Amoxicillin versus Placebo in patients with acute lower-respiratory-tract infection in primary care when pneumonia is not suspected\(^1\) (e.g. bronchitis)

**BOTTOM LINE**

- In adult primary care patients with acute lower-respiratory tract infections (LRTI) where pneumonia is not suspected, amoxicillin 1g po TID x 7 days, versus placebo:
  - did **not** ↓ the duration of symptoms (rated "moderately bad" or worse) or ↓ symptom severity within the first 2-4 days
  - did ↓ new or worsening symptoms (NNT=30) NS for those ≥60 years of age, but ↑ the risk of adverse events (e.g. nausea, rash, diarrhea, NNH=22)
- This study does not change how acute LRTIs are managed in adults when pneumonia is **not** suspected.

**Antibiotics are not recommended because of limited to no benefit & increased risk of harm.**

**BACKGROUND**

- Acute LRTIs in primary care include bronchitis and pneumonia.
  - Unless pneumonia is suspected, Canadian guidelines recommendation against the use of antibiotics as the etiology is usually viral.\(^2,3\)
  - A 2014 Cochrane review of antibiotics versus placebo for acute bronchitis (17 RCTs, n=3,936) showed patients given antibiotics were less likely to have cough (NNT= 6), but there was no difference in clinical improvement.\(^4\)
  - In an analysis of a database in the UK for respiratory tract infections that excluded pneumonia at baseline, researchers found that antibiotics decreased the risk of pneumonia as a complication (especially in ≥65 years).\(^5\)
  - With conflicting information, the authors wanted to determine the benefits (on symptoms) and harms of amoxicillin in acute LRTI.
  - They were also interested in determining whether certain subgroups of patients could benefit from treatment (e.g. ≥60 years).

**TRIAL BACKGROUND**

**DESIGN:** parallel, randomized, blinded (patients, clinicians, statisticians), placebo-controlled (appearance, taste, texture similar to active medication), ITT, Nov 2007-Apr 2010, primary care setting, multicentre (16 networks in 12 countries from the UK or Europe) with concealed allocation. Funding: European Commission Framework Programme, UK National Institute for Health Research, Barcelona Ciberde Enfermedades Respiratorias, Research Foundation Flanders.

**INTERVENTION:** amoxicillin 1g po TID x7 days vs. placebo

- for duration of illness (primary outcome): patients completed a validated, daily symptom diary for the duration of their illness (maximum 28 days), and each symptom was scored from 0 to 6. (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be)

**INCLUSION:** ≥18 yrs., acute cough (<28d duration) as main symptom, or an illness in which cough was not the main symptom but a clinician thought acute LRTI was the most probable diagnosis.

**EXCLUSION:** suspected or actual pneumonia (subjective), cough of non-infective cause, antibiotics used in previous month, could not provide informed consent, or complete a diary, pregnant, penicillin allergy, immunological deficiencies. Co-morbidities (e.g. asthma, COPD) were not excluded.

**POPULATION** at baseline: n=2,061 randomized, ~59% \(\geq 60\) yrs.

- mean baseline severity scores (4-point scale used): all symptoms = 2.1 (mild problem), cough = 3.2 (moderate problem); illness duration before index date ~9.4 days
- mean age ~49 years (±16.5years) (~29% ≥60 years), respiratory rate 16.9 bpm, body temperature 36.8°C
- past or present non-smoker ~46.5%, lung disease (asthma or COPD) ~15%, sputum production ~79%, discoloured sputum ~49%
- recruitment met sample sizes requirements for the primary outcome whole cohort, and subgroup analysis

**RESULTS**

**TABLE 1: EFFICACY & SAFETY**

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>AMOXICILLIN 1G PO TID X7DAYS (n=1038)</th>
<th>PLACEBO X7DAYS (n=1023)</th>
<th>GROUP</th>
<th>n</th>
<th>COMPARISON (95% CI)</th>
<th>NNT/NNH (TREATED X7D, FOLLOW UP MAX. 28D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY ENDPOINT</td>
<td></td>
<td></td>
<td>Whole cohort</td>
<td>1799/2061 (87.3%)^*</td>
<td>HR 1.06 (0.96-1.18)  HR 1.04 (excluded asthma or COPD &amp; found little difference)</td>
<td></td>
</tr>
<tr>
<td>Median duration of symptoms (rated by patients as “moderately bad” or worse after initial presentation)</td>
<td>6 days (IQR 3-11)</td>
<td>7 days (IQR 4-14)</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>≤60 yrs</td>
<td>550</td>
<td>HR 0.95 (0.79-1.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yrs</td>
<td>1249</td>
<td>HR 1.12 (0.98-1.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SECONARY ENDPOINTS</td>
<td></td>
<td></td>
<td>Whole cohort</td>
<td>1789/2061 (86.8%)</td>
<td>Difference -0.07 (-0.15 to 0.007)</td>
<td></td>
</tr>
<tr>
<td>Symptom severity (mean diary score for all symptoms on days 2-4)</td>
<td>1.69 (SD 0.84)</td>
<td>1.62 (SD 0.84)</td>
<td>Whole cohort</td>
<td>1789/2061 (86.8%)</td>
<td>Difference -0.07 (-0.15 to 0.007)</td>
<td></td>
</tr>
<tr>
<td>≥60 yrs</td>
<td>547</td>
<td>Difference -0.03 (-0.17 to 0.11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yrs</td>
<td>1242</td>
<td>Difference -0.08 (-0.18 to 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New or worsening symptoms (requiring visit to physician or hospitalization)</td>
<td>15.9% (162/1021)</td>
<td>19.3% (194/1006)</td>
<td>Whole cohort</td>
<td>2027/2061 (98.3%)</td>
<td>OR 0.79 (0.63-0.99)</td>
<td></td>
</tr>
<tr>
<td>≥60 yrs</td>
<td>584</td>
<td>OR 0.97 (0.64-1.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yrs</td>
<td>1443</td>
<td>OR 0.72 (0.55-0.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, rash, diarrhea</td>
<td>28.7% (249/867)</td>
<td>24% (206/860)</td>
<td>Whole cohort</td>
<td>1727</td>
<td>p&lt;0.025</td>
<td>NNH 22</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>Whole cohort</td>
<td>1727</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Authors state that symptoms were recorded in 1807 patients (amoxicillin n=908, placebo n=899). However, the numerator used is n=1799.
Adherence, as determined by medications taken on day 5 was 92.4% (778/842) for amoxicillin, and 90.1% (746/828) for placebo. It was unclear why the randomized denominator for each group was not used, which would result in amoxicillin adherence 75% (778/1038), and placebo 73% (746/1023).

Loss to follow up in the amoxicillin group was 12.5% (130/1038), and in the placebo group it was 12.1% (124/1023). Authors assessed effects of this loss by estimating the change in hazard ratio for several assumptions about resolution of symptoms. This did not affect the conclusions about the primary outcome.

**STRENGTHS, LIMITATIONS, & UNCERTAINITIES**

**STRENGTHS:**
- Likely the largest, multicentred, randomized, placebo-controlled study of antibiotics for acute LRTI, when pneumonia is not suspected in primary care.
- Daily symptom diary used was validated.
- Similar to real-world clinical practice where the patient diagnosis is initially unknown.
- The amoxicillin dose used (1g po tid) is double the usual Canadian dose (500mg po tid). This trial showed that high dose amoxicillin is no better than placebo for the most important endpoints.

**LIMITATIONS:**
- Recruitment took >30 minutes, so not all potential patients were screened. It’s possible that more complex and elderly patients were not included, so these results would not be applicable to them.
- Since a prediction rule for the diagnosis of pneumonia was not used (pneumonia was diagnosed clinically), it’s not possible to confirm whether all non-pneumonia patients were included, or whether all pneumonia was truly excluded. Older patients may have been more likely to be excluded, clinically.

**UNCERTAINITIES:**
- The high dose amoxicillin is recommended for AECOPD,\(^2\) Bugs & Drugs and the benefit in new or worsening symptoms may be due to this subgroup.
- It is unknown whether a lower dose could still decrease new or worsening symptoms while minimizing side-effects.

**RxFILES RELATED LINKS**


---

**ACKNOWLEDGEMENTS:** Contributors & Reviews: Loren Regier, Brent Jensen, Lynette Kosar  Prepared By: Anne Nguyen, Andrew Plishka

**DISCLAIMER:** The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of Saskatoon Health Region (SHR). Neither the authors nor Saskatoon Health Region nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of SHR, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources. Additional information and references online at [www.RxFiles.ca Copyright 2017 – RxFiles, Saskatoon Health Region (SHR)]

---