



**University of Dundee**

**Evaluation of severity score-guided approaches to macrolide use in community-acquired pneumonia**

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## **SUPPLEMENTARY METHODS**

### **INCLUSION/EXCLUSION CRITERIA FOR INDIVIDUAL COHORTS**

#### **Milan cohort**

##### ***Inclusion criteria:***

Pneumonia was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization associated with 1 of the following: (1) new or increased cough with/without sputum production; (2) fever ( $>37.8^{\circ}\text{C}$ ) or hypothermia ( $<35.6^{\circ}\text{C}$ ); or (3) abnormal white blood cell count (either leukocytosis or leukopenia), or C-reactive protein values above the local upper limit.

##### ***Exclusion criteria:***

Hospitalisation within 15 days prior to admission

#### **FAILCAP cohort**

##### ***Inclusion criteria:***

1. New pulmonary infiltrate seen on chest radiograph or CT Scan of the chest within 48 hours after hospitalization. (The finding of infiltrate by chest radiograph or other imaging technique is "required" for the diagnosis of pneumonia, according to the 2007 consensus guidelines from the Infectious Diseases Society of America and the American Thoracic Society (2). Patients identified during the screening process will be enrolled if a chest radiograph or CT Scan of the chest taken within 48 hours after hospital admission revealed a new infiltrate consistent with pneumonia

*plus at least one of the following:*

2. New or increased cough with/without sputum production
3. Fever (documented temperature -rectal or oral-  $>37.8^{\circ}\text{C}$ ) or hypothermia (documented temperature –rectal or oral-  $<35.6^{\circ}\text{C}$ )
4. Abnormal white blood cell count, either leukocytosis ( $>10,000/\text{cm}^3$ ) or leucopenia ( $<4,000/\text{cm}^3$ )

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***Exclusion criteria:***

Patients who meet at least one of the following definitions will be excluded from the analysis:

- 1) Patient has hospital-acquired pneumonia, defined as pneumonia that develops after 48 hours of the current hospitalization, or pneumonia that develops in a patient who had been discharged from the hospital within the prior 14 days of the current hospitalization.
- 2) Patient is re-admitted with a new episode of pneumonia during the 30-day follow up period.
- 3) Unstable psychiatric or psychological condition rendering the subject unlikely to be cooperative or to complete the study requirements.
- 4) Subject history that in the investigator's opinion would preclude subject compliance with the protocol.

**Edinburgh cohort**

***Inclusion criteria:***

Patients were included in the study if they presented with a new infiltrate on chest radiograph and had 3 or more of the following symptoms or signs (cough, sputum production, breathlessness, pleuritic chest pain or signs consistent with pneumonia on auscultation).

***Exclusion criteria:***

Hospital-acquired pneumonia (development of symptoms >48 hours following admission or discharge from an acute care facility <2 weeks prior to admission); active thoracic malignancy; immunosuppression (defined as current (>28 day) use of oral prednisolone at any dose or other immunosuppressive drugs (methotrexate, azathioprine, cyclosporin and anti-tumour necrosis factor alpha agents) or patients

with solid organ transplantation); pulmonary embolism and patients in whom active treatment was not considered appropriate (palliative care).

### **Barcelona cohort**

#### ***Inclusion criteria:***

Adult patients (>18 years) presenting with pneumonia, defined as the presence of a new infiltrate on a chest radiograph together with clinical symptoms that were suggestive of lower respiratory tract infection (*e.g.* fever, cough, sputum production, pleuritic chest pain).

#### ***Exclusion criteria:***

1) patients without a positive microbiologic diagnosis, 2) severe immunosuppression (AIDS, chemotherapy, immunosuppressive drugs [*e.g.*, oral corticosteroid  $\geq 10$  mg prednisone or equivalent per day for at least two weeks]), 3) health care-associated pneumonia cases, 4) active tuberculosis, 5) patients with cystic fibrosis, and 6) cases with a confirmed alternate diagnosis

### **Microbiological testing for atypical pathogens**

#### **Milan and FAILCAP cohorts:**

##### ***PCR based identification***

Nested PCR with primers amplifying 207-bp fragment of major outer membrane protein genes (*ompA*) of *Chlamydia pneumoniae*, 104-bp fragment P1 protein antigen of *Mycoplasma pneumoniae* and 403-bp fragment of the macrophage infectivity potentiator protein (MIP) of *Legionella pneumophila* were used. After amplification, 4% agarose gel electrophoresis and sybr safe DNA stain were used to visualise the PCR products.

##### ***Serology:***

*Chlamydia pneumoniae*: the presence of serum antibodies (IgG, IgA, IgM) was determined by the ANI Labsystems microimmunofluorescence (MIF) test. The serum

samples were considered positive when there were titers of >1:64 for IgG antibodies and >1:16 for IgA and IgM.

*Mycoplasma pneumoniae*: the detection of serum antibodies (IgG, IgM) was determined by an enzyme-linked immunosorbent assay (ELISA) (Viro-Immun Labor – Diagnostika GmbH).

**Edinburgh cohort:**

Testing for atypical pathogens (urine testing for Legionella and PCR based testing for *M. pneumoniae* and *C. pneumoniae*) was conducted in accordance with the British Thoracic Society/NICE guidelines, as previously reported<sup>9</sup>.

**Barcelona cohort:**

Blood samples for serology of atypical pathogens were performed at admission and within the third and sixth week thereafter. The etiology was considered definite if the following criteria was met: 1) elevated serum levels of IgM against *C. pneumoniae* ( $\geq 1:64$ ), *C. burnetii* ( $\geq 1:80$ ) and *M. pneumoniae* (any positive titre) 2) seroconversion (ie, a fourfold increase in IgG titres) for *C. pneumoniae* and *L. pneumophila* >1:128, *C. burnetii* >1:80

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