Clinical Context / Question: In patients with COPD, acute exacerbations are associated with a decreased quality of life, more rapid decline in lung function, and increased risk of death. In fact, the 30-day mortality of an acute COPD exacerbation is 26%, compared with 7.8% for a myocardial infarction. The cost of COPD exacerbations is also substantial, particularly when requiring hospital or ICU admission.

Macrolides have immunomodulatory and antiinflammatory effects, including the inhibition of pro-inflammatory enzymes and cytokines from bacteria and immune cells, stimulation of macrophages, and reduction of mucus secretion. As such, they have been used long-term in the treatment of cystic fibrosis to reduce airway inflammation.

With this in mind, can taking a macrolide regularly as an outpatient reduce the frequency with which patients with COPD present to the ER or are hospitalized for COPD exacerbations?

Search Strategy
Database: PubMed
- Limits: Randomized, controlled trial; humans; English
- Search terms: “Antibiotic COPD exacerbation prevention”
- Results: 40

Selected article:
Population screened
- Patients recruited from 17 sites associated with 12 academic health centers in the U.S.

Inclusion criteria
- People who were 40 years or older with a clinical diagnosis of COPD (definition: having at least a 10-pack-year history of smoking, a post-bronchodilator FEV1:FVC <70%, and a post-bronchodilator FEV1 <80% predicted value), who had not had an acute COPD exacerbation within the previous 4 weeks, and who met at least one of the following criteria: (1) used continuous supplemental O2, or, within the last year, (2) had received systemic glucocorticoids, (3) had gone to the ER for an acute COPD exacerbation, or (4) had been hospitalized for an acute COPD exacerbation

Exclusion criteria
- Asthma, resting heart rate >100 bpm, QTc interval >450 msec, use of medications that prolong the QT interval or are associated with toursades de pointes (except for amiodarone), hearing impairment documented by audiometric testing

Treatment group
- 250mg azithromycin daily x 1 year in addition to usual care

No treatment group
- Placebo pill (identical in appearance to azithromycin pill) daily x 1 year in addition to usual care

Primary endpoint:
- 1. Time to first acute exacerbation of COPD

Secondary endpoints:
- 1. Quality of life
- 2. Nasopharyngeal colonization with respiratory pathogens during study course
- 3. Adherence to taking study drug as prescribed
- 4. Hearing decrement

Are the Results of the Trial Valid?
- Randomized? YES
- All patients accounted for at end? YES
  - Follow-up rates by end of trial: 89% for treatment group, 90% for placebo group
  - Those who withdrew were accounted for; of the patients in the primary analysis, 13 from the treatment group and 9 from the placebo group were lost to follow-up
- Intention to treat? YES, except for adherence
  - Adherence was determined by clinic staff counting pills (excluded patients who did not attend any clinic visits)
- Blinding? DOUBLE
- Groups similar at start of trial? YES
  - There were no significant differences between groups at baseline in terms of age, sex, race/ethnic group, post-bronchodilator FEV1:FVC and FEV1, GOLD stage, current or past smoking history, medications taken for COPD, and entry criteria fulfilled
- Equal treatment of groups? YES
  - All received their usual care in addition to identical-appearing azithromycin or placebo pill. Use of ICS, LABA, and LAMA medications were not significantly different between groups at enrollment and at 12 months (P >0.10 for all).
- Did randomization work? YES
- Are the Results of the Trial important? YES, with caveats. COPD exacerbations were significantly less frequent in the treatment group. However, there was no significant difference in the mean number of ER visits or hospitalizations for COPD exacerbation.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Result</th>
<th>Significance</th>
<th>HR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first acute COPD exacerbation (1°)</td>
<td>266 days in treatment (tx) group; 174 days in placebo group</td>
<td>P &lt;0.001</td>
<td>0.73</td>
<td>n/a</td>
</tr>
<tr>
<td>Rate of acute COPD exacerbation / patient-year</td>
<td>1.48 in those receiving at least 1 dose azithromycin; 1.83 in those receiving at least 1 dose placebo</td>
<td>P &lt;0.01 (CI 0.72-0.95)</td>
<td>RR 0.83</td>
<td>2.86</td>
</tr>
<tr>
<td>Quality of life (2°) - Mean change in SGRQ - SF-36 scores</td>
<td>-2.8+/-12.8 units in tx group, 0.6+/-11.4 units in placebo group</td>
<td>-Did not exceed pre-specified mean change of &gt;4 units for clinical significance*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean rate of adherence (2°)</td>
<td>67.3% in tx group, 66.9% in placebo</td>
<td>P = 0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity: Nasopharyngeal colonization (2°)</td>
<td>12% of treatment group, 31% of placebo group</td>
<td>P &lt; 0.001</td>
<td>19%</td>
<td>5.26</td>
</tr>
<tr>
<td>Resistance to macrolides in those who became colonized during study</td>
<td>81% of treatment group, 41% of placebo group</td>
<td>P &lt; 0.001</td>
<td>40%</td>
<td>2.50</td>
</tr>
<tr>
<td>Hearing decrement</td>
<td>25% in tx group, 20% in placebo group</td>
<td>P = 0.04</td>
<td>5%</td>
<td>20</td>
</tr>
</tbody>
</table>

*However, the mean decrease in SGRQ and number of patients with a decrease in the SGRQ >4 was significantly different between treatment and placebo groups (P = 0.004 and P = 0.03, respectively)

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**Table 2. Effect of Treatment for Chronic Obstructive Pulmonary Disease (COPD) on Hospitalization Rates, Emergency Department or Urgent Care Visits, and Unscheduled Office Visits.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Azithromycin</th>
<th>Placebo</th>
<th>P Value*</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for any cause</td>
<td>0.74 (0.60–0.89)</td>
<td>0.95 (0.76–1.18)</td>
<td>0.13</td>
<td>0.94 (0.76–1.15)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization related to COPD</td>
<td>0.34 (0.26–0.43)</td>
<td>0.49 (0.31–0.67)</td>
<td>0.14</td>
<td>0.82 (0.64–1.07)</td>
<td>0.15</td>
</tr>
<tr>
<td>Emergency department or urgent care visit</td>
<td>0.43 (0.34–0.53)</td>
<td>0.48 (0.39–0.57)</td>
<td>0.47</td>
<td>0.81 (0.63–1.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>Unscheduled office visit</td>
<td>2.46 (2.08–2.48)</td>
<td>2.57 (2.21–2.60)</td>
<td>0.048</td>
<td>0.85 (0.74–0.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>Intubations</td>
<td>0.02 (0.01–0.04)</td>
<td>0.04 (0.01–0.06)</td>
<td>0.23</td>
<td>0.79 (0.04–1.75)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* The P value is for the rate of events per patient-year.
† The hazard ratio and P value are for the time to the first event in the azithromycin group as compared with the placebo group.

- All clinically important outcomes considered? MOST LIKELY
  - Inflammatory markers were not measured to determine if azithromycin had any quantifiable anti-inflammatory effect in these patients. Differences in these serologies may or may not have correlated with clinically significant outcomes.
- Likely benefits outweigh potential harms and cost? CASE-BY-CASE DECISION
• Benefits:
  • Decreased frequency of COPD exacerbation
  • Quality of life: improved but not to the pre-specified “clinically significant” level
  • Cost associated with COPD exacerbations vs. cost of macrolide: Would be more impressive if azithromycin shown to decrease frequency of hospital admissions
    • Administrative data from 602 hospitals \(\rightarrow\) mean costs of COPD care in 2008
      o $647 (SD $445) for ED visits \(n = 24,617\)
      o $7,242 ($7,987) for simple admissions \(n = 42,734\)
      o $20,757 ($41,370) for complex admissions \(n = 4142;\) defined as requiring intubation and/or ICU-level care.
        • 5.8% of hospital-based care, but 20.9% of costs
    • Retrospective study of Medicaid payments for long-term care expenditures and COPD: Twelve-month COPD-related direct expenditures per beneficiary (mean [SD])
      o LTC costs $5,629 [$12,562]
      o Pharmacy costs ($956 [$957]
      o Inpatient costs ($466 [$3,393]
      o Outpatient costs ($341 [$1,793]
  • Azithromycin: $1.11 / pill online ($400 / year)

• Harms:
  • Colonization with macrolide-resistant organisms
    • In this study, no evidence suggested that colonization increased the incidence of COPD exacerbation or PNA
    • However, could change resistance patterns in the community. For NHs, this could be particularly detrimental.
  • Hearing decrement: excess rate of 5%
    • Yet there were improvements in hearing on repeat testing regardless of whether azithromycin was stopped (?possible overestimate of incidence of hearing decrements), and other studies have not found this (?criteria too stringent)

Can I apply these results to my patient?

Perhaps – Mr. M meets all inclusion criteria for this study save that he was treated for a COPD exacerbation within four weeks of his presentation. It is unknown whether he has a hearing decrement at baseline, but he otherwise would not be excluded from randomization. Subgroup analyses, though based on small sample sizes, suggested that the effect of azithromycin was less with current smoking \( (*P = 0.012)\), hospitalization for COPD \( (*P = 0.053)\), ICS use at enrollment \( (*P = 0.032)\), and steroid use in the past year \( (*P = 0.074)\) and was greater with age >65 \( (*P = 0.012)\), most of which decrease the likelihood that Mr. M. would benefit from azithromycin. Furthermore, the patient has grown erythromycin-resistant MRSA from his sputum in the past; if he has macrolide cross-resistance, any benefit of azithromycin would likely be attributable to its immune-modulatory effects (though one could argue that he is not at risk of acquiring resistance to macrolides and exposing others in his NH further than he has thusfar). Of note, Seemungal’s study on erythromycin did not show any difference in inflammatory markers between treatment and placebo groups. Additionally, given that the aim of administering antibiotics to Mr. M is to keep him out of the ER and hospital, these data do not support the theory that daily azithromycin can accomplish that goal.


