



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

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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*

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pneumoniae, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* accounted for 83% of ALRIPS group positive cultures. *H. influenzae* and *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.

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.

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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 pleuritis 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 pleuritis 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, pleuro-pneumonia or pulmonary abscess and chest radiograph showing no signs of post-infectious sequelae.

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