"Complete the antibiotic course to avoid resistance"; non-evidence-based dogma which has run its course?

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Standfirst. Policy makers, educators and doctors should drop the message that stopping antibiotics early promotes antibiotic resistance.

Introduction

Antibiotics are vital to modern medicine and antibiotic resistance is a global, urgent threat to human health. There is an unambiguous relationship between antibiotic exposure and antibiotic resistance both at the population level[1] and in individual patients.[2] Therefore reducing unnecessary antibiotic use is a key measure to mitigate antibiotic resistance.

Avoiding antibiotic overuse requires healthcare professionals and the public to be well informed about antibiotic treatment. The first objective of the World Health Organisation (WHO) Global Action Plan 2015 is to *'Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.'*[3]

A major theme of public communication about antibiotics is that patients who fail to complete prescribed antibiotic courses put themselves and others at risk of antibiotic resistance. For example, in materials supporting this year's Antibiotic Awareness Week the WHO advises patients '*always complete the full prescription, even if you feel better, because stopping treatment early promotes the growth of drug-resistant bacteria'*.[4] Similar advice appears in national and local guidance (e.g. NHS choices,[5] the Mayo Clinic[6] and this idea is taught to UK secondary school children[7]). A key recommendation of the WHO's 2015 multi-country public awareness survey was to increase public awareness of the importance of completing antibiotic prescription courses.[8]

The idea that stopping antibiotic treatment early encourages antibiotic resistance is false in most situations. Furthermore, it is a significant barrier to optimising antibiotic treatment of individual patients. Following the example of Public Health England and the Centers for Disease Control, policy makers,

educators and doctors should stop using this message when communicating with the public. Further, they should publicly and actively state that this was not evidence-based and is incorrect.

Origins of the idea

Concern that giving too little antibiotic treatment could select for antibiotic resistance can be traced back to the dawn of the antibiotic era.

When Howard Florey's team treated Albert Alexander's staphylococcal sepsis with penicillin in 1941 they eked out all the penicillin they had (around 4g, less than one day's worth with modern dosing) over a period of four days by repeatedly recovering the drug from the patient's urine. When the drug ran out, the clinical improvement they had noted reversed and he subsequently succumbed to his infection.[9] There was no evidence that this was due to resistance but the experience may have planted the idea that prolonged therapy was needed to avoid treatment failure.

Fleming's early work had shown that sensitive bacteria could be 'acclimatised' to penicillin in the laboratory.[10] In his 1945 Nobel prize acceptance speech, Fleming painted a vivid clinical vignette in which an imagined patient with a streptococcal throat infection who takes insufficient penicillin, transmits the infection -- now in resistant form -- to his wife, and is thus responsible for her subsequent death from antibiotic-resistant disease.[11] Fleming advised 'If you use penicillin, use enough!' Ironically, *Streptococcus pyogenes* has never developed resistance to penicillin, and we now know that for most of the forms of antibiotic resistance which currently threaten patients, selection of resistance during treatment is of very limited importance.

Antibiotic treatment as a driver of antibiotic resistance

The scenario envisaged by Fleming was predicated on the concept of **target-selected antibiotic resistance** (see box). Infections typically begin when a small population of micro-organisms gain access to the host and replicate. Genetic mutations conferring antibiotic resistance may arise spontaneously during replication and be selected for during treatment. **Target-selected antibiotic resistance** is a clinically important process for major 'professional' pathogens

such as *Mycobacterium tuberculosis* and HIV. Transmission of professional pathogens during treatment or following incomplete treatment may allow resistant strains to spread from person to person. The early tuberculosis treatment trials demonstrated emergence of resistance during monotherapy[12] and underpin the need for combination therapy for this disease. Target-selected antibiotic resistance is however of very limited relevance to the bacterial species now posing the greatest problems due to antibiotic resistance.

For the main bacterial species in which antibiotic resistance is a clinical threat today (e.g. *Escherichia coli* and the so-called ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, Acinetobacter *spp*, Pseudomonas *spp*, Enterobacter *spp*.)) antibiotic use drives resistance primarily through **collateral-selection (see box).** These organisms are all found harmlessly in us, on us or in our environment. They can also act as 'opportunistic' pathogens. They are the commonest causes of urinary, abdominal and most forms of nosocomial infection. When a patient takes antibiotics for any reason, antibiotic sensitive species and strains present among their commensal flora or in the environment are replaced by resistant species and strains ready to cause infection in the future.[13] The longer the antibiotic exposure these 'opportunist' bacteria are subjected to, the greater the pressure to select for antibiotic resistance in them. Importantly for these opportunistic pathogens, resistant strains are transmitted between asymptomatic carriers, rather than people with infections (disease). Furthermore, many resistance-conferring genes can be easily passed between bacterial strains or species. Thus antibiotic selection may drive outbreaks of resistant infections independently of transmission of a specific strain or species.[14]

Minimum duration for maximum benefit

Traditionally antibiotics are prescribed in courses of recommended durations. Fundamental to the very concept of an antibiotic course is the notion that treatment for less than the course will be inferior. There is, however, a striking lack of evidence that current recommendations represent minimum durations below which patients will be at increased risk of treatment failure.

Historically, antibiotic course durations were set by precedent, driven by fear of under treatment, with little concern for antibiotic overuse. For many indications, recommended durations have got shorter as evidence for similar clinical outcomes with shorter course treatment has been generated (Table 1). However, the picture is patchy and complicated by comparisons of new against established agents having different pharmacological properties. For most indications, studies to identify the minimum effective treatment duration with commonly used agents simply have not been performed.[15] For example, pyelonephritis has historically been treated for two-weeks. Clinical trials have demonstrated the efficacy of shorter duration treatment using a quinolone (7-days ciprofloxacin[16] and 5-days levofloxacin[17]) but no such data exist for beta-lactams which are the main antibiotic class used. Current international guidelines continue to recommend 10-14 days' treatment with beta-lactams, based purely on absence of data for shorter courses.[18] In contrast, there are very few situations where shorter-duration treatment has been shown to have reduced clinical efficacy. A notable example is otitis media where 5 days' treatment is associated with a lower clinical cure rate (66%) than 10 days (84%).[19]

Common sense would indicate that if antibiotic exposure puts patients at risk of collateral-selection for antibiotic resistance, then less treatment, not more, should minimise this risk. A minority of therapy-duration studies have attempted to show whether this is true (Table 1). In hospital-acquired pneumonia, for example, randomised-controlled trial data indicate that short-duration treatment strategies are not only equivalent for clinical outcome but also associated with lower rates of infection recurrence and antibiotic resistance.[20,21] To our knowledge, for the opportunist pathogens which pose the greatest AMR threat, **no *clinical study has demonstrated increased risk of antibiotic resistance among patients take shorter duration treatment.***

It seems highly inappropriate to suggest patients risk contributing to antibiotic resistance by not following advice to complete a 'course' of treatment which is lacking in evidence, and which itself contributes to antibiotic use and hence resistance selection.

Is the concept of an antibiotic 'course' still valid at all?

The concept of an antibiotic course ignores the fact that patients may respond very differently to the same antibiotic treatment depending on diverse patient and disease factors. Currently we largely ignore this fact and instead make non-evidence-based indication-specific recommendations at the time of diagnosis. This situation is changing in hospital practice where biomarkers of treatment response, such as procalcitonin, have been used to guide stopping antibiotic treatment.[22] Outside hospital, where repeated testing may not be feasible, patients may be best advised to stop treatment when they feel better, in direct contradiction of WHO advice.[4] Of note, a recent clinical trial found that using fever resolution to guide stopping antibiotics in community-acquired pneumonia halved the average duration of antibiotic treatment with no reduction in clinical success.[23]

'Complete the course': a barrier to antibiotic conservation

The fallacious belief that completing a course of antibiotics minimises resistance is likely to be a significant barrier to reducing unnecessary antibiotic use. This idea is deeply embedded and both doctors and patients currently regard failure to complete a course of antibiotics as irresponsible behaviour.[24,25]

This belief is barrier to reducing unnecessary antibiotic use both in clinical practice and in developing a research evidence-base to guide optimal antibiotic use. In primary care strategies have been effective in avoiding unnecessary antibiotic courses being started for example through enhanced communication training, point-of-care tests, and use of delayed prescriptions.[26-8] However in secondary care, strategies to reduce unnecessary antibiotic aim to change or ideally stop antibiotics 48-72 hours after they have started but are challenging to implement[29]. Patient and healthcare professional concerns about the risks of incomplete treatment are likely to contribute to this. Designing trials of antibiotic-sparing treatment is notoriously difficult[30], not least because participants are invited to consent to receiving less antibiotic than they would outside the research on the basis that this could reduce their risk of antibiotic resistance, when they have been taught from school level that this increases the risk of resistance. It seems deeply ironic that when we prescribe antibiotic courses according to current recommendations there is no consent taken, and

likely to be little discussion of the evidence, but assessing course duration in a clinical trial requires informed patient consent.

What should we advise patients about duration of antibiotic treatment?

The 'complete the course' message has persisted despite good evidence to the contrary and previous arguments that it should be replaced.[15,31] One reason it may be such a resilient message is that – in the face of the overwhelming threat of antimicrobial resistance - it is simple and unambiguous, and the behaviour it advocates is clearly defined and easy to carry out. Nevertheless, there is overwhelming evidence that, in many conditions, stopping antibiotics sooner is a safe and effective way to reduce unnecessary antibiotic use. There are reasons to be optimistic that the public will accept that this message is wrong if the medical profession openly acknowledge that this is so. It goes against one of the most fundamental and widespread medication beliefs people have which is that one should take as little medication as necessary.[32] Concerted and consistent efforts have been successful in educating the public that antibiotics do not treat viral infections, for example. Instead, the public should be encouraged to recognise that antibiotics are a precious and finite natural resource which should be conserved. This will allow more patient-centred decision making about antibiotic treatment, where patients and doctors can balance confidence that a complete and lasting cure will be achieved against a desire to minimise antibiotic exposure unimpeded by the spurious concern that shorter treatment will cause antibiotic resistance.

Key messages

1) Antibiotic resistance is primarily the result of too much antibiotic use not too little.

2) There is no evidence for any common bacterial infection that stopping antibiotic treatment early increases a patient's risk of resistant infection.

3) Antibiotics are a precious and finite natural resource which should be conserved by tailoring treatment duration for individual patients.

Contributors and Sources

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Box 1: Antibiotic resistance selection

Target-selection. For certain 'professional' pathogens, such as *Mycobacterium tuberculosis*, spontaneous resistance-conferring mutants may be selected during treatment, can be transmitted before cure is achieved or can re-emerge following treatment failure. Other professional pathogens where this may apply include HIV, malaria, gonorrhoea and *Salmonella typhi.*

Collateral-selection. Many of the bacterial species which live harmlessly in the gut, on our skin and mucus membranes, or in the environment can also cause disease as 'opportunist' pathogens. For such organisms, resistance selection occurs predominantly during antibiotic treatment of other infections. Resistance in opportunists is passed easily to other strains of the same species of bacteria or to different bacterial species. Key examples include methicillin resistance in *Staphylococcus aureus,* Extended-spectrum beta-lactamase producing *Enterobacteriaceae* and carbapenem resistance in *Klebsiella pneumoniae.*

Table 1

Key indications for which duration of antibiotic treatment has been evaluated by randomised controlled trial

Indication	Treatment, days		Key evidence	Evidence on resistance
	Standard duration	Evaluated duration		
Otitis Media[19]	10	5	**Inferiority** of 5 days vs 10 days for clinical failure demonstrated in RCT	Similar short term selection of resistance in nasopharyngeal organisms.
Streptococcal pharyngitis[33]	10	3-6	**Comparable** effect of 3-6 days oral antibiotics to 10 days penicillin in children with streptococcal throat infection in Cochrane review of 20 studies	Not assessed
Community acquired pneumonia[23]	7-10	5	**Non-inferiority** of 5 day course once afebrile and clinical stability improving compared with physician guided therapy (median 10 days) for clinical success in RCT	Not assessed within RCT. Beta-lactam treatment >5 days associated with greater carriage of resistant *S. pneumoniae.*
Cellulitis[34]	7-14	5	**Non-inferiority** of 5 day course of levofloxacin compared with 10 days for clinical resolution in RCT	Not assessed
Pyelonephritis [16,17]	14	5-7	**Non-inferiority** of 7 v 14 days ciprofloxacin for cure[15] and 5 days levofloxacin vs 10 days ciprofloxacin for eradication of infection and clinical cure in RCTs[16]	Not assessed
Nosocomial pneumonia[20,21]	10-15	7-8	**Non inferiority** of short course treatment of suspected pneumonia among critical care patients for ICU mortality and infection recurrence in RCTs	Lower risk of further or resistant infection in patients receiving shorter duration therapy
Intra-abdominal sepsis[35]	7-14	4	**Non-inferiority** of fixed 4 day course compared with physician-guided therapy (median 8 days) for surgical-site infection, recurrent intraabdominal infection, or death in RCT	Statistically non-significant lower rates of extra-abdominal resistant infection in short course group

Note: RCT= randomised controlled trial

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