Understanding Therapy:
To treat or not to treat, that is the question!

June 8, 2016

Enas el Gouhary & Sheri Keitz
Objectives

✓ The evidence-based medicine cycle
✓ Start with a case scenario
✓ Ask the clinical question
✓ Key Concepts in RCT
  • Randomization
  • Allocation concealment
  • Blinding
  • Intention-to-treat
  • Treatment effect
✓ Return to case scenario
The Patient

Evidence-based Medicine Cycle

The 5 A's

ASSESS

APPRaise

APPLY

ACQUIRE

ASK
You are a general internist in a busy ambulatory practice. In the past week you have seen 3 patients with a chief complaint of “I think I need antibiotics.”

Two have bronchitis symptoms and one sinusitis. Clinically none of them have high risk comorbidities or red flags. You were on the fence about antibiotics prescription.

To treat or not to treat... that is the question.
One more thing...

- Your practice participates in Alternative Quality Contracting (pay for performance) and one of the metrics is Antibiotic Avoidance for adults with uncomplicated acute bronchitis.

- Your practice is doing poorly. The goal is for 90% of acute bronchitis patients to NOT receive antibiotics. Your practice is at 30%.
One more thing...

The fate of the entire world depends on your ability to pull this off.
American military researchers have identified the first patient in the US to be infected with bacteria that are resistant to an antibiotic that was last resort against drug-resistant germs.
And then this morning…

FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together

[ 05-12-2016 ]

Safety Announcement
Clinical question formation

**P**opulation

**I**ntervention

**C**omparison

**O**utcome

**T**ype of Question

**T**ype of (ideal) study design
Clinical question

Patient: Outpatients: uncomplicated bronchitis / sinusitis
Intervention: Delayed antibiotics
Comparator: Immediate antibiotics
Outcome: Symptoms, adverse events, antibiotics use, visits
Timeframe: Randomized controlled trial or meta analysis
ACP JournalWise®

An exciting complement to ACP Journal Club, ACP JournalWise, is now also available. Whereas ACP Journal Club takes an in-depth look at selected premier clinical studies and reviews, ACP JournalWise provides online access to all articles that pass the ACP Journal Club criteria. ACP JournalWise has these features:

- Quality-assessed, clinically rated original studies and reviews from over 130 clinical journals
Searching for "delayed antibiotic"

1. "Delayed antibiotics reduced antibiotic use in acute respiratory infection without increasing symptom duration"
   - Authors: Paul Glasziou, MBBS, PhD
   - Topics: antibiotics, follow-up, respiratory tract infections, time symptom lasts

   - Authors: Shmuel Shoham, MD; Annukka A.R. Antar, MD, PhD; Paul G. Auwaerter, MD, MBA; Christine M. Durand, MD; Mark S. Sulkowski, MD; Deborah J. Cotton, MD, MPH
   - Topics: antimicrobials
Therapeutics
Delayed antibiotics reduced antibiotic use in acute respiratory infection without increasing symptom duration


Clinical impact ratings: 6/6

Question
In acute, uncomplicated respiratory infections, do delayed antibiotic strategies reduce symptoms?

Methods
Design: Randomized controlled trial (RCT). ClinicalTrials.gov NCT01363531.
Allocation: Concealed.*
Blinding: Unblinded.*
Follow-up period: Up to 30 days.
Setting: 23 primary care centers in Spain.
Patients: 405 adults > 18 years of age (mean age 45 y, 66% women) who had acute, uncomplicated respiratory infections for which their physicians doubted the need for antibiotic treatment.

Intervention: Patient-led prescription, with antibiotics provided at the visit but not initiated immediately (n = 98); prescription collection, with antibiotics available for pick up 3 days after the visit (n = 100); immediate antibiotic initiation (n = 101); or no prescription (n = 99). Delayed groups (patient-led and collection) were told to consider taking antibiotics if they felt substantially worse in the first few days or if they had no improvement after 5 (for pharyngitis) or 10 (other infections) days (in which case they could also return to the physician). Immediate and no-antibiotic groups were told to consider visiting their physician if they had no improvement after 5 (for pharyngitis) or 10 (other infections) days.

Outcomes: Symptom duration (days) and severity (6-point Likert scale). Secondary outcomes included antibiotic use, unscheduled care, and adverse effects. 600 patients were needed to detect a 2-day difference between groups for symptom duration, given an expected mean duration of 12 days (80% power, α = 0.05).

Patient follow-up: 97% (intention-to-treat analysis).

Main results
Delayed groups and the immediate group did not differ statistically or clinically for duration of any symptoms or severe symptoms (Table). Median maximum symptom severity was higher for patient-led and no-prescription groups than for the immediate group, and lower for delayed groups than for the no-prescription group (P < 0.05). Fewer patients in the patient-led (33%) and collection (23%) groups used antibiotics than in the immediate group (91%) (P < 0.001). Groups did not differ for unscheduled care or adverse effects (overall P ≥ 0.27).

Conclusion
In acute, uncomplicated respiratory infections, delayed antibiotic strategies did not increase duration or severity of symptoms and reduced antibiotic use compared with an immediate antibiotic strategy.

*See Glossary.

Source of funding: Spanish Ministry of Health.

For correspondence: Dr. P. Alonso-Coello, Iberoamerican Cochrane Center, Barcelona, Spain. E-mail palonso@salut.gencat.cat.

Commentary
Antibiotic resistance has become a major threat to health care and is largely due to overuse of antibiotics. In the community, antibiotics are most commonly overused for acute respiratory infections. Although such infections are usually self-limiting, patient expectations and clinicians' fear of missing complications collude to sustain high rates of antibiotic prescribing. We have no magic bullets, but delayed prescribing seems to offer an acceptable compromise between immediate and no antibiotic prescription, and several previous trials have shown it is an effective strategy to reduce unnecessary antibiotic use (1). Despite that, uptake of delayed prescribing by doctors has been limited.

The RCT by de la Poza Abad and colleagues compared 4 prescription strategies including 2 variants of delayed prescribing: 1) a patient-led strategy (antibiotic prescription given but patients advised to take it only if symptoms worsen or do not improve within several days); 2) a collection strategy (patients could collect an antibiotic prescription on the 3rd day after the consultation). Self-reported antibiotic use in both the patient-led and collection strategies was lower than in the immediate prescription group (absolute reductions of 58% and 68%, respectively).

The major challenge with using delayed prescribing is choosing which strategy to use and working out how to adapt and deliver the strategy in different practice (e.g., fee-for-service health care systems) or cultural contexts (2). Using delayed prescribing seems to be the simplest effective way for clinicians to reduce antibiotic use without denying patients prescriptions.
Prescription Strategies in Acute Uncomplicated Respiratory Infections
A Randomized Clinical Trial

Mariam de la Poza Abad, MD; Gemma Mai Dalmau, MD; Mikel Moreno Baladano, MD, PhD; Ana Isabel Gonzalez Gonzalez, MD; Yolanda Canaliza Coode, MD; Silvestre Hernández Arbones, MD, PhD; Rafael Rousell del Campo, MD, PhD; Fara Torin Meneses, MD; Antonio Negreto Palma, MD; Laura Muñoz Ortiz, MD; Eulàlia Bonell Thió, MD; Carl Llo, MD, PhD; Paul Little, MD; Pablo Alonso-Casilla, MD, PhD; for the Delayed Antibiotic Prescription (DAP) Group

IMPORTANT
Delayed antibiotic prescription helps to reduce antibiotic use with reasonable symptom control. There are different strategies of delayed prescription, but it is not yet clear which one is the most effective.

OBJECTIVE
To determine the efficacy and safety of 2 delayed strategies in acute, uncomplicated respiratory infections.

DESIGN, SETTING, AND PARTICIPANTS
We recruited 405 adults with acute, uncomplicated respiratory infections from 23 primary care centers in Spain to participate in a pragmatic, open-label, randomized clinical trial.

INTERVENTIONS
Patients were randomized to 1 of 4 potential prescription strategies:
1. A delayed patient-led prescription strategy.
2. A delayed prescription collection strategy requiring patients to collect their prescription from the primary care center.
3. An immediate prescription strategy.
4. No antibiotic strategy.

DELAYED STRATEGIES CONSIST OF PREScribing AN ANTIBIOTIC TO TAKE only if the symptoms worsen or if there is no improvement several days after the medical visit.

MAIN OUTCOMES AND MEASURES
The primary outcomes were the duration of symptoms and severity of symptoms. Each symptom was scored using a 6-point Likert scale (scores of 3 or 4 were considered moderate, 5 or 6, severe). Secondary outcomes included antibiotic use, patient satisfaction, and patients' beliefs in the effectiveness of antibiotics.

RESULTS
A total of 405 patients were recruited, 398 of whom were included in the analyses; 196 patients (49.2%) were men; mean (SD) age, 45 (7) years. The mean severity of symptoms ranged from 18 to 3.5 points on the Likert scale, and mean (SD) duration of symptoms described on first visit was 6 (6) days. The mean (SD) general health status on first visit was 54 (20) based on a scale with 0 indicating worst health status; 100, best status. Overall, 314 patients (80.9%) were nonsmokers, and 372 patients (93.5%) did not have a respiratory comorbidity. The presence of symptoms on first visit was similar among the 4 groups. The mean (SD) duration of severe symptoms was 3.8 (3.3) days for the immediate prescription group and 4.7 (3.6) days for the no prescription group. The median (interquartile range [IQR]) of severe symptoms was 3 (1-4) days for the prescription collection group and 3 (2-6) days for the patient-led prescription group. The median (IQR) of the maximum severity for any symptom was 5 (3-5) for the immediate prescription group and the prescription collection group, 5 (4-6) for the patient-led prescription group, and 5 (4-6) for the no prescription strategy or to either of the delayed strategies used fewer antibiotics and less frequently believed in antibiotic effectiveness. Satisfaction was similar across groups.

CONCLUSIONS AND RELEVANCE
Delays strategies were associated with slightly greater clinically similar symptom burden and duration and also with substantially reduced antibiotic use when compared with an immediate strategy.

TRIAL REGISTRATION
clinicaltrials.gov identifier: NCT01363531

Orientation to paper (PICOT)

- **P**: 405 adults with acute, uncomplicated URI from 23 primary care centers in Spain

- **I & C**: 1 of 4 potential prescription strategies:
  - (1) delayed *patient-led* prescription strategy;
  - (2) delayed prescription *collection* strategy requiring patients to collect prescription from center;
  - (3) an *immediate* prescription strategy
  - (4) a *no* antibiotic strategy.
Orientation to paper (PICOT)

- **Primary outcomes** were the duration of symptoms and severity of symptoms.
  - Each symptom was scored using a 6-point Likert scale (scores of 3-4 → moderate; 5-6 → severe).

- **Secondary outcomes** included:
  - antibiotic use, patient satisfaction, and patients’ willingness to return to the provider.

- **T**: pragmatic (real world) RCT of different prescribing strategies in primary care
Randomization flow chart

Figure. Patient Randomization Flowchart

405 Patients enrolled

405 Patients randomized

7 Excluded to fulfill exclusion criteria or due to missing data on first visit

398 Patients included

99 No prescription strategy

101 Immediate prescription strategy

100 Prescription collection strategy

98 Patient-led prescription strategy
THE PATIENT

The 5 A's

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Evidence-based Medicine Cycle
### Critical appraisal

**Therapy Worksheet = Randomized Controlled Trial**

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<th>How serious is the risk of bias?</th>
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<td>Did intervention and control groups start with the same prognosis?</td>
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# Critical appraisal

**Therapy Worksheet = Randomized Controlled Trial**

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Flow of an RCT
To evenly distribute all known and unknown prognostic variables between the groups
Simple Randomization

Interactive Exercise #1
List generation

Heads: (A)

Tails: (B)
Instructions Interactive #1

• Carefully Open envelopes now

• Contents:
  – American randomization machine
  – Prognostic factor file card

• Please perform randomization and note your group assignment (heads or tails)

• Those who were randomized to HEADS, please pass your pennies to the aisle
While we count

• Is coin toss a random process?
• Why or why not?
Go to Document Reader
Goal vs. Outcome of randomization

We may not always achieve this goal
<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Age, mean (SD), y</th>
<th>Educational level</th>
<th>Respiratory comorbidity&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Smoking status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39 (38.6)</td>
<td>29 (29.0)</td>
<td>33 (33.7)</td>
<td>35 (35.3)</td>
<td>136 (34.2)</td>
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<tr>
<td>Age, mean (SD), y</td>
<td>48 (17)</td>
<td>42 (17)</td>
<td>45 (17)</td>
<td>45 (16)</td>
<td>45 (17)</td>
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<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary or less</td>
<td>26 (28.3)</td>
<td>19 (21.1)</td>
<td>32 (34.8)</td>
<td>26 (27.7)</td>
<td>103 (28.0)</td>
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<tr>
<td>Secondary</td>
<td>32 (34.8)</td>
<td>42 (46.7)</td>
<td>35 (38.0)</td>
<td>33 (35.1)</td>
<td>142 (38.6)</td>
</tr>
<tr>
<td>Higher</td>
<td>34 (36.9)</td>
<td>29 (32.2)</td>
<td>25 (27.2)</td>
<td>35 (37.2)</td>
<td>123 (33.4)</td>
</tr>
<tr>
<td>Respiratory comorbidity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (6.9)</td>
<td>5 (5.0)</td>
<td>4 (4.1)</td>
<td>10 (10.1)</td>
<td>26 (6.5)</td>
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<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nonsmoker</td>
<td>53 (54.1)</td>
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<tr>
<td>Smoker</td>
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<tr>
<td>Former smoker</td>
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</table>

Range 29% to 39%
## Back to Paper: Table #1

<table>
<thead>
<tr>
<th></th>
<th>Range 25% to 11%</th>
<th>25% to 11%</th>
<th>33% to 35%</th>
<th>35% to 37%</th>
<th>37% to 40%</th>
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Back to Paper: Table #1

What is the range here??

<table>
<thead>
<tr>
<th>Uncomplicated acute respiratory infection</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Rhinosinusitis</td>
<td>20 (19.8)</td>
<td>20 (20.0)</td>
<td>19 (19.4)</td>
<td>19 (19.2)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>47 (46.5)</td>
<td>46 (46.0)</td>
<td>45 (45.9)</td>
<td>46 (46.5)</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>32 (31.7)</td>
<td>32 (32.0)</td>
<td>32 (32.7)</td>
<td>32 (32.3)</td>
</tr>
<tr>
<td>Exacerbation of mild-to-moderate COPD</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
</tr>
</tbody>
</table>

How did that happen?
Randomization was performed by permuted block sizes of 4 and stratified by type of infection.
Stratified Blocked Randomization

Interactive Exercise #2
Today's question

People attending an EBM workshop in Canada

Opportunity to ask questions

Prohibition from asking questions

Learner satisfaction

“Therapy” question

Randomized controlled trial or meta analysis
Randomization:

(A) Allowed to ask questions
(B) NOT Allowed to ask questions

WE HAVE A LIST

Wanted to account for 2 key prognostic factors
1. Canadian vs. non-Canadian
2. Participant vs. Member of the tutorial teams
Instructions Interactive #2

• Need 10 volunteers and one of them must be Gordon

• Please come up to the stage and form a line

• ** no volunteers will be harmed in the performance of this exercise
Go to document reader
Randomization was performed by permuted block sizes of 4 and stratified by type of infection.
Focus on Randomization

P

R

List Generation

Stratification Blocking

O
Stratification and Blocking

- Stratification: is used to achieve approximate balance of important characteristics without sacrificing the advantages of randomization.

- Blocking: is used to keep the numbers in each group very close at all times.
Allocation concealment

✓ The person who is enrolling participants cannot know, predict, or manipulate the list

✓ Trials with inappropriate allocation concealment are associated with larger estimates of treatment effect

✓ Was allocation concealed in our exercise?
Allocation concealment

P  R  O

List generation  Allocation concealment
Allocation concealment vs. Blinding

• Why all the confusion?
Paragraph header: Randomization and masking

Sentences about randomization:
• Physicians randomized patients centrally using an electronic online platform.
• Randomization was performed by permuted block sizes of 4 and stratified by type of infection.

Sentence about blinding
• Neither patients nor health professionals were blinded.
Allocation concealment vs. Blinding

• Why all the confusion?

• Because both allocation concealment and blinding are about someone not knowing something.
### Allocation Concealment vs. Blinding

<table>
<thead>
<tr>
<th></th>
<th>Allocation Concealment</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>What?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td></td>
<td></td>
</tr>
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<tr>
<td><strong>Who?</strong></td>
<td>Enroller</td>
</tr>
<tr>
<td><strong>What?</strong></td>
<td>The list</td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td>Part of randomization</td>
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### Allocation Concealment vs. Blinding

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<tr>
<td><strong>Who?</strong></td>
<td>Enroller</td>
<td>Patients, caregivers, data collectors, outcome adjudicators, analysts</td>
</tr>
<tr>
<td><strong>What?</strong></td>
<td>The list</td>
<td>Group assignments</td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td>Part of randomization</td>
<td>Starts once allocated</td>
</tr>
</tbody>
</table>
What about Blinding?
is masking the group assignment to ensure all groups are treated the same apart from the intervention through the follow up period

Trials with inappropriate blinding are also associated with larger estimates of effect, but not as much as with inappropriate allocation concealment

Was the antibiotic study blinded?
Intention-to-treat and follow up

✓ ITT: Were patients analyzed in the groups to which they were randomized in the study?
Intention-to-treat

Cerebro-vascular disease

Surgery + ASA

ASA

200

100

100

10

10

Stroke

Stroke

Per Protocol

10/90 = 11%

RD = 9%

20/100 = 20%

ITT

20/100 = 20%

RD = 0%
Randomization flow chart

Figure. Patient Randomization Flowchart

405 Patients enrolled

405 Patients randomized

7 Excluded to fulfill exclusion criteria or due to missing data on first visit

398 Patients included

99 No prescription strategy

101 Immediate prescription strategy

100 Prescription collection strategy

98 Patient-led prescription strategy

97% follow up
Intention-to-treat... Why??

✓ Preserves prognostic balance between the groups (protects 'the list')

✓ Reflects real life
Back to the paper:
What are the results?
## Primary Outcomes

<table>
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<tr>
<th>Outcomes</th>
<th>Antibiotic strategy</th>
<th>Mean duration of symptoms (d)</th>
<th>( P ) value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Antibiotic strategy</td>
<td>Immediate antibiotics</td>
</tr>
<tr>
<td>Any symptoms</td>
<td>Patient led</td>
<td>13.1</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>Collection</td>
<td>12.3</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>No prescription</td>
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<td>Severe symptoms</td>
<td>Patient led</td>
<td>5.1</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Collection</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>No prescription</td>
<td>4.7</td>
<td>3.6</td>
</tr>
</tbody>
</table>
## Primary Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Antibiotic strategy</th>
<th>Mean duration of symptoms (d)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Antibiotic strategy</td>
<td>Immediate antibiotics</td>
</tr>
<tr>
<td>Any symptoms</td>
<td>Patient led</td>
<td>13.1</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>Collection</td>
<td>12.3</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>No prescription</td>
<td>14.4</td>
<td>11.7</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>Patient led</td>
<td>5.1</td>
<td>3.6</td>
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</tr>
</tbody>
</table>
Secondary Outcomes

• No difference in complications, unscheduled care or adverse effects (small # of outcomes)
• Overall patient satisfaction was high and similar
• More patients randomized to immediate strategy (85.7%) reported that they would return to their physician for a similar episode than in the other three groups (~70%)
• Fewer patients took antibiotics in the 3 groups that did not give immediate antibiotics
## Secondary Outcomes

91% (immediate) vs. 23%, 33%, 12%

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
<th></th>
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<th></th>
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<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic collected, No. (%)</td>
<td>90 (89.1)</td>
<td>&lt;.001</td>
<td>26 (26.0)</td>
<td>&lt;.001</td>
<td>34 (34.7)</td>
<td>&lt;.001</td>
<td>NA</td>
<td>NA</td>
<td>150 (50.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antibiotic used, No. (%)</td>
<td>92 (91.1)</td>
<td>&lt;.001</td>
<td>23 (23.0)</td>
<td>&lt;.001</td>
<td>32 (32.6)</td>
<td>&lt;.001</td>
<td>12 (12.1)</td>
<td>159 (39.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Nonantibiotic medication use, No. (%)</td>
<td>75 (74.3)</td>
<td>.90</td>
<td>75 (75.0)</td>
<td>79 (80.6)</td>
<td>.29</td>
<td>81 (81.8)</td>
<td>.20</td>
<td>310 (77.9)</td>
<td>.46</td>
<td></td>
</tr>
<tr>
<td>Need for unscheduled health care, No. (%)</td>
<td>4 (4.0)</td>
<td>4 (4.0)</td>
<td>6 (6.1)</td>
<td>6 (6.1)</td>
<td>20 (5.0)</td>
<td>.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General health status, mean (SD) $^b$</td>
<td>95 (90-100)</td>
<td>91 (85-100)</td>
<td>.86</td>
<td>95 (90-100)</td>
<td>.98</td>
<td>95 (90-100)</td>
<td>.77</td>
<td>95 (90-100)</td>
<td>.87</td>
<td></td>
</tr>
<tr>
<td>Adverse effects, No. (%)</td>
<td>1 (1.0)</td>
<td>0</td>
<td>1 (1.0)</td>
<td>3 (3.0)</td>
<td>5 (1.3)</td>
<td>.27</td>
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</tr>
<tr>
<td>Referral to the emergency department, No. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>2 (0.5)</td>
<td>.37</td>
<td></td>
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</tbody>
</table>
## Secondary Outcomes

### 91% (immediate) vs. 23%, 33%, 12%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
<th>P-value</th>
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Secondary Outcomes: Therapy Math

<p>| | | | |</p>
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</table>
Antibiotics used:

Step 1:

<table>
<thead>
<tr>
<th>Collection D#3</th>
<th>Immediate</th>
</tr>
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<tbody>
<tr>
<td>23%</td>
<td>91%</td>
</tr>
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</table>

Step 2: Subtract: \[91\% - 23\% = 68\%\]

Step 3: Divide: \[\frac{23\%}{91\%} = 0.25\]
What is the risk difference of 68% telling you?

In order to prevent antibiotic use in 68 pts, you need to offer delayed antibiotics to 100.

In order to prevent antibiotic use in 1, how many do you need to offer delayed antibiotics?

Formula
NNT: 100 / RD %
Number Needed to Treat

- Formula: \[ \text{NNT} = \frac{100}{\text{RD}} \]
  \[ \text{NNT} = \frac{100}{68} = 1.5 \rightarrow 2 \]
  \[ \text{NNT} = 2 \]

- You need to offer delayed antibiotic use to 2 patients in order to prevent one extra person from taking antibiotics for uncomplicated URI.
THE PATIENT

The 5 A’s

ASSESS

APPLY

ASK

ACQUIRE

Evidence-based Medicine Cycle
Back to our Scenario...

✓ Raises hands: how many would employ a delayed antibiotic strategy?

✓ What happened in real life: “Wait and See” or No antibiotics encouraged in clinic, working on implementation tools to standardize practices.

✓ Individual factors will drive implementation such as e-prescribing.
Take-home points

✓ The EBM cycle begins and ends with a patient

✓ Randomization intends to equally distribute prognostic factors between groups.

✓ There are multiple factors that may threaten the equal prognosis that we seek to achieve through randomization:
  ✓ Play of chance (small sample size)
  ✓ Improper allocation concealment
  ✓ Not following intention to treat
Take-home points

✓ Stratification and blocking are about making the list

✓ Allocation concealment is about the enroller not being able to manipulate the random list during enrollment

✓ Blinding is a later step (after allocation) that prevents 5 important groups from being able to treat patients differently based on their group allocation.

✓ Therapy math: simply subtract (Risk Difference) or divide (Risk Ratio).
Take-home points

✓ This is just the beginning...

And also the END...
Thank you!