Chapter 9
Principles of Antibiotic Policies

Judith Richards

Key points

- Resistant bacterial strains are selected in health care settings because of the large usage of antibiotics.
- To postpone development of resistance, antibiotics should be used carefully and rationally.
- Good antibiotic prescribing should be encouraged in hospitals and health care facilities.
- The microbiology laboratory service can guide clinicians to use targeted antibiotic treatment.
- Antibiotic stewardship programmes are important for reducing the risks of resistance.

Introduction [H1]

Background to resistance[1-6]

The discovery of antibiotics was a revolutionary event that has saved millions of lives; however, 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*) has created a vicious cycle, requiring new antibiotics which are invariably more expensive. Many medical services cannot afford such expensive agents, and so patients, especially in developing countries, will be denied appropriate treatment.

To preserve susceptibility, or at least postpone development of resistance, antibiotics should be used rationally. This is of prime interest to everyone – government, physicians and the public. Resistance can be delayed by better prescribing, this includes: 1) education, 2) antibiotic policies, and 3) surveillance of antibiotic usage and bacterial resistance with regular feedback to physicians. Effective infection prevention and control (IPC) activities are also required.

Antibiotic resistance develops through the natural process of mutation. As bacteria multiply rapidly (sometimes once every 20 minutes), mutations can be expressed very quickly. Resistance can be transferred not only to their offspring, but sometimes to totally different bacteria. The acquisition of resistance through plasmids, transposons, or direct genetic mutations can result in their progeny (daughter cells) exhibiting changes in the antibiotic target sites, in the production of detoxifying enzymes, or in decreased uptake of antibiotic. (See Figure 9.2)

If this happens in an environment where the antibiotic is commonly used, resistant strains of bacteria will be selected. In a health care facility with an inadequate IPC programme, they may spread and cause outbreaks.

Antibiotics 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 other patients. Therefore, narrow spectrum antibiotics should be used whenever possible.

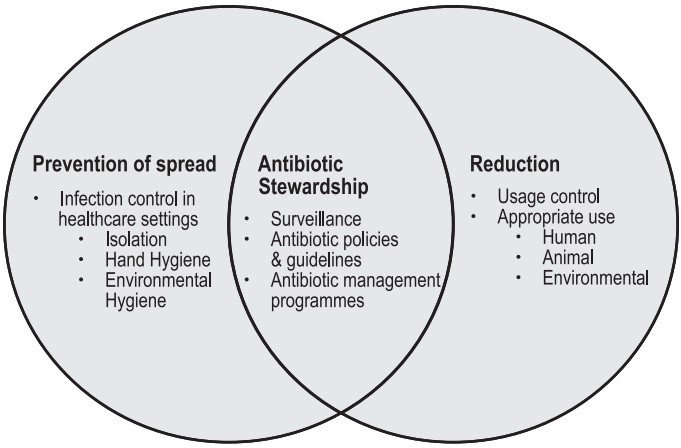

Figure 9.1 Methods to manage resistance

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; therefore good antibiotic prescribing practices should be encouraged. 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.

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. In the community, the treatment of diseases such as TB, especially autoimmune deficiency syndrome (AIDS)-related TB, is hampered by the emergence of multidrug-resistant strains (MDR-TB).

Antimicrobial uses

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 benefits of culture and sensitivity data; however, this information must be reviewed when 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, it must target the microorganisms most likely to cause infections following a procedure. 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 most effective.

Early review of prescribed antibiotics is essential for prudent therapy, especially for switching from intravenous (IV) to oral therapy. Suitable choices should be provided in local guidelines and formularies.

Antibiotic Stewardship[7]

Antibiotic stewardship programmes are seen as a key to modify prescribing practices of physicians, and decrease 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 use

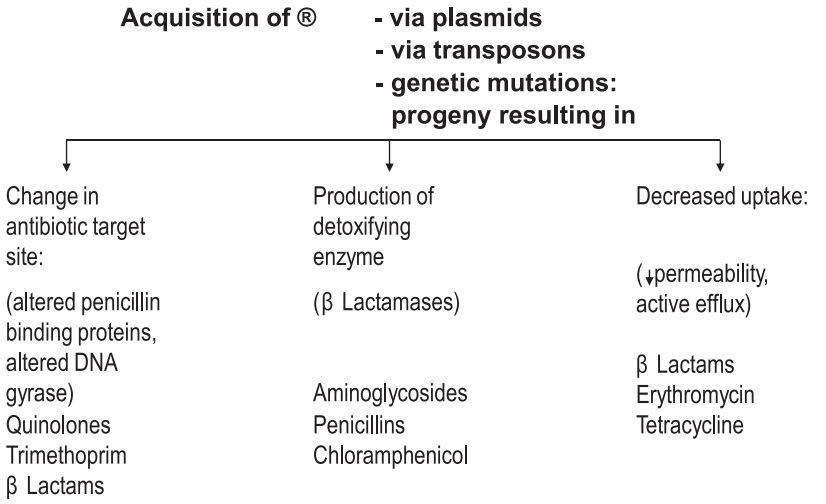

Figure 9.2 Bacterial responses

Table 9.1 Stewardship programme 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 and audit

shows 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.

Health care programmes which require the co-operation and interaction of multiple teams are shown in Figure 9.1. Key points are outlined in Table 9.1. Any 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.

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 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. The national policy should include education on antibiotic use and misuse at both graduate and postgraduate levels. There should be written guidelines for the treatment of important 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).

Management of Antibiotics in Health Care Facilities[8-11]

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." This often results from resistance by prescribers who believe that personal experience is more relevant than evidence-based recommendations, or who view 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.

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.

Important elements of a comprehensive stewardship programme include the following elements.

The antibiotic committee

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

- 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 are:

- 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 stop-orders after 24 hours).
- Protocols for de-escalation of parenteral use of antibiotics, including stop-orders after 3-5 days (depending on severity of infection) and recommendations for sequential treatment such as IV to oral switch protocols.
- 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.

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.

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 in the Model List for Essential Drugs[10] which is updated every two years. The most recent list (2009) includes 30 antibacterial antibiotics: 23 on the basic list, 2 for sexually transmitted diseases, and 5 on the complementary list for exceptionally severe healthcare-associated infections caused by resistant pathogens (ceftazidime, cefotaxime, imipenem+cilastatin, clindamycin and vancomycin), as well as listing 5 drugs for use as a reserve list for MDR-TB.

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.

Education

Correct use of guidelines/protocols requires education, especially of younger physicians. 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. Drug company presentations require the endorsement of the Antibiotic Committee and should not be provided unless a committee member is present.

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 recommended

in local guidelines. They should report first-line antibiotics if an isolate is sensitive; and only add the second line antibiotic if 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 selective reporting; active surveillance for resistance; antibiotic cycling policies (e.g., the regular changing of antibiotics reported); and molecular detection and surveillance for resistance of key microorganisms.

Important roles for the microbiology laboratory 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 9.2) 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.

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 Control Programme.
5. Education on antibiotic use and consequences of antibiotic misuse.
6. Regular, comprehensive audits, with feedback to prescribers.

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 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 stock controls.
    - 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?
    - 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.

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 decreasing 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 policies. 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 strain. Local policies should identify actions to be taken for the effective isolation of these patients, and appropriate environmental cleaning measures once they have been discharged.

Acknowledgement

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