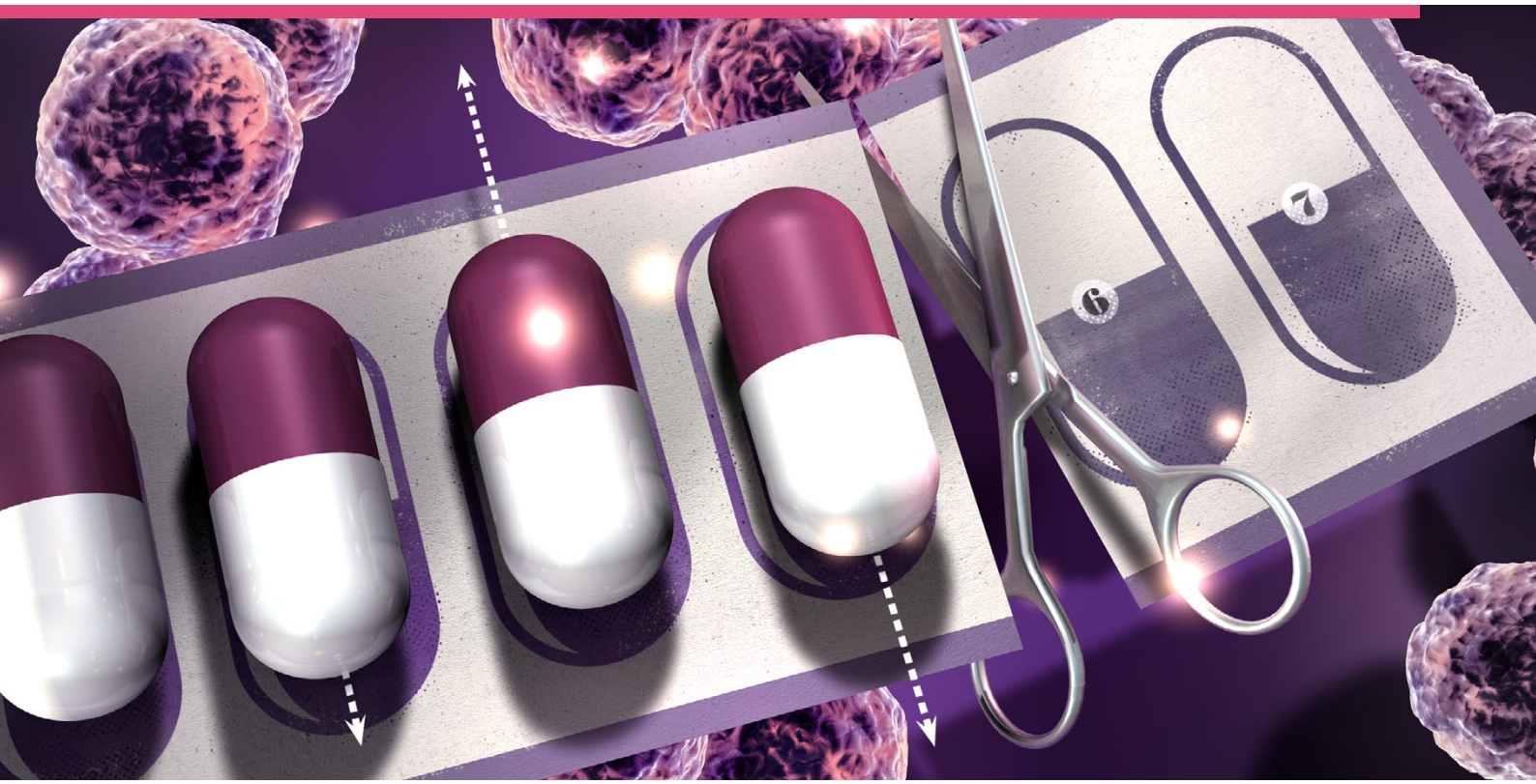

Antibiotics: the future is short

In general, the recommended durations of antibiotic treatment regimens are decreasing as evidence for the safety and efficacy of shorter courses accumulates. However, the key factor underpinning the debate about how long an antibiotic course should be is ensuring that antibiotics are only prescribed when they are likely to confer a significant health benefit.

KEY MESSAGES:

- Using antibiotics only when needed, and using short courses when appropriate, will avoid unintended adverse consequences for individuals and reduce the burden of antimicrobial resistance in the long-term
- Based on evidence of comparable clinical outcomes, shorter antibiotic courses are indicated for many conditions
- Clear communication is crucial when antibiotics are prescribed and dispensed to ensure that the patient knows why and how they should be taken
- Occasionally an antibiotic regimen may need to be individualised, e.g. a longer treatment course for patients who are immunosuppressed

Does this patient need an antibiotic? Using antibiotics only when needed

Resources such as the bpac[nz] antibiotic guide provide prescribers with information on whether an antibiotic is indicated for a particular infection.[1] In some cases, an antibiotic is always appropriate when an infection is present, e.g. bacterial pneumonia, meningitis, cellulitis, sexually transmitted infections, but in other cases, severity or persistence of symptoms and signs guides appropriate prescribing, e.g. sinusitis, otitis media, conjunctivitis, boils and some gastrointestinal infections.[1] The decision to prescribe an antibiotic for an individual patient, and for how long, can sometimes be uncertain. It is not always simple to determine immediately if the patient has a bacterial infection, and it can also be a subjective judgement as to whether the patient's symptoms are severe enough to warrant antibiotic treatment, or how their co-morbidities will impact on the course of their illness or recovery.

A prescribing guide may provide the "rules", but a clinical decision is made each time antibiotics are prescribed, for example:

- I know that an antibiotic is indicated for the infection, but how certain am I that the patient has this infection? Can the antibiotic be delayed while I investigate further?
- I think that the patient has an infection, but is this a self-limiting infection where severity or persistence of symptoms guides decisions about whether antibiotic treatment is beneficial?
- I am not certain that an antibiotic is required now, but what are the consequences of not prescribing? Will the patient return promptly if their condition deteriorates?
- Does the patient have co-morbidities or other clinical factors that increase the potential adverse outcomes of an infection, and therefore lower my threshold for prescribing an antibiotic?

In general, an antibiotic is needed if a patient has a bacterial infection (confirmed or very likely), in which the infection will cause clinical symptoms or complications and the infection is unlikely to resolve without antibiotic treatment in a reasonable length of time.

A lower threshold for prescribing an antibiotic, and/or a longer duration of treatment, may be appropriate for patients who are more likely to experience increased severity of infection or complications, or have an atypical presentation of infection. This includes frail elderly, infants, people taking immunosuppressant medicines, people with an autoimmune disorder, diabetes, severe hepatic or renal disease and people who are alcohol-dependent or malnourished.

In the context of primary care in New Zealand, clinicians are also likely to have a lower threshold for prescribing antibiotics for patients who are at significant risk of not returning if their condition deteriorates or who are living in circumstances detrimental to their health, e.g. over-crowded or damp housing.

For focused discussion on prescribing antibiotics for respiratory tract infections and other "winter ills", look out for our next article in the antibiotics theme.

Managing patient, and clinician, expectation

An additional aspect that may complicate the decision to prescribe an antibiotic is expectations about treatment; this can be the patient's expectation to receive an antibiotic, as well as the clinician's expectation that the patient wants an antibiotic. However, it should not be assumed that this is always the case – most patients will be just as happy with their treatment if they do not receive an antibiotic, as long as the reason why has been communicated effectively.[2] A goal of a clinical consultation is for the patient to feel satisfied and this can be achieved through appropriate listening, reassurance and validation that they made the right decision to seek medical assessment and advice.

If a patient asks for an antibiotic, it may be useful to check their understanding of this type of medicine. Some people may be unaware that antibiotics are a treatment for bacterial infections only, or they may be uncertain about what a bacterial infection is. Taking an antibiotic unnecessarily is not without risk – antibiotics can be associated with significant adverse effects, such as nausea, vomiting, diarrhoea, rash, and in rare

There is evidence that patients expect antibiotics less than clinicians believe they do

Patient satisfaction is more strongly associated with receiving understandable information and reassurance that an antibiotic is not always appropriate or effective than actually receiving an antibiotic prescription.[2, 4] A Cochrane systematic review found no significant differences in satisfaction between patients with acute respiratory tract infection (RTI) managed using a delayed or no antibiotic prescribing strategy.[5] In a primary care trial of antibiotic prescribing strategies for acute RTI, there were also no significant differences found in satisfaction between patients who did not receive an antibiotic (79% very satisfied) versus patients who were managed using the delayed antibiotic strategies (74 – 89%).[6] In a New Zealand study of perceptions about delayed antibiotic prescriptions, it was found that patients were not as concerned about being involved in decision-making about their health care as their clinicians perceived them to be.[7] Most patients preferred their clinician to decide whether they needed an antibiotic.[7]

cases obstructive jaundice, liver failure and death. Taking an antibiotic also causes disruption of the natural microbiota that normally helps theimmune system and prevents the overgrowth of harmful bacteria.[3] This can lead to infections caused by organisms such as *Candida albicans* and *Clostridium difficile*.

Provide a safety net

Sometimes the decision of whether to prescribe an antibiotic will change if symptoms worsen or persist or new symptoms develop. It can be explained to patients that this does not mean the wrong decision was made initially, it just means that their illness has evolved in a way that was not expected. Part of communicating why an antibiotic has not been prescribed is ensuring that patients know that their symptoms are still important, they are still unwell despite not requiring an antibiotic, and they should report back to their general practice if their condition deteriorates or they do not improve. Consider what barriers might prevent some patients from returning and if there are any solutions that the practice can offer, e.g. providing a "back pocket" prescription (see below), reduced or no cost follow-up visit, telephone follow-up, making an appointment at a convenient time in advance that can be cancelled if not required.

Consider if delayed antibiotic prescribing is appropriate

Delayed prescribing of antibiotics, i.e. a "back pocket prescription", is an option to reduce antibiotic use where there is clinical uncertainty regarding the need for antibiotics or where the patient may be unable to attend a follow-up consultation. This strategy involves providing a prescription but advising the patient not to fill it unless their symptoms worsen or persist, or if the results of laboratory testing subsequently indicate that a bacterial infection is present. Alternatively, a prescription could be provided free-of-charge and sent to the pharmacy if the patient phones, or be available for them to pick up at reception.

Further information is available from: "Delayed antibiotic prescriptions for respiratory tract infections: does the strategy work?", **www.bpac.org.nz/bpj/2015/june/delayed.aspx**

Prescribing antibiotics: the trend toward shorter courses

"For every bacterial infection for which trials have compared short-course with longer course antibiotic therapy [except tuberculosis], short-course therapy has been just as effective…" [8]

After making the decision to prescribe an antibiotic, the next decisions are selecting the right antibiotic for that infection, and prescribing it at an appropriate frequency and duration.

Short courses of antibiotics, i.e. seven days or less, are now standard for many uncomplicated infections treated in primary care. This recommendation is being driven by two factors:

1. Evidence that short courses of antibiotics are at least as safe and effective as longer courses
2. Increasing antibiotic resistance in commensal bacteria (part of the normal flora in the body)due to prolonged antibiotic exposure

In theory, in patients who are immuno-competent, antibiotics are only required to provide a "boost" to the body's phagocytic immune cells and other defence mechanisms which will eventually clear the infection.[9] The optimal duration of a course of oral antibiotics should therefore be sufficient to substantially reduce the patient's symptoms and prevent relapse, while minimising adverse effects and the development of antibiotic resistance. In most cases, a shorter course is better but there are some scenarios where antibiotics still need to be prescribed for a longer course (see: "Short courses of antibiotics are not appropriate in all situations").

The growing evidence in support of short courses of antibiotics

Numerous trials are providing evidence that short courses of antibiotics are safe and effective. For example, a systematic review of trials concluded that short courses of antibiotics (e.g. ≤ 5 days) are effective for the treatment of community-acquired pneumonia, and this is not dependent on the severity of infection or the antibiotic used.[10] The same review found some evidence that shorter course of antibiotics are effective in the treatment of skin and soft tissue infections, but concluded that clinical review should occur before antibiotics were stopped.[10]

Another study identified 19 trials comparing shorter versus longer courses of antibiotics in adults and adolescents who had been hospitalised with pulmonary, bloodstream, soft tissue, intra-abdominal or urinary infections. It was found that the rate of clinical and microbiological cure due to shorter courses of antibiotics was indistinguishable from that associated with longer courses, and there was no difference in risk of recurrence, adverse effects or mortality.[11] Although this study was carried out in a hospital setting rather than in the community, it does indicate that even severe infections can be treated effectively with shorter courses of antibiotics.

As more evidence accumulates, it is likely that the recommended duration of antibiotic treatments for many infections treated in primary care will be shortened.

Antibiotic dosing regimens for a range of common conditions are available in the guide "Antibiotic: choices for common infections", **www.bpac.org.nz/antibiotics/guide.aspx**

Short courses of antibiotics are not appropriate in all situations

Shorter is not always better when prescribing antibiotics and there are a number of clinical scenarios when longer treatment courses continue to be recommended.

Ensuring eradication of bacteria

In patients at increased risk of complications, e.g. a patient who is immunocompromised, longer durations of antibiotic treatment are recommended to eliminate the pathogenic bacteria as the consequences of residual bacteria remaining can be severe. For example, cystitis is treated for a longer duration in pregnant women; seven days instead of three to five days (depending on the antibiotic used).[1]

In New Zealand, there is a high rate of rheumatic fever among young Māori and Pacific peoples.[16] Rheumatic fever is a complication of group A streptococcus (GAS) infection. For this reason, people who are at high risk of rheumatic fever who present with a sore throat and have GAS isolated from a throat swab are prescribed a ten-day course of antibiotics (or a one-off IM dose) in order to eliminate the bacteria.[17] It is important that these patients take the entire course. Patients not at risk of rheumatic fever generally do not require antibiotic treatment for sore throat, including that caused by GAS.

Information on risk factors for rheumatic fever and a treatment algorithm for sore throat management are available from: **www.heartfoundation.org.nz/shop/heart-healthcare/non-stock-resources/sore-throat-algorithm.pdf**

Complicated infections require longer antibiotic treatment

Infections occurring in sites where antibiotic penetration or immune responses are relatively poor require a longer treatment duration, e.g. osteomyelitis (bone) or endocarditis (valvular tissue). Tuberculosis is caused by a slowly replicating bacterium that is only slowly killed by antibiotics and therefore an extended duration of antibiotic treatment, e.g. at least six months, is required. Patients with complicated infections such as these should usually have their treatment guided by an expert in infection management (infectious diseases physician or clinical microbiologist). It is important that patients do not cease treatment when they feel their condition has improved.

Short courses of antibiotics are not associated with increased rates of antimicrobial resistance

For many years the accepted wisdom has been that lengthy courses of antibiotics are necessary, sometimes long after symptoms have resolved, to prevent the development of antibiotic resistant bacteria and reduce the likelihood of a recurrent infection. However, it is now agreed that this logic only applies to infections where treatment aims to eradicate the causative bacteria entirely, e.g. in tuberculosis infection.[12] This precaution does not apply to the vast majority of infections managed in primary care where the bacteria will persist after the infection has resolved, e.g. most infections of the skin, urinary tract, upper and lower respiratory tract and abdomen. In these situations antibiotic courses that are longer than necessary actually increase the likelihood that commensal bacteria will develop resistance. For example, a meta-analysis of studies performed in primary care with a range of infections and treatment durations found that longer antibiotic regimens and multiple courses of antibiotics were associated with increased rates of antimicrobial resistance in urinary and respiratory bacteria and that increased antibiotic resistance could be detected for up to 12 months following antibiotic treatment.[13]

Short courses of antibiotics are less likely to cause adverse effects

Reducing the duration of antibiotic treatment means patients are less likely to develop dose-related antibiotic adverse effects. A systematic review of ten studies involving patients treated with antibiotics for chronic obstructive pulmonary disease (COPD) exacerbations found that courses of antibiotics of five days or less were associated with significantly fewer adverse effects than longer courses, i.e. seven days or more.[14] Another study found that even relatively small reductions in the duration of antibiotic treatment can result in fewer adverse effects. In 281 patients who had been admitted to hospital with a lower respiratory tract infection, there was a reduction in the incidence of gastrointestinal adverse effects, e.g. nausea, vomiting, diarrhoea and abdominal pain, from 20.6% to 13.6% when the average duration of treatment was reduced from 8.3 days to 6.8 days.[15]

Shorter courses means less antibiotic wastage

Prescribing a smaller quantity of antibiotics is likely to result in less antibiotic wastage, i.e. people are more likely to finish their course of antibiotics if prescribed for fewer days. This in turn decreases the risk of antibiotics being used inappropriately, e.g. self-directed use for another illness or used by other household members. Inappropriate use of antibiotics in the community contributes to antibiotic resistance as well as being a safety risk.

Prescribing an appropriate dose

Antibiotics must be dosed optimally in order to achieve a target concentration. Dosing recommendations should be followed where available, and depending on the clinical circumstances, give consideration to dosing at the maximum end of the range.

For recommended antibiotic dosing ranges, refer to the bpac^{nz} antibiotics guide: "Antibiotic: choices for common infections", **www.bpac.org.nz/antibiotics/guide.aspx** or the New Zealand Formulary: **www.nzf.org.nz**

Recommended antibiotic doses for adults are usually given as a "one-size fits all" dose or range in milligrams. There is debate over whether dosing should instead be weight-based (e.g. mg/kg) to account for people who are significantly under- or over-weight, but there is little clinical guidance to put this in practice. Several reviews concur that doses of some antibiotics should be increased, or at the least, used at the maximum recommended dose in people who are obese.[18–20] However, the pharmacokinetics of antibiotics in people who are obese are not predictable or uniform and there is insufficient data to make specific dosing recommendations. The maximum dose, or higher than the maximum, should be considered when prescribing beta-lactam antibiotics (e.g. penicillins, cephalosporins) and ciprofloxacin to patients who are significantly obese.[18–20] An alternate strategy is to use a loading dose where a short course of high-dose antibiotic is used to achieve satisfactory tissue penetration, followed by a standard dose for the rest of the course.[18]

If uncertain about an appropriate antibiotic dose in a significantly over- or under-weight patient, discuss with an infectious diseases physician or clinical microbiologist.

Should you stop antibiotics if symptoms resolve?

When antibiotics are prescribed, patients should not be given advice to stop taking them if their symptoms resolve as this may cause confusion and affect adherence to treatment. The decision to stop antibiotic treatment should be made in consultation with a clinician, either by follow-up appointment or phone call.

Ideally, if an antibiotic has been prescribed for an appropriate length of time, there will be no need to consider shortening the course. For example, trimethoprim is prescribed for uncomplicated cystitis in women for three days (if appropriate based on local resistance data); if the patient felt better after two days, there is no clear advantage of missing the third day's treatment and in fact this may be detrimental since there is evidence that three days treatment is optimal for this infection.[21]

However, there are some scenarios where a clinician may consider stopping antibiotic treatment early or conversely, continuing antibiotic treatment beyond the initial prescribed duration. Clinical guidelines give advice for an appropriate duration of antibiotic treatment that will manage infection in most patients, however, this may not be optimal for every patient, therefore tailoring duration of treatment based on individual clinical factors and response to treatment is a reasonable strategy for patients with uncomplicated infections.[12]

Clinical scenarios where antibiotic treatment should be stopped early:

- Empirical treatment was commenced but laboratory results subsequently show no bacterial infection
- Antibiotics were prescribed with uncertainty of bacterial infection, or for a self-limiting infection, and symptoms have now resolved
- Intolerable adverse effects occur; stop if the benefit of antibiotic treatment does not outweigh the adverse effects

Clinical scenarios where it might be appropriate to consider stopping antibiotic treatment early (or changing to another antibiotic):

- No clinical response to treatment; consider laboratory investigation (if not already done) to confirm bacterial infection and antibiotic sensitivity and consider discussing with an expert in infection management (infectious diseases physician or clinical microbiologist)
- Resolution of symptoms after a few days in an uncomplicated infection; there is evidence that symptom resolution is correlated with improvement in microbiological and biochemical markers of infection and stopping treatment when symptoms resolve does not adversely affect outcomes, e.g. in patients with cellulitis[22] and in patients with community-acquired pneumonia[23,24]

Clinical scenarios where it might be appropriate to consider extending antibiotic treatment:

- Infection was particularly severe and symptoms have not fully resolved
- The patient has co-morbidities that make them more vulnerable to the infection or its complications, e.g. taking immunosuppressants, diabetes, frailty
- The infection is recurrent

For further information, see: "Is it ok to stop antibiotics when symptoms resolve?", available from: **www.bpac.org.nz/bpj/2015/june/symptoms.aspx**

Encouraging adherence to an antibiotic regimen

Adherence is a critical component to antibiotic treatment and this requires good communication between the patient, prescriber and pharmacist. The patient should be provided with understandable information about how the antibiotic works and why they need to take it exactly as prescribed to maximise the benefit. If a patient has previously been prescribed a longer course of treatment, it may be necessary to explain why a shorter treatment is now "best practice".

Cost can be a barrier to people collecting a prescription for antibiotics. Ensure that patients know about the prescription subsidy scheme which entitles households (couples and dependent children aged 13–18 years) to free prescription items after more than 20 items have been dispensed; most pharmacies are able to electronically access this information and determine the number of prescription items that have been dispensed from their own and other pharmacies.

For further information about the Prescription Subsidy Scheme, see: **www.health.govt.nz/your-health/conditions-and-treatments/treatments-and-surgery/medications/prescription-subsidy-scheme**

Provide detailed instructions to go on prescription labels

Instructions for taking antibiotics need to be clear and unambiguous for patients. Most Patient Management Systems, e.g. Medtech, allow dosing instructions for a particular medicine to be customised and pre-populated for a methodical approach to prescribing. Instructions intended for prescription labels such as "take as directed" or "take until finished" are not ideal; more precise instructions should be given, e.g. take one capsule, every eight hours (three times per day), for five days. Ensure that these instructions are also communicated to the patient and they understand how often and for how long they should take the antibiotic. Discuss how many doses they should take on the first day of treatment, e.g. if they are collecting their prescription late in the day.

Reinforce the message in the pharmacy

Dispensing is an opportunity for the pharmacist to ensure that the patient understands their antibiotic dosing instructions and to reiterate the importance of taking the antibiotic as prescribed. This also provides the patient with another opportunity to ask questions; asking the patient to explain the instructions back is a good way to confirm that they have understood.

Often a good opening conversation is to ask the patient: "What has your doctor told you about how to take these antibiotics"?

Further discussion should cover:

- The dosing interval – some patients may like help to decide when they will take each dose, e.g. an eight-hourly dose could coincide with breakfast, afternoon tea and supper or the patient could set an alarm on their phone.
- Whether the antibiotic needs to be taken with or without food, and how the patient can arrange the dosing schedule around their meal times and school or work schedule.
- How many days the antibiotics should be taken for, e.g. your last day will be on Tuesday next week. It can sometimes be confusing for patients as to whether the first day they start taking their antibiotic is "day 1" or "day 0" if they, for example, collect their prescription late in the day and only have time for one or two doses. Do a calculation of the volume of supply and if necessary, explain that on their last day of treatment they will not need to complete a full days dosing.
- Antibiotic-related adverse effects and how these can be managed.
- Medicine interactions – the prescriber is likely to have considered medicine interactions, but another opportunity to check is when the medicine is dispensed
- The prescription subsidy scheme (if relevant)

Good adherence is arguably more important than duration of treatment

Prescribing the right antibiotic at an appropriate dose and dosing interval, and the patient taking the antibiotic as prescribed, is likely to be more influential on treatment success than the number of days that an antibiotic is taken. Antibiotic treatment is under threat worldwide due to increasing resistance largely as the consequence of inappropriate use; make your future use of antibiotics appropriately short, in order to keep antibiotics from a short future.

Further information: "Why are we using antibiotics as placebos? A webinar by Associate Professor Mark Thomas. Available from: **www.goodfellowunit.org/events/why-are-we-using-antibiotics-placebos**

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