The Rational Use of Antibiotics

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Summary

Antibiotics are one of the most commonly used group of drugs today. Inappropriate use of antibiotics has led to severe selection pressures resulting in the emergence of highly resistant strains. Inappropriate use also increases the cost of health care and exposes patients unnecessarily to the adverse effects of antibiotics. Before even choosing an antibiotic, it is important to ask whether an antibiotic is necessary in the first place. The choice of an antibiotic would depend on the aetiological agent as well as patient and antibiotic factors. An early review of the patient's response to the initial treatment is extremely important in order for the physician to either increase or decrease the level of therapy or to stop the treatment altogether. The availability of oral antibiotics with good pharmacokinetic properties would greatly encourage the switch from parenteral to oral agents whenever the situation warrants as oral therapy is far less expensive than parenteral. The optimum duration for treatment for many infections is not known but minimum periods of treatment has been recommended for some infections. Although no antibiotic is resistance-proof the judicious use of an agent will prolong its useful life.

Key Words: Antibiotic, Antimicrobial chemotherapy, Rational antibiotic usage, Switch therapy

Introduction

Antibiotics are one of the most commonly prescribed drugs today. It has been estimated that up to a third of hospitalised patients receive a course of antibiotics and antibiotics can account for up to 40% of the hospital's drug budget. Rational use of antibiotics is therefore extremely important as injudicious use can adversely affect the patient, cause emergence of antibiotic resistance and increase the cost of health care. Numerous studies from both developed and developing countries, including Malaysia, have shown that usage of antibiotics is still far from satisfactory[1-4].

When prescribing an antibiotic the following issues need to be addressed:

i) Is an antibiotic necessary?
ii) What is the most appropriate antibiotic?
iii) What dose, route, frequency and duration are needed?
iv) Is the treatment effective?

Is an antibiotic necessary?

Antibiotics are generally only useful for the treatment of bacterial infections. It is important to remember that not all fevers are due to infections and not all infections are caused by bacteria. The majority of infections seen in general practice are of viral origin and antibiotics can neither treat viral infections nor prevent secondary bacterial infections in these patients. Even where a bacterial aetiology is established, an antibiotic may not be always necessary. Many bacterial infections resolve spontaneously. Minor superficial skin infections may be more suitably treated with a local antiseptic. Collections of pus should be drained surgically and if drainage is adequate, antibiotics are often not required.

Choice of an antibiotic

The successful outcome of therapy would depend very much on the choice of the antibacterial agent. In the process of selecting an antibiotic, three main factors

need to be considered; the aetiological agent, the patient and the antibiotic.

The aetiological agent

Determination of the aetiological agent depends on a combination of clinical acumen and laboratory support. In many instances an antibiotic prescription has to be made based on the clinical diagnosis (empirical therapy). Clinical skill and a knowledge of both universal and local sensitivity patterns alone often enables a doctor to choose the correct antibiotic. Even where a bacteriology report is available it is necessary to interpret the report. Normal flora, colonisers or contaminants must be distinguished from true pathogens. Particular attention should be paid to the manner the specimen was collected and transported to the laboratory. Sensitivity results when available are at best only a guide to treatment. Laboratory reports should always be viewed in the light of clinical findings.

The patient

Several patient factors have to be considered in selecting an antibiotic. Age is an important factor. The very young and the very old tend to be more prone to the adverse effects of the antibiotics. Neonates have immature liver and renal functions which affect their ability to metabolise or excrete antibiotics. Antibiotics and their metabolites eg tetracyclines and the quinolones may adversely affect growing tissues and organs in children. Elderly patients are more likely to suffer from nephrotoxicity and allergic reactions. Dosage modifications would also have to be made in those patients with hepatic or renal impairment. Genetic factors can affect the way patients metabolise the drug (eg the acetylation of isoniazid) or the risk of suffering an adverse reaction (eg glucose-6-phosphate dehydrogenase and haemolytic anaemia). Antibiotics should as far as possible be avoided in pregnancy and when it is necessary to use an antibiotic, betalactam antibiotics and erythromycin are probably the safest. A history of allergy to antibiotics should always be sought before administration. Routine intradermal test doses for penicillin allergy is of little value and may even be dangerous. If in doubt avoid betalactams and use a macrolide or tetracycline (in adults) instead. In serious infections like meningitis and bacteraemic shock the immediate institution of the best available antibiotic for the suspected pathogen(s) is imperative as delay in treatment will increase both mortality and morbidity. In less serious situations such as otitis media where spontaneous recovery is common, an antibiotic that covers for the predominant organisms is adequate.

The antibiotic

The clinician should have adequate knowledge of the pharmacokinetic properties of the antibiotic he uses. Antibiotics vary in their oral absorption or their ability to cross the blood brain barrier and these factors will affect their routes of administration. The ability of the antibiotic to achieve therapeutic concentrations at the site of infection is another important consideration thus antibiotics used for treating urinary infections should ideally be concentrated in urine. Some antibiotics have very severe toxic effects and are best avoided in certain conditions. The doctor should also be aware of drug-drug interactions since many antibiotics can interact with other non-antibiotic drugs. Finally the cost of the antibiotic is also of major concern. In calculating costs it is perhaps more reasonable to take into account the total cost of treatment rather than just the unit cost of antibiotic per dose. The cost of disposables necessary for its administration, the necessity for monitoring antibiotic levels and the expected patient's length of stay in hospital must also be taken into account. The patient's compliance to medication is an important factor for consideration in the choice of antibiotics. Patients are more likely to comply to shorter durations of treatment and a once daily dosing regimen.

Choice of regimen

Parenteral or oral

Traditionally parenteral treatment has been preferred for severe sepsis. This is probably true in the past when potent oral antibiotics with good bioavailability were not readily available. Oral agents that are reliably absorbed and able to attain high levels in blood and tissues are now available. The use of these agents to treat serious infections deserves serious consideration. There has been studies showing that oral antibiotics

are as good as parenteral antibiotics in specific infections and at least one study has shown that oral ofloxacin is superior to intravenous ceftriaxone in treating typhoid fever[5].

Oral therapy has several advantages. The elimination of the need for intravenous access, an important source of bacteraemia, is perhaps the most significant advantage. The other complications related to an intravenous line like phlebitis and pulmonary embolism are also potentially reduced. Oral therapy reduces the length of hospitalisation and therefore the cost of treatment. Ancillary costs related to intravenous reconstitution, dilution fluids, syringes and needles are also avoided when oral therapy is given. A study conducted at the Johns Hopkins Hospital in the United States revealed that in 1991, the average daily cost for hospitalised patients on intravenous therapy was US$1100.00 compared to a daily cost of US$320.00 for home parenteral therapy. The average cost of treating a patient at home on oral antibiotics was only US$6.00 per day[6].

However, in patients unable to take oral treatment reliably parenteral therapy is obviously indicated and when doubt exists it is probably safer to commence intravenous treatment and review the treatment daily.

Duration of treatment

Except for a few conditions, the optimum duration of antibiotic treatment is unknown. Many antibiotics are often prescribed for a duration of 5-7 days. Nevertheless it is reasonable to discontinue therapy even after 3-5 days if the patient's symptoms have resolved. There are however certain infections where prolonged treatment is necessary (Table I). These include infections where a biofilm is present. In some conditions eg uncomplicated cystitis in women and gonococcal urethritis in males, single dose regimens have been shown to be effective.

Table I
Conditions where a minimum duration of treatment has been established

Infection	Minimum duration of treatment
Tuberculosis	4-6 months
Empyema and lung abscess	4-6 weeks
Endocarditis	4 weeks
Osteomyelitis	4 weeks
A typical pneumonia	2-3 weeks
Pneumococcal meningitis	7 days
Pneumococcal pneumonia	5 days

Monitoring efficacy

Early review of response

A routine early review (3 days after commencing treatment) of the patient's response is important in order to ensure that the patient is receiving appropriate treatment. After review the doctor will have to decide whether to:

i) continue with the present regimen
ii) increase the level of treatment by changing from oral to parenteral; increasing the dose or changing to a broader spectrum antibiotic
iii) decrease the level of treatment by changing from parenteral to oral, decreasing the dose or changing to a more specific narrow spectrum antibiotic
iv) stopping the antibiotic if the infection has resolved; the objective of treatment is achieved or the diagnosis has been changed.

Inconsistent microbiology reports

If the patient is responding there is no necessity to change antibiotic even when the laboratory reports a resistant organism. The isolate in question could have been a coloniser or a contaminant. Infections may resolve spontaneously and the antibiotic could have affected the bacteria in a way that makes it more susceptible to the host's immune defenses.

If the patient's condition fails to improve, a change in antibiotic may be necessary even when the laboratory reports a sensitive organism.

Causes of non-response to antibiotics

A patient may fail to respond to an antibiotic for a number of reasons which include:

i) the aetiological agent is resistant to the antibiotic
ii) the diagnosis is incorrect
iii) the choice of antibiotic is correct but the dose and/or route of administration is wrong
iv) the antibiotic cannot reach the site of infection
v) there is a collection of pus that should be drained surgically or a foreign body/devitalised tissue that should be removed
vi) there is secondary infection
vii) antibiotic fever
viii) non-compliance of the host

Changing from intravenous to oral

Wherever feasible intravenous therapy should be changed to oral therapy for all the reasons given earlier. The oral antibiotic (not necessarily the oral formulation of the intravenous antibiotic) should be selected based on clinical and laboratory findings. Four terms have been used to describe the change from intravenous to oral treatment.[7] They are:

i) *Streamlining* – where the antibiotic regimen is changed to one of narrower spectrum specifically targeted at the offending pathogen. This is often undertaken upon receipt of the culture and sensitivity reports eg changing from a third generation cephalosporin to cloxacillin upon when the infection is confirmed to be staphylococcal in nature.

ii) *Sequential* – where the change involves the use of the oral formulation of the intravenous antibiotic without any loss in potency eg changing from intravenous to oral ciprofloxacin.

iii) *Step-down* – where the intravenous antibiotic is changed to an oral agent of the same or different class with a reduction in potency eg changing from intravenous cefuroxime to oral cefuroxime axetil.

iv) *Switch* – where the intravenous antibiotic is changed to an oral formulation of another antibiotic without any loss in potency eg changing from intravenous ceftazidime to oral ciprofloxacin.

Similarly one should not hesitate to revert to intravenous therapy if the patient's condition warrants it.

Conclusion

Antibiotic resistance is a major clinical problem all over the world. There are now clinically significant isolates that are resistant to virtually all available antibiotics. It is pertinent to note that over the past two decades no major new class of antibiotics has been introduced for clinical use. No antibiotic is resistant-proof. How long an antibiotic will remain to be useful depends to a large extent on how it has been used.

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MCQs for the article on Rational Use of Antibiotics

1. Antibiotics

   A. are indicated for all bacterial infections
   B. prevent secondary bacterial infections when given for viral sore throats
   C. are an adjunct to surgical drainage in the treatment of abscesses
   D. do not cause fatal adverse reactions
   E. are prescribed in up to a third of hospitalised patients

2. Before prescribing an antibiotic

   A. the culture and sensitivity report should be available
   B. the liver and renal functions of the patient should be taken into consideration
   C. dermal tests for allergy should be performed
   D. the primary site of infection should be ascertained
   E. a history of G6PD-deficiency should be sought

3. The advantages of oral treatment include

   A. greater patient compliance
   B. decreased risk of line-associated bacteraemia
   C. less adverse side-effects from the antibiotic
   D. decreased length of hospitalisation
   E. decreased risk of emergence of antibiotic resistance

4. Prolonged antibiotic treatment (over 4 weeks) is generally recommended in

   A. typhoid fever
   B. osteomyelitis
   C. gram-negative bacteraemia
   D. infective endocarditis
   E. tuberculosis

5. Failure to respond to an antibiotic may be due to

   A. misdiagnosis
   B. antibiotic resistance
   C. a collection of pus
   D. secondary infection
   E. the inability of antibiotic to penetrate the infected tissues