EDITORIAL

Healthcare-associated pneumonia: meeting the yeti

S. Ewig* and A. Torres[#]

The concept of healthcare-associated pneumonia (HCAP) is based on three crucial notions: 1) a subgroup of patients with on-going contact with healthcare presents with community-acquired infections but nosocomial microbial patterns; 2) failure to cover multidrug-resistant (MDR) pathogens leads to inadequate initial antimicrobial coverage and, subsequently, accounts for excess mortality; and 3) HCAP patients must, therefore, be identified and treated with initial broad-spectrum antimicrobial treatment covering MDR pathogens [1].

To date, eight studies specifically addressing HCAP have been published, including six retrospective [2–7] and two prospective studies [8, 9], overall summing up to 2,056 patients. One study [8] has recently been extended to 557 patients [10]. Only two studies originated from Europe [8, 9]. All studies reported excess mortality of HCAP compared to community-acquired pneumonia (CAP) patients and five studies addressed the relationship of receiving inadequate initial antimicrobial treatment due to the presence of MDR pathogens [2, 4, 7–9]. However, none convincingly established a relationship between inadequate treatment and excess mortality.

In fact, the data reported to date suffer from severe methodological flaws, which we recently presented in detail [11]. In short, there are three main issues to consider. 1) The definitions of HCAP were highly heterogeneous with some including immunosuppressed patients. 2) Referring to microbiological data from hospital databases carries a high risk of misinterpretation, e.g. the original data supporting HCAP are simply invalid since they show that the rate of MDR is exceedingly high not only in HCAP but also in CAP patients [2]. There is no substitute for a microbiological investigation ensuring high standards of sampling, processing and reporting. 3) The HCAP definition encompasses an elderly and highly comorbid population with an intrinsically increased risk of death from pneumonia, confounding the relationship of lethal outcome to an MDR pathogen. In other words, excess mortality of HCAP as MDR pneumonia is as difficult to prove as that of MDR in ventilator-associated pneumonia, and, after all, is probably quite low. Actually, many patients meeting HCAP criteria receive restricted or even palliative treatment [12]. Therefore, simply

relating excess mortality to inadequate antimicrobial treatment may severely fail to recognise the true reasons behind.

Recent important data support this notion. First, in a Spanish study comparing HCAP and CAP patients with bacteraemic pneumococcal pneumonia, it was shown that despite low rates of inappropriate antibiotic therapy, mortality rates remained significantly higher in HCAP patients [13]. Secondly, in a Korean study, severity of illness, rather than type of pneumonia, was the main predicting factor for in-hospital mortality among patients with pneumonia hospitalised through the emergency department, despite a higher incidence of MDR in HCAP patients than CAP patients (29% *versus* 13%) [7]. Thirdly, in a large cohort study from 10 European countries including 119,699 patients admitted to the intensive care unit (ICU) for >2 days, excess risk of death for HCAP in the fully adjusted model ranged from 1.7 (95% CI 1.4–1.9) for drug-sensitive *Staphylococcus aureus* to 3.5 (2.9–4.2) for drug-resistant *Pseudomonas aeruginosa*. Resistance was defined as resistance to ceftazidime (*Acinetobacter baumannii* or *P. aeruginosa*), third-generation cephalosporins (*Escherichia coli*) and oxacillin (*S. aureus*). However, the risk of death associated with antimicrobial resistance (i.e. additional risk of death to that of the infection) was 1.2 (1.1–1.4) for pneumonia for a combination of four microorganisms and was highest for *S. aureus* pneumonia 1.3 (1.0–1.6). Overall, while HCAP increased mortality and length of stay in the ICU, the additional effect of the most common antimicrobial resistance pattern was judged to be comparatively low [14].

Without doubt, the study applying the best methodology was a Spanish prospective study [8] comparing HCAP and CAP patients and, therefore, this deserves more detailed comment. In this study, the incidence of MDR pathogens in HCAP patients was very low (methicillin-resistant *S. aureus* n=1, *P. aeruginosa* n=2 (1.6%) and Gram-negative bacilli n=5 (4%)). However, they more frequently had aspiration pneumonia (20.6% *versus* 3%). HCAP patients received inadequate initial antimicrobial treatment significantly more frequently (5.6% *versus* 2%), and in-hospital mortality was significantly higher (10.3% *versus* 4.3%). However, the relationship of higher mortality with inadequate initial empiric antimicrobial treatment and the microbial spectrum could not be proven. Instead, although mortality was approximately twice as high in HCAP patients, ICU admission was less frequent (6.3% *versus* 8.7%, i.e. the rate of ICU admission/death was 0.6 *versus* 2.0), suggesting treatment restrictions due to considerations of age and comorbidity [8].

The concept of HCAP is further challenged by the fact that two studies clearly showed that the HCAP definition is a poor predictor for the presence of MDR pathogens even in populations with supposedly high MDR prevalence. In one study,

*Thoraxzentrum Ruhrgebiet, Kliniken für Pneumologie und Infektiologie, Herne und Bochum, Bochum, Germany. [#]Servei de Pneumologia, Institut Clínic del Tórax, Hospital Clínic de Barcelona, Facultat de Medicina, Universitat de Barcelona, IDIBAPS, Ciber de Enfermedades Respiratorias, Barcelona, Spain.

CORRESPONDENCE: S. Ewig, Thoraxzentrum Ruhrgebiet, Kliniken für Pneumologie und Infektiologie, Evangelisches Krankenhaus Herne und Augusta-Kranken-Anstalt Bochum, Bergstrasse 26, 44791 Bochum, Germany. E-mail: ewig@augusta-bochum.de

neither single criteria of the HCAP definition nor a point scoring system achieved favourable predictive power [15]. Another showed a sensitivity of 78.3% and a specificity of 56.2%, *i.e.* false-positive predictions in nearly every second case [5].

In this issue of the *European Respiratory Journal*, ATTRIDGE *et al.* [16] report on outcomes from a national cohort of 15,071 non-critically ill patients meeting the HCAP definition in >150 Veterans Health Administration hospitals, the largest HCAP cohort studied to date. Treatment with guideline-concordant (GC)-HCAP therapy was not associated with improved 30-day mortality compared with GC-CAP therapy. In fact, GC-HCAP was associated with a longer length of hospital stay and increased mortality rates [16]. This finding is in line with another US study comparing outcomes of non-ICU hospitalised patients residing in nursing homes treated with GC-HCAP and GC-CAP therapy. No differences regarding in-hospital mortality or 30-day mortality were found between the GC-CAP and GC-HCAP groups, and GC-CAP patients actually had a decreased time to oral therapy and a decreased length of hospital stay [17]. Both studies are limited in that they are retrospective and that microbiological data are either scarce [16] or unavailable [17]. In the present study, a pathogen was identified in only 9.2% of cases; in addition, the quality of the data are questionable. A failure to demonstrate a protective effect of GC-HCAP treatment may be related to a high prevalence of patients with negative cultures, which may be treated like CAP, or to a low local prevalence of resistant pathogens obviating any need for broader coverage.

Nevertheless, these data reinforce our scepticism against the HCAP concept. Taken together, the HCAP concept is based on few and weak data. It has been shown to be a poor predictor for MDR pathogens. At least two studies now show that GC treatment does not seem to reduce mortality. However, the HCAP concept carries a high risk of heavy antimicrobial overtreatment if applied in routine practice. Although it has been argued that culture-negative patients are at a low risk of MDR pneumonia, *i.e.* HCAP, and can be safely treated like CAP patients [18], de-escalation after 2 or 3 days is a difficult tool to achieve in routine practice [19, 20]. Importantly, there are no data from Europe with MDR rates comparable to those reported in the USA, Japan and Korea in patients meeting HCAP definitions.

In our view, HCAP remains a misconception. Keeping immunosuppressed patients within the entity of pneumonia in immunosuppression, and conceding from available data that previous hospitalisation within the last 3 months should probably be addressed as nosocomial pneumonia instead of CAP [21], the only category that matters remains residence in a nursing home. To date, few studies support that MDR pneumonia is a frequent problem in these patients, at least in Europe [22, 23]. A recent Spanish study investigating 557 patients meeting HCAP criteria concluded that "most HCAP patients could be treated in the same way as patients with CAP, after carefully ruling out the presence of aspiration pneumonia" [10]. Of course, carefully designed studies should continuously address this issue. In our view, there is a particular need for studies including bronchoscopic microbial investigations. To date, only a few data in a selected population of nursing home residents are available [24].

Although HCAP was only recently reported to gain broad acceptance by US authors [25], this seems to be ambiguous in the USA. In one survey, although 79% of participants were reported to be in agreement with the HCAP guidelines, only 9% chose GC-HCAP treatment for hypothetical patients meeting HCAP criteria [26]. We argue that future studies evaluating the HCAP concept should be prospective, must provide clear patient characteristics including comorbidity, functional status and possible treatment restrictions, and apply sound microbiological standards.

STATEMENT OF INTEREST

A statement of interest for A. Torres can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES

- 1 American Thoracic Society. Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416.
- 2 Kollef MH, Shorr A, Tabak YP, *et al.* Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005; 128: 3854–3862.
- 3 Micek ST, Kollef KE, Reichley RM, *et al.* Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. *Antimicrob Agents Chemother* 2007; 51: 3568–3573.
- 4 Shindo Y, Sato S, Maruyama E, *et al.* Health-care-associated pneumonia among hospitalised patients in a Japanese community hospital. *Chest* 2009; 135: 633–640.
- 5 Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: is it time to refine the definition of health-care-associated pneumonia? *Chest* 2010; 137: 1283–1288.
- 6 Seki M, Hashiguchi K, Tanaka A, *et al.* Characteristics and disease severity of healthcare-associated pneumonia among patients in a hospital in Kitakyushu, Japan. *J Infect Chemother* 2011; 17: 363–369.
- 7 Park HK, Song JU, Um SW, *et al.* Clinical characteristics of health care-associated pneumonia in a Korean teaching hospital. *Respir Med* 2010; 104: 1729–1735.
- 8 Carratalà J, Mykietiuk A, Fernández-Sabé N, *et al.* Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med* 2007; 167: 1393–1399.
- 9 Venditti M, Falcone M, Corrao S, *et al.* Outcomes of patients hospitalised with community-acquired, health care-associated, and hospital-acquired pneumonia. *Ann Intern Med* 2009; 150: 19–26.
- 10 Garcia-Vidal C, Viasus D, Roset A, *et al.* Low incidence of multidrug-resistant organisms in patients with healthcare-associated pneumonia requiring hospitalization. *Clin Microbiol Infect* 2011; [Epub ahead of print DOI: 10.1111/j.1469-0691.2011.03484.x].
- 11 Ewig S, Welte T, Chastre J, *et al.* Rethinking the concepts of community-acquired and health-care-associated pneumonia. *Lancet Infect Dis* 2010; 10: 279–287.
- 12 Ewig S, Birkner N, Strauss R, *et al.* New perspectives on community-acquired pneumonia in 388406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009; 64: 1062–1069.
- 13 Rello J, Luján M, Gallego M, *et al.* Why mortality is increased in health-care-associated pneumonia: lessons from pneumococcal bacteremic pneumonia. *Chest* 2010; 137: 1138–1144.
- 14 Lambert ML, Suetens C, Savey A, *et al.* Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis* 2011; 11: 30–38.

- 15 Shorr AF, Zilberberg MD, Micek ST, *et al.* Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med* 2008; 168: 2205–2210.
- 16 Attridge RT, Frei CR, Restrepo MI, *et al.* Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. *Eur Respir J* 2011; 38: 878–887.
- 17 El Solh AA, Akinnusi ME, Alfarah Z, *et al.* Effect of antibiotic guidelines on outcomes of hospitalised patients with nursing home-acquired pneumonia. *J Am Geriatr Soc* 2009; 57: 1030–1035.
- 18 Labelle AJ, Arnold H, Reichley RM, *et al.* A comparison of culture-positive and culture-negative health-care-associated pneumonia. *Chest* 2010; 137: 1130–1137.
- 19 Kett DH, Cano E, Quartin AA, *et al.* Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis* 2011; 11: 181–189.
- 20 Ewig S. Nosocomial pneumonia: de-escalation is what matters. *Lancet Infect Dis* 2011; 11: 155–157.
- 21 Arancibia F, Bauer TT, Ewig S, *et al.* Community-acquired pneumonia due to Gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. *Arch Intern Med* 2002; 162: 1849–1858.
- 22 Lim WS, Macfarlane JT. A prospective comparison of nursing home acquired pneumonia with community acquired pneumonia. *Eur Respir J* 2001; 18: 362–368.
- 23 Polverino E, Dambrava P, Cillóniz C, *et al.* Nursing home-acquired pneumonia: a 10 year single-centre experience. *Thorax* 2010; 65: 354–359.
- 24 El-Solh AA, Aquilina AT, Dhillon RS, *et al.* Impact of invasive strategy on management of antimicrobial treatment failure in institutionalized older people with severe pneumonia. *Am J Respir Crit Care Med* 2002; 166: 1038–1043.
- 25 Zilberberg MD, Shorr AF. Healthcare-associated pneumonia: the state of evidence to date. *Curr Opin Pulm Med* 2011; 17: 142–147.
- 26 Seymann GB, Di Francesco L, Sharpe B, *et al.* The HCAP gap: differences between self-reported practice patterns and published guidelines for health care-associated pneumonia. *Clin Infect Dis* 2009; 49: 1868–1874.