2019; 82: 100–105.
- 44 Cillóniz Č, Polverino E, Ewig S, *et al.* Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest* 2013; 144: 999–1007.
- 45 Kofteridis DP, Giourgouli G, Plataki MN, *et al.* Community-acquired pneumonia in elderly adults with type 2 diabetes mellitus. *J Am Geriatr Soc* 2016; 64: 649–651.
- 46 Montull B, Menéndez R, Torres A, et al. Predictors of severe sepsis among patients hospitalized for community-acquired pneumonia. PLoS One 2016; 11: e0145929.
- 47 Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: an overview. *World J Crit Care Med* 2012; 1: 23–30.
- 48 Toledo D, Soldevila N, Torner N, *et al.* Factors associated with 30-day readmission after hospitalisation for community-acquired pneumonia in older patients: a cross-sectional study in seven Spanish regions. *BMJ Open* 2018; 8: e020243.
- 49 Millett ERC, De Stavola BL, Quint JK, et al. Risk factors for hospital admission in the 28 days following a community-acquired pneumonia diagnosis in older adults, and their contribution to increasing hospitalisation rates over time: a cohort study. BMJ Open 2015; 5: e008737.
- 50 Lin C-J, Chang Y-C, Tsou M-T, *et al.* Factors associated with hospitalization for community-acquired pneumonia in home health care patients in Taiwan. *Aging Clin Exp Res* 2020:32; 149–155.
- 51 Yeo HJ, Byun KS, Han J, *et al.* Prognostic significance of malnutrition for long-term mortality in community-acquired pneumonia: a propensity score matched analysis. *Korean J Intern Med* 2019; 34: 841–849.
- 52 Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet 2013; 381: 752–762.
- 53 Collard RM, Boter H, Schoevers RA, *et al.* Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012; 60: 1487–1492.
- 54 Flaatten H, De Lange DW, Morandi A, et al. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥80 years). Intensive Care Med 2017; 43: 1820–1828.
- 55 Rockwood K, Song X, MacKnight C, *et al.* A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173: 489–495.
- 56 Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018; 391: 1775–1782.
- 57 Eckart A, Hauser SI, Haubitz S, *et al.* Validation of the hospital frailty risk score in a tertiary care hospital in Switzerland: results of a prospective, observational study. *BMJ Open* 2019; 9: e026923.
- 58 Guidet B, Vallet H, Boddaert J, et al. Caring for the critically ill patients over 80: a narrative review. Ann Intensive Care 2018; 8: 114.

- 59 Faulkner CM, Cox HL, Williamson JC. Unique aspects of antimicrobial use in older adults. *Clin Infect Dis* 2005; 40: 997–1004.
- 60 Corsonello A, Abbatecola AM, Fusco S, *et al.* The impact of drug interactions and polypharmacy on antimicrobial therapy in the elderly. *Clin Microbiol Infect* 2015; 21: 20–26.
- 61 Gamble J-M, Hall JJ, Marrie TJ, *et al.* Medication transitions and polypharmacy in older adults following acute care. *Ther Clin Risk Manag* 2014; 10: 189–196.
- 62 Hoffman KR, Loong B, Haren FV. Very old patients urgently referred to the intensive care unit: long-term outcomes for admitted and declined patients. *Crit Care Resusc* 2016; 18: 157–164.
- 63 Fine MJ, Auble TE, Yealy DM, *et al*. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
- 64 Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in community acquired pneumonia: a validation study. *Thorax* 2000; 55: 219–223.
- 65 Sprung CL, Artigas A, Kesecioglu J, *et al.* The Eldicus prospective, observational study of triage decision making in European intensive care units. Part II: intensive care benefit for the elderly. *Crit Care Med* 2012; 40: 132–138.
- 66 Andersen FH, Flaatten H, Klepstad P, *et al.* Long-term outcomes after ICU admission triage in octogenarians. *Crit Care Med* 2017; 45: e363–e371.
- 67 Storms AD, Chen J, Jackson LA, *et al.* Rates and risk factors associated with hospitalization for pneumonia with ICU admission among adults. *BMC Pulm Med* 2017; 17: 208.
- 68 Heyland D, Cook D, Bagshaw SM, et al. The very elderly admitted to ICU: a quality finish? Crit Care Med 2015; 43: 1352–1360.
- 69 Valley TS, Sjoding MW, Ryan AM, *et al.* Association of intensive care unit admission with mortality among older patients with pneumonia. *JAMA* 2015; 314: 1272–1279.
- 70 Chen J-H, Chang S-S, Liu JJ, et al. Comparison of clinical characteristics and performance of pneumonia severity score and CURB-65 among younger adults, elderly and very old subjects. Thorax 2010; 65: 971–977.
- 71 Sanz F, Morales-Suárez-Varela M, Fernández E, et al. A composite of functional status and pneumonia severity index improves the prediction of pneumonia mortality in older patients. J Gen Intern Med 2018; 33: 437–444.
- 72 Charles PGP, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis 2008; 47: 375–384.
- 73 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44: Suppl. 2, S27–S72.
- 74 de Lange DW, Brinkman S, Flaatten H, *et al.* Cumulative prognostic score predicting mortality in patients older than 80 years admitted to the ICU. *J Am Geriatr Soc* 2019; 67: 1263–1267.
- 75 Blanch L, Abillama FF, Amin P, *et al.* Triage decisions for ICU admission: report from the Task Force of the World Federation of Societies of Intensive and Critical Care Medicine. *J Crit Care* 2016; 36: 301–305.
- 76 Bassford C. Decisions regarding admission to the ICU and international initiatives to improve the decision-making process. Crit Care 2017; 21: 174.
- 77 Capuzzo M, Volta C, Tassinati T, *et al.* Hospital mortality of adults admitted to intensive care units in hospitals with and without intermediate care units: a multicentre European cohort study. *Crit Care* 2014; 18: 551.
- 78 Leblanc G, Boumendil A, Guidet B. Ten things to know about critically ill elderly patients. *Intensive Care Med* 2017; 43: 217–219.
- Fung HB, Monteagudo-Chu MO. Community-acquired pneumonia in the elderly. Am J Geriatr Pharmacother 2010; 8: 47–62.
- 80 Fernández-Sabé N, Carratalà J, Rosón B, *et al.* Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. *Medicine (Baltimore)* 2003; 82: 159–169.
- 81 Gross AE, Van Schooneveld TC, Olsen KM, et al. Epidemiology and predictors of multidrug-resistant community-acquired and health care-associated pneumonia. Antimicrob Agents Chemother 2014; 58: 5262–5268.
- 82 Prina E, Ranzani OT, Polverino E, *et al.* Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. *Ann Am Thorac Soc* 2015; 12: 153–160.
- 83 Han X, Zhou F, Li H, et al. Effects of age, comorbidity and adherence to current antimicrobial guidelines on mortality in hospitalized elderly patients with community-acquired pneumonia. BMC Infect Dis 2018; 18: 192.
- 84 Ferrer M, Travierso C, Cilloniz C, *et al.* Severe community-acquired pneumonia: characteristics and prognostic factors in ventilated and non-ventilated patients. *PLoS One* 2018; 13: e0191721.
- 85 Villafuerte D, Aliberti S, Soni NJ, et al. Prevalence and risk factors for Enterobacteriaceae in patients hospitalized with community-acquired pneumonia. Respirology 2019; in press [https://doi.org/10.1111/resp.13663].
- 86 Simonetti AF, Viasus D, Garcia-Vidal C, *et al.* Management of community-acquired pneumonia in older adults. *Ther Adv Infect Dis* 2014; 2: 3–16.
- 87 Viasus D, Núñez-Ramos JA, Viloria SA, et al. Pharmacotherapy for community-acquired pneumonia in the elderly. Expert Opin Pharmacother 2017; 18: 957–964.
- 88 Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community-acquired pneumonia in adults: update 2009. Thorax 2009; 64: Suppl. 3, iii1–ii55.
- 89 File TM, Low DE, Eckburg PB, *et al.* FOCUS 1: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil *versus* ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother* 2011; 66: iii19–iii32.
- 90 Low DE, File TM, Eckburg PB, *et al.* FOCUS 2: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil *versus* ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother* 2011; 66: Suppl. 3, iii33–iii44.
- 91 Udeani G, Evans J, Cole P, *et al.* Ceftaroline fosamil for the treatment of community-acquired bacterial pneumonia in elderly patients. *Hosp Pract* (1995) 2014; 42: 109–115.
- 92 Nicholson SC, Welte T, File TM, *et al.* A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. *Int J Antimicrob Agents* 2012; 39: 240–246.
- 93 Amalakuhan B, Echevarria KL, Restrepo MI. Managing community-acquired pneumonia in the elderly the next generation of pharmacotherapy on the horizon. *Expert Opin Pharmacother* 2017; 18: 1039–1048.

- 94 Torres A, Sibila O, Ferrer M, *et al.* Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015; 313: 677–686.
- 95 Siemieniuk RAC, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. Ann Intern Med 2015; 163: 519–528.
- 96 Wan Y-D, Sun T-W, Liu Z-Q, *et al.* Efficacy and safety of corticosteroids for community-acquired pneumonia: a systematic review and meta-analysis. *Chest* 2016; 149: 209–219.
- 97 Bi J, Yang J, Wang Y, *et al.* Efficacy and safety of adjunctive corticosteroids therapy for severe community-acquired pneumonia in adults: an updated systematic review and meta-analysis. *PLoS One* 2016; 11: e0165942.
- 98 Nasa P, Juneja D, Singh O, et al. Severe sepsis and its impact on outcome in elderly and very elderly patients admitted in intensive care unit. J Intensive Care Med 2012; 27: 179–183.
- 99 Cillóniz C, Dominedò C, Magdaleno D, *et al.* Pure viral sepsis secondary to community-acquired pneumonia in adults: risk and prognostic factors. *J Infect Dis* 2019; 220: 1166–1171.
- 100 Dong T, Cursio JF, Qadir S, et al. Discharge disposition as an independent predictor of readmission among patients hospitalised for community-acquired pneumonia. Int J Clin Pract 2017; 71: e12935.
- 101 Neupane B, Walter SD, Krueger P, *et al.* Predictors of in-hospital mortality and re-hospitalization in older adults with community-acquired pneumonia: a prospective cohort study. *BMC Geriatr* 2010; 10: 22.
- 102 Jain S, Khera R, Mortensen EM, *et al.* Readmissions of adults within three age groups following hospitalization for pneumonia: Analysis from the Nationwide Readmissions Database. *PLoS One* 2018; 13: e0203375.
- 103 Bordon J, Wiemken T, Peyrani P, *et al.* Decrease in long-term survival for hospitalized patients with community-acquired pneumonia. *Chest* 2010; 138: 279–283.
- 104 Girard TD, Self WH, Edwards KM, et al. Long-term cognitive impairment after hospitalization for community-acquired pneumonia: a prospective cohort study. J Gen Intern Med 2018; 33: 929–935.
- 105 Eurich DT, Marrie TJ, Minhas-Sandhu JK, *et al.* Ten-year mortality after community-acquired pneumonia. A prospective cohort. *Am J Respir Crit Care Med* 2015; 192: 597–604.
- 106 Johnstone J, Eurich DT, Majumdar SR, *et al.* Long-term morbidity and mortality after hospitalization with community-acquired pneumonia: a population-based cohort study. *Medicine (Baltimore)* 2008; 87: 329–334.
- 107 Kaplan V, Angus DC, Griffin MF, et al. Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med 2002; 165: 766–772.
- 108 Yende S, Angus DC, Ali IS, *et al.* Influence of comorbid conditions on long-term mortality after pneumonia in older people. *J Am Geriatr Soc* 2007; 55: 518–525.
- 109 Eurich DT, Marrie TJ, Minhas-Sandhu JK, et al. Risk of heart failure after community acquired pneumonia: prospective controlled study with 10 years of follow-up. BMJ 2017; 356: j413.
- 110 Mortensen EM, Kapoor WN, Chang C-CH, et al. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. Clin Infect Dis 2003; 37: 1617–1624.
- 111 Sundin P-O, Udumyan R, Fall K, *et al.* Hospital admission with pneumonia and subsequent persistent risk of chronic kidney disease: national cohort study. *Clin Epidemiol* 2018; 10: 971–979.
- 112 Reyes LF, Restrepo MI, Hinojosa CA, et al. Severe pneumococcal pneumonia causes acute cardiac toxicity and subsequent cardiac remodeling. Am J Respir Crit Care Med 2017; 196: 609-620.
- 113 Corrales-Medina VF, Alvarez KN, Weissfeld LA, *et al.* Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA* 2015; 313: 264–274.
- 114 Corrales-Medina VF, Taljaard M, Yende S, *et al.* Intermediate and long-term risk of new-onset heart failure after hospitalization for pneumonia in elderly adults. *Am Heart J* 2015; 170: 306–312.
- 115 Violi F, Cangemi R, Falcone M, *et al.* Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. *Clin Infect Dis* 2017; 64: 1486–1493.
- 116 Cangemi R, Calvieri C, Falcone M, et al. Relation of cardiac complications in the early phase of community-acquired pneumonia to long-term mortality and cardiovascular events. Am J Cardiol 2015; 116: 647–651.
- 117 Restrepo MI, Reyes LF. Pneumonia as a cardiovascular disease. *Respirology* 2018; 23: 250–259.
- 118 Heyland DK, Garland A, Bagshaw SM, *et al.* Recovery after critical illness in patients aged 80 years or older: a multi-center prospective observational cohort study. *Intensive Care Med* 2015; 41: 1911–1920.
- 119 Ferrante LE, Pisani MA, Murphy TE, et al. The association of frailty with post-ICU disability, nursing home admission, and mortality: a longitudinal study. Chest 2018; 153: 1378–1386.
- 120 Becker S, Müller J, de Heer G, *et al.* Clinical characteristics and outcome of very elderly patients ≥90 years in intensive care: a retrospective observational study. *Ann Intensive Care* 2015; 5: 53.
- 121 Klapdor B, Ewig S, Pletz MW, *et al.* Community-acquired pneumonia in younger patients is an entity on its own. *Eur Respir J* 2012; 39: 1156–1161.
- 122 Arnold FW, LaJoie AS, Brock GN, *et al.* Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. *Arch Intern Med* 2009; 169: 1515–1524.
- 123 Torres A, Peetermans WE, Viegi G, *et al.* Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013; 68: 1057–1065.