Should you complete an antibiotic course or stop when better?

Richard Everts
Nelson Bays Primary Health
You have just filled a prescription for an antibiotic…

READ THIS IMPORTANT INFORMATION

- Take it exactly as your medical expert tells you
- Do not skip doses
- Do not share it with others
- Finish the prescription even if you feel better
- Do not save it for later

Why is this checklist so important?
Using an antibiotic the wrong way can make infections stronger and harder to treat. You can prevent this problem by getting smart about antibiotics.

Take antibiotics the right way.

For more information call 1-800-311-3435 or visit www.cdc.gov/getsman
Taking Antibiotic Medicines

Read the label every time you give or take the medicine.

Double check:
- who the medicine is for
- when to use it
- how much to use
- how to use it
- how long to use it for

Shake liquid medicine well before each dose.

Use a proper medicine measure:
- a dropper or syringe for a baby
- a syringe or dosing spoon for a child
- a measuring spoon or medicine measure for an adult

Use a different measure for each person to prevent cross-infection and wash it after use.

To check a child resistant lid, twist back one turn after closing.

Use the medicine only for the person whose name is on the label.

It is important to complete the full course of treatment even if the infection seems to get better.

REMEMBER... TAKE THE LOT, NO MATTER WHAT!
Antibiotic resistance

What can the public do?

People prescribed antibiotics should complete the full course of the medicine. Individuals who stop taking the antibiotics once the symptoms have lessened but before they have finished their complete course of medication often have not killed all the bacteria. Surviving bacteria can cause a reinfection, often with increased resistance to the antibiotic used in the attempt to control them.

Many common diseases are caused by viruses against which antibiotics, and most medicines, are ineffective. Prescribing and taking antibiotics in these instances increase the exposure of bacteria to antibiotics and may unnecessarily increase resistance to antibiotics.

Go to: Prescribing of antibiotics

Go to: Am I at risk?
Don't keep taking the tablets?

H P Lambert

Information about antibiotic drugs and instructions on their proper use usually include an injunction to finish the course. This is found in all patient-information leaflets and package inserts, some of which select the point for special emphasis in bold type or capital letters. “Keep taking the tablets” is a widespread dogma of medical practice. The supposed reasons for completing the course are that the patient either will not recover or will relapse if the course is not finished, and that completing the course will discourage the emergence of antibiotic resistance in the causal organism. Both suppositions are highly suspect. There is very little evidence for the optimum duration of antibiotic treatment for many infections, and courses shorter than those conventionally recommended are often appropriate. The other alleged reason for completing the course—that resistance will be discouraged—is rarely valid; on the contrary, antibiotic resistance is more likely to be encouraged by longer than by shorter courses of antibiotic.

How long is a course of treatment for infection?

For a few infections, there are fully validated trials that provide strong evidence on appropriate duration. Much the best evidence is available for tuberculosis, but optimum duration of antibiotic treatment has also been established for several other important infections—eg, gonorrhoea and infective endocarditis. For many infections, however, optimum duration of treatment is unknown. In particular, antibiotics are most commonly used in infections of the upper and lower respiratory tracts, which account for 75% of community prescriptions; for these infections there are great uncertainties and wide variations of opinion and practice about duration of treatment. Indeed, whether antibiotics are needed at all for some syndromes is disputed.

There is much controversy about the treatment of otitis media in children. Most British children with a diagnosis of otitis media receive antibiotics, and in the USA this condition is the most common reason for antibiotic use in outpatients. By contrast, antibiotics are not used routinely in otitis media in the Netherlands or Iceland, and there is evidence from several trials that antibiotics provide little or no benefit in this condition. As to duration of treatment, various trials have shown that courses of 2, 3, 5, and 10 days are equally effective (or presumably equally ineffective).

Similar doubts have emerged in acute sinusitis. Some controlled trials have shown the benefit of antibiotics, but 3 days’ treatment with trimethoprim-sulphamethoxazole was as effective as 10 days’ treatment. Other trials concluded that there is no advantage from their use, and in one study 28% of the treatment group and 9% of the placebo group had adverse effects.

There is also some dispute over the treatment of acute sore throat. Little and colleagues found no difference in outcome between no antibiotic, 10 days of antibiotic, or antibiotic given if symptoms had not settled within 3 days. But since antibiotics are of established benefit in streptococcal sore throat, a problem remains about how best to identify these bacterial infections.

It might be supposed that treatment guidelines would be firmly established in the more serious infections, but the widest gap in our evidence about duration of therapy is to be found in pneumonia and other infections of the lower respiratory tract. Acute lower respiratory tract infections are caused by many different organisms and vary greatly in severity, especially between different age groups and social conditions. A causal diagnosis is
Knowing when to stop antibiotic therapy

Empirical antibiotic therapy that turns out to be unnecessary, on review, can (and should) be stopped immediately.

After 50 years of widespread antibiotic use, we have reached the point where experts are seriously predicting “a postantibiotic era” and the World Health Organization has declared antibiotic resistance “a threat to global security”. No one can doubt the enormous benefits of antibiotics in curing or preventing serious sequelae of infections that were once the main causes of death and chronic illness, and enabling modern medical therapies that involve significant immune suppression.

These benefits are dramatic, and toxic side effects are apparently few. This makes it tempting — even now, when we know the risks — to prescribe antibiotics empirically at the first hint of infection, even viral infection, lest it progress to serious sepsis (and potential medicolegal or professional embarrassment). Although unnecessary antibiotic use is sometimes driven by patients’ expectations, they can be modified by public education.

During the first 30 years of the antibiotic era, the release of each new antibiotic was almost always followed by the emergence of resistance in some previously susceptible bacteria, but these were always estimated to cost the United States health system US$21–34 billion per annum; and

- all antibiotics have some specific adverse side effects such as allergy (or, rarely, anaphylaxis) or dose-related haematological, gastrointestinal, renal or hepatic toxicity.

Surveys of antibiotic use in hospital and community settings show that a third to a half of all prescriptions
Compliance with 10-day course of oral penicillin for strep pharyngitis

% compliance

Day

NEJM 1963;268:1116-8
Non-compliance survey

- 4514 adults in 11 countries recently prescribed antibiotics
- 912/4088 (22.3%) admitted non-compliance

Independent variables:
- Country – China 44%, Netherlands 9.9%
- Dosing regimen – OD 14.9%, TDS or QID 27%
- Age (inverse α non-compliance)
- Attitude of doctor and patient.

“If a patient feels much better but has only taken half of a prescribed course of antibiotics, should they stop the antibiotics early or complete the course?”

Results:
- Complete the course: 59%
- That depends …: 18%
- Stop: 23%
Non-bacterial infections

- Antibiotics are given to 52% of those presenting with uncomplicated URTI in the USA

  *JAMA 1997; 278:901-4*

- If no criteria for antibiotics or lab tests negative, don’t start antibiotics or tell patient to stop antibiotics.
Self-limited bacterial infections

Symptoms of conjunctivitis

Days of treatment

% Treatment

Placebo

Treatment

Placebo
Antibiotics for acute bronchitis?

- 17 trials with 3936 participants
- Antibiotics
  - ½ day fewer symptoms
  - 1 in 5 get side effects
- NSAIDs no benefit

*Cochrane Database Systemic Review 2014; 3: CD000245*
Antibiotics for acute bronchitis?

- 416 Spanish adults with ‘uncomplicated bronchitis’ = acute cough (< 7 days) plus discoloured sputum plus at least one other respiratory symptom (SOB, chest discomfort)
- 53% smokers or ex-smokers
- Augmentin vs ibuprofen vs placebo
- Outcome:
  - No difference in clinical features
  - GI side effects 12% vs 5% vs 3%

BMJ 2013; Oct4; 347:f5762
Antibiotics for non-pneumonia LRTI?

- 2061 patients with acute cough (< 4 weeks) and thought not to have pneumonia
- Randomised to amoxicillin 1g TDS or placebo
  - 79% produced sputum, half discoloured
  - Overall no reduction in severity or symptoms
  - Subgroup analysis:
    - No benefit in first 4 days; no benefit at day 7 in those who were worse or no better; no benefit in elderly, co-morbidity, smokers, green sputum
    - Mild benefit on day 5 to 7 if green sputum
    - 6.7% ↓ symptoms at day 5-7 ($p = 0.094$)
- Side effects:
  - Diarrhoea or nausea or rash 29% vs 24%

*Lancet Infect Dis 2013; 13: 123*
If antibiotics make no or little difference....

You may as well stop when feeling better. Or ideally not start antibiotics!
For infections in which antibiotics are clearly beneficial, how long is long enough?
Short-course Rx for cellulitis

- 87 patients, uncomplicated cellulitis
- RCT 5 days versus 10 days levofloxacin
- Cure without recurrence at 28 days
  - 5 days levofloxacin 42/43 (98%)
  - 10 days levofloxacin 43/44 (98%)

*Arch Intern Med* 2004;164:1669–1674
Short-course Rx for gonorrhoea

• Effective single dose treatments:
  • Cefixime 400mg po
  • Ceftriaxone 125mg IM
  • Ciprofloxacin 500mg po
  • Ofloxacin 400mg po
  • Levofloxacin 250mg po
Short-course Rx for meningococcus

- Retrospective audit CSF culture delayed > 1 hour after administration of Abs – no CSF taken more than 5 h after starting antibiotics grew *N. meningitidis*.
  
  *J Paed Child Health 2006; 42: 170-3 (D. Lennon)*

- Three days penicillin is enough to prevent relapse of meningococcal meningitis
  
  *CID 2003; 37: 658-62 (Ellis-Pegler, Galler, Roberts, Thomas, Woodhouse)*
Short course Rx for mild pneumonia in children

- 2000 children
- Randomised to amoxicillin for 3 d versus 5 d
- No difference in outcome

*Lancet* 2002; 360: 835-41
Duration of treatment for pneumonia

- Meta-analysis of 15 RCTs of 2796 patients with mild-moderate community-acquired pneumonia
  - Outcome same if < 7 or > 7 days duration
  - Drugs evaluated: azithromycin (10), beta-lactams (2), quinolones (2), ketolide (1)

*Am J Med 2007; 120(9): 783-90*
Short course Rx of childhood UTI

- 10 RCTs involving 652 children enrolled from OPC or ED with lower UTI
- Randomised to 2-4 days vs 7-14 days
  - No difference urine culture pos. at 0-7 d
  - No difference urine culture pos. at 10 d – 15 m
  - No difference resistant organisms
  - No difference recurrent UTI

Arch Dis Childhood 2002; 87: 118-23
Short-course Rx of adult UTI

- 3-days sufficient for trimethoprim, cotrimoxazole and fluoroquinolones
- 7 days required for beta-lactams and nitrofurantoin.
How short is too short?

- 96 elderly patients with acute UTI
- RCT trimethoprim single dose 200mg versus trimethoprim 200 mg BD for 5 days
- 7-day microbiological cure:
  - Single dose = 67%
  - 5-day course = 94%

*Age Ageing 1981;10:179-85*

Questions

- Is 1 day too short in general?
- Was 1 day too short for the 67%? (symptom duration?)
- Why would 1 day be enough for 67%?
Uncompl. UTI in non-pregnant ♀
All study entrants

Brit J Gen Pract 2002; 52: 729-34
Uncompl. UTI in non-pregnant ♀
Demonstrated bacteriuria

% symptomatic improvement and microbiologic cure

Day 3
Day 7

Nitrofurantoin (n=29)
Placebo (n=27)

Brit J Gen Pract 2002; 52: 729-34
RCT in Nelson – F versus F+P
If you stop antibiotics too soon, do you get more resistance?
Incomplete antibiotic course

Fittest and most resistant bacteria survive

More resistant normal flora

Relapse with more severe infection that is also more difficult to treat
Geometric mean minimum inhibitory concentration (MIC) for ampicillin of isolates from children according to whether or not they received antibiotics (error bars show 95% confidence intervals; P values based on t test)

Chung, A. et al. BMJ 2007;0:bmj.39274.647465.BEv1-bmj.39274.647465.BE
AB-failure relapses more severe?

- AB-resistant organisms are generally less “fit”
  - *E. coli*
  - *Salmonella typhimurium*
  - *E. faecium*
  - *Staphylococcus epidermidis*
  - TB
  - Penicillin-resistant pneumococcus…
- Immunity more effective?
Increasing duration of antibiotic treatment

After antibiotics
Eradicate the infecting organism?

- Yes – can do:
  - Gonorrhoea
  - Meningococcus
  - *Pseudomonas aeruginosa* in CF (if early)
  - MRSA carriage
  - TB

- But **not in most infections**, especially if causative organisms is normal flora.
Increasing duration of antibiotic treatment

After antibiotics
Too short is not good enough, but...

- 96 elderly patients with acute UTI
- RCT trimethoprim single dose 200mg versus trimethoprim 200 mg BD for 5 days
- 7-day microbiological cure
  - Single dose = 67%
  - 5-day course = 94%
- The single dose of trimethoprim was associated with less resistance in faecal enterobacteriaceae.

Resistance $\alpha$ duration

- 461 Canberra children < 4 years old
- Throat swabs yielded 631 pneumococcal isolates; 13.6% penicillin-resistant
- Penicillin resistance risk increased by 4% for each day of beta-lactam antibiotic taken in the preceding 6 months.

_BMJ_ 2002; 324: 28-30
Resistance \( \alpha \) duration

- 941 children (age 3-6 years) in Loiret, France
- Correlates with penicillin-resistant pneumococcal carriage:
  - Oral \( \beta \)-lactam use (\( \text{OR} = 3, \ P = 0.03 \))
  - Low-dose \( \beta \)-lactam use* (\( \text{OR} = 5.9, \ P = 0.002 \))
  - Longer than 5d course \( \beta \)-lactam (\( \text{OR} = 3.5, \ P = 0.02 \))

*lower than clinical recommendations

\( JAMA 1998; 279: 365-70 \)
Resistance $\alpha$ total use

Figure 1. Total outpatient antibiotic use in 26 European countries in 2002

Lancet 2005; 365(9459): 548-
Resistance $\alpha$ total use

Figure 6. Correlation between penicillin use and prevalence of penicillin non-susceptible S pneumoniae

AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.
Bring me Solo and the Wookie,

they will pay for this outrage.
If you feel better, is that a good sign that the bacteria are being killed?
Is eventual success related to rate of resolution of symptoms?

- Microbiological cure correlates with symptomatic cure (numerous studies)
- Persistent fever (and persistent positive blood cultures) predict complications of *Staphylococcus aureus* bacteraemia

*Arch Intern Med* 2003; 163:2066
*Clin Infect Dis* 1992; 14:75
*J Infect Dis* 1987
*J Infect* 2004; 48:245
Role of the immune system
When and how does the immune system need help from antibiotics?

- Early
  - Fever and hypotension (septic shock): every hour of antibiotic delay $\rightarrow$ survival falls by 7%
  
  *Clinical Infect Diseases 2008; 47: S3-13*

- Dose adequate?
  - Inadequate dosing $\rightarrow$ worse outcome

- Compliance
  - Poor compliance (not 3d vs 5d duration) associated with failure (OR = 4.5) in amoxicillin for childhood pneumonia study (n=2000)

  *Lancet 2002; 360: 835-41*
Stop when symptoms improved?

- 119 patients admitted to 9 hospitals in Netherlands
- All given 3 days IV amoxycillin
- Those who substantially improved after 3 days randomised to oral amoxycillin or placebo for 5 days
- No difference in clinical or radiological outcome at 10 days and 28 days.

*BMJ* 2006; 332: 1355-8
Duration of ABs commonly adjusted by clinical resolution
Duration of ABs commonly adjusted by clinical resolution

Australian TG Dec 2014 - prostatitis

Most antibiotics have good penetration into the inflamed prostate.

For mild to moderate infection, while awaiting the results of cultures and susceptibility testing, treat with oral antibiotic therapy. Use trimethoprim, amoxycillin + clavulanate or cepalexin—see Acute cystitis in men for doses; a longer duration of therapy is required (usually 2 to 4 weeks). Do not use nitrofurantoin because it does not achieve therapeutic levels in the prostate.

For severe infection, while awaiting the results of cultures and susceptibility testing, treat as for severe pyelonephritis; a longer duration of therapy is required (usually 2 to 4 weeks).

The appropriate duration of therapy is dependent on both disease severity and the response to treatment; while 2 weeks of antibiotic therapy is often adequate, it can be continued for up to 4 weeks for patients with severe disease or bacteraemia.

Adequate pain relief is also required; see Stepwise approach to acute pain management.
**Drug Interactions:** [DRUG ALERT] Warfarin.

**Patient Information:** Use with caution with occlusive dressings, incl babies nappies. Use for 14 day cleared.

**Pregnancy Category:** A

**Sport Category:** Permitted in sport

**Daktarin Cream (Cream)** Pharmacy Only
Miconazole nitrate; aqueous.

**Dose:** Skin infections: apply thin layer cream or lotion 2 times daily
Tinea versicolor: once daily. Rub well into skin
Continue uninterrupted treatment until lesions completely healed and for 2 weeks after.

**Pack:** 2 %30 g [1]
**Subsidy:** NS **Manufacturer Price:** $7.50 **Patient Charge:** $12.94
Advantages of stopping AB early

- Lower cost of antibiotics
- Fewer side effects
- Convenience
- Less resistance
- You’ve got some antibiotics left for next time.
Rational self-prescription of ABs?

- 1000 Finnish people living in Spain
- 115 purchased and took Abs (without medical input) in preceding 6 months
- Most common indication
  - Common cold 45%
  - Sore throat 17%

*Health Policy* 2006; 77: 166-71
Advantages of stopping AB early

- Lower cost of antibiotics
- Fewer side effects
- Convenience
- Less resistance.
- You’ve got some antibiotics left for next time.
When should you **not** stop antibiotics when you feel better?
When there’s no symptoms to start with..

- Asymptomatic UTI in pregnancy
- Eradication of MRSA
- Chlamydia urethritis
- Latent TB...
When the symptoms resolve long before the bacteria at the infection site have all died (studies: relapse)

- TB and other mycobacteria
- Endocarditis
- Chronic prostatitis
- Osteomyelitis
- Strep throat (RF)
When there is moderate-severe immune compromise
Randomised trial

• Nelson – December 2015 to February 2016
• Uncomplicated, moderate, community-acquired infections in adults:
  • Bladder (symptomatic + laboratory-proven)
  • Skin (length x width more than 75 cm$^2$)
  • Chest (meeting antibiotic criteria in local ‘Calculated Risk of Pneumonia’ score)
  • Sinus (meeting local antibiotic criteria).
• Exclusions: severe, moderate to severe immune compromise, treatment with an active antibiotic for that same infection in the last month.
Method

- AB choice – local guidelines, similar to 2014 ATG.
- Single dose IV or 2 days probenecid OK.

<table>
<thead>
<tr>
<th>STANDARD DURATION</th>
<th>SYMPTOM DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete full course</td>
<td>Stop when ‘substantially resolved’</td>
</tr>
</tbody>
</table>

- Trimethoprim x 3 d for cystitis
- Nitrofurantoin x 5 d for cystitis
- Flucloxacillin x 7 d for cellulitis
- Amoxicillin x 7 d for chest

- Symptom scores assessed daily.
- All patients followed up for 21 days after stopping.
- Approved by NZ H&D Ethics Committee.
### Results - baseline

- 71 patients with bladder (41), skin (19), chest (8) or sinus (3) infections.
- 3 patients withdrew: 1 non-compliant; 2 new different infections during treatment, required extra antibiotics.

<table>
<thead>
<tr>
<th></th>
<th>Standard duration (n = 32)</th>
<th>Symptom-based duration (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>8:24</td>
<td>10:26</td>
</tr>
<tr>
<td>Weight (mean, kg)</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td><strong>Type of infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Skin</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Chest</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Sinus</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Duration of symptoms before treatment (days, median)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Symptom score (out of 10) on Day 1 (mean (std dev))</td>
<td>5.6 (2.0)</td>
<td>5.1 (1.3)  (p=0.3)</td>
</tr>
<tr>
<td>IV antibiotic (up to 1 dose) at start of treatment</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Probenecid boosting (up to 2 days) at start of treatment</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Results – initial response

- 1 patient in each group failed oral antibiotics and required hospital admission for IV antibiotics

Figure 1. Mean daily symptom score of 66 patients who completed antibiotic treatment (and were still taking antibiotics on that day)
Results – key outcomes

- Symptom-based duration patients took antibiotics an average of 1 day less (range 4.5 days less to 2 days longer) than the ATG-recommended duration of treatment with that antibiotic for that infection.
- 3 of the 5 patients who needed more antibiotic at the end of treatment or who relapsed had skin infections.

<table>
<thead>
<tr>
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<th>Standard duration (n = 31)</th>
<th>Symptom-based duration (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of antibiotic treatment (mean (SD))</td>
<td>5.1 (1.7)</td>
<td>4.3 (1.9) <strong>p=0.057</strong></td>
</tr>
<tr>
<td>Defined daily dose (mean (SD))</td>
<td>7.4 (5.6)</td>
<td>5.4 (5.1) <strong>p=0.13</strong></td>
</tr>
<tr>
<td>Treatment-emergent adverse events (TEAE)</td>
<td>7 (23%, none severe)</td>
<td>6 (17%, none severe) <strong>NS</strong></td>
</tr>
<tr>
<td>Immediately needed more antibiotic at end of treatment</td>
<td>1 (3%)</td>
<td>- <strong>NS</strong></td>
</tr>
<tr>
<td>Relapse within 3 weeks of completing treatment</td>
<td>2 (6%)</td>
<td>2 (6%) <strong>NS</strong></td>
</tr>
</tbody>
</table>
**Cellulitis:** no relapse after 2.5 days of flucloxacillin 500 mg QID

**Cellulitis:** no relapse after 3.5 days of flucloxacillin 500 mg QID

**Cystitis:** no relapse after 1.5 days of nitrofurantoin 50 mg QID
Discussion

- Symptom-based prescribing reduced mean antibiotic consumption by 27% (DDD) without increasing relapse.
- Deciding when to stop antibiotics often was difficult and many patients needed guidance.
- The reduction in DDD may be less in real practice because many patients autonomously stop taking antibiotics when their symptoms have resolved.
- Antibiotic resistance was not measured in this study but reducing overall antibiotic consumption would probably reduce resistance.
My conclusion

• Prescribe the recommended dose and duration; encourage compliance
• There are a few circumstances when the AB course should be completed no matter how the patient feels – explain this
• For some conditions, stopping early when you feel better is common, logical, effective and has potential benefits on resistance and side effects
• Need more evidence before conservative official recommendations will change.
When radiologists take a selfie