Is it ok to stop antibiotics when symptoms resolve?

Traditionally, clinicians and health authorities advocate that patients should complete their full course of antibiotics as prescribed, even when their symptoms have improved, to prevent relapse of infection and the development of antibiotic resistance. A recent perspective in the Medical Journal of Australia has reignited debate on this guiding principle of antibiotic use.[1] The argument is that stopping antibiotic treatment once the patient's symptoms have resolved is a reasonable course of action in many situations, and is not likely to lead to relapse or promote antimicrobial resistance. Prescribers and patients are increasingly adopting this approach, in appropriate clinical situations.

> *"There is no risk – and every advantage – in stopping a course of an antibiotic immediately [after] a bacterial infection has been excluded or is unlikely; and minimal risk if signs and symptoms of a mild infection have resolved."*

—Professor Gwendolyn Gilbert, Clinical Professor in Medicine and Infectious Diseases, University of Sydney[1]

The most obvious circumstances in which it is appropriate to stop antibiotics when symptoms resolve are when the antibiotics were commenced without certainty of what infection is being treated, if any treatable bacterial infection is present at all, and for infections that are almost always self-limiting, e.g. conjunctivitis, bronchitis. Patient expectation often plays a role in the decision to start antibiotic treatment in these cases.

The debate around stopping antibiotics is essentially about ensuring that antibiotics are commenced appropriately in the first place. Important questions to consider include: is it more likely than not that the patient has a bacterial infection? Will prescribing an antibiotic result in a better clinical outcome? Will the infection resolve without treatment? Will the potential adverse effects of the antibiotics outweigh the benefits? Are laboratory investigations indicated? Can antibiotic treatment be delayed until infection is confirmed?

If antibiotics make little or no difference to clinical outcomes, it would seem logical that they could be stopped once symptoms have resolved – or ideally not be started in the first place. However, if an antibiotic is clearly beneficial, can it also be stopped if symptoms resolve? Although dependent on the individual clinical scenario, it has been suggested that stopping antibiotics earlier than a standard course might be considered for patients with moderate pneumonia, sinusitis, urinary tract infections, cellulitis or other substantial skin infections. For these patient groups, the main considerations for stopping antibiotics are whether the antibiotic course has been long enough for that particular bacterial infection, whether symptom resolution is a good marker of having taken enough antibiotic and whether stopping the antibiotic might increase the risk of relapse of infection and the development of antibiotic resistance.

There are many scenarios where stopping antibiotics upon resolution of symptoms is not appropriate, such as when eradication of the bacteria is the aim, e.g. treating group A streptococcal (GAS) pharyngitis in patients at risk of rheumatic fever, or in patients with more severe "deep-seated" or complex infections, e.g. osteomyelitis, endocarditis and tuberculosis, where small numbers of bacteria can persist despite a marked improvement in symptoms and signs. Early stopping of antibiotics in these conditions increases the risk of the patient experiencing a relapse. Antibiotic courses should also be completed for the full recommended duration in some cases where the patient has no symptoms, e.g. asymptomatic bacteriuria during pregnancy or the eradication of latent tuberculosis, and when the patient has severe immune deficiency.

Newer guidelines recommend shorter durations of antibiotics

Resolution of infection is dependent on a person's immune response and the ability of the antibiotic to target the site of infection and remain there for an adequate duration. The specific type of pathogen and tissue damage caused by the infection also affect resolution.[2] The optimal duration of a course of oral antibiotics should be sufficient to substantially reduce the patient's symptoms and prevent relapse, while minimising adverse effects and the development of antibiotic resistance. The choice and duration of antibiotic treatment should be based on the most up to date national or local antibiotic guidelines and local antibiotic susceptibility data, taking into account the patient's symptoms and signs, site of infection, co-morbidities, immune status and possible pathogens.

Newer treatment guidelines increasingly recommend shorter durations of antibiotic treatment, based on evidence that cure rates are similar to those with longer regimens, which have often been derived from original clinical trials. For example, three days of trimethoprim is sufficient to treat a woman with an uncomplicated UTI,[3,4] whereas, previously seven to 14 days of treatment was recommended.[5] A single dose of azithromycin (1 g) can be used to treat patients with chlamydia, as an alternative to seven days of doxycycline.[3,6] A 2011 systematic review concluded that shorter antibiotic courses (five to seven days) were as effective as longer courses (14 days or more) for patients with uncomplicated pyelonephritis or community-acquired pneumonia.[7] This finding was supported by a 2013 review which concluded that short courses of antibiotics (e.g. three days) were as effective as longer courses (e.g. ten days) in patients with mild to moderate community-acquired pneumonia.[8] Current New Zealand guidance for community-acquired pneumonia recommends five to seven days of treatment.[3,4]

Other examples of evidence for shorter durations of antibiotics include:

- 87 patients with uncomplicated cellulitis were randomised to five or ten days treatment with levofloxacin – no significant difference was found between groups in the rate of cure without recurrence at 28 days (98%)[9]
- 2000 children with mild pneumonia were randomised to three or five days treatment with amoxicillin – there were no difference in clinical outcomes between groups[10]
- A review of ten randomised controlled trials involving 652 children with lower urinary tract infection (UTI) randomised to two to four days or seven to 14 days antibiotic treatment – no difference was found between groups in positive urine cultures after treatment, resistant organisms or recurrent UTI[11]

Do the same antibiotic duration recommendations apply to all patients?

Guidelines on duration of antibiotic treatment reflect a regimen that is likely to be successful in most cases. This means that for some patients a shorter course is all that is needed and for others a longer course is required. The severity of infection often influences how long an antibiotic is given for, along with other factors such as the patient's immune status, co-morbidities and whether this is a recurrent infection. For example, in an analysis of optimal antibiotic treatment durations for UTI in children, some patients had resolution of symptoms after a single dose while others required up to ten days treatment.[12] The authors were able to conclude that for most children, two to four days treatment is sufficient,[12] but this recommendation will not apply to every patient that is treated.

Dose and compliance may be more important than duration of antibiotic treatment

Giving the right antibiotic at an adequate dose, along with good compliance with the daily regimen by the patient, i.e. taking the correct dose at the appropriate intervals, may be more important for treatment success than taking an antibiotic for a long period of time.

Prescribing an adequate dose of an antibiotic improves its clinical efficacy. Ideally, antibiotics should be dosed according to their pharmacokinetic and pharmacodynamic qualities to achieve the best clinical outcomes for the patient, as well as limiting the spread of antimicrobial resistance.[2] For example, fluoroquinolones (e.g. ciprofloxacin) have maximum bactericidal activity when their concentrations are high, even for a relatively short time; these are "concentration-dependent" antibiotics, and would be expected to be effective using shorter treatment courses. In contrast, beta lactam antibiotics (e.g. amoxicillin, cefalexin) are "time-dependent" antibiotics and the drug concentration needs to be above the minimum inhibitory concentration for the specific pathogen for a sufficient duration of time to achieve the greatest efficacy.[2]

Symptom resolution is often a good indicator of cure in mild to moderate infections

Resolution of symptoms is used as a criterion for treatment success in antibiotic trials and correlates very highly with microbiological cure. In a study involving 119 patients

admitted to hospital with community-acquired pneumonia in the Netherlands, it was found that stopping antibiotic treatment after symptom resolution did not adversely affect patient outcomes. All patients were treated for three days with IV amoxicillin. After this time, patients were rated on five-point scales which assessed four respiratory symptoms (dyspnoea, cough, sputum production and colour of sputum – worsening to complete recovery) and general improvement (not recovered to completely recovered). Those patients whose symptoms substantially improved after three days (improvement of two or more points on the scales and temperature < 38°C) were randomised to receive oral amoxicillin or placebo for five days. There were no differences in clinical or radiological outcomes between patient groups after 10 and 28 days.[13]

Shorter courses of antibiotics do not increase bacterial resistance

The association between antibiotic use and resistance is complex, however, longer courses of antibiotics have been associated with the greatest risk of antimicrobial resistance at both an individual and community level.[1, 14] Increased antibiotic use exerts a selective pressure for the development of resistance by eliminating antibiotic-susceptible bacteria and leaving antibiotic-resistant bacteria to multiply, making future treatment more challenging.[14] The concept of finishing the antibiotic course to prevent resistance may apply to infections for which treatment is expected to eradicate the causative bacteria entirely from the body (e.g. tuberculosis, gonorrhoea), but does not apply to infections caused by normal body flora (e.g. most infections of the skin, urinary tract, upper and lower respiratory tract and abdomen), in which the bacteria will persist long after the symptoms and signs of infection have resolved. Even if the bacteria causing the infection are eradicated, the antibiotic will exert resistance pressure on other natural bacterial flora – and the longer the course, the more resistance will develop.

It can be reasonably assumed, therefore, that stopping an antibiotic after a few days of treatment will be no more likely to contribute to antibiotic resistance than taking the full course. The systematic review that compared short vs. standard duration antibiotic treatment for UTI in children found no significant difference between treatment durations in the development of resistant bacteria.[12] Other studies on carriage of antibiotic-resistant *Streptococcus pneumoniae* and pneumococci have demonstrated that a high dose of antibiotic for a shorter duration results in less bacterial resistance than a lower dose for a longer duration.[15, 16]

In conclusion: patient education is most important

Stopping antibiotics when symptoms have substantially resolved appears to be effective and safe for many patients, especially those who are unlikely to have a bacterial infection or who have a self-limiting bacterial infection. The outcome of this approach in patients with moderate infections such as pneumonia, sinusitis, urinary tract infections or skin infections requires more study, but has the potential advantages of improved convenience, reduced adverse effects and less pressure on antibiotic resistance. Published evidence is increasingly supporting prompt treatment of bacterial infections, when appropriate, with higher doses of antibiotics, taken reliably and for shorter durations.

Clear expectations about duration of treatment, as well as daily adherence to a regimen, need to be agreed upon between the clinician and patient when antibiotic treatment is prescribed, ideally at the start of treatment. If an antibiotic is prescribed for a clear indication, and a minimum duration is supported by evidence-based guidance, patients should be advised not to stop treatment until the end of the course. For many other infections, where the optimal antibiotic treatment duration is less certain, the patient may be advised that it is acceptable to stop treatment when symptoms resolve. The decision to stop an antibiotic earlier than the agreed duration should ideally take place only after a follow-up discussion between the treating clinician (or designated clinical staff member, e.g. practice nurse) and the patient, to ensure that clinical features of infection have actually resolved and that there are no misunderstandings about the role of the antibiotic. This is also an opportunity to reinforce to the patient that the leftover antibiotic should be safely disposed of and not kept for future use or use by another family member.

A New Zealand-based randomised controlled trial is planned for the summer of 2015/16 to compare standard course antibiotic treatment versus stopping treatment once symptoms resolve in patients with skin, chest, sinus and urinary tract infections. It is hoped that this study will provide some definitive answers for this debate.

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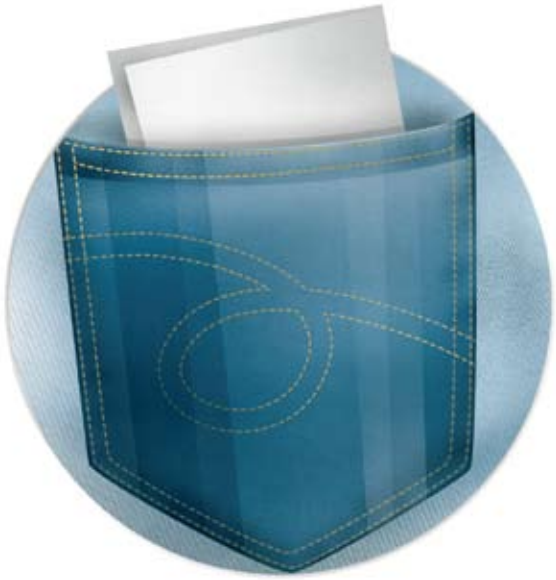

Delayed antibiotic prescriptions for respiratory tract infections: does the strategy work?

Delayed antibiotic prescribing, also known as a "back pocket prescription", is a strategy of providing a patient with a prescription for an antibiotic, but advising them not to fill it unless their symptoms persist or worsen, or if laboratory results (if requested) subsequently indicate a bacterial infection. Delayed antibiotic prescriptions are most often considered for patients with acute respiratory tract infections (RTIs), which is the focus of the following article.

Most patients with acute upper or lower RTI symptoms do not benefit from antibiotics and prescribing antibiotics inappropriately for these patients leads to unnecessary cost, adverse effects and the development of antibiotic resistance. Decades of observational and interventional studies involving thousands of patients have, however, identified subgroups of patients with conjunctivitis, sinusitis, sore throat and acute cough for whom antibiotics should be considered, based on the presence of key features in their history, examination or laboratory test results (see: "Antibiotics: choices for common infections", reference over page). These features may not be evident when the patient first presents to the general practice clinic, but may develop in the subsequent days to weeks. Options to capture this group of patients include immediate