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Antibiotic stewardship

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Introduction

Sir Frank MacFarlane Burnet, winner of the Nobel Prize for Medicine in 1960, wrote of the decline of infectious diseases in 1962: 'One can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious diseases'.[1] Any clinician who has cared for a patient with severe sepsis due to a multi-drug resistant (MDR) *Klebsiella pneumoniae* will recognise the significance of this misconception. Bacteraemias due to MDR bacteria are estimated to have caused more than 8,000 deaths and excess costs of €62 million in Europe in 2007, and prevailing trends indicate that infections caused by MDR Gram-negative bacteria are rapidly increasing, including in the UK.[2]

Drug resistance is an inevitable consequence of the evolution of microorganisms under antibiotic selection pressure. This phenomenon mandates a perpetual quest to discover new agents that can circumvent emerging resistance mechanisms. Drug discovery and development are expensive, and factors unique to antibiotics, such as relatively short treatment courses, have diverted investment to more profitable areas, leaving an increasingly unmet clinical need.[3] Although resistance is inevitable, the pace and extent of propagation of resistant organisms is governed by human behaviour – most importantly antibiotic consumption by humans and animals, as well as hygiene, sanitation and infection control. The profound consequences of antibiotic resistance for individual patients and society create an ethical imperative to protect public health by all available means, including antibiotic stewardship.

Stewardship is as an ethic that embodies responsible planning and management of finite resources. The term antibiotic stewardship has been adopted widely to encompass initiatives that promote the responsible use of antibiotics, with the goal of preserving their future effectiveness and safeguarding public health.[4–7] The physician may perceive the concept of stewardship as patronising or insulting and a threat to clinical freedom; nonetheless, physicians in the USA have recently called for mandatory implementation of antibiotic stewardship backed by legislation.[8] This article sets out the case for antibiotic stewardship and describes commonly used stewardship strategies and the evidence supporting their effectiveness.

Misuse of antibiotics

Antibiotic misuse (Table 1) is common in the UK and throughout the world. In 2009, family doctors in Britain prescribed 50% and 25% more antibiotics per head of population than their contemporaries in the Netherlands and Sweden, respectively.[9] A cross-sectional study of 8,057 general practices (GPs) in England revealed that antibiotic prescribing volumes varied fivefold between practices at the extremes of the study sample and twofold between practices on the 10th and 90th percentiles.[10] Only one-sixth of this variability could be explained by patient characteristics. A recent study of more than 1.5 million patient visits to GPs in the UK that resulted in a diagnosis of acute respiratory infection reported that the number needed to treat for antibiotics to prevent one admission to hospital due to pneumonia was 12,255.[11] Sixty-five per cent of patient visits resulted in a prescription, with prescribing rates varying from 3% to 95% by practice.

At any one time in hospitals in the UK, about one-third of inpatients are prescribed an antibiotic, with the main drivers being respiratory, urinary and skin and soft-tissue infections. Rates of antibiotic misuse in hospitals have remained unchanged at about 50%.[12,13] Overprescribing of broad-spectrum antibiotics is frequent, with such 'defensive prescribing' attributed to the precedence of treatment success in current patients at the expense of loss of effectiveness due to resistance in the future.[14]

Antibiotic prescribing and resistance

The relationship between antibiotic prescribing in the community and resistance is

Table 1. Examples of inappropriate use of antibiotics.[4,7]

Type	Example
Overuse	• Prescribing antibiotics for viral infections
	• Prescribing antibiotics for non-infectious processes (eg febrile patient with pancreatitis)
	• Treating minor bacterial infections that do not require antibiotics (eg small skin abscesses that resolve with incision and drainage)
	• Treating bacterial colonisation (eg positive catheter urine culture from an asymptomatic older patient)
	• Prescribing prolonged treatment courses (eg >24 hours for low-risk surgical prophylaxis)
Misuse	• Use of broad-spectrum antibiotics effective against multidrug-resistant organisms in a patient with a community-acquired infection
	• Failure to de-escalate broad-spectrum antibiotics according to culture results
	• Failure to adjust antibiotic prescription according to culture results when the isolated organism is resistant to initial therapy
Underuse	• Inadequate dosing of antibiotics
	• Premature discontinuation of antibiotics
	• Delay to prompt treatment of severe sepsis
	• Failure to prescribe an antibiotic regimen with an adequate spectrum of activity in a patient with a life-threatening infection
Abuse	• Prescribing antibiotics for financial incentive
	• Prescribing particular antibiotics as a result of pressure from a pharmaceutical industry representative

Table 2. ESKAPE pathogens: resistant micro-organisms identified as particularly problematic by the Infectious Diseases Society of America.[3]

Gram positive	Gram negative
• *Enterococcus faecium*	• *Klebsiella* species
– Vancomycin resistant (VRE)	– ESBL producer
• *Staphylococcus aureus*	– Carbapenemase β-lactamase producer
– Methicillin resistant (MRSA)	• *Acinetobacter baumannii*
– Vancomycin intermediate (VISA)	– Carbapenem resistant
	• *Pseudomonas aeruginosa*
	– Carbapenem resistant
	• *Enterobacter* species and *Escherichia coli*
	– ESBL producers
	– Carbapenemase β-lactamase producers

ESBL = extended-spectrum β-lactamase.

Key points

1. Resistance to last-line antibiotics is emerging and spreading globally but few new antibiotic classes have been discovered or are close to market
2. Antibiotic resistance increases morbidity and mortality for individual patients as well as posing a threat to public health
3. Doctors have a responsibility to prescribe antibiotics judiciously and participate actively in antibiotic stewardship
4. Antibiotic treatment must be prescribed only for patients with evidence of (or a reasonable suspicion of) infection and administered promptly
5. Narrow-spectrum antibiotics should be selected where safe and effective, to minimise collateral damage to normal flora and preserve the effectiveness of broad-spectrum agents

KEY WORDS: Antibiotic, antimicrobial, stewardship, resistance, prescribing

well characterised.[15] Exposure to antibiotics in primary care is consistently associated with a subsequent twofold risk of antibiotic resistance in respiratory and urinary bacteria for up to 12 months after treatment.[16]

Antibiotic prescribing in hospitals also selects for resistance at both the patient and institutional levels.[17] The risk of acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) was increased 1.8-fold in patients exposed to antibiotics.[18] Prescribing of ineffective antibiotics for patients harbouring resistant organisms was associated with a 1.6-fold increased risk of mortality from infection.[19] Table 2 lists MDR organisms that are currently problematic according to the Infectious Diseases Society of America.

Knowledge and confidence among doctors

A survey of doctors in a teaching hospital in the USA in 2004 reported that 90% of doctors wanted more education about antibiotics, with only 21% of doctors feeling very confident that they were using antibiotics optimally.[20] A more recent survey of junior doctors in Scotland suggested that 75% were confident about choosing the correct antibiotic, but only 36% felt confident about planning the duration of treatment.[21] Of all antibiotic stewardship interventions, junior doctors rated the availability of guidelines most highly for promoting appropriate prescribing. A 2010 survey of more than 300 medical students in the USA reported that at least three-quarters of students expressed a desire for more education about choice of antibiotic.[22]

The impact of lack of knowledge of antibiotic pharmacology and pathogen epidemiology in practice is illustrated by a recent study of guideline adherence for patients admitted to a Dutch university hospital with sepsis.[23] Off-guideline treatment had a broader spectrum than on-guideline treatment in 87% of 108 off-guideline prescriptions, but the antibiotic susceptibility of isolated pathogens was similar for off- and on-guideline regimens (93% and 91% respectively).

Professional standards

The General Medical Council (GMC) and Academy of Medical Royal Colleges have

endorsed *A single competency framework for all prescribers*, a report published in May 2012 by the National Prescribing Centre on behalf of the National Institute for Health and Care Excellence (NICE).[24] Competency statements from this that are relevant for antibiotic prescribing include:

- Competency group 1: Knowledge – has up-to-date clinical, pharmacological and pharmaceutical knowledge relevant to own area of practice:
  - Competency 11: Understands antimicrobial resistance and the roles of infection prevention, control and antimicrobial stewardship measures
- Competency group 7: Understands and works within local and national policies, processes and systems that impact on prescribing practice; sees how own prescribing impacts on the wider healthcare community:
  - Competency 59: Understands and works within local frameworks for medicines use as appropriate (eg local formularies, care pathways, protocols and guidelines).

Aims of antibiotic stewardship

Antibiotic stewardship has two primary goals:[25]

- to ensure effective treatment for patients with bacterial infection
- to reduce unnecessary antibiotic use and minimise collateral damage.

Collateral damage is defined as the increased risk of colonisation and infection with antibiotic-resistant bacteria following damage to the normal bacterial flora after antibiotic treatment. At the patient level, stewardship has been defined as 'the optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance'.[26] The Royal College of Physicians issued guidance on effective antibiotic prescribing in 2011 (Box 1).[27]

At the organisational level, stewardship refers to evidence-based programmes and interventions to monitor and direct antimicrobial use.[28] Table 3 summarises

Table 3. Examples of hospital antibiotic stewardship interventions.[6,25]

Type of intervention	Example
Governance structures	• Organisational strategy for antibiotic stewardship • Antibiotic prescribing policy (statement of principles of responsible prescribing and expected quality standards), which may include: – 48-hour review – intravenous-to-oral switch – automatic stop orders (termination of prescriptions after a specified interval unless authorisation to continue obtained) – compulsory order forms (prescribers required to complete a form with clinical details to justify use of restricted antibiotics) – expert approval (prescriptions for restricted antibiotics authorised by infection specialist or head of department) – dedicated antibiotic prescription chart – removal by restriction (restrictive policy imposed in target wards, units or operating theatres – eg by removing restricted antibiotics from drug cupboards) – therapeutic substitution (pharmacists authorised to substitute alternative antibiotics) – antibiotic cycling and rotation policy – mixing, diversity and heterogeneous prescribing policy • Antibiotic stewardship committee (including medical microbiologist or infectious diseases physician, specialist pharmacist and information analyst)
Operational delivery	• Antibiotic formulary – may incorporate limited list of antibiotics subject to prescribing restrictions such as requirement for preauthorisation • Guidelines for initial treatment of common infections (evidence based, peer reviewed and informed by local resistance data where possible) • Guidelines for perioperative prophylaxis for common surgical procedures • Reminder systems (eg preprinted adhesive labels for medical case notes) • Computerised physician order entry (electronic prescribing) – may incorporate computerised decision-support systems • Mobile device software applications for point-of-care information and guidance
Risk management	• Guidelines for management of infection in patients with allergy to antibiotics • Information on safe administration of intravenous antibiotics • Guidelines for dosing and monitoring of serum levels of toxic antibiotics
Clinical microbiology/ infectious disease specialist and laboratory support	• Validation and interpretation of microscopy, culture and susceptibility results for laboratory reporting • Surveillance and reporting of trends in antibiotic resistance • Telephone consultation for advice on infection management • Bacteraemia follow-up service • Antibiotic stewardship ward rounds • Point-of-care rapid tests for bacterial infection • Advanced sepsis biomarkers (eg procalcitonin)
Controls and quality assurance	• Surveillance of antibiotic prescribing trends • Public reporting and benchmarking of antibiotic consumption data (eg World Health Organisation-defined daily doses) • Audit and feedback of adherence to prescribing policy • Audit and feedback of adherence to guidelines
Education and training	• Induction training on antibiotic stewardship • Revalidation training • Distribution of printed educational materials (eg pocket guidelines and patient information leaflet) • Educational meetings • Electronic learning • Antibiotic prescribing competency assessment • Academic detailing or educational outreach (one-on-one educational intervention) • Nominated clinical champions for antibiotic stewardship • Provision of patient information and counselling

Table 4. Cochrane review of effectiveness of antibiotic stewardship interventions: antibiotic prescribing outcomes.[25]

Type of intervention	Number of studies	Median effect size (%)*				
		ITS	Controlled ITS	CBA	RCT	CRCT
Persuasive†	44	42.3	31.6	17.7	3.5	24.7
Restrictive**	24	34.7	–	17.1	–	40.5
Structural‡	8	–	–	–	13.3	23.6

ITS = interrupted time series; CBA = controlled before-and-after study; RCT = randomised controlled trial; CRCT = cluster-randomised controlled trial.
*Meta-analysis by study design; results reported as a change in direction of intended effect. †Dissemination of educational materials in printed form or via educational meetings, reminders, audit and feedback, and educational outreach. **Compulsory order form, expert approval, restriction by removal, and review and change prescription. ‡Introduction of new technology for laboratory testing, changes to laboratory turnaround time, and computerised decision support.

Box 1. Royal College of Physicians' insight into effective antibiotic prescribing – top ten tips.[27]

Antibiotics are essential to modern medicine and may be life saving, but their abuse leads to resistance. All physicians who prescribe antibiotics have a responsibility to their patients and for public health to prescribe optimally.

1 Institute antibiotic treatment immediately in patients with life-threatening infection
2 Prescribe in accordance with local policies and guidelines, avoiding broad-spectrum agents
3 Document the indications for prescribing antibiotics in the clinical notes
4 Send appropriate specimens to the microbiology laboratory, draining pus and removing foreign bodies if indicated
5 Use antimicrobial susceptibility data to de-escalate, substitute and add agents, and to switch from intravenous to oral therapy
6 Prescribe the shortest antibiotic course likely to be effective
7 Always select agents to minimise collateral damage (ie selection of multi-resistant bacteria/*Clostridium difficile*)
8 Monitor antibiotic drug levels, when relevant (eg for vancomycin)
9 Use single-dose antibiotic prophylaxis wherever possible
10 Consult your local infection experts

examples of antibiotic stewardship interventions commonly deployed in hospitals. A primary focus of hospital stewardship programmes is prevention of the indiscriminate use of broad-spectrum antibiotics. The rationale for this strategy is twofold. Firstly, broad-spectrum antibiotics, as well as being effective against a wide range of bacteria, are also frequently active against MDR bacteria and must be held in reserve for when they are genuinely needed (life-, limb- or sight-threatening infections of unknown cause or known MDR pathogens) to avoid selecting for extensively or pan-drug-resistant bacteria. Secondly, broad-spectrum agents cause extensive destruction of normal commensal flora, thereby compromising host immune function and rendering patients vulnerable to opportunist pathogens such as MRSA and *Clostridium difficile*.[18,29] The importance of this is increasingly recognised, as the presence of the human microbiota interferes with colonisation by potential pathogens by depletion of nutrients, production of enzymes and toxic metabolites, and modulation of the innate immune response.[29]

The use of broad-spectrum antibiotics for patients with severe or life-threatening sepsis is unquestionably justified. However, evidence supports a more conservative approach for the vast majority of hospitalised patients, in whom a strategy that starts with narrow-spectrum antibiotics and escalates to broader-spectrum agents in the event of clinical failure or microbiological evidence of resistance is safe and proportionate.[30]

The evidence for antibiotic stewardship

A recently-updated Cochrane review summarises the evidence for interventions to improve antibiotic prescribing in hospital inpatients (Table 4).[25] When comparable studies were analysed by meta-regression, restrictive interventions were found to have a greater impact on prescribing than persuasive interventions at one month after implementation, but restrictive and persuasive interventions had similar effects at six months and beyond.

Clinical and microbiological outcomes of stewardship interventions

Interventions intended to reduce antibiotic prescribing were found to be associated with reductions in *Clostridium difficile* infections and colonisation and infection with aminoglycoside- or cephalosporin-resistant Gram-negative pathogens, MRSA and vancomycin-resistant enterococci.[25] Four interventions intended to increase effective prescribing for pneumonia were associated with a significant reduction in mortality (risk ratio 0.89 [95% confidence interval (CI) 0.82 to 0.97]).

Unintended consequences of antibiotic stewardship

A meta-analysis of interventions that aimed to decrease unnecessary prescribing in 11 studies including 9,817 patients found no detrimental impact compared with controls, with a trend towards lower mortality in intervention arms (0.92 [0.81 to 1.06]).[25] A subset of five studies reporting hospital readmission suggested a higher risk in the intervention arms (1.26 [1.02 to 1.57]), but the quality of evidence was very low. Length of stay, reported in six studies, was comparable for the intervention and control arms.

Conversely, interventions intended to increase effective prescribing can be associated with unintentional increases in unnecessary antibiotic prescribing and associated collateral damage.[25] Unintended consequences of prescribing restrictions, such as compulsory order forms and pre-authorisation restrictions, have been reported, including delays in starting restricted antibiotics and a pseudo-outbreak of nosocomial infection caused by an altered threshold for documentation of nosocomial infection following implementation of an antibiotic management programme.[25] Such problems must be anticipated and managed.

Conclusions

Antibiotic resistance, particularly in Gram-negative bacteria, is rapidly increasing,

including in the UK, and few new antibiotics are likely to be developed in the near future. Acute and general physicians commonly prescribe antibiotics and therefore have an ethical obligation to understand, support and adhere to the principles of antibiotic stewardship.

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