APPROPRIATE ANTIBIOTIC PRESCRIBING

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INTRODUCTION

In the UK, approximately 5,000 hospital patients per year die of nosocomial infection.[1] A significant proportion of these cases is caused by antimicrobial-resistant pathogens, in particular methicillin-resistant *Staphylococcus aureus* (MRSA), now endemic in British hospitals. Alarmingly, other bacteria, such as vancomycin-resistant enterococci (VRE) and penicillin-resistant pneumococci (PRP), are increasingly prevalent. Worldwide, antimicrobial resistance is widespread and has been documented in all of the major classes of pathogens.[2] In some European countries, parts of the US and many developing nations, common community-acquired pathogens (e.g. *Streptococcus pneumoniae*) are frequently resistant to 'traditional' first-line therapy. This global ecological problem has evolved through the acceleration of Darwinian natural selection among bacteria. The widespread use of broad-spectrum antimicrobial agents, in both human and veterinary medicine, continues to fuel this process. Increasingly, national and international organisations are recognising the clinical impact of pathogen resistance and have published recommendations.[2-4]

It is against this background, and in a climate of limited health care resources, that policy-makers, hospital managers and clinicians have become increasingly aware of the high costs, financial and otherwise, of antimicrobial therapy. Strategies, such as intravenous to oral switch therapy,[5] are being developed to try and curb the inappropriate use of antimicrobials and thereby improve the quality of patient care whilst reducing the costs of antimicrobial prescribing. Ongoing ecological changes and a lack of oral narrow-spectrum antimicrobials for resistant pathogens, however, are likely to result in the increased use of broad-spectrum intravenous agents, further perpetuating the resistance problem and hampering the impact of antibiotic control interventions. In this environment, appropriate and responsible antibiotic prescribing, both in the community and in hospitals, is increasingly important. This paper summarises the symposium *Appropriate Antibiotic Prescribing*, run jointly by the Royal College of Physicians of Edinburgh and the Royal Pharmaceutical Society of Great Britain.*

RESISTANCE AND PRESCRIBING: THE MISSING LINK

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Mathematical models can help us understand microbial resistance and predict the impact of infection control interventions. Although the selection of resistance by antibiotic pressure is important, it is the spread of resistant organisms that is at the crux of the problem in hospitals. Hand washing reduces the risk of a health care worker (HCW) becoming colonised. If a HCW does become colonised, however, a subsequent high number of patient contacts, as is the case in many UK hospitals, encourages spread from the HCW to a non-colonised patient, and from that now colonised patient to a non-colonised HCW. Additionally, the increasing practice of transferring patients for tertiary care has aided the inter-hospital spread of antibiotic-resistant pathogens. The restriction of antibiotic prescribing within this environment limits the selection of resistance and therefore the likelihood that a patient becomes colonised in the first place.

This relationship can be represented by the following equation where the basic reproductive number (BRN) is the number of secondary cases caused by an index case:

> BRN = Numbers of HCWs contaminated ↔ Numbers of patients colonised by contaminated HCWs

When this is applied to the intensive care unit (ICU) setting, resistant bacteria appear to be no less transmissible than sensitive strains. Employing strict infection control measures, however, can reduce the BRN to below 1 (the BRN must be >1·0 for the organism to continue to spread in an environment) and thereby reduce the prevalence of resistant organisms. It should be remembered, however, that greater statistical fluctuations occur in small populations. In an ICU, for example, large fluctuations in the number of patients colonised by MRSA occur from one month to the next, whereas the number of patients colonised in the population as a whole is more stable. This is important when interpreting the impact of an infection control intervention, because any improvement seen may simply reflect expected fluctuation.

Most antibiotics, however, are consumed in the community.[2] Unfortunately, few longitudinal studies have measured both antibiotic consumption and bacterial resistance. Arason *et al.* studied the correlation between antibiotic consumption and the carriage rate of penicillin-resistant and multi-resistant pneumococci in Icelandic children, following the introduction of a clonal strain of PRP from Spain in the late 1980s.[6] Defined daily doses (the proportion of the population receiving treatment at any one time) ranged from 9·6 to 23·2 per 1,000 children daily (1·1 to 2·6 courses yearly per child). Pneumococci were carried by 52·7% (n = 484) of children with 9·7% of isolates being either penicillin- or multi-resistant. Multivariate analysis showed that an age of less than two years, living in an area with high antibiotic consumption and high individual use of antibiotics significantly increased the likelihood of colonisation by PRP.

* *Meeting held in the Royal College of Physicians of Edinburgh on 16 June 2000*

Unfortunately, in favourable conditions (as was the case in Iceland) the prevalence of bacterial resistance increases rapidly. However, following the implementation of appropriate counter-measures, the reverse does not occur, with the prevalence of resistance falling slowly. This is because sensitive organisms are likely to have either no or only a subtle inherent survival advantage over resistant strains. Under a constant selection pressure, doubling the amount of antibiotic consumption will half the time taken to reach a certain level of resistance. The aim, therefore, is to try and maintain a low prevalence of resistant bacteria and avoid the exponential phase. This can be achieved by keeping community antibiotic prescribing below a certain threshold, thereby enabling antibiotic sensitive organisms to remain ahead. In Iceland, doctors have subsequently reduced their antibiotic prescribing and the prevalence of PRP has reduced.

The important public health question is: once a certain prevalence of antibiotic resistance is established, how long does it take to reverse evolution? Crucially, it must be understood that even with appropriate control measures, resistance will never fall to pre-antibiotic prevalence. If a high level of selection is re-established in Iceland, for example, the prevalence of PRP will increase more rapidly than initially.

KEY POINTS

1. In the community, the prevalence of antibiotic resistance is directly proportional to (inappropriate) antibiotic prescribing.
2. In hospitals, it is the spread of resistant organisms that is at the crux of the nosocomial infection problem.

COMMUNITY PRESCRIBING: PILLS OR PLATITUDES?

Dr William Holmes, General Practitioner and Special Lecturer in Respiratory Medicine, University of Nottingham

Theorising about reducing antibiotic prescribing is all very well, but patients presenting to GPs do not understand it. Respiratory illness is the commonest reason for a patient to consult his or her GP and, unsurprisingly, antibiotic prescribing for this indication is correspondingly high. George Bernard Shaw said 'What people like to do is to take medicine'; it is this that GPs need to overcome if they are to reduce antibiotic prescribing in the community.

Patients admitted to hospital with respiratory tract infection (RTI) form only the tip of an enormous iceberg. Most antibiotic prescriptions occur in the community although, paradoxically, most of the evidence for the treatment of RTI is derived from hospital-based studies. In contrast to ACE inhibitors, for which there is a considerable evidence base, patients with minor respiratory tract infections often ask their GP for an antibiotic prescription. Surprisingly, given that no evidence to support efficacy exists, 75% of patients presenting to their GP with acute bronchitis receive an antibiotic.[7]

While it is easy to blame patients for one's prescribing inadequacies, it is undoubtedly true that many GPs use antibiotics as a 'get out' clause during busy periods. The patient and workload pressure is demonstrated by Macfarlane *et al.*, who asked GPs to write down how certain they were that an antibiotic prescription was clinically indicated.[7] When GPs felt an antibiotic was definitely indicated, the patient received one. When they felt that an antibiotic was probably indicated, the patient usually got the benefit of the doubt. When an antibiotic was probably not indicated, a significant proportion of patients still got a prescription. Even when GPs thought that an antibiotic was definitely not indicated, 1% of patients still received one. Taking the 'probably not' and 'definitely not' indicated groups together, one in five patients received an unnecessary antibiotic prescription, as perceived by GPs. Unfortunately, the pharmaceutical industry has capitalised on this phenomenon and it is somewhat worrying to see that in the US and Canada advertisements for antibiotics are now directly aimed at the patient.

Both the public and medical profession poorly understand the natural history of acute bronchitis. Most patients present to their GP on day seven of their illness and usually consult a pharmacist or buy over-the-counter medication beforehand.[7] Two-thirds of patients still have a cough ten days after their initial GP consultation and one-quarter have not returned to normal activities.[8] A cough not responding to antibiotics, therefore, is unlikely to be a failure of treatment, but is part of the natural history of the condition. Patient re-attendance for the same symptom, irrespective of any previous treatment received, however, is common (20% of all patients).[9] In a study of 518 patients with cough, it was found that fever, chest pain, discoloured sputum and antibiotic prescribing had no influence on re-attendance. Dyspnoea and previous ill health had a small impact on re-attendance, but by far the most important factor was the patient's previous consulting behaviour.[10] Patients therefore often re-attend their GP because of their nature, and not because of illness severity or whether they have received an antibiotic. Given this, patient education is likely to be the most successful strategy for reducing re-attendance and community antibiotic prescribing. A study using a simple education leaflet stating that coughing is a good thing and part of the body's natural defence mechanism, for example, reduced re-attendance from 21% to 15%.[9]

In conclusion, the management of respiratory tract infections in the community needs to be improved. The nomenclature is inconsistent and should be changed. Patient and doctor education is likely to be the most successful approach to reducing community antibiotic prescribing. Importantly, research about how a GP can identify the patients that need an antibiotic during routine consultations, is vital.

KEY POINTS

1. There is little evidence to suggest that antibiotics affect the natural history of acute bronchitis.
2. Patient and clinician education is likely to be the most effective strategy for reducing community antibiotic prescribing.

INTERACTIVE SESSION

APPROPRIATE ANTIBIOTIC PRESCRIBING IN THE COMMUNITY

Dr Ian Williamson, Senior Lecturer in Primary Medical Care, University of Southampton, and Ms Angela Timoney, Specialist in Pharmaceutical Public Health, Tayside Health Board

The aim of the interactive sessions was to present a multi-disciplinary audience with a range of common clinical scenarios seen in primary and secondary care. Following each case presentation, the evidence to justify the use of an antibiotic was reviewed. This evidence is summarised below.

Proposition: an antibiotic should be prescribed for the majority of respiratory tract infections seen in general practice

There is no convincing evidence that an antibiotic is useful in the management of an uncomplicated cough or cold. Complications of tonsillitis, such as otitis media, quinsy and rheumatic fever, are rare in developed nations. Although antibiotics reduce these complications, the actual numbers that have to be treated are high (e.g. to prevent one case of otitis media 30 children must be treated (in adults the figure is 145)).[11] A recent Dutch study suggested that patients with three out of four Centor criteria (history of fever, tonsillar exudate, tender anterior cervical lymph nodes and an absence of cough) benefit from penicillin V 500 mg three times daily.[12]

Antibiotics appear to reduce or cure symptoms in 84% of patients with acute sinusitis compared to 69% taking placebo.[11] This moderate benefit, however, must be balanced against the risk of adverse events and the wider implications of antimicrobial prescribing for a self-limiting illness. Amoxycillin appears to be as effective as other agents for this indication.

Proposition: a topical antibiotic should be prescribed to a child with suspected infective conjunctivitis

Bacterial and viral conjunctivitis are difficult to differentiate clinically and many clinicians therefore manage all cases with a topical antimicrobial. Epidemics in school-age children are usually self-limiting adenovirus infections. Other cases may be caused by *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Staphylococcus aureus*. A recent systematic review of 527 cases found that acute bacterial conjunctivitis is frequently self-limiting and resolves itself within five days (64%). No sight- or life-threatening complications were reported in either the treated or placebo patients. Topical antibiotic therapy, however, was associated with earlier clinical remission.[13]

Proposition: ciprofloxacin should be prescribed for patients with community-acquired infective diarrhoea

In developed countries, community-acquired infective diarrhoea, whether viral or bacterial, is usually self-limiting. Dehydration is the most common reason for hospital admission, but this feature of the disease is not dependent on receiving antimicrobial therapy. Randomised controlled trials have shown ciprofloxacin to reduce the duration of diarrhoea by one to two days.[14] The British Infection Society recommends that only those with risk factors for invasive bacterial disease (i.e. hypochlorhydria (including patients taking H_2 antagonists or proton-pump inhibitors), the elderly, patients with underlying inflammatory bowel disease, the immunocompromised, those with a prosthetic intravascular device and patients with dysenteric symptoms) should receive ciprofloxacin.[15]

Proposition: a narrow range rather than a broad-spectrum antibiotic is advisable for acute otitis media

A recent systematic review (n = 2,202 children) found that two-thirds of children at 24 hours after the start of treatment had recovered regardless of whether they received antibiotic or placebo. Antibiotic therapy appeared to have no effect on hearing outcome, progression of illness or relapse. Antibiotics did, however, result in 5% fewer children having pain at two to seven days.[16]

If an antibiotic were prescribed then it would make sense to choose an agent that minimises the ecological impact but provides activity against the common bacterial pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae* and beta-haemolytic streptococci). Penicillin V or amoxycillin are the drugs of choice. Erythromycin is an alternative for those with penicillin allergy. Five days of antibiotic therapy appears to be as effective as longer courses.[17]

Proposition: a three day course of antibiotic rather than a longer course is preferred for uncomplicated urinary tract infection in otherwise healthy females

Several studies have shown that short course antibiotic therapy (three days) is as effective as longer treatment for uncomplicated urinary tract infections in healthy women.[18, 19] This has now been adopted as a Department of Health recommendation.[3]

Proposition: there is scientific evidence that intramuscular benzylpenicillin, given by GPs to patients with suspected meningococcal disease, improves outcome

No high quality evidence exists to support this strategy, but given that randomised controlled trials are not feasible, almost all experts agree that this is the correct approach. There is evidence that patients with rapidly progressing infection who receive delayed antibiotic therapy have a poorer prognosis.[20] The British Infection Society endorses this in a recent consensus statement.[21]

Proposition: there is uncontroversial evidence that antibiotics are always indicated for the treatment of exacerbations of chronic bronchitis

A meta-analysis published in 1995 found that antibiotics conferred a small benefit in the management of exacerbations of chronic obstructive pulmonary disease (10·75 l/min improvement in peak expiratory flow rate). Antibiotic therapy is likely to be most beneficial for patients with advanced disease and for severe cases requiring admission to hospital.[22] Amoxycillin is the first-line drug of choice.

APPROPRIATE ANTIBIOTIC PRESCRIBING IN HOSPITALS

Professor Peter Davey, Professor of Pharmacoeconomics, University of Dundee

1. A 56-year-old woman is admitted to hospital with dysuria, loin pain and rigors. Her temperature is 38·5 °C, pulse rate 110/minute, respiratory rate 22/minute, blood pressure 90/50 mmHg and white cell count 15·0 x 10^9/l. Which of the following terms most appropriately describes her condition?

- Septicaemia
- Sepsis
- Severe sepsis
- Septic shock

According to the systemic inflammatory response syndrome (SIRS) criteria, this patient has severe sepsis.[23] The SIRS system is based on the presence or absence of simple clinical parameters. Sepsis is said to exist if two or more of: pulse rate >90/minute; respiratory rate >20/minute; temperature <36 °C or >38 °C; and white cell count <4·0 or >12·0 x 10^9/l are present in a patient with symptoms of infection. Severe sepsis is when a patient with sepsis has evidence of multi-organ dysfunction, hypoperfusion or hypotension. Septic shock exists if hypotension is present in a patient with severe sepsis despite adequate fluid resuscitation. This system allows rapid severity assessment of patients with suspected infection. For example, patients with one or no positive SIRS criteria have a good prognosis and are unlikely to have life-threatening infection requiring intravenous antibiotics. Depending on the clinical circumstances, such patients could be managed conservatively until further investigations are available or prescribed narrow-spectrum oral therapy. Septicaemia is now an obsolete term and is best avoided.

2. Which empirical treatment would you use for the above patient?

- IV co-amoxiclav
- IV co-amoxiclav + gentamicin
- Oral trimethroprim
- Oral cephalexin
- Oral ciprofloxacin

Given that this woman has pyelonephritis causing severe sepsis, intravenous therapy is initially indicated. Those with a resistant organism do worse than those with a sensitive strain.[24] The addition of gentamicin to co-amoxiclav is therefore advisable in a patient who is clearly ill and who has more to lose by receiving ineffective antibiotic therapy than a 'well' patient. A clearly defined and locally adapted IV to oral switch programme should guide the switch to oral therapy.[5]

3. A 36-year-old male is admitted from the Accident and Emergency Department with a chest radiograph-confirmed community-acquired pneumonia (CAP). His temperature is 38·2°C, respiratory rate 18/minute, diastolic blood pressure 65 mmHg, urea 6 mmol/l and his pulse oximetry is 93%. He is not confused and is able to take oral fluids. What is the most appropriate antibiotic regimen?

- IV cefuroxime + clarithromycin
- IV amoxycillin + clarithromycin
- Oral amoxycillin + erythromycin
- Oral azithromycin
- Oral levofloxacin

This man has a non-severe pneumonia according to the British Thoracic Society (BTS) and modified BTS severity criteria (severe pneumonia equates to a 21–36-fold risk of death and exists if two or more of respiratory rate ≥30/minute, diastolic blood pressure ≤65 mmHg, urea >7 mmol/l and confusion are present).[25, 26] Unless the oral route is compromised, non-severe pneumonia should be treated with oral therapy.

There is no high quality evidence to support one antibiotic regimen over another.[27] It would seem sensible, however, to choose a regimen that provides activity against the two common causal organisms of CAP, *Streptococcus pneumoniae* (60–75%) and *Mycoplasma pneumoniae* (5–18%).[25] Amoxycillin with erythromycin is therefore the most suitable regimen above. Although azithromycin is convenient (once daily for three days) and provides appropriate antimicrobial activity, it is expensive and has poor bloodstream bioavailability (37%). There is therefore doubt about its efficacy in patients who may have pneumococcal bacteraemia.[5] No convincing evidence is available as yet to support the use of the new fluoroquinolones over 'traditional' antimicrobials.[28] Widespread use of these agents in either the community or hospitals may encourage fluoroquinolone resistance and would seem foolish antibiotic stewardship.

4. A *Candida* species is isolated from the blood culture of a 55-year-old male with a subphrenic abscess following abdominal surgery. He has remained febrile (temperature >38 °C) and tachycardic (pulse = 110/minute) despite drainage of the abscess and intravenous cefuroxime and metronidazole. Culture from the abscess fluid is awaited. What is the most appropriate management strategy?

- Observe the patient
- IV amphotericin
- IV amphotericin + flucytosine
- IV fluconazole
- Oral fluconazole

In the scenario of a clearly unwell patient with risk factors for fungaemia, intravenous anti-fungal therapy is required. If the patient is clinically stable, previously unexposed to azole anti-fungal therapy and if *Candida krusei* infection is unlikely, IV fluconazole or IV itraconazole are suitable initial agents. However, if the patient has severe sepsis or is stable but previously exposed to fluconazole or itraconazole, or if *Candida krusei* infection is suspected, IV amphotericin (with or without an additional agent) is the regimen of choice.[29] Flucytosine is mainly active against yeast species and has good tissue penetration. It is, however, myelosuppressive and is therefore best reserved for the combination therapy of deep tissue infections, such as endocarditis and meningitis.[30]

ANTIBIOTIC PRESCRIBING IN THE FUTURE

Dr Jonathon Cooke, Director of Pharmacy, South Manchester University Hospitals NHS Trust

All hospital pharmacists have experience of the use of inappropriate intravenous antibiotics, unmonitored gentamicin and other antibiotic misdemeanours. With drug costs contributing approximately 5% of the average hospital's budget, and antibiotics forming 20% of this, the NHS can ill afford such practice. Additionally, doctors are being increasingly scrutinised and asked to justify their decisions. It is vital that care pathways are studied and developed to aid the diagnostic and decision-making process.

Antibiotic formularies, pharmacists attending hospital

ward rounds, specialist guidelines, audit and intravenous to oral switch programmes are just some of the approaches that are currently being used to try and improve antibiotic prescribing. NHS direct, PRODIGY (a GP prescribing system), the electronic British National Formulary (BNF) and electronic hospital formularies are all part of the NHS information management and technology strategy and will be used by clinicians as prescribing aids in the future. It is intended that the National Institute of Clinical Excellence and the Scottish Health Technology Board will link into these.

One of the main advantages of electronic prescribing is that, for the first time in hospitals, it will allow antibiotic usage data to be linked with important clinical parameters, such as patient demographics, diagnosis and outcome. If such systems are not user friendly, however, clinicians may ignore their advice. The current sub-optimal practice will only improve if doctors, nurses and clinical pharmacists take advantage of such technology and learn to work as harmonious multi-disciplinary prescribing teams.

KEY POINTS

1. In the future, electronic drug prescribing will become routine practice in the NHS. To use such systems to their full potential, however, clinicians must embrace this new technology.
2. To improve clinical practice, doctors, pharmacists and other prescribing health care professionals must learn to work in multi-disciplinary prescribing teams.

WHOSE RESPONSIBILITY IS APPROPRIATE ANTIBIOTIC PRESCRIBING?

Dr Derek Maclean, Medical Director, Tayside University Hospitals NHS Trust

What responsibility does hospital management currently have for antibiotic prescribing? Do hospital managers know what doctors are prescribing? Will clinical governance change anything?

The NHS has failed to control the spread of resistant nosocomial pathogens. Reversing this trend requires realisation of the impending financial consequences of this failure at all levels of NHS management. The current divide between primary and secondary care does not facilitate coherence of antibiotic policy. Additionally, the increasing population of residential and nursing home patients, high consumers of both antibiotics and acute hospital services, is likely to heighten the resistance problem. Local drugs and therapeutics committees, and antibiotic subcommittees thereof, must bridge this divide and provide coherent antimicrobial prescribing policy across the whole of Scotland. Once developed, if clinicians are unable to adhere to such policy, a higher level of antimicrobial regulation, such as controlled drug status for some antibiotics, may be needed. It seems likely that such issues will be of major concern for the Health Technology and Clinical Standards Boards of Scotland.

NHS managers may know about the financial costs of antibiotics in their trust, but few have knowledge of local antimicrobial prescribing patterns, or when antimicrobials should and should not be used. This ignorance will only improve when the litigation costs of hospital-acquired infections exceed the costs of effective prevention. Many trusts are now reaching this situation, and universal systems of surveillance to identify where patients acquire their nosocomial pathogens need to be established. Adequate case note documentation should be compulsory as it is central to this and the audit of antibiotic prescribing practice. Hopefully, the move towards more evidence-based practice will improve the diagnosis of infection and antimicrobial prescribing. With this in mind, antibiotic subcommittees must be increasingly involved in the clinical governance agenda.

Acute medical admissions are an ever-spiralling problem and encourage physicians, who are under pressure to discharge patients, to prescribe antibiotics. As a result, there will be an increasing need for 'roving' infection specialists, with acute medical training, to play an active role in acute medical admissions units. If NHS trusts and the medical profession are to be persuaded to adopt this new, more professional approach to antimicrobial prescribing, a sound evidence base must exist. The challenge to NHS management is to promote and develop strong and productive links between infection specialists, hospital infection control teams, antibiotic subcommittees, public health and primary care physicians and clinical directors. Clinical governance will drive such links and encourage trusts to develop evidence-based antimicrobial resistance action plans. Ultimately, accountability for the control of antimicrobial prescribing and resistance within a trust, however, must lie with the chief executive.

KEY POINTS

1. The cost of nosocomial infection-related litigation is beginning to exceed the cost of effective prevention. Hospital managers must be aware of local antimicrobial prescribing patterns and, under the clinical governance agenda, develop evidence-based antimicrobial resistance action plans.
2. A national antimicrobial prescribing policy, with flexibility for local adaptation, that bridges the gap between primary and hospital care should be developed to guide clinicians across the whole of Scotland.

ANTIBIOTIC PRESCRIBING: LEARNING FROM THE PAST AND PLANNING FOR THE FUTURE

Professor Fernando Bacquero, National Institute of Health, Madrid, Spain

Microbial adaptation and the development of resistance usually occur slowly. Microbes can achieve high level antimicrobial resistance gradually by ascending a resistance ladder. This is the concept of 'silent resistance'. For example, when *Streptococcus pneumoniae* and *Staphylococcus aureus* are exposed to quinolone antibiotics, they cryptically evolve so that the first mutants selected are no more phenotypically-resistant on the basis of standard microbiological techniques than are sensitive bacteria. These primary mutations are not observed in clinical

practice, but they exist. This phenomenon explains why low level-resistant *Streptococcus pneumoniae* organisms were isolated in Spain before intermediate and highly resistant strains. In this scenario, using high doses of antibiotics may overcome low and intermediate level resistance and minimise the clinical impact; this is the case for community-acquired pneumonia due to PRP.[31] In contrast, other forms of resistance (e.g. methyltransferase gene mutation mediated pneumococcal macrolide resistance) do not require ascent of the resistance ladder and immediately impose high level resistance. Clinically, this means that increasing the dose of antibiotic will not overcome resistance.

In a patient receiving antibiotic therapy, gradients of antibiotic concentration exist within and between different tissues. The selection of resistance only occurs between critical low and high thresholds of tissue antibiotic concentration. A low concentration of antibiotic above a critical level will select low level mutants, whereas higher concentrations will either select high level mutants or, if above a critical level, will prevent selection. In the appropriate environment, most bacteria can achieve low level resistance, as there are many potential mechanisms. High level resistance is usually more difficult, because highly specialised mechanisms that may have a high genetic price are required. Bacteria that are highly exposed to antibiotics (e.g. *Pseudomonas aeruginosa* in cystic fibrosis patients) hypermutate and thereby become highly resistant.[32] These 'clonal jackpots' are important because not only do they increase the likelihood that resistance genes will spread to sensitive strains of *Pseudomonas aeruginosa*, but also to other different bacteria, thus amplifying the ecological impact.

So what can we expect in the future? Using *Streptococcus pneumoniae* as an example, it is likely that low- and intermediate-resistant strains will be increasingly isolated around the world. This is already the situation in Spain where 60% of commensal pneumococci in children are resistant to penicillin. Currently, the clinical consequences of this are low, because high concentrations of beta-lactam antibiotics occur in the lung following standard community-acquired pneumonia antimicrobial regimens. If higher level resistance becomes common, however, penicillin-resistant pneumococci may have a greater clinical impact. The key question for the medical profession is: will this actually happen? It is possible, for example, that the genetic mutations required to achieve clinically significant resistance impose a high physical penalty on the bacterium cell wall, thereby reducing pathogenicity and the ability to compete with less resistant strains.

KEY POINTS

1. Antimicrobial resistance evolves insidiously over many years, and the absence of phenotypic resistance in a bacterium does not necessarily mean that the first steps have not been taken up the resistance ladder.
2. For some bacteria, the achievement of clinically significant resistance may have too high a genetic price; for the time being, however, the medical profession should assume a worst-case scenario.

CONCLUSIONS

Antimicrobial resistance is an ecological problem caused by human misuse of a precious resource. This perpetual and slowly evolving process cannot be cured, but to some extent it could be reversed and curtailed. This requires a realisation of the impending consequences of failure at all levels of world society and the development of evidence-based interventions to reduce inappropriate antibiotic prescribing in both human and veterinary medicine. Such strategies must be inclusive of the developing nations, where poor access to appropriate antimicrobials and high infection-related mortality still occur. Research into the appropriate use of the available agents, new antibiotics and vaccine development remains important. Careful stewardship of any new antimicrobials is also clearly essential if the lessons of today are not to haunt us in the future.

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