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

June 6, 2017

Enas el Gouhary & Sheri Keitz
Objectives

✓ Incorporate best evidence about a treatment using evidence cycle

✓ Define Selected Key Concepts in RCT
  • Randomization
  • Allocation concealment
  • Blinding
  • Treatment effect

✓ Apply knowledge through an interactive exercises in a large group setting
The 5 A’s

Evidence-based Medicine Cycle

THE PATIENT

ASK

ASSESS

ACQUIRE

APPLY

APPRaise
✓ 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.
• 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%. 
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.
THE PATIENT

The 5 A's

ASSESS

ASK

Evidence-based Medicine Cycle

ACQUIRE

APPLY

APPRAISE
Clinical question formation

P: Population
I: Intervention
C: Comparison
O: Outcome
T: Type of Question
T: Type of (ideal) study design
Clinical question formation

**P**

Outpatients: uncomplicated bronchitis / sinusitis

**I**

Delayed antibiotics

**C**

Immediate antibiotics

**O**

Symptoms, adverse events, antibiotics use, visits

**T**

Therapy question

**T**

Randomized controlled trial or meta analysis
The Patient

The 5 A's

ASSESS

ASK

ACQUIRE

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APPRAISE

Evidence-based Medicine Cycle
ACP Journal Club
The Best New Evidence for Patient Care™

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
Showing 1 – 20 of 4848
SORT: | Best Match | Most Recent | Basic | Expanded

**Delayed antibiotics reduced antibiotic use in acute respiratory infection without increasing symptom duration**
Paul Glasziou, MBBS, PhD

**TOPICS:** antibiotics, follow-up, respiratory tract infections, time symptom lasts

**Antimicrobial Access in the 21st Century: Delays and Critical Shortages**
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
Delayed antibiotics reduced antibiotic use in acute respiratory infection without increasing symptom duration

Clinical impact ratings: 5

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 visits, and adverse effects.

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@santpau.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 approach.
Prescription Strategies in Acute Uncomplicated Respiratory Infections
A Randomized Clinical Trial

Mariam de la Poza Abad, MD; Gamma Mas Dalmau, MD; Mikal Moreno Bakadano, MD, PhD; Ana Isabel González González, MD; Yolanda Canellas Criado, MD; Silvia Hernández Anadón, MD, PhD; Rafael Rotaacha del Campo, MD; Pau Torán Monserrat, MD; Antonio Negrata Palma, MD; Laura Muñoz Ortiz, MD; Eulàlia Borrell Thió, MD; Carl Llor, MD, PhD; Paul Little, MD; Pablo Alonso-Coello, MD, PhD; for the Delayed Antibiotic Prescription (DAP) Group

**Importance** 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; or (4) a no antibiotic strategy. Delayed prescription 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).
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
  – (2) delayed prescription collection
  – (3) an immediate prescription
  – (4) a no antibiotic
Four Arms of the Trial

Patient Led

Rx: Gorillacillin
2 pills twice daily

Given same instructions

Collection

Rx: Come back in 3 days if still sick

Immediate

No prescription

Rx: Nothing for You

Rx: Gorillacillin
2 pills twice daily
Orientation to paper (PICOT)

• **Primary outcomes:**
  – Duration and severity of symptoms
  – Symptom Severity: 6-point Likert scale
  – 2 day difference in duration = clinically relevant

• **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
The 5 A’s

THE PATIENT

The Evidence-Based Medicine Cycle

- Assess
- Ask
- Acquire
- Appraise
- Apply
**Critical appraisal**

Therapy Worksheet provides framework to assess a Randomized Controlled Trial

<table>
<thead>
<tr>
<th>How serious is the risk of bias?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did intervention and control groups start with the same prognosis?</td>
</tr>
<tr>
<td>Were patients randomized?</td>
</tr>
<tr>
<td>Was randomization concealed?</td>
</tr>
<tr>
<td>Were patients in the study groups similar at baseline with respect to prognostic factors?</td>
</tr>
<tr>
<td>Was prognostic balance maintained as the study progressed?</td>
</tr>
<tr>
<td>To what extent was the study blinded?</td>
</tr>
<tr>
<td>Were groups prognostically balanced at the study’s conclusion?</td>
</tr>
<tr>
<td>Was follow-up complete?</td>
</tr>
<tr>
<td>Were patients analyzed in the groups to which they were randomized?</td>
</tr>
<tr>
<td>Was the trial stopped early?</td>
</tr>
</tbody>
</table>
Flow of an RCT
Goal of randomization

To evenly distribute all known and unknown prognostic variables between the groups
Randomization: Part I

P \rightarrow R \rightarrow \text{List generation} \rightarrow O
Simple Randomization

Interactive Exercise #1
List generation

Heads: (A)

Tails: (B)
Random?

- Is coin toss a random process?
- If your answer is YES raise your hand
- Why or why not?
Go to Randomization page
Goal vs. Outcome of randomization

We may not always achieve this goal
Back to our paper
Did Randomization Work?

Table 1: baseline demographics
## Back to Paper: Table #1

### Range 29% to 39%

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>26 (29.0)</th>
<th>33 (33.7)</th>
<th>35 (35.3)</th>
<th>136 (34.2)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<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>
</tr>
<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(^b)</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>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>53 (54.1)</td>
<td>50 (50.5)</td>
<td>61 (62.2)</td>
<td>51 (52.6)</td>
<td>215 (54.8)</td>
</tr>
<tr>
<td>Smoker</td>
<td>22 (22.4)</td>
<td>25 (25.3)</td>
<td>11 (11.2)</td>
<td>20 (20.6)</td>
<td>78 (19.9)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>23 (23.5)</td>
<td>24 (24.2)</td>
<td>26 (26.5)</td>
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\(^b\) Indicates respiratory comorbidity data.
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<tr>
<td>Respiratory comorbidity b</td>
<td>7 (6.9)</td>
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Range 25% to 11%
Back to Paper: Table #1

Range 19% to 20%

<table>
<thead>
<tr>
<th>Uncomplicated acute respiratory infection</th>
<th>20 (19.8)</th>
<th>20 (20.0)</th>
<th>19 (19.4)</th>
<th>19 (19.2)</th>
<th>78 (19.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinosinusitis</td>
<td>47 (46.5)</td>
<td>46 (46.0)</td>
<td>45 (45.9)</td>
<td>46 (46.5)</td>
<td>184 (46.2)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>32 (31.7)</td>
<td>32 (32.0)</td>
<td>32 (32.7)</td>
<td>32 (32.3)</td>
<td>128 (32.2)</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>8 (2.0)</td>
</tr>
<tr>
<td>Exacerbation of mild-to-moderate COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How did that happen?
Here’s How...

• 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:

WE HAVE A LIST

(A) Allowed to ask questions

(B) NOT Allowed to ask questions

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
Random List Generation:
Sentence from the paper

• Randomization was performed by permuted block sizes of 4 and stratified by type of infection.
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.
Random List Generation

P  R  O

List Generation
Stratification Blocking
Randomization: Part II

- Stratification
- Blocking
- List Generation
- ??
Allocation Concealment: Sentence from the paper

- Physicians randomized patients centrally using an electronic online platform

- Note: the words “allocation concealment” are almost never stated explicitly in the text
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 1?
- What about exercise 2?
Allocation concealment
• Neither patients nor health professionals were blinded.
Were patients, caregivers, collectors of outcome data, adjudicators of outcome, and data analysts aware of group allocation?

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.
Among most common sources of confusion in teaching randomized trials

Why?

Allocation concealment and blinding are both 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>Patients, caregivers, data collectors, outcome adjudicators, analysts</td>
</tr>
<tr>
<td><strong>Doesn’t know</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td></td>
<td></td>
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<td>When?</td>
<td>Part of randomization</td>
<td></td>
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<td>enroller</td>
<td>the list</td>
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<tr>
<td>doesn’t know</td>
<td>group assignments</td>
</tr>
<tr>
<td>part of randomization</td>
<td>starts once allocated</td>
</tr>
</tbody>
</table>
Back to the paper
How Serious is Risk of Bias?

• Randomized: Yes
• Allocation: Concealed
• Similar at Baseline: Mostly
• Blinding: Not patients or providers (? others)
• Follow up: 30 days; 97% complete
• Stopped early for benefit: No
• Intention to treat: Yes**
What are the Results?
## Primary Outcomes: Symptom Duration

<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>
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<td>No prescription</td>
<td>14.4</td>
<td>11.7</td>
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<td>3.6</td>
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<td>3.6</td>
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Secondary Outcomes

- Complications, unscheduled care or adverse effects (small # of outcomes): NO DIFFERENCE
- Overall patient satisfaction: HIGH & 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: Therapy Math

<table>
<thead>
<tr>
<th>Antibiotic collected, No. (%)</th>
<th>90 (89.1)</th>
<th>26 (26.0)</th>
<th>&lt;.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic used, No. (%)</td>
<td>92 (91.1)</td>
<td>23 (23.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Antibiotics used:

Step 1:

Collection D#3 | Immediate
--- | ---
23% | 91%

Step 2: Subtract: 91% – 23% = 68% Absolute Risk difference

Step 3: Divide: 23% / 91% = 0.25 Risk ratio
In Words...

• Risk Difference (absolute risk reduction or increase):  
The absolute reduction in risk is 68% between the 3-day collection group and the immediate antibiotics group

• Risk Ratio (relative risk):  
The risk of taking antibiotics in the 3-day collection group is a quarter (25%) of that with the immediate prescription strategy.
Number Needed to Treat

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: \( NNT = \frac{100}{RD} \)
  \( NNT = \frac{100}{68\%} = 1.5 \rightarrow 2 \)
  \( NNT = 2 \)

✓ Words: You need to offer delayed antibiotic use to 2 patients in order to prevent one extra person from taking antibiotics for uncomplicated URI.
Relative Risk Reduction

✓ Formula: $\text{RRR} = 1 - \text{Risk Ratio}$
   
   $\text{RRR} = 1 - 0.25$
   
   $\text{RRR} = 0.75$

✓ Words: The risk of taking antibiotics for an uncomplicated URI in the 3 day collection group is reduced by 75% compared to immediate strategy.
Evidence-based Medicine Cycle

THE PATIENT

ASSESS

AKS

ACQUIRE

APPLY

APPRAISE

The 5 A’s
Back to our Scenario...

✓ Raise hands: how many would consider a delayed antibiotic strategy?

✓ What happened in real life: Implemented a quality improvement project to educate providers and provide tools for counseling patients on antibiotic avoidance

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

✓ Randomization intends to equally distribute prognostic factors between groups.

✓ Multiple factors 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 (for small groups)
Take-home points

✓ Stratification and blocking are about making the list

✓ Allocation concealment is about the enroller not being able to know, predict, or 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.
Take-home points

✓ Therapy math:
  ✓ Subtract (Absolute Risk Difference)
  ✓ Divide (Risk Ratio)

✓ Number Needed to Treat = 100/Risk Difference (%)
✓ Relative Risk Reduction = 1 – Risk Ratio
Take-home points

✓This is just the beginning...

And also the *END*...
Thank you!
Handouts for math
Antibiotics used:

Step 1:

Collection D#3: 23%
Immediate: 91%

Step 2: Subtract:

Step 3: Divide:
Number Needed to Treat

✓ NNT = 100/ RD (%)

Relative Risk Reduction

✓ Relative Risk Reduction = 1 – Risk Ratio