The cost-effectiveness of using the newer antibiotics in primary health care

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The use of newer antibiotics in primary care may substantially increase the cost of antimicrobial therapy, and the additional expense may or may not result in commensurate additional benefit to the patient. This question is considered in respect of older and newer drugs among the ß-lactams, macrolides, and quinolones. The benefits considered are primarily those to the patient, but also those to other parties involved in providing the medication or otherwise concerned with the patient's health. The costs quoted are those for oral forms of the drugs. In addition, other intrinsic and incidental costs to the patient are discussed, as well as the costs arising from inappropriate use of the drugs. It is argued that avoidable use of the newer drugs in primary care may adversely affect antimicrobial therapy in tertiary care by promoting increased prevalence of resistance, and may thus give rise to additional costs to the community at large.

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Introduction

The responsible use of new drugs in primary heath care requires an awareness of costs and how they arise. The purchase of an antimicrobial drug for the treatment of a patient in the community is only one part of the cost of that treatment. If laboratory tests are needed to check bacterial sensitivity, renal function, or—during the course of the treatment—to monitor drug levels, the costs of these have to be added. There is also cost involved in dispensing the drug and in administering it. Even when taken orally, cost arises if nursing help or supervision is needed, and if tests have to be done to check the patient's compliance. If the drug is given parenterally, the route, frequency, and length of the course will all help to determine the cost. If the treatment fails because bacterial resistance develops, or if adverse effects of the drug necessitate further consultation, hospitalisation, or additional laboratory investigations, extra costs will be incurred which are potentially measurable. Such events tend to injure the practitioner's reputation with the patient, and that of the drug with the practitioner—these are also costs, albeit indirect ones.

Individual costs

In addition to the costs mentioned above, there are other costs to the individual receiving antimicrobial treatment in the community. There are costs of the illness which will vary widely from patient to patient, such as the cost of travel from home to the clinic or doctor's office, the cost of lost working time, either to an adult patient or to a sick child's parent, the cost to the employer if the patient's replacement is only a temporary one, and the cost to the sick child of lost schooling at some critical period. These variables are outside the prescriber's control, but others are not. How many visits will have to be made and how much time will be lost will depend on the efficacy of the treatment, the route and dosage schedule, and also on whether adverse side effects occur. Whenever possible, these matters should be taken into account when the doctor is selecting antimicrobial drugs.

Effectiveness of antimicrobial drugs

Antimicrobial drugs serve to inhibit or kill harmful microorganisms, and all the antibiotics that are available for prescription for treating infections will do these things effectively—provided they are used for suitable indications, in a suitable dosage, and for

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the correct length of time. Given these conditions, it is hard to distinguish between them on the grounds of their effectiveness. Advertisements often carry the message that a particular drug is more powerful, and this is often misunderstood. The term should be interpreted simply as broad spectrum, which becomes an undesirable characteristic when the sensitivity of the infecting organism is known.

Benefits from appropriate antimicrobial use

Assuming effectiveness, there are benefits to be considered both to the patient and to others. The patient obviously benefits when an antibiotic is used appropriately and successfully. He or she is relieved of symptoms, the infection is controlled or eliminated, and the individual can return to work or school, or generally get on with life. The general practitioner benefits from having a satisfied patient. The community benefits, because the patient once again becomes a productive member of society, ceases being a liability to his or her family or a source of infection to others, and all this has been achieved economically at the primary health care level. The pharmaceutical company profits by the sale and also benefits from the drug's improved reputation with the prescribing practitioner.

Cost of inappropriate antimicrobial use

If a drug is used inappropriately, either as an unsuitable choice or when no antimicrobial was indicated, there is no possible benefit to the patient's health and even if not actually harmed, he or she has been exposed to unnecessary risk and expense. If such treatment is recognised by the patient to be costly and unhelpful, this again is to the detriment of the doctor's reputation.

A cost of a different kind that arises from the inappropriate use of antimicrobials is the cost to the community. This deserves serious consideration, because primary care is, or should become, community-oriented.[1] Even when an antibiotic is used appropriately and the therapeutic aim is achieved, the patient's normal bacterial flora have been exposed to a selective force which favours any bacterium which happens to be resistant to it, or is resistant because of either a mutation, or the acquisition of a plasmid from another bacterium. The effect is similar as the patient's population of resistant bacteria is temporarily increased. If not exposed to more antibiotic, in this patient or another one, the bacterium with acquired resistance will tend to die out, no longer having a selective advantage. However, if many people in the community are taking antibiotics, the resistant bacterium may find a suitable new host, and this is particularly likely in the case of a multiply-resistant organism. The result is that antibiotic resistance becomes more prevalent in the community. This too is a cost, because it compels the more frequent use of more costly newer antibiotics, until they in turn cease to be reliable weapons against pathogenic bacteria.

Factors influencing the speed of resistance development

The sequence of events described has happened repeatedly over the years, and can be considered an inevitable effect of the widespread use of any antimicrobial drug. The rapidity with which it has happened has varied from organism to organism, with their varied abilities to develop or acquire resistance, and from place to place, depending on the countries' abilities to purchase the drugs and on the efforts made to control their use—the more effective the control, the lower the prevalence of resistance. Whether subsequently transferable or not, genes coding for resistance appear as the result of mutations. These may occur at frequencies so low as to appear to be highly improbable events. For example, the mutations needed for ciprofloxacin resistance occur at a frequency of 10^{-14} or lower.[2] Against this are the enormous numbers of bacteria to which each human being is host, and the rapidity with which their genomes are copied. These turn low-frequency events into likely ones, particularly if the drug is widely used.

Pharmaceutical companies' promotional efforts tend to accelerate the increase in resistance. In one Singapore hospital, a pharmaceutical company's major promotion of a new third generation cephalosporin produced a very substantial increase in the use of the drug. Within six months, resistant organisms among the Enterobacteriaceae had increased in prevalence,[3] and the new drug was soon sharing the market with similar products whose limitations were already well known.

Comparing older with newer drugs

In comparing advantages and costs of older and newer drugs, only three categories of antimicrobials are considered here—ß-lactams, macrolides, and fluoroquinolones. Costs are quoted for drugs that can be administered orally. The questions to be addressed are how much more the patient will have to pay for the newer antimicrobial, and what benefit may be gained by using it.

Costs and benefits

Beta-lactams

The newer ß-lactam antimicrobials are products of the battle between bacteria with their ß-lactamase enzymes and pharmaceutical companies armed with more

resistant ß-lactam antimicrobials and ß-lactamase inhibitors. Resistant broad-spectrum drugs are countered by extended-spectrum ß-lactamases, and the escalation continues. In general, the risk of side effects with newer ß-lactams is of the same order as that of the older drugs. In assessing reported allergy to a penicillin, a distinction may be made between the rapid IgE-mediated anaphylactic reaction and the more common late, relatively mild symptoms, such as a rash following ampicillin. The latter would not necessarily preclude the use of a cephalosporin if there were strong indications for it.

The remaining considerations are cost and effectiveness, and in this context effectiveness depends on the prevalence of resistance to the drug. One recent paper provides a measure of the resistance problem in this community (Table 1).[4] The majority of isolates of *Escherichia coli* from urinary tract infections (UTIs) were ampicillin-resistant, with coverage substantially improved by the addition of clavulanic acid. This was also true of the small number of urinary isolates of *Klebsiella* and *Proteus* spp. The usefulness of ampicillin plus clavulanic acid against the community isolates is notably greater than that observed among hospital isolates of ampicillin-resistant *E coli*.[5]

Of the cephalosporins reported (Tables 1 and 2), cephalexin resistance was most frequent, reflecting the fact that it has been the drug most widely used. Cefuroxime remained more useful, perhaps protected from excessive use by its high price, but ampicillin plus clavulanic acid appeared at least as effective and less expensive.

Table 1. Resistance among urinary tract *Escherichia coli* isolates in the Hong Kong community

Antimicrobial	Resistant isolates (%)
Ampicillin	62.5
Ampicillin + clavulanic acid	1.9
Cephalexin	41.5
Cefuroxime	7.5
Ceftriaxone	0.0
Nalidixic acid	24.5
Ofloxacin	5.6
Co-trimoxazole	39.6

Source: Ling JM, et al. Hong Kong Practitioner 1993.[4]

Table 2. Resistant isolates obtained from community-acquired respiratory infections

Organism	Resistant isolates (%)
Haemophilus influenzae	
Ampicillin	64.2
Ampicillin + clavulanic acid	46.3
Cephalexin	94.8
Cefuroxime	8.2
Erythromycin	79.1
Co-trimoxazole	11.2
Streptococcus pneumoniae	
Ampicillin	4.3
Ampicillin + clavulanic acid	4.3
Cephalexin	17.4
Cefuroxime	0.0
Erythromycin	56.5
Co-trimoxazole	65.2

Source: Ling JM, et al. Hong Kong Practitioner 1993.[4]

Among the isolates found in community-acquired respiratory tract infections,[4] 64.2% of *Haemophilus influenzae* isolates were ampicillin resistant, 4.7% of *Streptococcus pneumoniae* were resistant, more than 80% of *Staphylococcus aureus* strains were resistant, but none of the ß-haemolytic streptococci were. The addition of clavulanic acid achieved relatively little in this context. Again, resistance to cephalexin was relatively frequent, with less resistance to cefuroxime. The figures quoted give an indication of the risk of meeting antibiotic resistance in the community, but for any patient who has recently been in a hospital or nursing home, the risks are considerably greater. In both UTIs and respiratory infections, ceftriaxone and ceftazidime were still generally effective, but some resistant strains were in evidence among *Klebsiella* spp., *Pseudomonas aeruginosa*, *S aureus*, and *S pneumoniae*. The same would be expected to hold true for the newest oral cephalosporins.

Macrolides

Generally, the cost of treatment is considerably higher with newer drugs—the importance of this varies with the patient's circumstances and the mode of payment. Among the macrolides, the difference in cost between old and new is considerable (Table 3). For a small

Table 3. Commercial drug prices

Antimicrobial	Content	HK$ per tablet or capsule
Amoxycillin	250 mg	0.31*
Augmentin	375 mg	3.90*
Cephalexin	500 mg	2.00*
Cefuroxime	250 mg	8.41*
Cefetamet	500 mg	8.70†
Erythromycin	250 mg	0.24*
Clarithromycin	250 mg	6.85*

* Information from Hong Kong Hospital Authority, Prince of Wales Hospital Drug List, Shatin, Hong Kong

† Information from Roche Pharmaceuticals and Chemicals Ltd., Hong Kong

number of conditions (e.g. disseminated infection with *Mycobacterium avium-intracellulare*), clarithromycin may be the drug of choice. However, in many more common infections, the organisms concerned may show cross-resistance among the macrolides. Although this is not invariably the case, erythromycin resistance makes clarithromycin resistance likely. In the community, erythromycin appears fairly effective against ß-haemolytic streptococci (17.4% resistant),[4] however, the situation may deteriorate over time. Workers in Finland recently reported widely varying resistance between different communities, including up to 44% resistance to erythromycin.[6] Resistance is prevalent among *S pneumoniae* isolates in Hong Kong. An important characteristic of the macrolides is their activity against organisms in the genera *Mycoplasma*, *Campylobacter*, *Helicobacter*, *Chlamydia*, and *Legionella*. What the patient will certainly get for buying one of the newer macrolides rather than erythromycin is a far smaller risk of adverse effects, particularly involving the gastrointestinal tract. However, successful completion of a course of erythromycin might be anticipated in a patient who has taken the drug without adverse effects in the past.

Quinolones

Of the quinolones, the only long-used drug to consider is nalidixic acid, with in vitro results indicating that the drug still covers approximately 75% of *E coli* isolates (UTIs). For such infections, ofloxacin would be the appropriate fluoroquinolone as in vitro results indicate that it gives 90% to 95% coverage of community-acquired UTIs. The fluoroquinolones are excellent drugs, but it is arguable that their use in primary health care should be minimised. While current recommendations against use of fluoroquinolones in children or pregnant women remain in place, a large proportion of primary care patients are excluded, and the need for reduced dosage when renal function is impaired (creatinine clearance < 50 ml/min) complicates their use in the elderly.

From the hospital standpoint, fluoroquinolones are still quite precious in tertiary care, sometimes proving to be the drug of choice when multiple antibiotic resistance is a problem, particularly in cases of severe gram negative sepsis. The more widely they are used, the shorter their useful life will be. The only available method of prolonging that life is to restrict their use to cases in which there is no reasonable alternative.

Using the latest drugs

Is it a sound principle to prescribe the newest drugs in primary health care? Cynically, one might answer "Yes, prescribe them while they still work". It must be remembered that the various clinical trials carried out before licensing expose only moderate numbers of people to the drug on trial and may not necessarily have established the ideal dosage and schedule. The rarer side effects may not appear until the drug has been more widely prescribed. Temofloxacin might be taken as an example of a drug that was tested, licensed, marketed, and promoted, but then had to be withdrawn because of an uncommon but very severe adverse effect. When one tries to assess the merits of an advertised new drug, the promotional material may prove less helpful than one might wish. References given may be few, and the independence of the studies quoted may be uncertain.

We rely on the research and development work of the pharmaceutical industry to add to the antimicrobial armamentarium and—of course—the industry must sell its products. What are needed are doctors who can interpret drug advertisements critically, who not only read the lines, but between them noting—for example—what common pathogens are not mentioned and any questions that are not answered.

However, even the best educated doctor would find it difficult to practise in a way consistent with his or her knowledge when treating patients whose information about health and disease is very inadequate, or mistaken. The patient complaining of a cold who demands an antibiotic is an often-quoted example—the patient is not seeking health education, but a treatment of their own choosing. The education of adults regarding health matters is a slow process, often with disappointing results.

Schoolchildren may be more amenable, and if the medical profession helps to make such teaching as good as it can be, perhaps the next generation may have a more sophisticated and informed approach to the use of antimicrobials. Such well-informed patients' expectations would then be met if they were treated without extravagance, with well-targeted antibiotics given only when clear indications exist.

This article has considered cost-effective antibiotic use mainly in terms of the prescribing practices of the individual practitioner. Some countries are more regulated, and control of new drugs is exercised by government departments responsible for health. In Canada and Australia, guidelines have been developed by which economic analyses of advantages and costs of new drugs may affect their listing and pricing.[7] In comparison, the United Kingdom—while not without guidelines on these matters—seems to have adopted a somewhat *laissez-faire* attitude, which may be currently influential in Hong Kong.

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