Chapter 9

Principles of Antimicrobial Stewardship

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Key Points
• Overuse of antibiotics drives bacterial resistance. • To postpone development of resistance, antibiotics should be used carefully and rationally. • Antibiotic stewardship programmes are essential in our efforts to reduce the risks of resistance. • Good antibiotic prescribing should be encouraged in hospitals and health care facilities. • The microbiology laboratory service can guide clinicians to use targeted antibiotic treatment.

Introduction

Background to resistance [1-7]

The discovery of antibiotics was a revolutionary event that has saved millions of lives; however, considering they have been in use for just over 7 decades, their effectiveness has lessened because microorganisms have developed resistance. The emergence of bacteria resistant to many antibiotics (such as multidrug-resistant tuberculosis [TB], beta-lactamase-producing Gram-negative bacteria, carbapenemase producers, and methicillin-resistant *Staphylococcus aureus* [MRSA]) has created a vicious cycle, constantly requiring new and more powerful antibiotics, which are invariably more expensive and increasingly less available. Many medical services, especially in developing countries where the burden is high and resources are limited, cannot afford such expensive agents, and so patients may be denied appropriate treatment.

The clinical impact of antibiotic resistance is huge, with increased morbidity and mortality. Patients with resistant microorganisms have extended hospital stays, leading to increased costs and loss of bed days. Multiresistant microorganisms, such as MRSA, are now also prevalent in the community, and surveillance programmes have identified worryingly high levels of stool carriage of extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae in asymptomatic volunteers.[8] The treatment of diseases such as TB, especially acquired immunodeficiency syndrome (AIDS)-related TB, is hampered by the emergence of multi-drug-resistant strains (MDR-TB). Invasive carbapenemase-producing Gram negative infections can carry mortality rates of 40 to 50%.

The economic burden is also worryingly high, with estimated societal costs estimated to be around $55 billion for the United States alone.[9] While the burden of drug resistance is more difficult to quantify in low income countries, the long term consequences in terms of lost productivity, excessive deaths, and rapid spread are well documented.

To preserve susceptibility, or at least postpone development of resistance, antibiotics should be used rationally. This is of prime interest to everyone – government, medical carers, and the public.

Resistance develops through changes made to a bacterium's genetic inheritance either through the natural process of mutation (changes to the deoxyribonucleic acid of the cell, without the addition of new genes), or by acquisition of new genetic material by transfer from - usually- other bacteria, using the mechanisms of transformation, transduction or conjugation. Since bacteria multiply rapidly (sometimes once every 20 minutes), mutations can be expressed very quickly. Resistance can be transferred not only to their off-spring, but sometimes to totally different bacteria.

The acquisition of resistance through plasmids, transposons, or direct genetic mutations can thus result in their progeny (daughter cells) exhibiting changes that include target protection, target substitution, entry blockage, and detoxification, as shown in Figure 9.1. If this happens in an environment where the antibiotic is commonly used, such as health care institutions, resistant strains of bacteria will be selected. In a health care facility with an inadequate IPC programme, they may spread and cause outbreaks.

Antibiotics also affect normal human bacterial flora, which can become resistant and act as a reservoir of resistance genes. This poses a unique problem, as treatment of one patient's infection may then affect the flora of other patients. Therefore, narrow spectrum antibiotics should be used whenever possible.

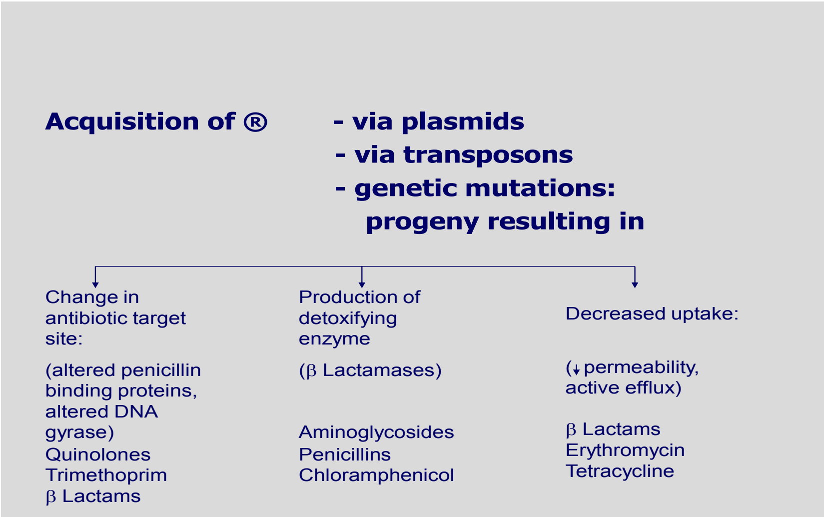

Figure 9.1. Bacterial responses

Antibiotics are also used extensively in veterinary medicine (for infections and as growth promoters) and agriculture, creating additional reservoirs of antibiotic-resistant microbes that may infect humans.

Excessive antimicrobial use is directly responsible for development of resistance; however it can be delayed by improving prescribing practices. To achieve this, better education; use of antibiotic prescribing and usage policies; surveillance of antibiotic use and consumption; and microbiological surveillance of bacterial resistance with regular feedback to physicians should be included in any programme.

Effective IPC interventions should also be used, although mathematical models suggest that in situations where there is both a high level of antibiotic resistance and high antimicrobial consumption, control of antibiotic use provides the best solution.

How are antimicrobials used?

Definitions

Empirical therapy

Empirical therapy is treatment for a possible or likely infection before laboratory results become available, or when they are impossible to obtain. Empirical choices may have to be made on the basis of microscopy, without the benefit of culture and sensitivity data. This type of use is most common in low resource settings and in ambulatory/community or outpatient care. However, it is strongly recommended that the use of antibiotics is reviewed if and when laboratory data are available.

Pathogen-directed therapy

Pathogen-directed therapy is antibiotic treatment guided by the results of microbiological investigations, with choices determined by specific sensitivity/resistance data.

Prophylaxis

Prophylaxis is use of antibiotics to prevent infection. Generally used just prior to surgery or other invasive procedures, it must target the microorganisms most likely to cause infections following the procedure (e.g., colo-rectal surgery, prevention of subacute bacterial endocarditis, use in prolonged ruptured membranes prior to delivery). It can also be applied to prevent infections in immunocompromised patients (e.g., AIDS, cancer patients, transplants) and contacts of known infected cases (e.g., meningococcal meningitis, TB). Prophylaxis must be used for the shortest possible time and given when antibiotics are likely to be most effective.

Antibiotic Stewardship[10-12]

Antibiotic stewardship is a coordinated program that seeks to promote appropriate use of all antimicrobials, including antibiotics, antivirals, and antifungals. An effective program helps to reduce microbial resistance, improve patient outcomes, and reduce the opportunity for the spread of microorganisms, including those that are multidrug resistant. Such progammes are seen as a key to modify prescribing practices of physicians and other healthcare providers, decreasing antibiotic use. Antibiotic guidelines or policies, which can be national or local/health care facility-specific, demonstrate a commitment to the prudent use of antibiotics. Their application demonstrates that government, medical societies, and the public are aware of the problem and committed to solving it. Local policies should focus on using antibiotics with the narrowest spectrum, least expensive, minimal toxicity, and the least impact on development of resistance.

These health care programmes require the co-operation and interaction of multiple teams and interventions. These methods are outlined in Figure 9.2.

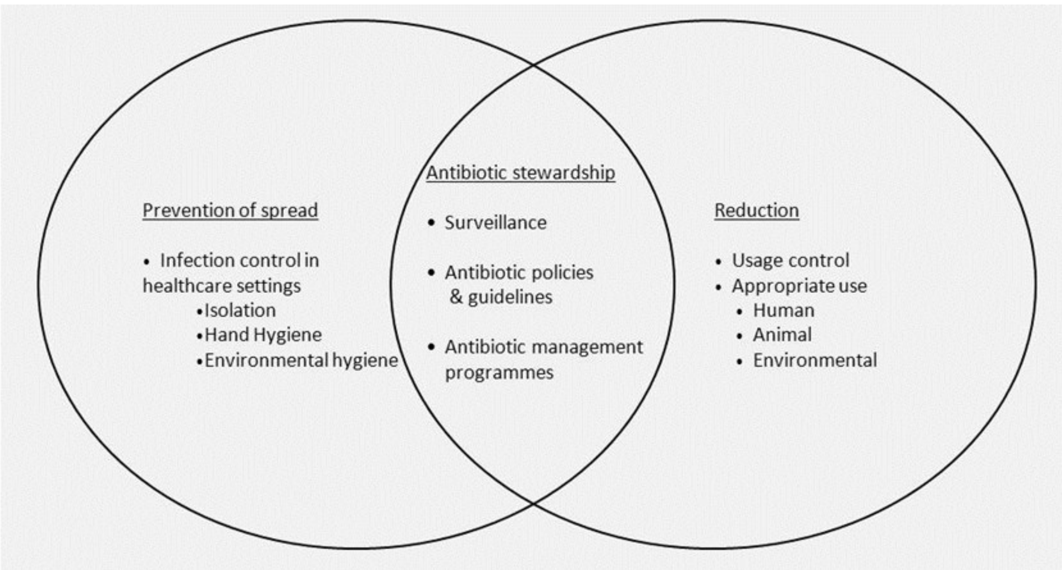

Figure 9.2. Methods to manage resistance[13]

Any stewardship programme should be well designed and implemented through a mixture of voluntary, persuasive, or restrictive means. Education is important, as is the production and dissemination of guidelines. The programme should be audited regularly and feedback provided both to users and programme directors. If an audit indicates that voluntary methods are not working, restriction of certain classes of antibiotics may be necessary. Key points are outlined in Table 9.1.

Table 9.1. Stewardship programmes' key points

- National policies
- Local hospital/health care facility policies
- Formularies and guidelines appropriate to local needs
- Effective infection control teams (ICT)
- Effective microbiology laboratory support
- Education
- Audit and feedback

National Antibiotic Policies

Initiatives should start at the national level with regulation of production and import of antibiotics, as well as control of local production. Legislation aimed at reducing the use of over-the-counter (OTC) antibiotics, imposing strict limitations on veterinary uses, and educating the public, is an important role for governments. The government must ensure enough essential antibiotics are available for local needs and that every health care facility has access to effective microbiology and IPC services. Legislation aimed at regulating the importation and local manufacture of antimicrobials should be introduced to reduce the risks of counterfeit drugs, which may not work, and contribute to resistance.

National policies should include education on antibiotic use and misuse at both graduate and postgraduate levels. To encourage and support appropriate use in ambulatory and out-patient settings, there should be written guidelines for the treatment of important and/or prevalent community-acquired infections. The general population should be educated about the consequences of antibiotic misuse.

Antibiotics for humans should be prescribed only by medical doctors or appropriately trained healthcare workers using carefully supervised protocols. OTC medications should be avoided. Antibiotic use in veterinary practice should be confined to disease treatment, and not for normal husbandry (growth) or welfare (group/herd prophylaxis), and use of antibiotics effective for human treatment discouraged for animals. Education of farmers is thus essential.

Management of Antibiotics in Health Care Facilities

Improper antibiotic prescribing has been described as "too many patients receiving unnecessary broad spectrum antibiotics by the wrong route, in the wrong dose, and for too long".[14] This is often the result of prescribers believing that personal experience is more relevant than evidence-based recommendations, or viewing initiatives as excuses to cut costs. Physicians often question why they should not use any available antibiotic. The answer is simple: antibiotics do not act on the patients; they act on their microorganisms. Individual treatments can and do impact other patients through spread of resistance. In addition, infections happen in patients under the care of many different medical specialists, most of whom are not specially educated in infectious diseases.

The impact of excessive use of antibiotics in the community/outpatient setting must not be underestimated. Countries vary enormously in their prescribing patterns, even in the developed world, and access to OTC medications has a huge influence in the levels of resistance found. The increase in use of broad-spectrum antibiotics, and their use to treat conditions that generally do not require an antibiotic at all (otitis media, sinusitis, upper respiratory tract infection, etc.) should be discouraged, and more judicious application of policies encouraged.

Careful management of antibiotics in health care settings requires a holistic approach including prioritisation by administrators and involvement of multiple stakeholders, as well as dedicating sufficient manpower and financial resources.

Healthcare stewardship programmes (HCSP)

Core elements for an effective HCSP include strong leadership commitment, the appointment of a single strong leader responsible for the programme, the use of “drug expertise” through a lead pharmacist, and effective action, education and monitoring. These elements, described in more detail, should all be considered as part of a comprehensive stewardship programme. See Tables 9.2 and 9.3.

The antibiotic committee

This committee can be either stand-alone, or part of an institution’s Drug and Therapeutics Committee. Antibiotic Committees must prepare local guidelines / protocols for antibiotic use. The members should include:

- doctors who prescribe antibiotics (specialists in infectious diseases, intensive medicine, internal medicine, paediatrics, clinical pharmacology, surgery);
- nurses, especially in countries where they prescribe antibiotics;
- specialist pharmacists (will provide data about antibiotic use);
- microbiologists (will provide data about bacterial resistance, as well as mechanisms and development of resistance);
- members of management;
- members of the Infection Control Committee (often, especially in small facilities, this is the microbiologist);
- Others may be co-opted as needed.

The antibiotic management team

Larger hospitals and other health care facilities should have a team to advise on antibiotic use and audit prescribing. It could include infectious disease physicians, clinical pharmacologists, pharmacists (ideally with specialist training), clinical microbiologists, and any doctors authorised to use reserve antibiotics. An antibiotic pharmacist (at least part-time) with the support of the Infection Control Doctor (ICD) is a minimum requirement for smaller institutions.

Guidelines and protocols

Health care facilities should have antibiotic policies containing guidelines and protocols for antibiotic use. Protocols may be ward specific, especially if there are special problems due to bacterial resistance – for example in oncology or intensive care wards. The areas most often covered by an antibiotic policy include:

- List of antibiotics in the formulary - no antibiotic outside the list should be used.
- Guidelines for empiric and targeted treatment of common infections, including dosage and duration of treatment, first and second line therapy, and what to use for allergic patients.
- Protocols for surgical prophylaxis (including automatic stop orders after 24 hours). Antibiotics for surgical prophylaxis should vary with the type of operation and epidemiological situation. Prophylactic antimicrobials should be different from those normally used to treat surgical infections.
- Protocols for de-escalation of parenteral use of antibiotics (i.e., switch therapy), including stop orders after an appropriate length of time (as early as 3-5 days depending on severity of infection).
- Recommendations for sequential treatment such as intravenous (IV) to oral switch protocols Suitable choices and guidance regarding when the patient is deemed clinically stable and able to move from IV to oral therapy, should be provided in local guidelines and formularies.
- Protocols for a reserve antibiotic, to include how to order and who can authorise its use (usually the microbiologist, ICD, or infectious disease physician).

The guidelines and protocols should be developed after discussions with all physicians, and take into consideration their views on type of antibiotic, route of administration, dosing, and duration of therapy. They will then be owned by everyone and easier to implement.

The list of antibiotics available depends on a country's politics and funding of the health care system. The World Health Organisation recommends a list of essential antibiotics for adults and children in its ”Model List for Essential Drugs” that is updated every two years.[15] The most recent ones include a core list that addresses minimum medicine needs for a basic healthcare system, and a complementary list for priority diseases or conditions including healthcare-associated infections caused by resistant pathogens, and drugs reserved for MDR-TB. The international charity organization, Medicine sans Frontieres, has also produced a comprehensive list of antibiotics recommended for specific common clinical conditions, based on effectiveness, and alternatives.[1]

Antibiotics recommended in local guidelines/protocols should be chosen according to local bacterial resistance patterns. If a health care facility does not have a microbiological service, regional or national resistance data can be used. If such data do not exist, then guidelines/protocols could be based on international resistance data, although this is least appropriate.

Table 9.2. Minimal requirements for an effective local antibiotic programme

1. Antibiotic Committee producing a formulary and guidelines for empiric and targeted therapy for infection in the particular setting.
2. Microbiology service - in the health care facility or contracted out.
3. Surveillance of antibiotic consumption and antimicrobial resistance; regular feedback to prescribers.
4. Effective Infection Prevention and Control Programme.
5. Education on antibiotic use and consequences of antibiotic misuse.
6. Regular, comprehensive audits, with feedback to prescribers.

Table 9.3 Core elements of a Stewardship Programme [17]

- Leadership commitment
- Appointment of a single, respected, effective Leader that can effect change
- Involvement of an antibiotic pharmacist
- Monitoring and reporting
- Education

Education

Correct use of guidelines/protocols requires education, especially of younger physicians and prescribers. This includes formal meetings, clinical rounds with antibiotic committee members or antibiotic management team, and formal lectures. Education must focus on new antibiotics, new methods of administration, and the influence on bacterial ecology. Education has to be provided by employees or an independent professional; it must not be provided by individuals from the pharmaceutical industry, unless a member of the antibiotic committee is present, and the presentation is free of bias.

Role of the microbiology laboratory

The microbiology laboratory plays a crucial role in helping to manage the use of antibiotics in health care settings. The routine application of sensitivity tests (antibiograms) helps to identify individual levels of sensitivity and resistance to specific antibiotics, and helps clinicians choose appropriate therapy.

Microbiology laboratories should only test the antibiotics that are used to treat that particular microorganism and testing practices should be included as part of local guidelines. They should report first-line antibiotics if an isolate is sensitive; and only add the second line antibiotic if the first is resistant. This makes it less likely that second line antibiotics (usually broader spectrum, more toxic, more expensive) will be prescribed.

Additional information from the microbiology laboratory which can offer general guidance in the choice of antibiotics and reduce unnecessary use includes:

- Surveillance of bacterial resistance with regular feedback to prescribers.
- Screening for carriage of resistant microorganisms and molecular detection and typing.
- Restricted reporting of antibiotic sensitivities to narrow spectrum agents, only reporting second and third line antimicrobials when first-line will not work.
- Regular reporting of changing resistance patterns to users, via newsletters, etc.

A number of strategies for testing and reporting of antibiotic sensitivities have been recommended, all aimed at reducing the risks of resistance development. They include restricted, selective reporting; active surveillance for resistance; support for locally agreed antibiotic cycling policies by the regular changing of antibiotics reported; and molecular detection and surveillance for resistance of key microorganisms.

Important roles for the microbiology laboratory additionally include early and regular notifications of resistant bacterial isolates to the infection control team (ICT) (to help control their spread) and feedback to clinicians on antibiotic use and cost, as well as resistance on their wards (often the best way to change prescribing habits).

Audit of compliance

Compliance with all the policies/guidelines needs to be audited. (See Table 9.4) Feedback of audit data reinforces the educational messages and helps to highlight areas where further work is required. Audits usually require a multidisciplinary team, generally lead by a clinical microbiologist or an infectious disease physician, as clinical notes have to be reviewed and interpreted correctly. If performed as part of teaching ward rounds, they can be a very powerful tool to develop sensible prescribing.

Key areas for audits are

- Adherence to agreed protocols and guidelines: are drugs being used in accordance with protocols?
    - Are empirical vs. targeted treatments clearly specified?
    - Are drugs stopped at the correct time?
    - Is IV to oral step-down properly implemented?

  - Is there appropriate use according to clinical need and microbiology results?
  - Is there correct and appropriate use and application of surgical prophylaxis guidelines?
- Effectiveness: are policies and guidelines being followed?
  - Consumption data: based on pharmacy stock controls - evidence of use at expected levels
  - Signed prescriptions
  - Usage data: Defined Daily Doses based on patient bed days/length of stay
- Appropriateness: Are the policies being used effectively?
  - Dosage: too much - too little?
  - Timeliness: start - stop dates? Administration times?
  - Appropriateness: compliant with local policies?

Audit questions can also be used to build a bundle. The development and use of audit bundles are based on an "all or nothing" approach, where each element of the bundle is as important as the others. Together they reflect the strategy for a comprehensive policy for antibiotic management.

Table 9.4 Key areas for audit activities

- Adherence to local protocols?
- Effectiveness and compliance with local policies and guidelines
- Appropriateness (dosage/timeliness/compliance)

Control of Healthcare-Associated Infections

Resistant bacterial strains are selected by excessive antibiotic use, but may also enter a facility when patients come from another hospital, nursing home, or even the community. If IPC is effective, there is an equilibrium between introduced, selected, and 'discharged' resistant strains and containment of resistance will be possible.

Effective IPC should decrease healthcare-associated infections, stopping outbreaks and limiting transmission of pathogens. This will decrease antibiotic usage and reduce antibiotic pressure; hence, there will be less selection of resistant strains. However, it cannot stop the emergence of new resistance patterns, and so will only be successful in combination with effective antibiotic stewardship programmes. Of course, poor IPC leads to more infections, more antibiotic usage, more resistance, etc., and so a vicious cycle occurs.

The ICT should work in close collaboration with the local microbiology department and receive regular early reports of patients who are detected as carrying a resistant pathogen. Local policies should identify actions to be taken for the effective isolation of these patients, and appropriate environmental cleaning measures while in the facility and once they have been discharged.

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Further Reading

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