Acute lower respiratory infections on lung sequelae in Cambodia, a neglected disease in highly tuberculosis-endemic country

Blandine Rammaert a,b,*, Sophie Goyet a, Arnaud Tarantola a, Sopheak Hem a, Sareth Rith a, Sokleaph Cheng a, Vantha Te c, Patrick Lorn Try d, Bertrand Guillard a, Sirenda Vong a, Charles Mayaud e, Philippe Buchy a, Laurence Borand a

a Institut Pasteur du Cambodge, Phnom Penh, Cambodia
b Université Paris-Descartes, Sorbonne Paris Cité, Hôpital Necker-Enfants Malades, Service des Maladies Infectieuses et Tropicales, APHP, Institut Hospitalo-Universitaire Imagine, Paris, France
c Donkeo Provincial Hospital, Takeo, Cambodia
d Kampong Cham Provincial Hospital, Kampong Cham, Cambodia
e Université Pierre et Marie Curie, Centre de Pneumologie et Réanimation Respiratoire, Hôpital Tenon, APHP, Paris, France

Received 21 April 2013; accepted 23 July 2013
Available online 9 August 2013

KEYWORDS
Bronchiectasis;
Airway remodeling;
Pseudomonas aeruginosa;
Haemophilus influenzae;
Countries;
Developing

Summary
Background: Little is known about post-infectious pulmonary sequelae in countries like Cambodia where tuberculosis is hyper-endemic and childhood pulmonary infections are highly frequent. We describe the characteristics of hospitalized Cambodian patients presenting with community-acquired acute lower respiratory infections (ALRI) on post-infectious pulmonary sequelae (ALRIPS).

Methods: Between 2007 and 2010, inpatients ≥15 years with ALRI were prospectively recruited. Clinical, biological, radiological and microbiological data were collected. Chest radiographs were re-interpreted by experts to compare patients with ALRIPS, on previously healthy lungs (ALRIHL) and active pulmonary tuberculosis (TB). Patients without chest radiograph abnormality or with abnormality suggestive as other chronic respiratory diseases were excluded from this analysis.

Results: Among the 2351 inpatients with community-acquired ALRI, 1800 were eligible: 426 (18%) ALRIPS, 878 (37%) ALRIHL and 496 (21%) TB. ALRIPS patients had less frequent fever than other ALRI (p < 0.001) and more productive cough than ALRIHL (p < 0.001). Streptococcus
Introduction

The United Nations Millennium Development Goals aim to reverse the tuberculosis (TB) epidemic by 2015 [1]. Despite a clear reduction in TB incidence between 2010 and 2011, post-TB pulmonary sequelae remain under-recognized in most countries. The direct link between the number of TB episodes and lung damage is well documented [2]. In addition, widespread lung destruction may occur in spite of effective anti-tuberculous therapy. Subsequent healing may result in extensive fibrosis, bronchostenosis, pleura remodeling with loss of pulmonary volume and traction bronchiectasis [3]. According to the World Health Organization (WHO), Cambodia was the country with the highest documented TB prevalence worldwide at 817/100 000 population in 2012 [1]. Other under-treated bacterial infections such as pulmonary abscesses or purulent pleurisies may also cause pulmonary and/or pleural sequelae. Finally, bronchiectasis may result from acute lower respiratory infections (ALRI) with both tuberculous and severe non-tuberculous pathogens, which are highly prevalent in Cambodian children [4].

Surveillance of ALRI (the SISEA project, Surveillance and Investigation of Epidemics in South-East Asia) conducted in two Cambodian provincial hospitals found a high proportion of pulmonary sequelae diagnosed by systematic chest radiographs [5]. Local clinicians were unaware of this form of chronic respiratory disease. As such – and in absence of systematic microbial identification - patients are denied appropriate antibiotics and usually referred to a specialized TB ward for a standard 6-months anti-TB therapy. We undertook this study to describe the clinical, radiological and microbiological characteristics of patients presenting with ALRI on post-infectious pulmonary sequelae (ALRIPS) included in the project, comparing them to other types of ALRI; the management of ALRIPS patients is also discussed.

Methods

Data from patients in this study were prospectively collected through the community-acquired ALRI surveillance SISEA from April 2007 to July 2010 in two provincial Cambodian hospitals. This surveillance project focused on ALRI epidemiology in Cambodia, a Southeast Asian tropical country. The patient recruitment and assessment methodology is described elsewhere [5–8]. SISEA was approved by the Cambodian National Ethics Committee for Health Research (number 024-NECHR). Patients’ informed consent was obtained prior to any investigation.

Briefly, after including inpatients with lower tract respiratory symptoms for less than 14 days and excluding patients with known immunodeficiency [5–7], hospital physicians recorded demographic, clinical, and therapeutic data as well as on-site biological testing results and outcome. They assigned a final diagnosis to each patient, including that of lung sequelae superinfection. On admission, blood, non-induced sputum, throat and nasopharyngeal samples were collected for direct examination, cultures and molecular diagnostic techniques, performed at Institut Pasteur du Cambodge. Procedures for viral and bacterial assessment have previously been described [6,7,9–12]. Direct sputum examination for acid-fast bacilli (AFB) were performed at the hospital laboratories for each patient on admission and repeated during the following two days. In accordance with Cambodia’s national TB recommendations, culture was not systematically performed. A single chest radiograph per patient was performed on admission. Expert pulmonologists blinded to the patient’s condition re-interpreted chest radiograph and then reviewed patients’ medical files to assign a final diagnosis to each included case.

We extracted from the SISEA database adult patients (aged 15 years and above) with ALRI and abnormal chest radiograph on admission. We then excluded from analysis patients with other respiratory diseases such as pulmonary fibrosis, post-tobacco emphysema, pneumothorax and thoracic deformation. We thus classified patients into three groups: ALRIPS, ALRI on presumed previously healthy lung (ALRIHL), and pulmonary TB. We finally excluded patients with positive AFB smears and pulmonary sequelae to avoid confusion in groups’ comparison (Fig. 1).

The ALRIPS group was defined as patients with clinical and biological signs compatible with ALRI and presenting post-infectious pulmonary sequelae on chest radiograph on admission. Post-infectious pulmonary sequelae were defined as radiologically-diagnosed lung lesions highly suggestive of a previous lung infection such as TB, abscesses, purulent pleurisies or bronchiectasis. Severe sequelae were defined by at least combination of two features such as retraction, pleural thickening, fibrosis, bronchiectasis and cavities. Fig. 2 illustrates severe sequelae. Moderate sequelae were defined by the above features taken separately.

The ALRIHL group was defined as patients with clinical, biological and radiological signs compatible with pneumonia, pleurisy, pleuropneumonia or pulmonary abscess and chest radiograph showing no signs of post-infectious sequelae.

\textit{pneumoniae, Haemophilus influenzae, and Pseudomonas aeruginosa} accounted for 83% of ALRIPS group positive cultures. \textit{H. influenzae} and \textit{P. aeruginosa} were significantly associated with ALRIPS compared with ALRIHL. Treatment was appropriate in 58% of ALRIPS patients. Finally, 79% of ALRIPS were not recognized by local clinicians. In-hospital mortality was low (1%) but probably underestimated in the ALRIPS group.

\textbf{Conclusion:} ALRIPS remains often misdiagnosed as TB with inappropriate treatment in low-income countries. Better-targeted training programs would help reduce the morbidity burden and financial costs.

© 2013 Elsevier Ltd. All rights reserved.
As recommended by WHO, pulmonary TB, was confirmed by bacteriology or diagnosed by a clinician [13]. Smear-positive and smear-negative cases met the WHO definition [13].

The definitions of clinical conditions, diabetes, renal impairment, cardiovascular disease and severity were described elsewhere [6,7]. First-line antibiotherapy was defined as the antibiotics regimen received during the first three days of hospitalization.

**Statistical analysis**

Median and interquartile range (IQR) were calculated for continuous data. Number and percentages were determined for categorical data. Characteristics of patients with ALRIPS were initially compared to those of patients with ALRIHL and to those of active pulmonary TB cases using either Chi-square, or non-parametric tests (Kruskal–Wallis), as appropriate.

To identify clinical risk factors of having a superinfection on pulmonary sequelae on admission, the following variables with p values <0.2 were then introduced in backward stepwise logistic regression analysis: age in 10-year classes, gender, comorbidities, clinical signs, and severity.

Statistical significance was defined at a 5% threshold (p < 0.05). Odd ratios (ORs) are shown only for variables remaining significant within the final model. Analyses were performed using Stata 12® (Stat Corp., College Station, TX, USA) software program.

**Results**

**Demographic, clinical, microbiological and therapeutic characteristics of ALRIPS**

Among 2351 patients aged 15 years and above included in the surveillance project, 1831 cases with abnormal chest
were susceptible to amoxicillin. S. pneumoniae and Pseudomonas aeruginosa accounted for 91 (83%) of the 109 positive sputum and one blood culture. Of the 51 strains with antibiograms, 23 (45%) produced a positive antibiotic susceptibility testing results, 23 (45%) of the 51 H. influenzae strains with antibiotic susceptibility testing results, 23 (45%) produced a penicillinase, but all of those remained susceptible to amoxicillin-clavulanate. All the isolated strains of S. pneumoniae were susceptible to amoxicillin. P. aeruginosa presented no resistance, except to ciprofloxacin in two (13%) strains. Concurrent virus detection was noted in 15 (3.5%) patients. Four chest radiographs were highly suggestive of aspergilloma but fungal culture of sputum samples could not be performed.

The first-line antibiotic prescribed in ALRIPS was penicillin A for 283 (66%) patients, in combination with aminoglycosides for 47 (11%). Only 33 (8%) patients received amoxicillin-clavulanate, which was not available at hospital pharmacies, and 15 (3.5%) ceftriaxone. Treatment was correctly adapted to subsequently available antibiotic susceptibility testing results for 198 (61%) patients, including 58% (30/52) of patients with H. influenzae, 74% (17/23) with S. pneumoniae, none (0/15) with P. aeruginosa, and 42% (5/12) with Klebsiella pneumoniae. The median duration of treatment was seven days (IQR 5–10 days). The median length of stay at hospital was ten days (IQR 7–14 days). In total, six (1%) patients died in hospital; 350 (82%) went home with or without medical discharge.

According to experts’ review, ALRIPS were recognized by local clinicians in 108 (25%) patients, while 56 (13%) were misdiagnosed as TB cases including 29 (52%) who were transferred to another hospital and 8 (9%) to another ward (mainly TB ward).

### Table 1  Demographic, clinical characteristics and univariate analysis comparing patients aged ≥15 years with acute lower respiratory infections (ALRI) on pulmonary sequelae (ALRIPS) (reference group), ALRI on previously healthy lungs (ALRIHL) and active pulmonary tuberculosis (TB), SISEA study, Cambodia, 2007–2010.

|                         | ALRIPS        | ALRIHL        | p   | TB             |
|-------------------------|---------------|---------------|-----|----------------|
|                         | n = 426       | n = 878       |     | n = 496        |
| Demographic             |               |               |     |                |
| Age in years, median (IQR) | 60 (52–70)    | 55 (42–66)    | <0.001 | 52 (40–65) |
| Male gender             | 198 (45.9)    | 439 (50.0)    | 0.233 | 268 (54.0) |
| Co-morbidities          |               |               |     |                |
| At least one co-morbidity | 143 (33.6)    | 402 (45.8)    | <0.001 | 178 (35.9) |
| Cardiovascular disease  | 25 (5.9)      | 151 (17.2)    | <0.001 | 19 (3.8)  |
| Diabetes                | 42 (9.9)      | 124 (14.1)    | 0.03  | 58 (11.7) |
| Liver disease           | 2 (0.5)       | 9 (1.0)       | 0.304 | 6 (1.2)   |
| Renal impairment        | 4 (0.9)       | 8 (0.9)       | 0.961 | 3 (0.6)   |
| Tobacco use             | 47 (11.0)     | 89 (10.10)    | 0.619 | 67 (13.5) |
| Excessive alcohol consumption | 71 (16.7)  | 142 (16.2)    | 0.821 | 100 (20.1) |
| Clinical characteristics |               |               |     |                |
| Severity                | 11 (2.6)      | 83 (9.4)      | <0.001 | 22 (4.4)  |
| Hypoxemia               | 18 (4.2)      | 64 (7.3)      | 0.03  | 21 (4.2)  |
| Hemoptysis              | 68 (16.0)     | 54 (6.1)      | <0.001 | 59 (11.9) |
| Cough                   | 423 (99.3)    | 871 (99.2)    | 0.857 | 491 (99.0) |
| productive cough        | 372 (87.3)    | 576 (65.6)    | <0.001 | 413 (83.3) |
| Fever                   | 185 (43.4)    | 611 (69.6)    | <0.001 | 261 (52.6) |
| Treated prior to admission | 264 (62.0)  | 416 (47.4)    | <0.001 | 290 (58.5) |
| Outcome                 |               |               |     |                |
| Discharged alive        | 350 (82.2)    | 600 (68.3)    | <0.001 | 156 (31.5) |
| Transferred to another ward | 70 (16.4)   | 235 (26.8)    | <0.001 | 331 (66.7) |
| Died or was discharged for death at home | 6 (1.4) | 43 (4.9) | 0.002 | 9 (1.8) |
| Length of hospital stay (days) | 10 (7–14) | 7 (4–11)  | <0.001 | 6 (3–9) |

Results are expressed as n (%), otherwise specified. Significant values (p < 0.05) are in bold.
Comparison of ALRIPS with ALRIHL and TB patients

Results of univariate analysis are shown in Table 1. In comparison with ALRIHL and TB, ALRIPS patients were significantly older, 338 (80%) being aged 50 years and above (Fig. 3), and had less fever (43.4% vs. 69.6%; \( p < 0.001 \); [vs. 52.6%; \( p = 0.005 \]), respectively). They also stayed significantly longer at hospital than both other groups, even though they were more frequently alive at discharge.

Bacteria cultures were more often positive in ALRIPS than in both other groups (26.6% vs. 18.9%; \( p < 0.03 \); [vs. 10.5%; \( p < 0.001 \), respectively]. \( H. \) influenzae, \( Pseudomonas \) aeruginosa and \( K. \) pneumoniae were more frequently isolated in samples from patients with ALRIPS than from both other groups (Table 2). There was no significant difference for virus yield between groups.

Results of the multivariate analysis are presented in Table 3. Briefly, the ALRIPS group differed from ALRIHL in terms of: older age (over 50 years); less known cardiovascular disease and diabetes; less fever; more productive cough; more hemoptysis; and less severity on admission. In comparison with TB patients, patients with ALRIPS were 40 years and over, had less fever and more hemoptysis.

Discussion

Our findings indicate that clinicians and public health specialists are little aware of the burden of unrecognized sequelae in a TB-endemic country. In our study, nearly one in four adult patients admitted for ALRI presented superinfection on post-infectious sequelae. These patients were mostly aged 50 and above. Chronic pulmonary disease was often very advanced and associated with Gram-negative bacilli and \( S. \) pneumoniae. Although AFB smears remained negative, these cases of superinfected sequelae were misdiagnosed and sometimes treated as active TB. Furthermore, the empiric first-line antibiotic treatment used was inappropriate according to the antibiotic susceptibility testing results in nearly one in three cases.
Clinical features were not helpful in distinguishing between active TB, ALRIHL and ALRIPS. Patients in the ALRIPS group had more productive cough and were less often febrile than in the other groups. But taken individually, these symptoms are poor clinical indicators. Hemoptysis was more prevalent in the ALRIPS group compared to both other groups, which is unsurprising due to the frequency of bronchiectasis in post-infectious sequelae. The relatively high proportion of hemoptysis in ALRIHL group may be due to necrotizing bacteria, *K. pneumoniae* or *B. pseudomallei*, which have previously been described by our team, or to environmental contaminations cannot be excluded[25]. Clinical features were not helpful in distinguishing between active TB, ALRIHL and ALRIPS. Patients in the ALRIPS group had more productive cough and were less often febrile than in the other groups. But taken individually, these symptoms are poor clinical indicators. Hemoptysis was more prevalent in the ALRIPS group compared to both other groups, which is unsurprising due to the frequency of bronchiectasis in post-infectious sequelae. The relatively high proportion of hemoptysis in ALRIHL group may be due to necrotizing bacteria, *K. pneumoniae* or *B. pseudomallei*, which have previously been described by our team, or to environmental contaminations cannot be excluded[25].

As *Aspergillus* spp. may also colonize bronchiectasis and pre-existing cavities, enhancing hemoptysis when aspergillosis erode bronchial arteries[23]. A short prevalence assessment from the same prospective study performed in 2010 among 138 consecutive patients showed that 21 (15%) were infected with non-tuberculous mycobacteria (i.e *Mycobacterium avium intracellulare*, *M. scrofulaceum*, *M. abscessus*, *M. fortuitum*, *Mycobacterium* spp.) in at least one of three consecutive sputum samples (Institut Pasteur in Cambodia unpublished data). Of these 21 patients, nine presented with ALRIPS. It has been shown that patients with bronchiectasis and post-TB sequelae have a higher risk than other chronic respiratory diseases to develop non-tuberculous mycobacteriosis[24]. Nevertheless, the pathogenicity of atypical mycobacteria is difficult to establish in this study and environmental contaminations cannot be excluded[25].

The currently first-line empirical antibiotic used for ALRI in Cambodia is penicillin A, which remained active on 74% of *Streptococcus pneumonia* strains found in the ALRIPS group. However, 42% of isolated *H. influenzae* and all *P. aeruginosa* strains were resistant to this antibiotic. Cambodian antibiotics guidelines for ALRI are currently under revision and will be adjusted to the local epidemiology. In theory, amoxicillin-clavulanate, ceftriaxone or cefotaxime, or fluoroquinolones are possible choices for first line therapy. There are, however, two major obstacles to the broad use of fluoroquinolones as first-line empirical treatment in Cambodia. On one hand, ofloxicine and ciprofloxacine are not effective as anti-pneumococcal drugs and 13% of *P. aeruginosa* were resistant to ciprofloxacin in our study. On the other hand,
fluroquinolones currently remain active in TB. [26]. Generalization of fluroquinolones use could therefore delay TB diagnosis, and trigger widespread emergence of resistant TB strains [27]. Since the presentation of the ALRIPS patients was less severe on admission, fluroquinolones could be proposed in this group only as a second-line therapy if the first-line treatment is found to be ineffective upon re-evaluation and after the results of AFB screening.

Hospital stay was longer in the ALRIPS group contributing to direct and indirect cost for patient’s family. In addition, the low percentage of mortality in this study may be due to under-reported deaths. Patients frequently died at home just after discharge, as already shown in another Cambodian publication about ALRI patients infected with K. pneumonia and in a Vietnamese study in HIV-TB co-infected patients [7,28].

One limitation of the study is that diagnosis was based on only one chest radiograph performed on admission. The SISEA project lacked funding to perform follow-up radiological assessment. Most (86%) of the radiographs in our ALRIPS group showed obvious sequelae, which could have easily been recognized by clinicians. However, chest radiographs have limited sensitivity to detect mild abnormalities, and especially bronchiectasis. Some cases with mild bronchiectasis could have been classified in ALRIHL group. In a Thai study on bronchiectasis, 10% of the patients with bronchiectasis detected by computed tomography (CT) scan had a normal chest radiograph [19]. CT scan would have been a better diagnosis tool than chest radiograph in this case, but unfortunately it is not available in Cambodian provincial hospitals.

Conclusion

In conclusion, clinical misdiagnosis and mismanagement of superinfections on post-infectious pulmonary sequelae are frequent and represent a serious threat to patients, to public health and to healthcare finances in a TB-hyperendemic country such as Cambodia. Improving the detection of chronic bronchitis signs, training clinicians on chest radiograph interpretation, implementing mycobacteria culture in Cambodian’s laboratories, and implementing the use of simple spirometric measures could help this diagnosis. Further studies are needed to assess the decline of forced expiratory volume and the reduction of the long-term functional prognosis and quality of life of Cambodian patients, in addition to assess the generating added costs to families and the Cambodian health system.

Funding

Substantial contribution to conception and design: LB, PB, CM, BG, SV, AT, SG, BR; acquisition of data: VT, PLT, SG, SH, BR, SR, SC, BG; analysis and interpretation of data: BR, SG, LB, AT, CM; drafting the article: BR, SG, LB; revising it critically for important intellectual content: PB, CM, SV, AT; final approval of the version to be published: all authors; BR, SG and LB are the guarantors of the paper.

Surveillance and Investigation of endemic situations in South-East Asia (SISEA) was funded by the French Agency for Development (Agence Française de Développement, AFD) and the US Department of Human and Health Services (US DHHS). Blandine Rammaert received a grant from the Fondation Pierre Ledoux Jeunesse Internationale and the Société de Pathologie Infectieuse de Langue Française.

Conflict of interest

All authors declared no competing interests for the present work. BR received a travel grant from MSD and Gilead.

Acknowledgments

We gratefully acknowledge the patients who agreed to participate to this study. We are also grateful to Kampong Cham and Donkeo hospitals’ care givers for their contribution to this study and for patients’ care.

References

[1] WHO/Global tuberculosis report 2012 [Internet]. WHO. Available from: http://www.who.int/tb/publications/global_report/en/index.html [cited 2012 Oct 31].
[2] Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax 2000;55:32–8.
[3] Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GAW. Lung remodeling in pulmonary tuberculosis. J Infect Dis 2005;192:1201–9.
[4] WHO/Cambodia [Internet]. WHO. Available from: http://www.who.int/countries/khm/en/ [cited 2012 Jun 23].
[5] Vong S, Guilhard B, Borand L, Rammaert B, Goyet S, Te V, et al. Acute lower respiratory infections in >5 year-old hospitalized patients in Cambodia, a low-income tropical country: clinical characteristics and pathogenic etiology. BMC Infect Dis 2013;13:97.
[6] Rammaert B, Beauté J, Borand L, Hem S, Buchy P, Goyet S, et al. Pulmonary melioidosis in Cambodia: a prospective study. BMC Infect Dis 2011;11:126.
[7] Rammaert B, Goyet S, Beauté J, Hem S, Te V, Try PL, et al. Klebsiella pneumoniae related community-acquired acute lower respiratory infections in Cambodia: clinical characteristics and treatment. BMC Infect Dis 2012;12:3.
[8] Guerrier G, Goyet S, Chheng ET, Rammaert B, Borand L, Te V, et al. Acute viral lower respiratory tract infections in Cambodian children: clinical and epidemiologic characteristics. Pediatr Infect Dis J 2013;32:e8–13.
[9] Arnott A, Vong S, Sek M, Naughtin M, Beauté J, Rith S, et al. Genetic variability of human metapneumovirus amongst an all ages population in Cambodia between 2007 and 2009. Infect Genet Evol [Internet]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21292032; 2011 Feb 1 [cited 2012 Jun 20].
[10] Arnott A, Vong S, Mardy S, Chu S, Naughtin M, Sovann L, et al. A study of the genetic variability of human respiratory syncytial virus (HRSV) in Cambodia reveals the existence of a new HRSV group B genotype. J Clin Microbiol 2011;49:3504–13.
[11] Arnott A, Vong S, Rith S, Naughtin M, Ly S, Guilhard B, et al. Human bocavirus amongst an all-ages population hospitalised with acute lower respiratory infections in Cambodia. Influenza Other Respir Viruses [Internet]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22531100; 2012 Apr 25 [cited 2012 Jun 20].
[12] Buecher C, Mardy S, Wang W, Duong V, Vong S, Naughtin M, et al. Use of a multiplex PCR/RT-PCR approach to assess the
viral causes of influenza-like illnesses in Cambodia during three consecutive dry seasons. J Med Virol 2010;82:1762–72.

[13] WHO. Table 5. Definitions of tuberculosis cases and treatment outcomes [Internet]. WHO. Available from: http://www.who.int/tb/publications/global_report/2007/table_5/en/ [cited 2013 Feb 3].

[14] WHO/Cambodia. Tuberculosis profile [Internet]. Available from: https://extranet.who.int/sree/Reports;op=Replet&name=WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=KH &outtype=html [cited 2012 Oct 23].

[15] Weinreich UM, Korsgaard J. Bacterial colonisation of lower airways in health and chronic lung disease. Clin Respir J 2008; 2:116–22.

[16] King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Microbiologic follow-up study in adult bronchiectasis. Respir Med 2007;101:1633–8.

[17] Angrill J, Agustı´ C, de Celis R, Rahó A, Gonzalez J, Solé T, et al. Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. Thorax 2002;57: 15–9.

[18] Albertson TE, Chan AL. Antibiotic therapy in elderly patients with acute exacerbation of chronic bronchitis. Expert Rev Respir Med 2009;3:339–48.

[19] Palwatwichai A, Chaoprasong C, Vattanathum A, Wongsa A, Jatakanon A. Clinical, laboratory findings and microbiologic characterization of bronchiectasis in Thai patients. Respirology 2002;7:63–6.

[20] Ho PL, Chan KN, Ip MS, Lam WK, Ho CS, Yuen KY, et al. The effect of Pseudomonas aeruginosa infection on clinical parameters in steady-state bronchiectasis. Chest 1998;114: 1594–8.

[21] Kelly MG, Murphy S, Elborn JS. Bronchiectasis in secondary care: a comprehensive profile of a neglected disease. Eur J Intern Med 2003;14:488–92.

[22] Wilson CB, Jones PW, O’Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. Eur Respir J 1997;10: 1754–60.

[23] Cesar JM, Resende JS, Amaral NF, Alves CM, Vilhena AF, Silva PL. Cavernoectomy x resection for pulmonary aspergiloma: a 32-year history. J Cardiothorac Surg 2011;6:129.

[24] Andréjak C, Nielsen R, Thomsen VØ, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax 2012;68:256–62.

[25] Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367–416.

[26] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JM, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med 2012;9: e1001300.

[27] Chen T-C, Lu P-L, Lin C-Y, Lin W-R, Chen Y-H. Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis. Int J Infect Dis 2011;15:e211–216.

[28] Ngo AT, Duc NH, Lan NH, Maynart M, Mayaud C, Quy TH. Mechanisms and causes of death in 143 Vietnamese HIV-infected patients hospitalized for tuberculosis. Rev Pneumol Clin 2007;63:139–46.