

# Amoxicillin versus Placebo in patients with acute lower-respiratory-tract infection in primary care when pneumonia is not suspected<sup>1</sup> (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.<sup>2,3</sup>
- 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.<sup>4</sup>
- 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).<sup>5</sup>
- 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% ♀

- 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

follow-up: 28 days

TABLE 1: EFFICACY & SAFETY

CLINICAL ENDPOINTS	AMOXICILLIN 1G PO TID x7DAYS n=1038	PLACEBO x7DAYS n=1023	GROUP	n	COMPARISON (95% CI) AMOXICILLIN VS. PLACEBO	NNT/NNH (TREATED x7D, FOLLOW UP MAX. 28D)
<b>PRIMARY ENDPOINT</b>						
Median duration of symptoms (rated by patients as “moderately bad” or worse after initial presentation)	6 days (IQR 3-11)	7 days (IQR 4-14)	Whole cohort	1799/2061 (87.3%)*	HR 1.06 (0.96-1.18) HR 1.04 (excluded asthma or COPD & found little difference)	NS
			≥60 yrs	550	HR 0.95 (0.79-1.14)	
			<60 yrs	1249	HR 1.12 (0.98-1.24)	
<b>SECONDARY ENDPOINTS</b>						
Symptom severity (mean diary score for all symptoms on days 2-4)	1.69 (SD 0.84)	1.62 (SD 0.84)	Whole cohort	1789/2061 (86.8%)	Difference -0.07 (-0.15 to 0.007)	NS
	1.5 (SD 1.02)	1.47 (SD 0.94)	≥60 yrs	547	Difference -0.03 (-0.17 to 0.11)	
	1.78 (SD 0.85)	1.69 (SD 0.85)	<60 yrs	1242	Difference -0.08 (-0.18 to 0.01)	
New or worsening symptoms (requiring visit to physician or hospitalization)	15.9% (162/1021)	19.3% (194/1006)	Whole cohort	2027/2061 (98.3%)	OR 0.79 (0.63-0.99)	NNT 30
	18.9% (54/285)	19.4% (58/299)	≥60 yrs	584	OR 0.97 (0.64-1.47)	NS
	14.7% (108/736)	19.2% (136/707)	<60 yrs	1443	OR 0.72 (0.55-0.95)	NNT 22
Nausea, rash, diarrhea	28.7% (249/867)	24% (206/860)	Whole cohort	1727	p=0.025	NNH 22
Death	0	0	Whole cohort	-	-	-

\*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, & UNCERTAINTIES**

- 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 >30minutes, 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.
- UNCERTAINTIES:**
- The high dose amoxicillin is recommended for AECOPD,<sup>2</sup> 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.

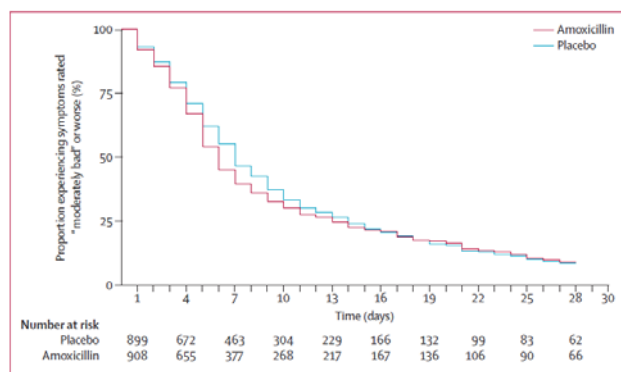


Figure 2: Kaplan-Meier estimates for duration of symptoms rated "moderately bad" or worse

**RxFILES RELATED LINKS**

- RxFiles Acute Bronchitis: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/ABX-Acute%20Bronchitis.pdf>
- RxFiles Viral Prescription Pad (available in 14 languages): <http://www.rxfiles.ca/rxfiles/uploads/documents/ABX-Viral-Prescription-Pad-Languanges.pdf>
- RxFiles Poster for Patient Exam Rooms (Bronchitis): <http://www.rxfiles.ca/rxfiles/uploads/documents/BRONCHITIS-ABX.pdf>

X =non-formulary in SK ⊗=not covered by NIHB ☞=Exceptional Drug Status in SK ♀=female AECOPD=acute exacerbation of chronic bronchitis bpm=breaths per minute CI=confidence interval HR=hazard ratio IQR=interquartile range ITT=intention to treat NNH=numbers needed to harm NNT=numbers need to treat NS=not statistically significant OR=odds ratio SD=standard deviation RCTs=randomized controlled trials yrs=years old

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<sup>1</sup> Little P, Stuart B, Moore M et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013;13:123-29.  
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<sup>3</sup> Balter MS, LaForge J, Low DE et al. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. *Can Respir J* 2003;10(Suppl B): 3B-32B.  
<sup>4</sup> Smith S, Fahey T, Smucny J et al. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2014;3: CD000245.  
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