Rethinking the concepts of community-acquired and health-care-associated pneumonia

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The increasing numbers of patients who are elderly and severely disabled has led to the introduction of a new category of pneumonia management: health-care-associated pneumonia (HCAP). An analysis of the available evidence in support of this category, however, reveals heterogeneous and misleading definitions of HCAP, reliance on microbiological data of questionable validity, failure to recognise the contribution of aspiration pneumonia, failure to control microbial patterns for functional status, and failure to recognise frequently applied restrictions of treatment escalation as bias in assessing outcomes. As a result, the concept of HCAP contributes to confusion more than it provides a guide to pneumonia management, and it potentially leads to overtreatment. We suggest a reassignment of the criteria for HCAP to reconstruct the triad of community-acquired pneumonia (with a recognised core group of elderly and disabled patients and a subgroup of younger patients), hospital-acquired pneumonia, and pneumonia in immunosuppressed patients.

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Introduction

The 2005 update of the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guidelines on nosocomial pneumonia[1] introduced the new term health-care-associated pneumonia (HCAP). On the basis of data published at the same time as the guidelines, a population with frequent or chronic contact with health care was found to be at risk of multidrug-resistant pathogens frequently not covered in empirical initial antimicrobial treatment recommended in guidelines for the management of community-acquired pneumonia. Mortality was around 20%, twice as high as that in patients with community-acquired pneumonia and almost as high as that in non-ventilated patients with nosocomial pneumonia.[2] The recommendation of the guidelines was to treat patients classified as having HCAP intensively with a combination of broad-spectrum antimicrobial drugs, which is similar to recommended treatment for patients at risk of multidrug-resistant pneumonia.[1]

Since the publication of the 2005 guidelines, nine studies have provided original data on HCAP,[2–10] one of these studies is an abstract,[10] and only two were prospective.[6,10] However, 14 published reviews[11–24] suggest widespread acceptance of HCAP. In view of the worldwide threat of increasing resistance to antimicrobial drugs, acceptance of HCAP without good evidence would increase the use of antimicrobial drugs and produce selection pressure for drug-resistant organisms. Therefore, a critical review of available data to put the clinical problems underlying HCAP into perspective is needed.

Until recently, the basic classification of pneumonia was as the triad of community-acquired pneumonia, hospital-acquired pneumonia, and pneumonia in immunosuppressed patients. Table 1 lists the core elements of the definition of these types of pneumonia. These types of pneumonia are not solely a textbook classification but also a clinical concept. The classification incorporates two principal notions: first, host immunity (and the types of immunosuppression) and environment of pneumonia acquisition are associated with a predictable microbial spectrum; and, second, empirical initial antimicrobial treatment can rely on a predictable microbial spectrum.

Although the triad was clearly a simplification with uncertainties at the edges of these definitions (and the need to take into account severity, local epidemiology, and particular risk factors), the concept worked in clinical practice: it allowed clinicians to be confident when making important clinical decisions.

Challenges to the concept of community-acquired pneumonia

The first challenge to the concept of community acquired pneumonia was the emergence of the new entity, so-called community-acquired pneumonia in the elderly, in view of the increasing number of elderly patients with pneumonia.[25–33] Disease in elderly patients seemed to differ in microbial spectrum. However, there were conflicting results. In general, studies from the USA had an increased incidence of Gram-negative Enterobacteriaceae (and, in part, *Pseudomonas aeruginosa*)[30,34] compared with that found in studies elsewhere.[26,27,31] Some studies focused on community-acquired pneumonia in the very elderly (ie, aged 80 years and more) without substantially different results,[34–36] and some suggested functional status was the main determinant of outcome rather than age.[37–38]

Another approach to a similar, but not identical, population was to study nursing-home-acquired pneumonia.[39–48] Patients residing in nursing homes were thought to be at increased risk of Gram-positive or Gram-negative multidrug-resistant pathogens. Again, results differed substantially but with similar trends in studies from inside and outside the USA. Conforming to the definitions listed (table 1), the concept of nursing-home acquired pneumonia changed both elements of definition: the host at risk and the environment of pneumonia acquisition. The host at risk remained ambiguous, since it would usually mean elderly patients and, to some extent, severely disabled patients. The environment also

	Host*	Environment
Community-acquired pneumonia	Immunocompetent	Community
Hospital-acquired pneumonia†	Immunocompetent	Hospital
Pneumonia in patients that are immunosuppressed‡	Immunosuppressed	Community or hospital

*Immunosuppression is difficult to define, but usually refers to a relevant risk for opportunistic pathogens. †Including hospital-acquired pneumonia in patients who are non-ventilated (non-ventilator-associated pneumonia) and ventilated (ventilator-associated pneumonia), with or without tracheostoma. ‡Including iatrogenic immunosuppression (eg, steroids), inherited immunosuppression, solid-organ transplantation, neutropenia or stem-cell transplantation, and HIV/AIDS.

***Table 1*: Definitions of the three types of pneumonia**

remained uncertain, because nursing homes are not specified in terms of the type of care provided. Finally, pneumonia acquired within home care was thought different from community-acquired pneumonia.[49]

For the reasons above, the definitions of community-acquired pneumonia in the elderly and nursing-home acquired pneumonia were not generally accepted as separate categories of pneumonia, and patients continued to be included in the community-acquired pneumonia concept (table 2), with substantial overlaps, in a manner not satisfactorily settled.

HCAP—the reference data

Data supporting the concept of HCAP were derived from a retrospective 2-year (2002–03) cohort analysis in 59 US hospitals in 4543 non-immunosuppressed patients with pneumonia (table 3).[2] Microbiological data were culture results from the first 5 days after admission to hospital. The analysis resulted in three main messages: HCAP was frequent (988 patients; 21·9%); many patients had Enterobacteriaceae and multidrug-resistant pathogens (ie, 26·5% meticillin-resistant *Staphylococcus aureus* [MRSA], 25·3% *P aeruginosa*, 2·6% *Acinetobacter* spp, and 25·8% Enterobacteriaceae); and mortality was high, 19·8% compared with 10% in community-acquired and 18·8% in hospital-acquired pneumonia, reaching 29·3% in ventilator-associated pneumonia. Length of stay and cost were also substantially increased compared with community-acquired pneumonia. The investigators concluded that "the present analysis justified HCAP as a new category of pneumonia".

A detailed analysis of these data, however, seriously challenges the main conclusions drawn from this study.[2] First, the definition of a health-care facility was unclear. Second, numbers of Enterobacteriaceae and multidrug-resistant pathogens were unexpectedly high. Even more concerning, when looking at the microbial patterns of patients with community-acquired pneumonia, similar high frequencies of Enterobacteriaceae and multidrug-resistant pathogens (8·9% MRSA, 17·1% *P aeruginosa*, 1·6% *Acinetobacter* spp, and 21·3% Enterobacteriaceae), as well as *Streptococcus pneumoniae* and *S aureus* (16·6% and 25·5%) were noted. To our knowledge, comparable microbial patterns in community-acquired pneumonia have not previously been reported. If these data were to be accepted as presented, the most evident conclusion would be to reject the concept of community-acquired pneumonia as a whole, since the risk of inadequate treatment from complying with existing guidelines would be extremely high, and to recommend triple to quadruple treatment for all patients that are admitted to hospital. Finally, only patients with culture-positive results were entered into the analysis, which might be accurate for the microbiological analysis but not for the comparison of outcomes.

A subsequent retrospective cohort analysis reporting the experience in a single centre in St Louis (MO, USA) was based on very similar methods.[3] The analysis covered 3-years (2003–05), merged data from the hospital and microbiological database and pharmacy records, and assessed all culture-positive patients within the first 2 days of admission to hospital. However, the definition of HCAP was clarified and widely extended (table 3). Many types of immunosuppression (including chemotherapy for cancer treatment) were introduced as new criteria. On the basis of this definition, HCAP was very common (67·4% of all cases), had similar differences in microbial patterns to those of community-acquired pneumonia (MRSA 30·6%, *P aeruginosa* 25·5%, other

	Host	Environment
Community-acquired pneumonia	Immunocompetent	Community
Community-acquired pneumonia in the elderly	Age >60 years (community) or >65 years; immunocompetent; functional status undefined	Community or nursing home*
Community-acquired pneumonia in the very elderly	Age >80 years; immunocompetent; functional status undefined	Community or nursing home*
Community-acquired pneumonia in the functionally impaired	Usually elderly without defined threshold; immunocompetent; functional status impaired	Community or nursing home†
Nursing-home-acquired pneumonia	Usually elderly without defined threshold; immunocompetent; functional status undefined	Nursing home

*Most studies did not exclude residents of nursing homes. †Typically most are residents of nursing homes.

***Table 2*: Concepts of community-acquired pneumonia**

	Host	Environment	Hospital exposure	Immunosuppression
ATS/IDSA guideline update (2005)[1]	Home-infusion therapy, chronic dialysis within 30 days, home wound care	Nursing home, extended-care facility, family member with multidrug-resistant pathogen	Previous admission to hospital for at least 2 days in the past 3 months	..
Kolleff et al (2006)[2]	Long-term haemodialysis	Transfer from health-care facility	Admission to hospital in the past 3 months	..
Micek et al (2007)[3]	Outpatient dialysis, peritoneal dialysis, infusion therapy necessitating regular visits to a hospital-based clinic	Nursing home, rehabilitation hospital, other long-term nursing facility	Admission to hospital in the past 12 months	Corticosteroids (5 mg/day or more), HIV infection, solid organ or bone-marrow transplant, radiation or chemotherapy for cancer in the past 6 months, inherited or acquired immunodeficiency (eg, common variable immunodeficiency)
Carratalà et al (2007)[6]	Intravenous treatment at home, self-administered intravenous therapy 30 days before pneumonia, attended at hospital or haemodialysis clinic	Wound care or specialised nursing care through a health-care agency, family, or friends; residence in nursing home or long-term care facility	Admission to hospital in the past 90 days	Intravenous chemotherapy 30 days before pneumonia
Venditti et al (2009)[7]	Haemodialysis in the past 30 days	Residence in nursing home or long-term care facility	Admission to hospital in the past 30 days, admission to acute-care hospital for 2 days or longer or surgery in the past 180 days	Intravenous chemotherapy in the past 30 days
Shindo et al (2009)[8]	Home-infusion therapy, chronic dialysis within 30 days, wound care at home	Nursing home, extended-care facility	Admission to hospital for at least 2 days in the past 3 months	..

HCAP=health-care-associated pneumonia. ATS/IDSA=American Thoracic Society and Infectious Diseases Society of America.

***Table* 3: Definitions of HCAP used in the ATS/IDSA guideline and different studies according to four criteria**

non-fermenters 1·9%, and Enterobacteriaceae 19·7%), and was associated with inadequate initial antimicrobial treatment of 28·3% and mortality of 24·6%.

Like the 2002–03 study, this report lacked microbiological quality control. It also included only culture-positive patients in outcome analysis. Unfortunately, the study contaminated the community-acquired pneumonia or HCAP group with pneumonia in patients with any type of immunosuppression.

In a study dedicated specifically to HCAP caused by *S aureus*,[5] 28 patients (including 16 meeting HCAP criteria, eight of these with primary pneumonia) monitored during 2 years (2000–02) were analysed retrospectively. Compared with patients with community-acquired pneumonia, patients with HCAP were older, more acutely severely ill, and had greater mortality.

The data presented do not support the conclusion that "the study supports recommendations for treatment guidelines directed toward the entity of HCAP and the empirical coverage of *S aureus* among certain high-risk groups". First, only seven (44%) of 16 patients were residents of long-term care facilities, and most remaining risk factors were skin portals (eight patients), device-related (three), recent admission to hospital (four), immunosuppression (six), and cancer chemotherapy (two). Second, the triad of higher age, higher severity score, and higher mortality does not justify a new entity—otherwise entities should have been constructed around severity and outcome criteria. Third, wounds and decubitus ulcers are probably more prevalent in the group classified as having HCAP, and such patients are therefore likely at higher risk of *S aureus* than are others; however, even that cannot be proven with this small retrospective series, and in view of the small sample retrieved (16 cases from 2008 patients with blood cultures), it does not seem to be a major problem. Finally, MRSA was almost absent.

Validation studies outside the USA

Three studies outside the USA have attempted to validate the concept of HCAP: two in southern Europe[6,7] and one in Japan.[8] In a prospective study of epidemiology, antimicrobial treatment, and outcome in Barcelona, Spain,[6] 727 patients admitted to hospital with pneumonia were included, of whom 17·3% met the criteria of HCAP (table 3). Overall, patients with HCAP were older, had greater comorbidity, and more severe pneumonia at presentation than those with community-acquired pneumonia as assessed by pneumonia severity index. There were some statistically significant differences in causative organism: compared with patients with community-acquired pneumonia, more patients with HCAP were infected with *Haemophilus influenzae* (11·9% *vs* 6·0%), *S aureus* (2·4% *vs* 0%), and Enterobacteriaceae (4·0% *vs* 1·0%). Patients with HCAP

were also more likely to have aspiration pneumonia (20·6% *vs* 3%) but less likely to be infected with *Legionella* spp (2·4% *vs* 8·8%). Accordingly, patients with HCAP were substantially more likely to receive inadequate empirical initial antimicrobial treatment (5·6% *vs* 2%), and in-hospital death was more common (10·3% *vs* 4·3%). The investigators concluded that HCAP "should be regarded as a separate category of respiratory infection".

Compared with previous studies in the USA,[2–5] the study design and microbiological methods of this Spanish study were more robust. However, several points deserve special attention. First, differences of age, comorbidity, and severity of pneumonia at presentation were directly related to the criteria for selecting patients, and not a proof for a concept. Second, by contrast with the data from the USA, the Spanish investigators could not confirm relevant numbers of multidrug-resistant pathogens (only one patient infected with MRSA in HCAP or *P aeruginosa* [1·6% *vs* 0·5%]), and also the incidence of Enterobacteriaceae was low (4%). The only clue from this part of the analysis was the far higher incidence of aspiration pneumonia, a fact totally neglected in the US studies. Third, the crucial relation of higher mortality to inadequate initial empirical antimicrobial treatment to the peculiarities of microbes present in patients with HCAP could not be proven. Instead, what really matters is a fact not commented on in this study: although mortality was roughly twice as high in patients with HCAP when compared with community-acquired pneumonia, admission to intensive-care units was less common (6·3% *vs* 8·7%; ie, the rate of admission to intensive-care units compared with death was 0·6 *vs* 2·0). This finding is related to another important point disregarded in the concept of HCAP—namely, the presence of a treatment ceiling for patients who are elderly and severely disabled.

The second study from southern Europe is a multicentre prospective observational study from Italy,[7] including 55 hospitals and 362 patients admitted to hospital with pneumonia during two 1-week surveillance periods in January and June–July. 90 patients (24·9%) had HCAP (table 3), and more of these patients were more severely acutely ill and were more frequently malnourished (11·1% *vs* 4·5%), and more died (17·8% *vs* 6·7%). Inadequate empirical initial antimicrobial treatment (treatment not recommended by ATS/IDSA guidelines) was an independent predictor of increased intrahospital mortality.

This study, although prospective and multicentric, included few patients. The main criterion for HCAP was admission to hospital within 90 days (80%), only 10% of participants were residents of nursing homes. The key issue of HCAP, excess mortality because of the presence of drug-resistant pathogens, was not assessed. Moreover, information on rates of admission to intensive care units versus mortality was not given. The study does not prove much more than patients admitted to hospital within 180 days have a similar mortality compared with patients with hospital-acquired pneumonia.

The Japanese study[8] was retrospective and included 371 patients admitted to hospital during a 14-month period in 2005–07. 141 patients (38·0%) had HCAP, largely according to the ATS/IDSA defintion (table 3). The proportion of patients with severe disease was higher in patients with HCAP than in patients with community-acquired pneumonia. 11·1% of patients with moderate HCAP died in hospital compared with 1·9% of patients with moderate community-acquired pneumonia (p=0·008). In patients with moderate severity disease in whom pathogens were identified, potentially drug-resistant pathogens were isolated from more patients with HCAP than patients with community-acquired pneumonia (22·2% *vs* 1·9%; p=0·002). The presence of potentially drug-resistant pathogens was associated with initial treatment failure (risk ratio [RR] 4·2, 95% CI 2·2–8·1) and inappropriate initial antimicrobial treatment (RR 14·0, 95% CI 4·5–43·6).

This study largely investigated patients with HCAP admitted to hospital for 2 days or longer in the preceding 90 days (39%) and those who resided in nursing homes or extended-care facilities (61%). Immunosuppression was present in both the HCAP and community-acquired pneumonia groups (9·2% *vs* 7·4%). The quality of the microbiological investigation was questionable because of the lack of standardised and validated methods. Taken as reported, pathogen patterns of HCAP and community-acquired pneumonia differed mainly in the incidence of Enterobacteriaceae and non-fermenters (21% and 13%). MRSA was rare in both pneumonia groups (0·9% *vs* 3·5%). Importantly, initial antimicrobial treatment differed substantially between both groups, hinting at different approaches to patients meeting HCAP criteria. Since monotherapy was much more common (42·6% *vs* 10%) and standard combination treatment (β-lactam with macrolide or quinolone) much more rarely applied (27·6% *vs* 83·9%) in patients with HCAP, despite a higher severity of disease (2·8% *vs* 26·1% mild and 43·1% *vs* 23·5% severe pneumonia), treatment restrictions were likely applied on the basis of prognostic and ethical considerations.

Drug-resistant pathogens as defined in this Japanese study were present in 17 patients (12%) with HCAP compared with six (2·9%) with community-acquired pneumonia, with initial treatment failures and inappropriate initial antimicrobial treatment in 12 patients (70·6% and 75%, respectively) and death of five patients (29·4%). Detailed analysis of initial antimicrobial treatment and the rate of admission to intensive-care units in this group and the five patients who died was not provided but would be crucial to determine whether drug-resistant pathogens and not treatment restrictions were the main reasons for excess death.

56·7% of patients with HCAP and 35·2% of patients with community-acquired pneumonia who died were

infected with drug-resistant pathogens. However, the suggested relation of drug resistance and outcome is challenged by the comparison of mortality. Among patients with community-acquired pneumonia group and drug-resistant pathogens, two (33%) of six died. Thus, although the drug-resistance was more common in HCAP than in community-acquired pneumonia, a similar proportion of patients died.

These three validation studies did not show HCAP to be a valid classification of pneumonia, at least for southern Europe and Japan.

Attempts to refine the concept

According to the concept of HCAP, the presence of more drug-resistant pathogens implies less adequate initial empirical antimicrobial treatment, resulting in excess mortality. Therefore, more aggressive diagnostic and therapeutic approaches, including broader initial empirical antimicrobial treatment, are recommended to reduce mortality. However, validation studies do not support this concept. No consistent pattern of drug-resistance exists in HCAP, and inadequate empirical antimicrobial treatment (according to current community-acquired pneumonia guidelines) does not seem to be the leading reason for excess mortality. Furthermore, broader initial antimicrobial treatment might not be indicated in those patients with drug-resistant pathogens because of prognostic and ethical considerations.

Shorr and colleagues[9] compared rates of resistant infection among patients meeting any criteria for HCAP with those who did not and explored the individual components of the definition, consisting of recent admission to hospital, residence in a nursing home, long-term haemodialysis, or immunosuppression. Overall, 639 patients were included in the study, and drug-resistant pathogens were found in 289 (45·2%). Each component of the definition of HCAP was identified in more patients with resistant infections than in those without; however, the broad definition had a specificity of only 48·6% and misclassified a third of patients. A scoring system on the basis of the four predictive variables was only moderately predictive.

By contrast, Brito and Niederman[50] acknowledge that the concept of HCAP is in need of revision. In their recent review, they found HCAP to be a heterogeneous group, with only some patients at risk of multidrug-resistant organisms. Patients at risk of multidrug-resistant pathogens were those with severe illness or those with other risk factors including admission to hospital in the past 90 days, antimicrobial treatment in the past 6 months, poor functional status as defined by activities of daily living score, and immune suppression. On the basis of the risk factors identified in recent studies, they developed an algorithm for initial empirical antimicrobial treatment of patients with HCAP, suggesting that not all such patients need a broad-spectrum multidrug regimen for appropriate and effective treatment.

However, in view of the risk factors described by the authors, one can argue against a need for an additional category of pneumonia. Previous admission to hospital might represent a part of the definition of hospital-acquired pneumonia, and the threshold of 3 months instead of 1 might be the most appropriate. Antimicrobial treatment in the past 3–6 months is an important risk factor for subsequent drug-resistance modifying treatment recommendations, which is already included in the recent updates of community-acquired pneumonia guidelines. The inclusion of immune suppression in any category of pneumonia (community or hospital acquired) supersedes the pneumonia triad. The only highly important predictor not covered by the concept of community-acquired pneumonia or hospital-acquired pneumonia is poor functional status. This finding should prompt special recognition in alternative concepts.

A misconception to be revised

The concept of HCAP has the merit of including a population under-recognised in guidelines so far—ie, patients who are elderly or severely disabled with repeated or chronic contact with health care, leading to a risk of infection with drug-resistant pathogens. However, as defined at present, the concept has contributed to significant confusion, creating the risk of overtreatment.

Definitions of HCAP are highly diverse (table 3), in part uninterpretable, and deleterious for any useful classification of pneumonia. Core points of the concept of HCAP such as the increased incidence of drug-resistant pathogens, resulting in inadequate treatment and, therefore, excess mortality are highly questionable. By contrast, important findings in patients with HCAP, such as a limit to the escalation of treatment, a higher frequency in aspiration pneumonia, and functional status as a predictor of drug-resistance have not been adequately recognised. The ATS/IDSA guideline recommendation for initial antimicrobial treatment of patients with HCAP will substantially increase the use of antimicrobial drugs. Data suggest that, at least for non-bacteraemic *P aeruginosa* and other non-fermenters in patients with HCAP, regular empirical coverage might not be indicated.[51,52]

Where to go from here

The most obvious change in pneumonia epidemiology is the increasing number of patients who are elderly or severely disabled, have chronic contacts with health care, and are residents of nursing homes: all such patients have a raised risk of infection with drug-resistant pathogens. This change reflects demographic developments and increases in life expectancy. A nationwide quality assurance programme in Germany[53] included all adults with community-acquired pneumonia admitted to hospital during 2 years consecutively. Of 388 406 patients, 81% were 60 years or older, and 28·4% were age 80–89 years.[53] These numbers allow us to conclude that elderly people are no longer a subgroup of community acquired

pneumonia but the core group. Instead, younger people with community-acquired pneumonia form a relevant subgroup. The same database shows that of those patients who died in hospital, only 15·7% were admitted to an intensive-care unit at any time of hospital stay before death. This finding hints at a frequent practice of limiting treatment escalation on the basis of prognostic and ethical considerations.

Since pneumonia is a common cause of death in elderly and severely disabled people, prognostic and ethical considerations might lead to a limit of treatment escalation—eg, restriction of admission to intensive-care units. This fact has to stand before all clinical and investigational approaches to these patients. In clinical terms, decisions about potential treatment limitations have to be made before any decision on diagnostic and therapeutic interventions. In investigations of the disease and treatment, any conclusions and recommendations based on excess crude mortality are meaningless. Instead, clinically relevant analyses must be based on outcome data from patients judged to have had an indication for unrestricted treatment. Phrases about unacceptably high mortality have to be avoided in general, and in particular when commenting on data including a relevant proportion of patients that are severely disabled and died from pneumonia as a terminal event.

Selection pressure either in populations with repeated antimicrobial treatment cycles or in a population with repeated admission to hospital or chronic contacts with health care create the conditions needed for the development of drug-resistant pathogens. Thus, drug-resistant pathogens are a potential problem in elderly people or those with comorbidities. However, care has to be taken when risk factors for drug-resistance are defined. Age alone is not a risk factor, neither is comorbidity. Each comorbidity has a specific risk profile that in turn tends to depend strongly on the stage of the disease (eg, chronic obstructive pulmonary disease is a risk factor for *P aeruginosa* particularly in advanced stages).[54]

Moreover, health-care facilities and nursing homes are not a homogeneous environment with comparable prevalence of drug-resistant pathogens. Many nursing homes are attractive buildings were elderly people live as tenants, paying the rent with the option of support if necessary. But nursing homes can also provide full nursing, including tube feeding, for patients who are bedridden. Home care might be restricted to the visit of an ambulatory nurse caring for wounds or include full nursing care comparable to a nursing home. Nursing homes might have outbreaks of MRSA or pathogens producing extended-spectrum β-lactamases but typically be almost free of these.[55] Thus, the possibility of drug-resistant pathogens in patients cared for at home by health-care agencies and in nursing homes should be taken into account, but it probably makes little sense to view these as a risk factor for HCAP. For such patients the classification of community-acquired pneumonia seems appropriate, and whether residence status should influence the selection of antimicrobial treatment should be judged on the basis of each individual institution.

Any epidemiological data on patients with risk factors for drug-resistant pathogens should strictly be based on prospective investigation with defined microbiological methods and assessment. Retrospective databases are not appropriate because of the high risk of misinterpretation of non-quality controlled culture results. Particular caution is needed in the reporting of incidences of Enterobacteriaceae and *P aeruginosa*. In a recent study assessing the incidence of these pathogens in 5130 patients with community-acquired pneumonia, applying strict quality criteria, 72% of the Enterobacteriaceae isolates and 55% of the *P aeruginosa* isolates did not meet predefined quality criteria and associated mortality was near to that in the general population without such isolates.[54] Thus, most isolates probably cannot be considered as the causes of disease.

The main challenges in the elderly disabled population might be aspiration (with and without drug-resistant pathogens) and functional disability (also independently of distinct underlying comorbidity). Some data suggest that the relation of aerobic and anaerobic pathogens in aspiration pneumonia depends on functional status as assessed as activities of daily living (ADL).[39] Moreover, some data show a relation of ADL score on the incidence of Enterobacteriaceae or *P aeruginosa* and on drug-resistant pathogens, modified by previous antimicrobial exposure.[40] In the previously mentioned Japanese study,[8]

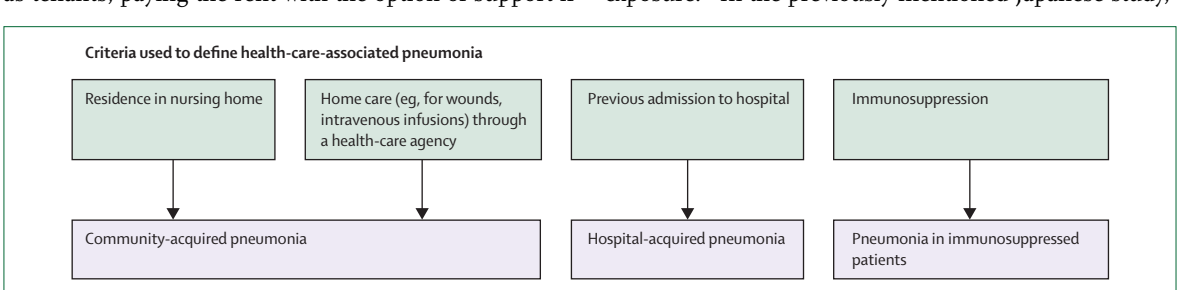

Figure 1: **Rearrangement of criteria used to define health-care-associated pneumonia**
The criteria used to define health-care-associated pneumonia (HCAP), showing that the triad pneumonia classification system is still more consistent than the inhomogeneous category of HCAP. Haemodialysis and chemotherapy for active cancer have not been studied and categorised.

enteral tube feeding (as well as poor functional status and aspiration) was predictive of drug-resistant pathogens. In another study,[54] enteral tube feeding was associated with an odds ratio of 13·8 (95% CI 3·4–56·7) for infection with *P aeruginosa*. Taken together, these data seem to support the clinically plausible hypothesis that functional impairment is the most relevant determinant of the risk for drug-resistant pathogens. Therefore, the assessment of the risk of aspiration as well as functional assessment by one of the usual scores (eg, ADL or Barthel) should probably form part of the management of these patients.

The category community-acquired pneumonia must not be contaminated with immunosuppression, which clearly relates to the category of pneumonia in immunosuppressed patients. The criterion of "relevant risk for opportunistic pathogens" although clearly not very strict seems to work after all.

There are some conditions that have not been addressed sufficiently in the past but clearly deserve to be studied in the future. These include patients with chemotherapy in the past 30 days (but without neutropenia) and patients on different kinds of haemodialysis. However, the category of community-acquired pneumonia must no longer include patients previously admitted to hospital. Instead, it should prompt classification as hospital-acquired pneumonia.[56] In fact, the aforementioned Italian study,[7] which included the highest proportion of patients classified as HCAP because of recent admission to hospital (80%), supports the view that these patients should be classified as having hospital-acquired pneumonia because they have a mortality comparable to that in patients with hospital-acquired pneumonia. The optimum threshold (30 days, 90 days, 180 days or longer) should be further investigated.

Younger people with community-acquired pneumonia should form a new subgroup and attract substantial new investigational efforts to understand the genetic basis for the acquisition of pneumonia, which is probably different from that in older people.

Towards a new concept of community-acquired pneumonia

All criteria used to define HCAP can be plausibly integrated in the classical triad pneumonia classification system (figure 1).

However, approaches to community-acquired pneumonia in patients admitted to hospital need to change to address concerns about drug-resistant pathogens (panel and figure 2). Patients with community-acquired pneumonia aged 65 years or older are the core group in view of higher incidence, specific microbial patterns and risk factors for drug-resistant pathogens, and different prognosis of comorbidity and acute pneumonia.

The main subgroups of community-acquired pneumonia relate to performance status. This should be assessed by validated methods such as the ADL score.

***Panel:* Factors modifying the expected microbial pathogens in the suggested concept of adult community-acquired pneumonia**

In all community-acquired pneumonia

Severity

Probably does not have an independent bearing on drug-resistance; however, increasing severity of community-acquired pneumonia needs broader initial antimicrobial treatment to avoid excess mortality.

Comorbidities

Comorbidity might be more heterogeneous in patients age 18–64 years and includes many conditions with unknown implications for pathogen patterns. Chronic health-care contacts in patients in this age group should lead to classification in the core group. Severity of comorbidities has to be staged.

Previous antimicrobial treatment

Number of antimicrobial treatment cycles and antimicrobial drugs must be assessed.

Factors specific to elderly patients (>65 years)*

Home care

Have to be judged locally and individually for the risk of conveying drug-resistance.

Residence in nursing home

Have to be judged locally and individually for the risk of conveying drug-resistance.

Aspiration

*Functional status good to moderate (ADL 14 or less). Functional status severely disabled (ADL 14 or more).

Selection of treatment for severely disabled patients needs special prognostic and ethical consideration. Having decided on the extent of treatment (a decision that might be revised in any direction during follow-up), heightened awareness of drug-resistant pathogens is needed in this group. Main additional risk factors for drug-resistant pathogens include home care, residing in a nursing home, and aspiration. In all patients in home care or in nursing homes, the potential increased risk of drug-resistant pathogens must be judged on an individual basis. Whether this concept also applies to outpatients is unknown. Almost all data on nursing-home-acquired

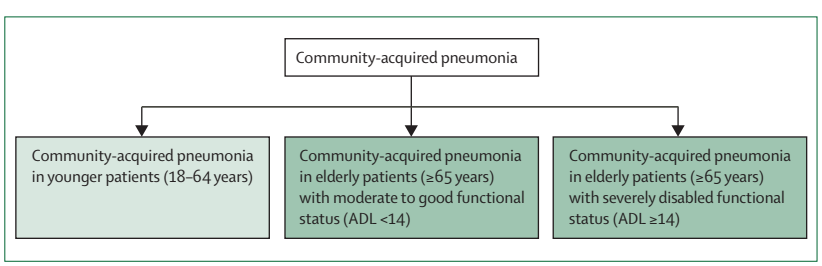

***Figure* 2: Suggested subdivision of community-acquired pneumonia according requirements and risk factors modifying the expected microbial spectrum**
ADL=activities of daily living score.

pneumonia and definitely all on HCAP refer to patients admitted to hospital. Thus, studies addressing this issue are urgently needed.

Evidently, parts of this concept need validation. The validation of the factors "home care" and "residence in nursing home" should be on the basis of strict definitions, indicating the type and extent of care, and should always be adjusted for functional status. Additionally, the differences in epidemiology of drug-resistant pathogens among countries and regions should be taken into account.

Contributors

All authors contributed to the design of the article. SE wrote the paper. All authors discussed and revised the Review.

Conflicts of interest

JC has served on the board of Pfizer, Bayer, Janssen-Cilag, and Cerexa; has received grants from Kalobios Pharmaceutical and Kenta Biotech; and has received honoraria from Pfizer, Brahms, Janssen-Cilag, Wyeth, and Astellas. SE, TW, and AT declare no conflicts of interest.

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Role of multidrug-resistant pathogens in health-care-associated pneumonia

We read with interest Santiago Ewig and colleagues' article[1] discussing the validity of a new classification scheme for pneumonia, including for health-care-associated pneumonia (HCAP). The investigators reviewed the available evidence, including our 2009 study.[2] They conclude that this study does not prove much more than that patients admitted to hospital within 180 days have a similar mortality as patients with hospital-acquired pneumonia, and that the key issue of HCAP—excess mortality due to drug-resistant pathogens—was not assessed. Here we present microbiological data from this prospective study, which was undertaken in Italy between January and July, 2007.

Microbiological data were culture results from the first 5 days after admission to hospital, or within 5 days of diagnosis with pneumonia. An aetiological diagnosis was definitive if one of the following criteria were met: (1) blood cultures yielded a bacterial pathogen (in the absence of an apparent extrapulmonary focus); (2) pleural fluid and cultures of transthoracic needle aspiration yielded a bacterial pathogen; (3) a respiratory sample that was representative of the lower respiratory tract (fiberoptic bronchoscopy with protected catheter) yielded a bacterial pathogen; (4) isolation of *Legionella pneumophila* in sputum, or detection of *L pneumophila* serogroup 1 or pneumococcal antigen in urine; (5) an increase of four times in the antibody titre, or seroconversion for atypical pathogens. An aetiological diagnosis was regarded as presumptive when a predominant microorganism was isolated from a purulent sample (more than 25 polymorphonuclear leucocytes and fewer than ten squamous cells per low-power field [original magnification×10]) with compatible findings from Gram stains.

Overall, an aetiological diagnosis was obtained in 22·4% of patients (95% CI 20·2–24·6). 28·4% (23·4–33·4) had a presumptive microbiological diagnosis, and 71·6% (66·6–77·6) a definitive diagnosis. Bacteraemia occurred in six patients with HCAP (*Streptococcus pneumoniae* in two, *Staphylococcus aureus* in three, and *Escherichia coli* in one), in four patients with hospital-acquired pneumonia (*S aureus* in three, and *E coli* in one), and in seven patients with community-acquired pneumonia (*S pneumoniae* in four, *E coli* in two, and *Pseudonomas aeruginosa* in one). No statistically significant differences were noted in the rates of bacteraemia between the three groups. A microbiological documentation was more frequently obtained in patients with HCAP (31·1%, 95% CI 19·7–42·5) than in those with community-acquired (18·4, 11·9–24·8) or hospital-acquired pneumonia (24·5, 9·2–39·8).

The distribution of pathogens varied among the three pneumonia categories (table), with *S aureus* predominating in the HCAP and hospital-acquired pneumonia groups, and *S pneumoniae* in the community-acquired group. The rate of meticillin resistance among *S aureus* isolates was 37·5% in the community-acquired group, 63·6% in the HCAP group, and 50% in the hospital-acquired group. These results seem to confirm the role of potentially multidrug resistant pathogens such as *S aureus, P aeruginosa,* and other Gram-negative bacilli, in patients with HCAP. As noted by other investigators,[3-5] patients with HCAP have a higher incidence of multidrug-resistant bacteria and, consequently, an increased likelihood of receiving inappropriate antibacterial therapy at the start.[2] This factor seems to be crucial in explaining the increased mortality recorded for HCAP.

In our study, features of patients with community-acquired pneumonia and HCAP were not substantially different in terms of median age, presence of comorbidities, or immunosuppression. Thus, the proposed classification of community-acquired pneumonia based on mean age or functional status is questionable. The review by Ewig and colleagues underestimates the value of clinical and microbiological studies undertaken in different areas of the world (Europe, Japan, and the USA). Future prospective clinical trials are needed to delineate the pathogens and risk factors associated with HCAP. However, the available evidence supports HCAP as a new category of pneumonia, which is distinct from community-acquired

	CAP n=41	HCAP n=28	HAP n=12	p value
Staphylooccus aureus	7 (17·1%)	11 (39·3%)	6 (50·0%)	0·034
Streptococcus pneumoniae	18 (43·9%)	2 (7·1%)	0	<0·001
Gram-negative bacteria				
Pseudonomas aeruginosa	4 (9·7%)	2 (7·1%)	2 (16·7%)	0·65
Enterobacteriaceae and other Gram negative bacilli	5 (12·2%)	9 (32·1%)	2 (16·7%)	0·11
Haemophilus influenzae/parainfluenzae	1 (2·4%)	1 (3·6%)	1 (8·3%)	0·68
Atypical bacteria				
Mycoplasma, Chlamydia, Legionella spp	3 (7·3%)	1 (3·6%)	1 (8·3%)	0·77
Others*†	3 (7·3%)	2 (7·1%)	0	0·69

Data are number (%) of patients. CAP=community-acquired pneumonia. HCAP=health-care-associated pneumonia. HAP=hospital-acquired pneumonia. *CAP: one atypical mycobacterium, one *Aspergillus fumigatus,* and one *Mycobacterium tuberculosis;* †HCAP: one atypical mycobacterium, one *M tuberculosis*.

***Table*: Frequency of microbial pathogens associated with community-acquired, health-care-associated, or hospital-acquired pneumonia**

pneumonia, both epidemiologically and microbiologically.

We declare that we have no conflicts of interest.

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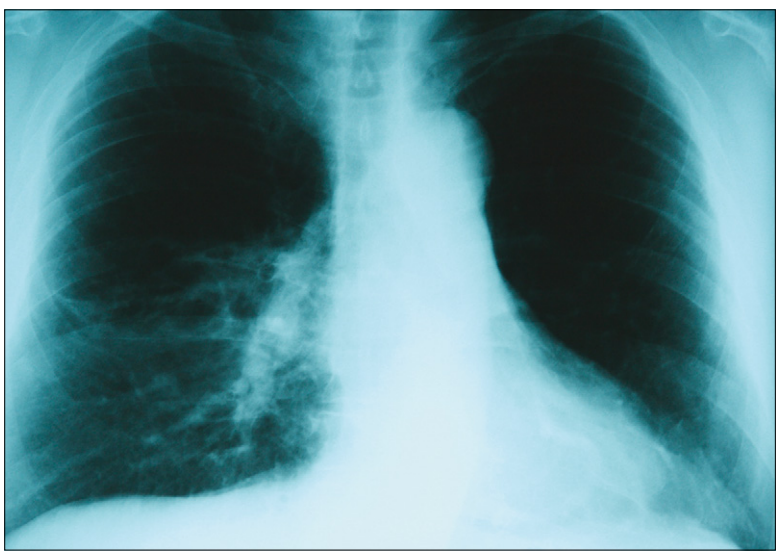
Authors' reply

We appreciate that Mario Venditti and colleagues now present their microbiological data for the Italian multicentre study of community-acquired, hospital-acquired, and health-care-assisted pneumonia (HCAP).[1] They claim that these data support the idea that HCAP is distinct from community-acquired pneumonia, a view with which we disagree. Microbiological data included samples from patients from the first 5 days after admission to hospital or within 5 days of diagnosis with pneumonia. Standards generally indicate that samples should be obtained at diagnosis. Results from samples obtained after diagnosis carry a significant risk for representing nosocomial colonisation or superinfection, particularly after introduction of antimicrobial treatment. This risk is a concern, particularly in view of the failure to undertake quantitative cultures of respiratory samples retrieved bronchoscopically. Overall, the diagnostic yield was low, with an aetiological diagnosis obtained in only 81 patients (22·4%). Of these 81, two had *Mycobacterium tuberculosis* and two had non-tuberculous mycobacteria, which are not usually regarded as pathogens of pneumonia. Of the patients with HCAP, only 28 had an aetiological diagnosis (26 excluding mycobacteria), which preclude valid conclusions about the aetiology of the populations studied.



Dr P Marazzi/Science Photo Library

Classification of pneumonia on the basis of where it was acquired is under debate

The microbial range is statistically significant for only *Streptococcus pneumoniae*, which were more frequent in community-acquired pneumonia, and for meticillin-resistant *Staphylococcus aureus* (MRSA), which were more common in health-care-associated and hospital-acquired pneumonia. However, reported rates of MRSA are excessively high, reaching 17·1% even in community-acquired pneumonia, and if representative, would need guidelines of community-acquired pneumonia to be revised immediately. Moreover, caution should be taken when results of MRSA cultures are interpreted. In the absence of quantitative cultures, only bacteraemic episodes, or positive cultures from sites that are normally sterile, would be definite evidence for infection. *Pseudomonas aeruginosa* was even slightly higher in community-acquired than in hospital-acquired pneumonia (9·7% *vs* 7·1%), and Gram-negative enterobacteriaceae were more frequent in HCAP than in hospital-acquired pneumonia (32·1 *vs* 16·7). The unusually high rates of *P aeruginosa* and Gram-negative enteric bacilli in community-acquired pneumonia add to our reservations about the validity of the microbiological data. The investigators do not provide data for resistance patterns of *P aeruginosa* and Gram-negative enteric bacilli; we cannot therefore know the true rate of multidrug-resistant pathogens, although they claim to have identified an excessive rate of multidrug resistance in patients meeting the definition for HCAP.

Venditti and colleagues try to convince us that HCAP is different from community-acquired pneumonia with just 22 patients (11 with MRSA, two with *P aeruginosa*, nine with