بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ
Delayed antibiotics reduced antibiotic use in acute respiratory infection without increasing symptom duration

Question

In acute, uncomplicated respiratory infections, do delayed anti-biotic strategies reduce symptoms?
Methods

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.
Randomized controlled trial (RCT). ClinicalTrials.gov NCT01363531.

23 primary care centers in Spain

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, $a = 0.05$).
**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.
### Table & figure

#### Patient-led, collection, or no-prescription antibiotic strategies vs immediate antibiotics in acute, uncomplicated respiratory infection

<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>
</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>
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 anti-biotic strategies did not increase duration or severity of symptoms and reduced antibiotic use compared with an immediate antibiotic strategy.
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.
Commentary

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.
6 weeks of antibiotics was noninferior to 12 weeks for clinical cure in pyogenic vertebral osteomyelitis

Reference: Lancet 2015;385:875-82
Question

In patients with pyogenic vertebral osteomyelitis (PVO), is 6 weeks of antibiotic therapy noninferior to 12 weeks of therapy?
**Methods**

359 adults ≥ 18 years of age (mean age 61 y, 69% men) who had microbiologically confirmed PVO with typical radiologic features.

**Patients:**

Exclusion criteria: inclusion of vertebral implants; pregnancy or breast-feeding; recurrence of spondylodiscitis; fungal, brucellar, or mycobacterial infection; or life expectancy < 1 year.

**Exclusion criteria:**

Exclusion criteria included presence of vertebral implants; pregnancy or breast-feeding; recurrence of spondylodiscitis; fungal, brucellar, or mycobacterial infection; or life expectancy < 1 year.
Randomized controlled noninferiority trial (Duration of Treatment for Spondylodiscitis [DTS] study). ClinicalTrials.gov NCT00764114, EudraCT 2006-000951-18.

Infectious disease, rheumatology, and internal medicine departments in 71 clinical centers in France

Clinical cure (sustained absence of fever, pain, and the inflammatory syndrome), cured and alive, and cured without further antibiotic therapy at 1 year. Secondary outcomes included adverse events.
Main results

The most common causative organisms were Staphylococcus aureus (41%, 2% of patients had methicillin-resistant S. aureus [MRSA]), Streptococcus species (18%), coagulase-negative Staphylococcus (17%), and enterobacterial species (11%). 6 weeks of antibiotic therapy was noninferior to 12 weeks of therapy.
### 6 vs 12 wk of antibiotic therapy for pyogenic vertebral osteomyelitis†

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Event rates</th>
<th>At 1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 wk</td>
<td>12 wk</td>
</tr>
<tr>
<td>Cured‡</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>Cured and alive</td>
<td>89%</td>
<td>86%</td>
</tr>
<tr>
<td>Cured without further antibiotic therapy</td>
<td>81%</td>
<td>81%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>RRI (CI)</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 adverse event</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>1% (27 to 41)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
Conclusion

In patients with pyogenic vertebral osteomyelitis, 6 weeks of antibiotic therapy was noninferior to 12 weeks of therapy for clinical cure.
In their multicenter, noninferiority randomized controlled trial (RCT) comparing 6 and 12 weeks of antimicrobial therapy in patients with PVO, Bernard and colleagues used a pragmatic design that allowed physicians to choose antimicrobial regimens for their patients. Concerns arising from the open-label design are partly allayed by the comparable antibiotics used in the 2 groups.
Commentary

The representativeness of enrolled patients is a primary consideration in pragmatic trials (1), and the wide inclusion criteria in the RCT helped to achieve representativeness. However, the low prevalence of MRSA should be taken into account in centers with different epidemiology. Time to diagnosis was not reported, which reduces confidence in generalizing the results, particularly because the mean time to diagnosis for PVO is 42 to 59 days after symptom onset.
Commentary

Overall, the trial by Bernard and colleagues provides strong evidence for the noninferiority of 6 weeks of antibiotics compared with 12 weeks for PVO. Uncontrolled use of antimicrobial agents has been associated with an increase in antimicrobial resistance. Trials evaluating shorter antimicrobial courses are a crucial step in guiding evidence-based decisions that decrease this antimicrobial pressure (3).
Review: Peripheral thermometers do not have clinically acceptable accuracy for measuring core body temperature

Clinical impact

Question

What is the accuracy of peripheral thermometers for estimating core body temperature?
Methods

Patient;
Included studies evaluated peripheral index thermometers (tympanic membrane, temporal artery, axillary, or oral) in adults or children in acute care or ambulatory settings with paired reference standard measurements taken within 5 minutes using central reference thermometers (pulmonary artery catheter, rectal, urinary bladder, or esophageal).

Exclusion criteria included studies of healthy volunteers or noncontact infrared thermometers.
75 studies (n = 8682) met selection criteria; 42 included adults (median age 61 y), 32 included children (median age 16 mo), and 1 included both. Comparisons included patients with unrestricted temperatures (71%), fever (21%), or hypothermia (8%). Tympanic membrane (52 studies), axillary (34 studies), temporal artery (14 studies), and oral thermometers (11 studies) were compared with pulmonary artery catheter (31 studies), rectal (30 studies), bladder (12 studies), or esophageal thermometers (3 studies) as reference standards.
Main results

In adults and children, calibrated tympanic or oral thermometers met LOA, but all types of peripheral thermometers exceeded the LOA compared with central thermometers (Table).
### Estimates of pooled mean difference in temperature between peripheral and central thermometers in adults and children*

<table>
<thead>
<tr>
<th>Peripheral thermometer</th>
<th>Patient group</th>
<th>Number of studies</th>
<th>95% limits of agreement, °C</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibrated tympanic membrane</td>
<td>All</td>
<td>26</td>
<td>0.49 to 0.47</td>
<td>98%</td>
</tr>
<tr>
<td>Calibrated oral</td>
<td>All</td>
<td>8</td>
<td>0.39 to 0.46</td>
<td>98%</td>
</tr>
<tr>
<td>Ty mpanic membrane</td>
<td>Adults</td>
<td>32</td>
<td>1.42 to 1.26</td>
<td>99%</td>
</tr>
<tr>
<td>Temporal artery</td>
<td>Adults</td>
<td>6</td>
<td>0.64 to 0.82</td>
<td>99%</td>
</tr>
<tr>
<td>Axillary</td>
<td>Adults</td>
<td>13</td>
<td>0.94 to 0.27</td>
<td>99%</td>
</tr>
<tr>
<td>Oral</td>
<td>Adults</td>
<td>10</td>
<td>0.76 to 0.63</td>
<td>99%</td>
</tr>
<tr>
<td>Ty mpanic membrane</td>
<td>Children</td>
<td>18</td>
<td>0.67 to 0.37</td>
<td>99%</td>
</tr>
<tr>
<td>Temporal artery</td>
<td>Children</td>
<td>8</td>
<td>0.61 to 0.42</td>
<td>97%</td>
</tr>
<tr>
<td>Axillary</td>
<td>Children</td>
<td>16</td>
<td>1.40 to 0.55</td>
<td>99%</td>
</tr>
</tbody>
</table>
Conclusion

Calibrated tympanic or oral thermometers are accurate, but peripheral thermometers do not have clinically acceptable accuracy for measuring core body temperature compared with central thermometers.
Commentary

that peripheral thermometers have poor sensitivity for detecting fever. On the basis of their analyses, they reasonably suggest use of a calibrated electronic oral thermometer or tympanic membrane thermometer when a central thermometer is “best avoided or impractical.”
Detecting fever is clinically important, and this review reminds practitioners that peripheral thermometers are unreliable for detecting fever and can contribute to missed or delayed diagnosis.
Review: In older persons at vascular risk, statins do not prevent dementia or cognitive decline at 3.5 to 5 years.

Question

In persons at risk for dementia because of age or at risk for vascular events, do statins prevent dementia? What are the harms?
Methods

2 RCTs met inclusion criteria. 1 UK RCT (n = 20 536; age 40 to 80 y, with 28% ≥ 70 y; mean follow-up 5 y) evaluated simvastatin, 40 mg/d, in persons at high risk for vascular events; persons with dementia or any condition that could affect long-term compliance were excluded. The other RCT (n = 5804; age 70 to 82 y, with mean age 75 y; mean follow-up 3.2 y), done in Scotland, Ireland, and the Netherlands, evaluated pravastatin, 40 mg/d, in persons with a history of, or at risk for, vascular disease; persons with poor cognitive function (Mini-Mental State Examination score < 24) were excluded. Both studies used concealed allocation; had adequate follow-up data; and blinded participants, clinicians, and outcome assessors.
Main results

Statins did not reduce risk for dementia or cognitive impairment at 5 years or improve scores on cognitive tests at 3.5 years compared with placebo (Table). Statins and placebo did not differ for treatment discontinuations due to adverse events (Table).
# Table & figure

## Statins vs placebo for preventing dementia in older persons at risk for vascular events*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>RRR  (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Dementia at 5 y</td>
<td>1 (20 536)</td>
<td>0.30%</td>
<td>0% (64 to 39)</td>
</tr>
<tr>
<td>Cognitive impairment† at 5 y</td>
<td>1 (20 536)</td>
<td>23.7%</td>
<td>2% (3 to 7)</td>
</tr>
<tr>
<td>Treatment discontinued due to adverse events at 3.5 to 5 y</td>
<td>2 (26 340)</td>
<td>4.56%</td>
<td>6% (5 to 16)</td>
</tr>
</tbody>
</table>

### Mean difference in change from baseline at 3.5 y (CI)‡

- **Mini-Mental State Examination score**: 1 (5804) 0.06 (0.04 to 0.16)
- **Time to complete Stroop Color Word Test (sec)**: 1 (5804) 0.80 (0.38 to 1.98)
- **Picture-Word Learning Test score**: 1 (5804) 0.02 (0.12 to 0.16)
- **Letter Digit Coding Test score**: 1 (5804) 0.01 (0.25 to 0.23)
Conclusion

In older persons at risk for vascular events, statins do not pre-vent dementia or cognitive decline compared with placebo.
Commentary

In societies with increasingly aging populations, minimizing cognitive decline and onset of late-life dementia is an important goal. In late life, mixed dementias related to both Alzheimer disease and vascular brain injury become more common.
Commentary

large trials included in the Cochrane review by McGuinness and colleagues found that, although statins reduce targeted vascular events, their benefits do not extend to prevention of dementia or cognitive decline.
Barriers to a definitive RCT evaluating statins for preventing dementia include high cost, long duration of follow-up, and ethical concerns related to not offering beneficial treatment to a control group.
Commentary

Multiple risk factor reduction may be a better strategy for reducing risk for late-life dementia. The recently published, long-term FINGER trial in Finland found that a combination of diet, exercise, cognitive training, and vascular risk monitoring improved or maintained cognitive function in at-risk persons.
Images in Clinical Medicine
Dahl's Sign

A 76-year-old woman was admitted to the hospital with shortness of breath. She had tachypnea and was breathing through pursed lips. The patient had a long history of advanced chronic obstructive pulmonary disease (COPD), with a forced expiratory volume in 1 second of 21% of the predicted value. The pulmonary examination showed inspiratory retraction of the intercostal muscles and the suprasternal notch, along with diffuse, polyphonic expiratory wheezing with a prolonged expiratory phase. Symmetric, slanting regions of hyperpigmentation were noted on both thighs, a finding consistent with Dahl's sign, also known as Thinker's sign. Described in 1963 in a patient with severe COPD, Dahl's sign is caused by repeated pressure from the elbows on the epidermis of the thighs in patients spending large amounts of time in the tripod position, resulting in hyperpigmented, hyperkeratotic plaques. Although characteristically found on the thighs, Dahl's sign can also be seen on the elbows of patients who chronically lean forward on a hard surface, essentially creating a callus. As in our patient, this finding provides supporting evidence of disease chronicity and severity. Oral glucocorticoids and nebulized bronchodilators were prescribed, which provided minimal relief, and the patient was discharged home with hospice care.