Author's response to reviews

Title: Severe Enterobacter pneumonia developing outside the hospital setting: a plea for greater awareness of the concept of health-care-associated pneumonia

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Version: 2 Date: 15 April 2011

Author's response to reviews: see over
Re: BMC Infect Dis
MS: 5382136254959140
Answers to reviewers

We wish to thank both reviewers for their insightful comments that have helped us improve the manuscript.

Reviewer #1

Minor revisions

1. I suggest the authors should re-position the article using the following draft:
- At the time patients with Enterobacter pneumonia presented to the hospital, they did not meet the criteria for HCAP. Hence, they were treated like CAP.
- The authors decided to describe Enterobacter pneumonia
- Describing Enterobacter pneumonia, striking differences with usual CAP were noticed. To search for significant differences between Enterobacter pneumonia and CAP related to other pathogens, each Enterobacter pneumonia was matched with any other CAP. (The comparison between 2 kinds of CAP seems to me more accurate than comparing HCAP with CAP).
- The article would so describe Enterobacter pneumonia, state that they share more characteristics with HCAP than with CAP, and corroborate some limits of the ATS guidelines.

We fully agree with the reviewer. As a matter of fact, the first version of the article intended to shed some light on the HCAP concept, that is the key message of the paper, rather than describe how the study really happened. The reviewer is correct in suggesting that it contributes “to scramble the message”. The new version of the manuscript basically describes how the study was performed. We initially considered Enterobacter pneumonia as community-acquired pneumonia (CAP) (and consecutively treated them as CAP). Then we compared them with CAP due to common bacteria. Indeed, at the same time, we were progressively aware of the recently published HCAP concept and we therefore introduced HCAP criteria in the comparison. As suggested by the reviewer, and following this comment, we substantially modified the structure of the article, mostly in the result section. The title and method section were also clarified. Also in response to Reviewer #2, the comparison between groups is now presented as a logistic regression including both univariate and multivariate analysis. HCAP criteria are now included as one among several variables (which were already compared in the initial version of this manuscript such as demographic, clinical, biological or radiographic variables).
From now on, the plan of this section is

**Results**

EnCAP clinical description and radiographic findings

EnCAP bacteriological findings

Univariate analysis of factors associated with CAP due to Enterobacter sp compared with CAP due to common bacteria

Clinical and biological findings

Radiographic findings There was no significant difference in radiographic findings

Criteria for HCAP

Multivariate analysis

Antimicrobial therapy and sepsis outcome

Moreover, the introduction section was also modified to clarify the objective of the study (page3, line 6-11) and we reserved the discussion about the HCAP concept in the discussion section (page 7, line 12-28). We hope it is now clearer that this study was designed for the comparison of two groups of CAP, one of them including a particular species with more criteria for HCAP than the other group.

2. *The authors classified pneumonia as healthcare-related when patients had been admitted in a hospital during the past 12 months. This classification refers to larger criteria (Antimicoribial Agents and Chemotherapy 2007 (51)10: 3568-73) for HCAP than those cited in the references 6 and 14...*

and

... in 2007 related to healthcare infections were also defined by French guidelines; the authors being french, this reference should be cited (Mai 2007, Comité Technique des infections nosocomiales et des infections associées aux soins, Ministère de la Santé)

of the emerging threat—Proceedings of the HAI summit. Clinical Infectious Diseases 2008;47:555–99). These papers propose to modify the definition of a HCAP criterion, namely to extend the period during which a patient was previously hospitalised (from 3 months in previous papers to one year in these). We then completed old references by these more recent ones (reference 10-11)(page 4, line 19,22) and by the French guideline (as suggested by the Reviewer) which however proposes less clear-cut definitions. This point is further addressed in the discussion section page 7, line 30 and page 8, line 1-3.

3. The introduction should be clarified, briefly summarizing how nosocomial pneumonia (ATS 1996) were splitted into VAP, HAP, and HCAP (ATS 2005).

As suggested by the reviewer, the following explanation was added to the introduction section page 3, line 9-12: “HCAP refer to a new category of pneumonia apparently developing in the community with the particularity to apply to patients who have recently interfaced with the health care system [6]. Bacteria responsible for HCAP can share the same susceptibility profile than hospital-acquired bacteria.”

4. The term “from outside the hospital setting” is confusing and repeated many times in the article. Clearly defining the terms in the introduction could allow to use CAP or HCAP infections, or non-nosocomial infections...

The term “from outside the hospital setting” was deleted in the whole text except in the discussion part page 7, line 15 and 20 where it holds a particular signification.

5. Page 3: “Each eligible Enterobacter HCAP” at this time of the article, it is not known if Enterobacter pneumonia are HCAP or CAP. “Each eligible Enterobacter pneumonia
and
page 4: data collection, last 4 words: “included”, prefer “monitored”?
and
-page 4 definitions:
 . “Sputum cultures were accepted” prefer “Sputum cultures were considered significant”
and
 . “CAP was defined as pneumonia in patients who did not met” à “did not meet”
and
The table 1 should be corrected: Line “Male/female, n” the corresponding values are percentages, not numbers; Line “comorbidities, %” the corresponding values are mean number of comorbidities, not percentage of patients having comorbidities; Lines COPD, cancer…to chronic renal failure: it should be mentioned that the values are %; Line: “Time between onset of symptoms”...it should be specified if it is mean time or median time; Line “Fever” maybe simply replace “fever” by T°>37.5°C (ask the editor, should the temperature be expressed in °C, °F, or both?); Line “shivering”: the usual term is “chills”; Line “sepsis classification” what does the p value at the end of the line mean?; Lines “leukocytosis” and “C-reactive protein”: please specify the units; Line “blood urea” :”mmol/L” à”(mmol/L)”

and

The table 2 should be corrected: P value à p value; “Prior antimicrobial treatment”, please change to “antimicrobial treatment started <24h before admission” or specify the delay in the legend.

All these corrections have been completed. Please pay attention that “Enterobacter pneumonia” has been cited as “EnCAP” throughout the new version of the manuscript, precluding any confusion with HCAP as the initial version did. Please also note that table 1 and 2 have been modified following the Reviewer #2’s suggestion of performing a logistic regression. Please note that some results of the univariate analysis have been modified by logistic regression in comparison with the khi² or Student T test comparisons initially performed in the previous article version. Actually, non available data are taken into consideration differently by logistic regression.

6. “all patients were living at home and one was treated at home“ : what does “treated at home” mean: peritoneal dialysis? Else?

The term “treated at home” refers to the French definition of “hospitalisation à domicile”. After English editorial assistance, we now propose page 6, line 14-15 “All patients were living at home but one was considered as a home care patient since he received intravenous therapy at home.”

7. it might be interesting for readers to know if ESBLE were resistant to ciprofloxacin, but also to aminoglycosides, since HCAP are usually treated with antibiotic combination including aminoglycosides, and ESBLE are commonly resistant to aminoglycosides
The reviewer is correct and we thank him for this observation. Actually, in our study “ESBL-producing strains were isolated in four cases, including ciprofloxacin resistance in two, gentamicine resistance in one and amikacine resistance in another strain.” (page 5, line 26-27). We agree that this detail is somewhat important since the rationale of aminoglycoside in addition to βlactamins as the empiric treatment of such infections remains debated. We added a comment in discussion part, page 8, line 9.

**Other modifications:**

Please note that, in line with Reviewer #2’s suggestion, a logistic regression was performed by an epidemiologist of our group (Brice Amadeo, Univ. de Bordeaux, INSERM, U657, F-33000 Bordeaux) subsequently cited as a new co-author of the paper.
Reviewer # 2

Major revisions

1. A case control study is performed to identify factors associated with healthcare-associated (HCA) Enterobacter pneumonia. Cases are defined as HCA-Enterobacter pneumonia and controls as community-acquired pneumonia caused by non-Enterobacter species. Cases and controls should be chosen from the same population of patients in order to reduce the chance that some other difference between the two groups is accounting for the difference in factors under investigation. In this study, controls are patients with community-acquired pneumonia, which differs from HCA pneumonia. A more appropriate control group would therefore be patients with HCA pneumonia caused by non-Enterobacter species.

We fully agree with the Reviewer. Furthermore, this major comment is complementary to the first comment of Reviewer #1, namely

I suggest the authors should re-position the article using the following draft:
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- The authors decided to describe Enterobacter pneumonia
- Describing Enterobacter pneumonia, striking differences with usual CAP were noticed. To search for significant differences between Enterobacter pneumonia and CAP related to other pathogens, each Enterobacter pneumonia was matched with any other CAP. (The comparison between 2 kinds of CAP seems to me more accurate than comparing HCAP with CAP).
- The article would so describe Enterobacter pneumonia, state that they share more characteristics with HCAP than with CAP, and corroborate some limits of the ATS guidelines.

As a matter of fact, we did initially intend to compare CAP due to Enterobacter sp. with CAP due to more common and typical bacteria (Pneumococci ...). As the unusually high inappropriate empiric antibiotic treatment of Enterobacter CAP was drawn to our attention, criteria for HCAP were included in the analysis. Indeed, this concept was progressively described at the time of the study completion and could explain the inappropriateness of empiric treatment. These criteria rapidly appeared to be the cornerstone of this study. Subsequently, the study presentation was focused on this message but we admit that it undoubtedly scrambled its understanding.

As suggested by the Reviewers, we substantially modified the structure of the result section. The method remains unchanged but was clarified, as did the title. From now on, the new version of the manuscript basically describes how the study was performed. Also in response to the second major comment 3 and 4 of the Reviewer (see below), the comparison between groups is now presented as a logistic regression including both univariate and multivariate analysis and odds ratio. HCAP criteria are included as one among several other variables.
(which were already compared in the initial version of this manuscript, i.e. demographic, clinical, biological or radiographic variables).

From now on, the plan of the result section is

**Results**

- EnCAP clinical description and radiographic findings
- EnCAP bacteriological findings
- Univariate analysis of factors associated with CAP due to Enterobacter sp compared with CAP due to common bacteria

  **Clinical and biological findings**

  **Radiographic findings** There was no significant difference in radiographic findings

  **Criteria for HCAP**

  **Multivariate analysis**

  **Antimicrobial therapy and sepsis outcome**

Moreover, the introduction was also modified to clarify the objective of the study (page 3, line 6-11) and we reserved the discussion about the HCAP concept in the discussion section (page 7, line 12-28). We hope that it is now clearer that this study was designed for the comparison of two groups of CAP, one of them including a particular species with more criteria for HCAP than the other group.

2. The definition for HCA needs revision. The authors cite reference 14 for their definition which requires in addition to the criteria listed in the paper, also prior antibiotic therapy, chemotherapy and wound care. Also, the time limit for prior hospitalization is 90 days and not 1 year are stated in the paper

The reviewer is correct in pointing out that we cited reference 14, i.e. “Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health-care-associated pneumonia (2005) Am J Respir Crit Care Med 171:388-416.” for HCAP criteria whereas we used more recently proposed criteria. We now corrected this point and modified the references cited for these criteria (reference 10-11)(page 4, line 19,22), i.e. a recent study by Micek et al. (2007 Health-care-associated pneumonia and community-acquired-pneumonia: a single-center experience. Antimicrob Agents Chemother 51:3568-3573) and a recent expert statement (Kollef MH, Napolitano LM, Solomkin JS, Wunderink RG, Bae IG, Fowler VG, Balk RA, Stevens DL, Rahal JJ, Shorr AF, Linden PK and Micek ST. Health care–associated infection (HAI): a critical appraisal of the emerging threat—Proceedings of the HAI summit.
Clinical Infectious Diseases 2008;47:S55–99. These papers propose to extend the period during which a patient was potentially previously hospitalised (from 3 months in previous papers to one year in these). We added a French guideline in the references as suggested by Reviewer #1 even if its definitions are less clear-cut. Finally, the advantage of whether this period should be of 3 months or 12 months is addressed in the discussion section page 7, line 30 and page 8, line 1-3.

3 and 4. Given the small number of cases (only 10) it is important to include odds ratio and 95% confidence intervals in the results section.

and

A univariate analysis is performed. However, it is important to also follow this analysis with logistic regression which will control for potential confounders.

In line with the reviewer’s suggestion, a logistic regression was performed by an epidemiologist of our group (Brice Amadeo, Univ. de Bordeaux, INSERM, U657, F-33000 Bordeaux) subsequently cited as a new co-author of the paper.

First, a univariate analysis was conducted including the variables of table1. Several variables were introduced in the model in a different way from their initial description. For example, comorbidities were not presented as a continuous variable but rather as a categorical variable (cf. table 1 of new version). HCAP criteria, whether patients presented with no or at least one criterion, were also introduced in the model in line with the modification of the article discussed above. Then a multivariate analysis was completed (see statistical method page 5 line 4-9, result section page 6, line 16-17). Final results and odds ratio are presented in the new table 1. Please note that some results of the univariate analysis have been modified by logistic regression in comparison with the khi² or Student-T test comparisons initially performed in the previous article version. Actually, non available data are taken into consideration differently by logistic regression.

5. The major difference in outcomes between cases and controls was a difference in average temperature of 0.6 degrees Celsius. There was no statistically significant difference with regards to sepsis. The discussion should address this issue.

In the logistic regression model, this difference was not observed (see statistical explanation above). Except leukocytosis, no difference on clinical characteristics or severity of sepsis was
observed in the multivariate analysis. We agree with the reviewer that this is important. Indeed, it is likely that physicians may expect more severe sepsis with community-acquired bacteria sharing the same profile than hospital-acquired bacteria such as \textit{Enterobacter sp.} or \textit{Pseudomonas sp.} in other studies. This point is addressed in the discussion page 7 line 9-11.

6 and 7. \textit{The identification of one case with Enterobacter pneumonia was based on positive blood cultures and not respiratory data. One could argue that this case did not have Enterobacter pneumonia and may have been due to another pathogen. Consideration for deleting this case should be addressed.}

and

\textit{In another case of Enterobacter pneumonia, Moraxella was also recovered from respiratory cultures. This case should be excluded as it does not represent only Enterobacter pneumonia.}

The reviewer is correct in pointing that both cases need to be discussed. Regarding the first one, a reference article published by Ruiz et al. in the American Journal of Respiratory and Critical Care Medicine (see reference 3) proposed that the \textit{“etiology was considered definite if one of the following criteria was met: (1) blood cultures yielding a bacterial...(in the absence of an apparent extrapulmonary focus)...”}. We think our case meets this criterion since he exhibited no apparent extrapulmonary infection and presented with a clear clinical and radiographic picture of CAP. We did not discuss this case in our second version of the article. However we could do it if the reviewer wants to.

We agree with the reviewer about the second case. However, we initially intended to keep this case assuming that BAL is a highly specific method, that \textit{Enterobacter sp.} grew to a higher threshold than \textit{Moraxella catarrhalis} (1.5 x 10^6 CFU/mL vs 10^4 CFU/mL) and finally that the empiric antibiotic treatment of this patient (i.e. coamoxiclav) covered \textit{Moraxella sp.} but not \textit{Enterobacter sp.} explaining the delay in the improvement of clinical signs of pneumonia.

To take into account the reviewer’s suggestion, we tested the robustness of the uni/multivariate model whether or not this patient was excluded. No significant change was observed. These results are shown in next table (n=10 patients vs n=9 patients, the latter case being excluded)

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=10</td>
</tr>
<tr>
<td>Male Sexe</td>
<td>0.33</td>
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<tr>
<td></td>
<td>(0.06-1.81)</td>
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</tbody>
</table>


We then propose to keep this patient in the study provided a limitation is added in the discussion part (page 8, line 15-17).

**Discretionary revisions**

1. *In Table 1, HCA Enterobacter pneumonia should be specified in the column heading*

Table 1 and 2 were modified as discussed above
2. A description of the ICU should be included, regarding number of admissions per year and total number of beds.
Done (page 3, line 18)

3. A clarification of how aspiration pneumonia was defined and total numbers would be helpful since this is one of the exclusion criteria.

The definition refers to the classical definition (Aspiration pneumonitis and aspiration pneumonia. Marik PE. N Engl J Med 2001;344,665-671), even if we recognize that no clear cut criteria are yet defined (page 3, line 24-26). Aspiration pneumonia are excluded from our epidemiological monitoring but we don’t screen them, unfortunately. We can add a limitation about aspiration definition and absence of screening if the Reviewer wants it.