Author’s response to reviews

Title: RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS IN BRONCHIECTASIS EXACERBATIONS

Authors:

Rosario Menéndez (rosmenend@gmail.com)
Raúl Méndez (rmendezalcoy@gmail.com)
Eva Polverino (EPOLVERI@clinic.cat)
Edmundo Rosales-Mayor (edmundo.rosales@gmail.com)
Isabel Amara-Elori (milisaelori@gmail.com)
Soledad Reyes (reyes@comv.es)
José Miguel Sahuquillo-Arce (wadjur@hotmail.com)
Laia Fernández-Barat (lfernan1@clinic.cat)
Victoria Alcaraz (victoriaalcarazserrano@gmail.com)
Antoni Torres (ATORRES@clinic.cat)

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Dear editor, please find below the information required. We hope to meet the requirements for acceptance of the manuscript as original for BMC Infectious Disease.

Author’s response to reviewers:

Title: Risk Factors For Multidrug-Resistant Pathogens In Bronchiectasis Exacerbations

Authors:

R. Menéndez rosmenend@gmail.com
Dear Sir or Madam:

Thank you for consideration of our manuscript for publication in your journal. We have reviewed the manuscript according to your reviewer’s comments and we hope that our new version fulfills the criteria to be published.
Reviewer 1. Dr. Silvano Esposito

This is a good original paper investigating prospectively the possible risk factors for an MDR etiology in patients with exacerbation of chronic bronchitis and bronchiectasis.

The paper is well done, well designed and well written, but it would deserve some revision

1. Title: I would say ... in patients affected by exacerbations of chronic bronchitis and bronchiectasis

   • We have considered that suggestion, however we prefer to maintain only bronchiectasis in order to avoid misinterpretation with other patients with chronic bronchitis and/or COPD.

2. Patients and methods

   Identification methods. Please specify which identification method was adopted and what susceptibility test was utilized as well.

   If an automatic conventional test was utilized please note in the discussion its limits compared with newer molecular test citing the following paper

   • In the new version we have added the identification method used and the susceptibility tests. The sentence is now as follows:

   “Microorganism identification was consider positive as in previous publications,[9] Briefly, bacterial identification was achieved by means of the MALDI-TOF MS (Biomerieux, Marcy l’Etoile, France). Antimicrobial susceptibility was tested by the Kirby-Bauer disk diffusion technique on Muller-Hinton or sheep blood agar, depending on the microorganism growth requirements; E-test and in-house PCR were used to assess unexpected resistance patterns”.

• With regard to the comment about automated conventional tests we have added a sentence in discussion (3rd paragraph) and the suggested reference (Yeliz Çetinkol Y et al, reference 14) as follows:

“We evaluated resistance using conventional methods usually performed in daily routine and we don’t perform automated methods or clonal analysis of resistance.[14]”

3. Blood cultures and BAL. In the same section you report that patients were investigated also for blood cultures, and bronchoalveolar lavage specimens but you don’t mention any result about that. It would be interesting to know the results of these investigation. Also for possible viral etiology no data is reported.

• Blood cultures and BAL specimens were only required if indicated by the attending physicians. In the new version the sentence is as follows: “The microbiological diagnosis was performed with the following tests: sputum (208 patients), urine antigen test for S. pneumoniae (126) and L. pneumophila (128), two blood samples (87) and nasopharyngeal swabs (125) (for influenza A and B, parainfluenzae, syncytial respiratory virus, adenovirus). Sputum and bronchoalveolar lavage (11) were processed for Gram and Ziehl–Neelsen stains and for cultures of bacterial, fungal and mycobacterial pathogen”

• Viral etiologies are incorporated in the Table 2.

4. References. The risk factors for MDR microorganisms have been investigated by several authors and they are well defined. I would add the following references.


• Following the suggestion of the reviewer, the two prior references have been added in the discussion of the new version (references 22 and 25). Reference 22 in Page 11, 3rd paragraph: “and for Enterobacteriacea mainly related to exposure to III/IV generation of cephalosporins or broad-spectrum penicillins.[22].” Reference 25 in Page 11, 4rd paragraph: “Prior MDR colonization is a recognized risk factor for MRSA[24,25].”

5. Severity and MDR. But none has investigated about the bronchiectasis and exacerbation on chronic bronchitis. The severity of respiratory dysfunction and the severity of bronchiectasis itself (you mentioned that a severity score was calculated) could play an important role also on the MRD etiology. This should be mentioned.

• We totally agree, the severity of bronchiectasis plays a very important role on MDR etiology. In fact, almost 80% of MDR exacerbations occurred in patients with higher punctuations in the well-validated specific bronchiectasis scores: FACED and BSI. However, in the multivariate analysis prior hospitalization was more decisive in prediction of MDR. It has been more extensively commented in the new version. Page 11, last paragraph as follows: “Almost 80% of MDR exacerbations occurred in patients with higher punctuations in prognostic scales such as FACED or BSI whereas MDR in mild scales were lower 6.2% and 40.6% respectively. However, after entering in the model other independent factors, these scales are not remaining independently associated with multi-drug resistance.”

Reviewer 2. Dr. Sithembiso Velaphi

Summary of the article from my understanding: This is a descriptive study with its objective being to determine risk factors associated with isolation of multi-drug resistant organisms
MDRO) in adults with non-cystic fibrosis bronchiectasis. A total of 233 patients were included in the study of which 159 had an organism isolated from the sputum or specimen sent. Of the 159 patients 32 grew multi-drug resistant organisms. Patients with multi-drug resistant organisms were more likely to require hospitalization. The risk factors associated with growing multi-drug resistant organisms were having renal disease, prior multi-drug resistant organism isolation and hospitalization previous year.

My Comments:

1. Abstract: Under results, the statement that MDRO were more frequent in hospitalized patients give impression that the specimens were taken in patients who were hospitalized already, yet it was not the case, rather those who had MDRO were more likely to require hospitalization. They must rephrase the sentence. They must put a p-value next to percentages comparing hospitalization rates. I suppose they meant Enterobactericeae when they used the word Enterobacteria- please recheck. They must include confidence intervals next to the Odds ratios.

• The sentence has been rewritten in order to improve the information. Exacerbations caused by MDR microorganisms were more frequent in those with prior isolation of MDR, that is those with chronic colonization and/or infection (Table 1). Besides, during the current exacerbation, MDR microorganisms were more frequent isolated in patients that required hospitalization due to the exacerbation compared to those treated as outpatients. Results sentence is as follows: “233 exacerbations were included and microorganisms were isolated in 159 episodes. Multidrug-resistant pathogens were found in 20.1% episodes: Pseudomonas aeruginosa (48.5%), methicillin-resistant Staphylococcus aureus (18.2%) and Extended spectrum betalactamase + Enterobacteriaceae (6.1%), and they were more frequent in exacerbations requiring hospitalization (24.5% vs. 10.2%, p: 0.016)”

• P value was added next to percentages comparison hospitalization rates

• Enterobacteriaceae word is added

• 95% Confidence Intervals to the odds ratio were included.
2. Methods: My understanding is that they included first exacerbations, suggesting that they included patients who never had bronchiectasis exacerbations before. They need to describe what they meant by first, because when they present the results they include patients with previous hospitalizations which is not clear whether the hospitalizations were related to bronchiectasis exacerbations or not. Because if they were then they cannot say the patient had first exacerbation. Therefore they need to describe what they meant by first or if first is what I understand they meant then should exclude patients with previous bronchiectasis exacerbations.

- Bronchiectasis is a chronic disease and patients have been referred to our specific clinics in two tertiary care centers in different phases of the disease. We mean that we consider almost impossible to enroll patients in the first exacerbation in their natural course of their diseases. That circumstance is identical for all hospitals. In fact, in international registries for bronchiectasis in adults (EMBARC), it is allowed to enroll chronic patients not naïve and with prior hospitalizations as other colleagues in the world do. In our two clinics of bronchiectasis we assist patients from other hospitals, from primary care or other facilities, and in all cases after referral we confirm the bronchiectasis diagnosis, perform a diagnosis study according to Spanish guidelines and follow up patients. For this study, we have obtained approval from the ethics committee and then the signed consent of the patients; after that process we initiate the recruitment for exacerbations; that is why we have included the first exacerbation after obtaining the informed consent to recruit patients for this study. In the new version it has been more extensively explained. The two paragraphs in the new version are as follows:

“In our specific specialized clinic, patients are referred from primary care, other hospitals, other specialties or any other medical facilities. We confirmed the diagnosis of bronchiectasis by computerized tomography scan of lungs along with compatible symptoms and aetiology of bronchiectasis had been investigated according to Spanish guidelines [5] previous to study recruitment. Local committees approved the study and patients gave written informed consent (Biomedical research ethics committee Hospital La Fe 2011/0342). Patients were enrolled in the study when they presented the first exacerbation (after signing the informed consent) and required new antibiotic treatment or hospital admission and no subsequent exacerbations for every patient were included.

3. Results. The authors state that there were 32 patients with MDRO which was 20.1% of 159 patients with microorganisms isolated, and but they also state that the 32 MDRO accounted for 20.1% of microorganisms isolated which is not correct as there were 241 microorganisms
isolated according to Table 2 and therefore 32/241 is not 20.1% - they need to correct the statement in the first sentence under microbiological results. And number of MDRO listed is 31 not 32. They must state as to which other bacteria other than MRSA and Pseudomonas were MDR and which Enterobactericeae were MDR. What does the superscript 'a' in Table 2 next to MDR denote as it is not explained at the top or bottom of the Table?

- In the new version, the numbers have been corrected
- Other MDR pathogens are detailed now
- Superscript ‘a’ is now explained at the bottom of the Table 2

4. Follow-up. The first sentence under the sub-heading Follow-up is difficult to understand - what are the numbers in parenthesis represent especially the numerators, as the totals 153 and 73 have not been explained or mentioned before.

- In the new version, the sentence has been rewritten as suggested as follows: “Patients who required admission were more likely to grow MDR organisms than those who did not require admission (27/153 vs 5/80, p:0.016)(Figure 1).”

5. Table 4. In Table 4 - they should include all the other variables that were included in the multivariate analysis even though they were not significant so that the readers can see what was included and what were the odds ratios or p-values.

- In the new Table 4 we have included non-significant variables

6. Figure 1. In Figure 1 - the last blocks must be changed to 'Required or Not Requiring Hospitalizations' because as they stand now, it appears as if the specimens were taken from patients who were in hospital and those who were outpatients which is not my understanding, as all patients were coming in with new exacerbations therefore could not have been hospitalized already.
• In the new Figure 1 the blocks have been changed to “Required or not requiring hospitalization” as suggested

7. Conclusion. Under discussion: In their conclusion to also relate to the main objectives of the study, regarding risk factors.

• In the conclusion the independent risk factors have been specifically related and the paragraph now is as follows:

“Our findings have identified three independent risk factors - hospitalization in the previous year, chronic renal disease, and prior multidrug-resistant isolation - for identification multidrug-resistant pathogens in BE exacerbations. This information may be useful for clinicians in guiding initial antibiotic therapy in exacerbations of BE. A further validation in different BE cohorts including distinct phenotypes and larger follow-up periods should be performed. MDR risk prediction in BE exacerbations is a new field that requires validation for clinical decision-making in selecting initial appropriate antibiotics and for safely avoiding anti-MDR coverage”