Antimicrobial stewardship

Antimicrobial resistance is a global concern threatening patient safety directly, and through secondary impact on patients undergoing chemotherapy, surgery, transplantation and other areas of care reliant upon effective anti-infective therapy. To address antimicrobial resistance, ongoing programmes of activity in human and animal health, and in environmental care, are being enacted.

In medicine, antimicrobial stewardship focuses on optimization of antimicrobial prescribing to improve patient outcomes, while minimizing the development of antimicrobial resistance for patients and wider society. The context, strategies and delivery of antimicrobial stewardship vary markedly between countries and health-care providers, but central to all antimicrobial stewardship programmes is the overarching goal of ensuring that patients who require an antimicrobial receive the right agent, at the right dose, at the right time, for the right duration. Inherent in this is the need to ensure that patients who do not require an antimicrobial do not receive one inappropriately.

Antimicrobial resistance

The development of antimicrobial resistance among micro-organisms is a natural response to selective pressures from antimicrobial agents. Although many antimicrobials are derived from natural products, it is the excess use of antimicrobials in human health (in both primary and secondary care), veterinary medicine and animal production, and environmental effluents which have contributed to the global rise of antimicrobial resistance (Årdal et al, 2016).

Generation of antimicrobial resistance from suboptimal antimicrobial use is compounded by transmission of resistant pathogens from patient to patient in some settings, often as a result of breakdown in infection control practice, most commonly inadequate hand hygiene. International travel and health tourism have accelerated the transmission of resistant organisms worldwide, compounding this issue further (van der Bij and Pitout, 2012).

Antimicrobial resistance impacts greatly upon the most vulnerable patients in hospitals, typically those requiring multiple antimicrobial therapies and those in critical care areas. Empiric antimicrobial guidelines, which are often rule-based, do not routinely target antimicrobial-resistant organisms; the exception is in neutropenic sepsis where empiric antimicrobial regimens are intentionally broad from the outset.

Where there is unexpected antimicrobial resistance, there can be a delay in effective therapy (typically taking 48–72 hours until antimicrobial susceptibility results become available). Even with targeted therapy, where second- and third-line antimicrobial agents are needed, they can be associated with higher rates of mortality (e.g. vancomycin for meticillin-resistant *Staphylococcus aureus*) (Naylor et al, 2018) or morbidity because they have less favourable adverse event profiles (e.g. colistin and drug-induced acute kidney injury) (Ordooei Javan et al, 2015).

It has been estimated that by 2050, if solutions to antimicrobial resistance are not found, up to 10 million deaths each year and a cumulative US$100 trillion global output will be directly attributed to this issue (O'Neill, 2016). The pharmaceutical industry has provided few new agents to combat antimicrobial-resistant organisms over the last two decades, resulting in a waning therapeutic armamentarium. Pharmaceutical companies have been incentivized to develop new therapies and invest in research and development through coordinated programmes such as the Global Antibiotic Research and Development Partnership and 'New drugs for bad bugs' (Infectious Diseases Society of America, 2010). There is therefore a clear need to optimize and rationalize the antimicrobials that are available at present. This can only be achieved through collaborative approach to stewardship of these limited antimicrobials and promoting good infection control practices.

Defining antimicrobial stewardship

Antimicrobial stewardship is an organizational system to promote and monitor the optimal use of antimicrobials. Nathwani (2012) describes antimicrobial stewardship to be:

- 'An inter-professional effort, across the continuum of care
- involves timely and optimal selection, dose and duration of an antimicrobial
- for the best clinical outcome for the treatment or prevention of infection
- with minimal toxicity to the patient
- and minimal impact on resistance and other ecological adverse events such as *C. difficile*'.

A successful antimicrobial stewardship programme should improve patient treatment outcomes, improve patient safety, and reduce the impact of antimicrobial resistance in patients and the wider society. A coordinated effort is required from all antimicrobial users across all areas of health care. Engagement by health-care leaders, microbiology and infectious disease specialists, and antimicrobial pharmacists with all clinical areas of health care is required for antimicrobial quality improvements. Such

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initiatives should be structured to reduce suboptimal prescriptions, which include:

- Unnecessary use of antimicrobials
- Use of unnecessarily broad-spectrum antimicrobials
- Inappropriate dosage or duration of antimicrobials.

Antimicrobial stewardship in practice

Presentation with acute infection or sepsis necessitates prompt initiation of antimicrobials. The initial decision to treat is often taken with limited clinical information and without confirmation of the nature or antimicrobial susceptibility of the causative pathogen. Initiation of therapy must be timely, follow local evidence-based antimicrobial prescribing guidelines, and be tailored to individual patient needs.

Assessing the need for antimicrobial therapy initiation

Antimicrobials are well tolerated, and were initially thought to have limited adverse effects. A greater understanding of antimicrobial resistance has evolved this risk–benefit balance. Patients presenting to primary care with self-resolving infections are being encouraged to avoid antimicrobial therapy (Royal College of General Practitioners, 2013) and offered advice for symptomatic relief. Delayed (or 'back-up') antibiotic prescriptions, in which a prescription is issued to a patient to use at a later date if the symptoms fail to resolve, may also be used. In secondary care, the acuity and severity of infection presentations makes this less appropriate, and sepsis programmes aim for prompt therapy (<1 hour) to improve patient outcomes (National Institute for Health and Care Excellence, 2017).

Taking appropriate microbiology samples pre-therapy

Microbiology results help inform future prescribing decisions and direct therapies to optimize patient outcomes. Successful sampling is best done in the absence of any antimicrobial exposure and should be collected before initiating empiric therapy in all hospital patients (National Institute for Health and Care Excellence, 2017). In non-severe self-limiting infections, it may be appropriate to withhold antimicrobial treatment until the microbiology results are available.

> "Antimicrobial therapy should be reviewed daily, and certainly by 48–72 hours, to assess antimicrobial effectiveness."

The right drug, at the right dose, via the right route, at the right time

Selecting the most appropriate antimicrobial for an infection requires a detailed knowledge of the antimicrobial's pharmacokinetic properties, activity against targeted organisms, relevant tissue penetration, bactericidal activity and local resistance rates. To reduce the complexity of this decision for each patient reviewed, antimicrobial prescribing guidelines are often created for each hospital or local primary care group. These guidelines provide evidence-based practice adapted for local needs, reflecting the patient population and local antimicrobial resistance rates. Typically they include optimal drug dosing, route of administration and suggested durations of therapy for a variety of common infective syndromes.

Tailoring empiric therapy to individual patient needs

The increased prevalence of antimicrobial-resistant organisms challenges current prescribing practices. Patients with risk factors for resistant organisms, including past colonization or infection with antimicrobial-resistant organisms, or recent antimicrobial exposure or failure, should warrant further investigations and may necessitate tailored empiric therapy following consultation with an infection specialist (Moore et al, 2012). Patients with antimicrobial allergies, particularly with beta-lactams, may require alternative treatment options or re-challenging of allergy status.

Ongoing review of antimicrobial therapy

Antimicrobial therapy should be reviewed daily, and certainly by 48–72 hours, to assess antimicrobial effectiveness (Public Health England, 2015). Microbiology results and patients' clinical response should be used to inform this review. Antimicrobial therapy should be assessed for appropriateness with options to stop, switch (intravenous to oral administration to facilitate early discharge), change (antimicrobial choice), continue current therapy with future review date, or discharge on outpatient parenteral therapy.

National strategies to improve antimicrobial stewardship

In the UK, all NHS trusts are mandated to implement an antimicrobial stewardship programme to manage and survey the usage and adverse impact of antimicrobials within the organization (Department of Health, 2015). Mandatory reporting of healthcare-associated infections includes toxin-positive *Clostridioides difficile* infection, meticillin-resistant *S. aureus* bacteraemia, and recently *Escherichia coli* bacteraemia. Financial penalties for inappropriate healthcare-associated infection acquisition has coincided with a vast reduction of these reported cases through improvement work overseen by local antimicrobial stewardship programmes, in collaboration with infection control programmes.

National toolkits on good antimicrobial stewardship practice have heavily influenced practice and draw on the initiatives of successful interventions in specific countries. The English Start Smart and Focus (Public Health England, 2015) programme has introduced the 48–72-hour review of antimicrobial therapy into practice to encourage de-escalation and early switch of empiric therapy from intravenous to oral thus facilitating early discharge and reducing line-associated infections. The UK Department of Health (2013) antimicrobial resistance strategy 2013–18 identified several key areas for antimicrobial stewardship promotion. Clinician education around antimicrobial stewardship awareness, both undergraduate and in clinical practice, has instigated the development of core prescribing competencies. In addition, surveillance of antimicrobial usage linked with local antimicrobial resistance is published by many trusts to identify the developing trends and consequences of antimicrobial resistance (e.g. Public Health England's Fingertips website https://fingertips.phe.org.uk/).

In parts of UK the commissioning for quality and innovation and quality premium frameworks have also promoted good antimicrobial stewardship practice (NHS England, 2016). A reduction in broad spectrum antimicrobial use, particularly piperacillin-tazobactam and carbapenems,

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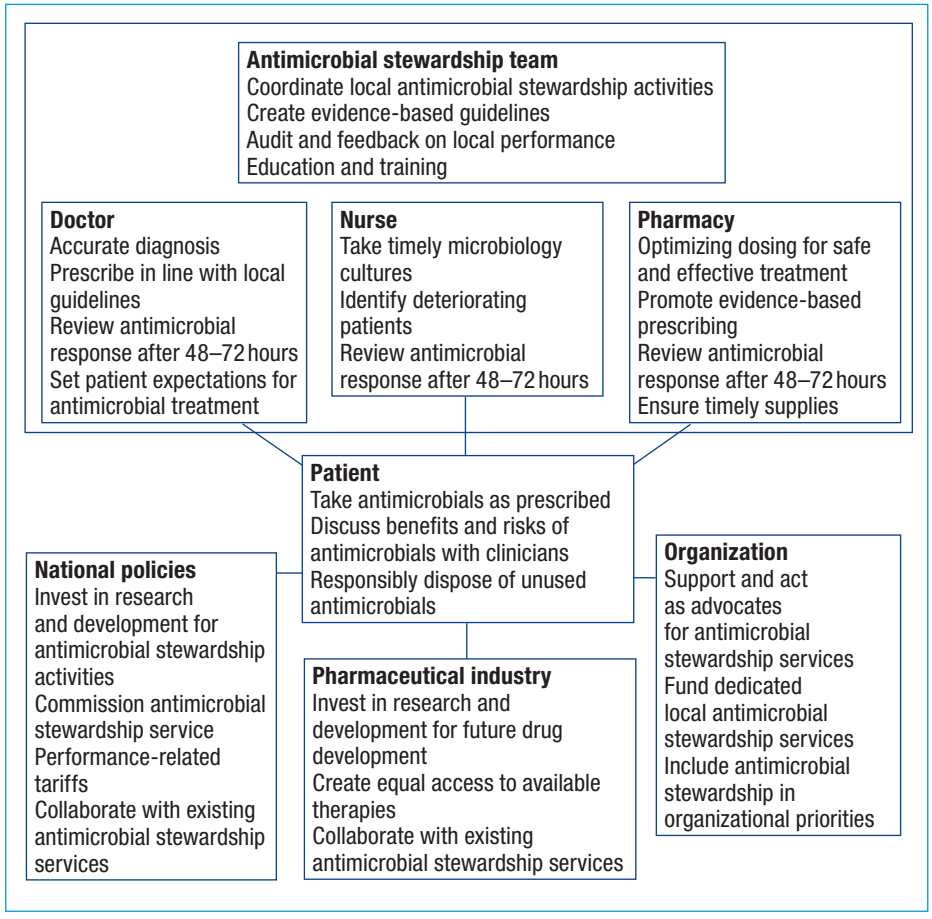

Figure 1. Antimicrobial stewardship networks are multi-professional and patient centred, with varied but complementary roles.

and concerted effort to promote the traditionally 'narrow spectrum' therapies in their place is encouraged to address the rising antimicrobial resistance pressures. Instead, antimicrobials which spare the use of these broad spectrum agents are encouraged to increase the heterogeneity of prescribing and reduce the selective pressures that prescribing homogeneity imparts upon antimicrobial resistance.

Successful strategies for influencing antimicrobial prescribing

Public expectation of antimicrobial treatment can increase unnecessary usage. A reported 75% of antibiotic prescribing originates in primary care, often for self-limiting disease. One of the key strategies to reduce demand for antimicrobials has been enacted through awareness-raising initiatives for the public (Royal College of General Practitioners, 2013; Kesten et al, 2018).

Strategies to influence health-care professionals towards antimicrobial stewardship goals include a wide array of interventions, which have been trialled with varying degrees of success. Largely, they fall within two broad areas: restriction or enablement.

Restrictive techniques

Control of antimicrobial supply, typically from hospital pharmacies, can be successfully used to control use of restricted antimicrobials. Through order forms or expert approval, antimicrobials of high cost or broad spectrum can be limited to use under infection specialist approval only. This controls antimicrobial misuse but the long-term benefits are less clear. The negative interprofessional relationships this restriction develops may erode interprofessional trust as well as contributing to delays in time to first dose, negatively impacting upon sepsis management while approval is sought.

Microbiology laboratory reporting can also be used to influence on the choice of antimicrobial therapy; the selective reporting of antimicrobial susceptibility by microbiology laboratories (practiced in many areas across Europe) will influence prescribing behaviours (Al-Tawfiq et al, 2015).

Enablement techniques

Enablement techniques empower individual clinicians to take responsibility for the prescribing appropriateness of antimicrobials. A short feedback loop on prescribing and antimicrobial stewardship performance review is possible through the advances in electronic prescribing systems and clinical decision support systems (Rawson et al, 2017). Point-of-care stewardship interventions help provide direct and timely feedback to the prescriber at the time of prescription or laboratory diagnosis, and provide an opportunity to educate clinical staff on appropriate prescribing antimicrobial stewardship-targeted interventions (Nathwani, 2012).

Corrective feedback from real-time practice, regardless of whether a restrictive or enabling technique is used, is associated with sustainable improvements in prescribing habits and should be used in combination with any antimicrobial stewardship quality improvement initiative (Davey et al, 2017).

The local antimicrobial stewardship team

Although good antimicrobial stewardship practice should be embedded among all clinicians, often a multidisciplinary antimicrobial stewardship team is responsible for and leads on good antimicrobial prescribing practices within health-care organizations. The team often consists of microbiology or infectious disease consultants, specialist pharmacists, and the infection control team working with the clinical leads within the wider organization (*Figure 1*).

The group will feed back on prescribing practices, antimicrobial usage, medication safety incidents and local antimicrobial resistance patterns. The group implements changes in evidence base, and national guidelines and policies, into local practice. Horizon scanning of new therapeutic options and novel diagnostic investigations is overseen by this group. The antimicrobial stewardship team, often in collaboration with infection specialists, often provides a consult service for antimicrobial resistance-related or complex infections (Moore et al, 2012) and this has demonstrated improved patient outcomes (Goto et al, 2017).

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Outcomes of the antimicrobial stewardship team

Reduction in total antimicrobial usage is a widely adopted performance indicator, with lower antimicrobial usage expected to reduce selective pressure on resistant microbes. Elements of prescribing, including documentation of indication, adherence to guidelines and 48–72-hour follow up, are common antimicrobial stewardship process measures. However, there is only a tentative link demonstrating improved antimicrobial resistance outcomes with these measures. A lack of robust interventional studies or (cluster) randomized trials for antimicrobial stewardship services has resulted in disparate antimicrobial stewardship activities and outcome measures, making benchmarking and peer review challenging.

Conclusions

Antimicrobial resistance is a cause for global concern because of the current and potential impact on global population health and the global economy. This complex issue respects none of the traditional boundaries of health care and requires a unified antimicrobial stewardship response from all clinicians. While appropriate antimicrobial usage is everyone's responsibility, antimicrobial stewardship teams act to coordinate and support the practice of all prescribers. **BJHM**

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KEY POINTS

- Antimicrobial stewardship is a coordinated response to optimize antimicrobial use by all users in the face of antimicrobial resistance.
- Unchecked, antimicrobial resistance is expected to negate many of the medical advances made through the last century as many routine health-care interventions become an unacceptable risk in the absence of effective antimicrobials.
- Antimicrobial stewardship aims to improve individual patient outcomes through evidence-based practice while minimizing the population level impact of antimicrobial resistance
- Any reduction made to total antimicrobial usage will help reduce the selective pressure for antimicrobial resistance, with the easiest reductions from avoiding antimicrobial usage for self-limiting infections in primary care.
- A follow-up review after 48–72 hours of empiric antimicrobial therapy is recommended to identify any patients with evidence of treatment failure and ensure corrective action in line with available microbiology and/or consultation with infection specialists.

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