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Cost Effectiveness of Quinolones in Hospitals and the Community

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Abstract

In hospitals, oral quinolone therapy has lower daily associated costs (acquisition and administration) than most intravenous regimens. In addition, oral switch therapy shortens the duration of hospital stay for most patients. However, randomised trials are required to measure the economic impact of the switch to oral therapy in terms of hospital care costs and the burden imposed on community health services, on relatives or carers and on the patient.

Evidence about the reliability of absorption of quinolones in hospitalised patients is more likely to be obtained from large population kinetic studies than randomised effectiveness trials.

The existing literature on cost effectiveness of quinolones in the community is disappointing. The principal problems are poor definition of diagnostic criteria, inclusion of irrelevant comparator drugs and a failure to include infections caused by bacteria that are resistant to the comparator. Consequently, there is little evidence to support the use of economic models to determine the consequences of antibiotic resistance in the community.

This review will focus on 2 broad areas of quinolone prescribing: (i) oral switch therapy in hospital and (ii) community use of oral quinolones; the main topics being the economic consequences of antibiotic resistance and their potential impact on the cost effectiveness of quinolones in the community. The aim of the review is to summarise current knowledge in these areas and to identify key questions for future research (i.e. this is not a systematic review of all of the available literature). For a more detailed analysis of some of the points covered, the reader is referred to 2 recent publications.[1,2]

1. Considerations of Oral Switch Therapy

1.1 Acquisition and Administration Costs

The acquisition cost of defined daily doses of oral formulations of any antibiotic are usually 2- to 10-fold lower than the cost of the corresponding intravenous formulation. In addition, intravenous therapy has administration costs (consumables, staff time required for preparation and administration, wastage resulting from administration of a quantity less than the vial contents).[1,2] Once costs of preparation and administration are added to drug acquisition costs, the cost of oral quinolone therapy is usually less than the cost of intravenous therapy.[1,2] An economic analysis that simply sets out to prove that this is the case will be of little value to the decision-maker. Thus, the aim should be to prove that savings in drug acquisition and administration costs translate into savings in clinical practice and to reassure the decision-maker that there are no hidden additional costs to oral therapy, for example those arising from reduced efficacy.

Importantly, switching from intravenous therapy to an oral quinolone is only cost effective if continued antibiotic therapy is clinically indicated[3] and there is no cheaper oral alternative.[1]

1.2 Potential for Shortening the Duration of Hospital Stay

The potential for shortening hospital stay with oral switch quinolone therapy has been demonstrated in a large multicentre study,[4] in which 766 patients receiving intravenous antibacterials for infections arising from the respiratory tract, urinary tract, skin, soft tissue, bones or joints were switched to oral ciprofloxacin therapy. Subsequently, 496 of these pa-

tients were discharged before completion of ciprofloxacin treatment.

If the patients had not been switched to oral ciprofloxacin, the majority would have continued on intravenous therapy, either as inpatients or outpatients. Only 82 (11%) were considered suitable for other oral antibacterial treatment. It was estimated that switching to oral ciprofloxacin resulted in earlier discharge of 427 (56%) of the patients.

The most common reasons for patients remaining in hospital despite changing to oral ciprofloxacin were the patient's concurrent medical condition (303/339; 76%) and difficulty in placement into a nursing home or other chronic-care institution (62/339; 16%). Poor response to oral ciprofloxacin delayed discharge in only 24 (6%) patients. In addition, the longer the planned duration of antibacterial treatment, the greater the potential for improving concurrent medical problems and resolving social requirements before completion of antibiotic therapy.

This study showed that the potential for early discharge was greatest for patients with bone and joint infections, which is likely to be a result of relatively prolonged treatment together with a lower probability of concurrent medical conditions influencing hospitalisation.

Clearly oral switch therapy has the potential to shorten hospital stay, especially in countries in which home intravenous antibiotic services are not widely available.[2] However, patients are often kept in hospital for some days after switching to oral therapy without obvious clinical need.[5,6] For example, 86 patients switched from intravenous to oral therapy in Dundee remained in hospital for a median of 4 days but only 22 (26%) had either medical or social problems which justified continuing hospitalisation.[6]

1.3 The Economic Value of Shortening the Duration of Hospital Stay

There are 5 common fallacies in estimating the economic gain of early hospital discharge.[7]

- The savings will be equal to the average cost per day in hospital before implementation of the programme for promoting early discharge

In practice, the savings attributable to patients who are discharged early are usually offset by an increase in the average cost per day of hospitalisation (i.e. patients who can be discharged early are almost always replaced by patients requiring more aggressive investigation and treatment)

- Early discharge will shorten hospital waiting lists

This will only occur if the availability of hospital beds is the only factor influencing admission to hospital. In reality this is also influenced by the availability of resources such as operating theatres and/or diagnostic facilities.

- Early discharge will not increase the cost of care in the community.
- Early discharge will not impose any financial burden or inconvenience on carers or family.
- Early discharge will not impose any burden on the patient.

The importance of considering these 5 issues has been demonstrated in recent studies of accelerated discharge programmes,[8,9] including the use of outpatient or home intravenous antibiotic services.[10] However, I am not aware of any study of oral switch therapy that has measured the impact of early discharge on the hospital, the community services, the patient or their carers and relatives.

1.4 Costs of Treatment Failure

When considering oral switch therapy, one must also consider the high cost of treatment failure.

The costs of failure of antibiotic treatment in hospital were quantified in one study of patients treated with gentamicin regimens.[11] Compared with patients who had a successful outcome, treatment costs were an average of £357 higher per patient who died [95% confidence interval (CI) £31 to £682] and an average of £418 higher per patients who failed to respond to initial therapy (95% CI £89 to £747). Removal of patients with Gram-negative bacteraemia had little impact on these results: treatment costs were £431 per patient higher in the nonbacteraemic patients who did not respond to initial treatment (95% CI £61 to £802).

The potential costs of inadequate treatment were graphically illustrated for one patient. This patient received 6 days of treatment for a wound infection and was discharged to home with no further antibiotic treatment. Total treatment cost for the first admission was £186. The patient was readmitted after 2 days with gross suppuration of the wound and the total treatment cost for the second admission was £1757 (antibiotics, equipment and staff time).

1.5 Evidence for the Effectiveness of Oral Quinolone Therapy

Clinicians are concerned about the effectiveness of oral therapy and need to be reminded that the right oral therapy can be more effective than the wrong intravenous therapy. For example, in an open randomised trial,[12] treatment of uncomplicated enteric fever with oral ofloxacin resulted in complete cure of all 22 patients, whereas only 18 of 25 patients treated with intravenous ceftriaxone were completely cured ($p <$

0.01). The UK costs for the regimens used would be £108.00 for ceftriaxone (3g/day intravenously for 3 days) compared with £10.26 for ofloxacin (200mg twice daily by mouth for 5 days).

Overall, the quality of randomised controlled trials (RCTs) of oral switch therapy is uneven. In one review, only 6 of 32 trials satisfied the rules of evidence.[13] Mandell et al. used 6 general criteria to assess articles and to determine the validity and applicability of the results:[13]

1. Was the assignment of patients to treatment truly randomised?
2. Were all clinically relevant outcomes reported?
3. Were the study patients recognisably similar to your own?
4. Were both statistical and clinical significance considered?
5. Is the therapeutic manoeuvre feasible in your practice?
6. Were all patients who entered the study accounted for by its conclusion?

Because the critical issue was considered to be whether switch therapy was as effective as intravenous therapy, the authors considered that if both the experimental and control arms of a study included switch therapy then that study was confounded. They reviewed 32 published studies and rejected 19 because they were not randomised trials. They rejected 7 of the remaining 13 RCTs because of inappropriate control regimens (inclusion of switch therapy in the control as well as the experimental arm), leaving 6 RCTs that were considered to provide adequate evidence of the effectiveness of switch therapy in comparison with intravenous therapy.

Moreover, even when trial design issues have been resolved, the patients in the switch arm have usually received 3 to 5 days of intravenous therapy before changing to oral therapy.[13,14] Given that 5 days of intravenous treatment may be enough for most cases of intra-abdominal infection,[3] it could be argued that demonstrating the equivalence of intravenous/oral switch and intravenous-only regimens does not establish the need for any oral therapy following intravenous treatment in the switch arm.

1.6 Concerns about Drug Absorption with Oral Quinolones

We now have abundant information about the clinical effectiveness of quinolones in treating a wide variety of infections. We also have evidence about the serum concentrations which must be achieved to provide the best chance of successful treatment. However, concerns remain about the absorption of quinolones in patients, because of the potential effect of concomitant disease or sepsis during drug absorption. These concerns are probably best addressed by population kinetic studies in patients. Trials comparing the clinical outcome of oral quinolone therapy with parenteral treatment are a very indirect way of answering the question: do patients with infection absorb quinolones reliably? Clinical outcome will be affected by many factors besides the absorption of the quinolone. Moreover, it is difficult to design a protocol which avoids the problems of either fixing the duration of oral and intravenous therapy or of leaving this decision to the whim of clinicians (i.e. making the trial a study of clinician behaviour rather than of effectiveness of oral quinolone treatment). It would be preferable to define particular patient groups in whom absorption of quinolones might be impaired (e.g. patients with postoperative ileus or diarrhoea or signs of sepsis). Absorption of quinolones or other oral antimicrobials could then be studied by measurement of serum concentrations, while giving intravenous treatment with an alternative drug if necessary.[15]

2. Drug Utilisation Studies of Oral Quinolones

Further drug utilisation reviews are required to document the use of quinolones in practice[16] with the aim of identifying 3 groups of patients:

- those who switch to oral quinolones as recommended by local guidelines
- those who could receive oral quinolones but continue to receive parenteral antibiotics
- those who are receiving oral quinolones when cheaper oral drugs would be appropriate.

Documentation in this way should allow the hospital to calculate the net cost saving being achieved through maintaining oral quinolones as part of the hospital formulary, as well as quantifying the additional benefits that could be realised by better compliance with policy. This in turn should assist in deciding how much effort is worth putting into improving compliance with policies and in designing studies of the cost effectiveness of drug utilisation review.[17]

Indeed, one recent study suggested that switch therapy from intravenous to oral ofloxacin was easier to implement than sequential therapy from an intravenous regimen to a different oral formulation.[18] This is an interesting possibility that requires further study.[2]

Ideally, hospitals should monitor indicators of outcome of antibacterial treatment. These include death in hospital, escalation or reintroduction of antibacterial treatment and readmission within 2 weeks of dis-

charge.[11] As most hospitals do not have information systems that allow routine collection of such data, hospital management should be encouraged to invest in better information technology.[19]

The drive to contain drug costs through encouraging oral switch therapy should not be allowed to obscure 3 key points:[2]

- (i) if the costs of treatment failure are high then they can easily wipe out savings from reduced drug acquisition costs
- (ii) the cost effectiveness of any treatment is crucially dependent on the accuracy of diagnosis, particularly for regimens that have both high drug acquisition costs and a risk of serious adverse effects
- (iii) efficient disease management for serious infections requires that all patients with confirmed infection receive effective empirical treatment. This inevitably means that some patients receive unnecessary treatment. Modifying or stopping unnecessary treatment as soon as possible[20] will be a crucial component of disease management.

3. Meta-Analysis of Quinolone Use in a Variety of Community-Acquired Infections

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) recently completed a systematic review of the clinical and economic evidence supporting the use of quinolones for uncomplicated urinary tract infections, prostatitis and community-acquired pneumonia.[21] In total, 893 titles were found on MEDLINE and 235 on Embase, of which 217 were considered worthy of detailed review. Each paper was reviewed by 2 observers and differences resolved by discussion. In total only 41 (19%) of the papers were considered eligible for meta-analysis (table I). All of the papers reporting trials in community-acquired pneumonia were rejected, mainly because of inclusion of ineligible patients (i.e. those with nosocomial pneumonia or undifferentiated lower respiratory tract infections) or because of comparison with regimens which are not considered standard therapy for community-acquired pneumonia in Canada. Although 16 reports of RCTs in prostatitis met the criteria for inclusion, the total number of patients was small, thus the confidence intervals for estimates of efficacy were extremely wide. Taken together with the problems of comparing drugs across rather than within studies, it was considered that the evidence was too weak to form the basis for an economic analysis of quinolone therapy in chronic prostatitis. Thus, despite an apparently impressive amount of evidence (table I) the CCOHTA team concluded that analysis of the cost effectiveness of quinolones was only possible for cystitis.

3.1 Cost Effectiveness in the Treatment of Cystitis

Of the 25 studies on community-acquired cysitis reviewed by CCOHTA, 9 were comparisons between different quinolones (ciprofloxacin, norfloxacin or ofloxacin) and 16 were comparisons between co-trimoxazole and quinolones (ciprofloxacin 1 trial, norfloxacin 7 trials and ofloxacin 8 trials). The quality of the trials was variable. There were no significant differences between quinolones in effectiveness or side effects. Of the trials comparing quinolones with co-trimoxazole, a minority reported both clinical and microbiological end-points and most trials were restricted to infections caused by bacteria that were sensitive to both of the drugs (table II).

The trial results were used as the basis for a decision analysis that calculated the total cost of care, including repeat visits made either because of lack of recurrent cystitis, or because of adverse effects. The total cost of care was similar for co-trimoxazole ($Can80 per patient) and the 3 quinolones ($Can83 for ofloxacin, $Can84 for ciprofloxacin and norfloxacin). Effectiveness was measured in morbid days, which included symptoms due either to cystitis or to drug side effects. Patients had an average of 4.7 morbid days with co-trimoxazole versus 4.0 days with either

Table I. Reasons for exclusion of studies from a meta-analysis of clinical and economic considerations in the use of fluoroquinolones in community-acquired infections[21]

	Community-acquired pneumonia		Prostatitis		Uncomplicated cystitis	
	number	%	number	%	number	%
Total trials reviewed	36		60		121	
Number of trials rejected from final meta-analysis	36	100	44	73	96	79
Reason for rejection:						
Ineligible inclusion criteria	25	69	18	40	61	69
Ineligible comparator drugs	9	25	9	20	23	24
Not randomised controlled trial	2	6	5	11	7	7
Outcomes not reported	0		10	22	0	
Duplicate publication	0		1	2	0	
Not in English	0		1	2	0	

Table II. Content of 15 clinical trials that compared co-trimoxazole with norfloxacin or ofloxacin for the treatment of uncomplicated, community-acquired cystitis[21]

	Norfloxacin (n = 7 trials)			Ofloxacin (n = 8 trials)		
	yes	no	not clear	yes	no	not clear
Blinding of treatment allocation	1	1	5	1	3	4
Entry restricted to women with infections caused by bacteria sensitive to both study drugs	5	2	0	3	3	2
Clinical and microbiological end-points included. (No indicates that the trial only reported microbiological end-points)	1	6	0	4	4	0

Table III. Costs of quinolones in selected countries. Data were obtained in 1999 and use the lowest price based on the available pack size in each country. For example, in Germany the price of 400mg ofloxacin is based on the cost of 50 x 400mg tablets (DM448.36/50 = DM8.97), whereas the price for the same dose would be DM11.34 calculated from the cost of 10 x 200mg tablets (DM56.94). The point of this table is to show that the price ratio of levofloxacin or ofloxacin to ciprofloxacin varies markedly between countries. The doses in this table are based on the defined daily doses (DDD) published by the WHO in 1997. DDD are simply an indication of commonly prescribed daily doses and are not intended to signify therapeutic equivalence for any specific infection

	France (F)	Ratio to ciprofloxacin	Germany (DM)	Ratio to ciprofloxacin	Italy (L)	Ratio to ciprofloxacin	UK (£)	Ratio to ciprofloxacin
Oral								
Levofloxacin (500 mg/day)	NA	NA	7.30	0.38	10.73	1.95	2.78	0.98
Ofloxacin (400 mg/day)	30.00	0.97	8.97	0.47	5.98	1.09	2.04	0.72
Ciprofloxacin (1000 mg/day)	31.00	Referent	18.98	Referent	5.49	Referent	2.84	Referent
Intravenous								
Levofloxacin (500 mg/day)	NA		NA		119.99	0.98	28.39	0.95
Ofloxacin (800 mg/day)	NA		NA		NA	NA	44.01	1.45
Ciprofloxacin (800 mg/day)	NA		NA		122.40	Referent	30.45	Referent

ciprofloxacin, norfloxacin or ofloxacin. The authors concluded that any of the 3 quinolones provided more cost-effective treatment than co-trimoxazole at a modest cost per morbid day avoided ($Can3.90) for ofloxacin and $Can5.60 for ciprofloxacin or norfloxacin).

3.2 The CHEST Study in Chronic Bronchitis

This was a randomised, multicentre, parallel-group open-label study comparing ciprofloxacin with standard care for the management of acute exacerbations of chronic bronchitis.[22] In the control arm, doctors were allowed to choose any antibiotic but were provided with a classification of antibiotics into first and second line. The authors believed that doctors would choose a first-line antibiotic for a first exacerbation of chronic bronchitis but, in reality, 56% (108/194) antibiotic prescriptions were for second-line drugs, and a total of 18 different drugs were used in the control arm. This makes interpretation of the results very difficult and illustrates the lack of consensus about usual care for this condition.

The aim of the CHEST study was to show that ciprofloxacin treatment increased the interval between exacerbations of chronic bronchitis. However, there was no difference between the experimental and control arms in the trial. Nonetheless, there was a slight, but not statistically significant, improvement in all quality-of-life measures with ciprofloxacin over usual care, which the authors attributed to more rapid resolution of an exacerbation with ciprofloxacin.

The CHEST study does put the costs of antibiotic treatment into perspective against the overall costs of management of advanced chronic bronchitis (in order to be eligible for the study patients had to have 3 or more exacerbations during the previous year). Costs were highly variable in both arms, e.g. mean annual costs per patient in the ciprofloxacin arm were $CAN3194 but the standard deviation was $CAN6575. The variance in costs was most marked for concomitant medications, hospitalisations and time lost from work. Antibiotic costs were only 6% of the total ($CAN188/3194) in the ciprofloxacin arm and 4% of the total ($CAN116/2617) in the standard care arm.

4. Adapting Cost-Effectiveness Data to Different Countries

There are marked differences between countries in the acquisition costs of drugs which will inevitably alter the results of cost-effectiveness analyses (table III). There is similar variation in the costs of other healthcare resources such as medical visits and investigations. However, it is relatively easy to adapt a decision analysis to another setting by inserting local costs. The results of such an analysis with costs adapted from $US to UK pounds and German DM are summarised in table IV. This study was based on a decision analysis that used the results of 2 randomised

Table IV. Total costs of management of uncomplicated cystitis in women: data from a decision analysis from the US adapted for local costs of healthcare in the UK and Germany.[23] The original study included data about 2 outcomes: recurrent cystitis and vaginal candidosis as a complication of antibiotic treatment. The probability of successful outcome is the probability of having no further symptoms due to either cystitis or candida vaginitis within 28 days of treatment. Total cost includes the cost of the original visit plus any additional visits, investigations or drugs required to manage recurrent cystitis or vaginal candidosis

	Probability of successful outcome (%)	US ($US)	UK (£)	Germany (DM)
Ofloxacin	84	114	16	74
Co-trimoxazole	67	116	14	65
Amoxicillin	55	132	15	105
Nitrofurantoin	42	160	19	88
Cefadroxil	28	171	22	109

clinical trials to compare the cost effectiveness of amoxicillin, cefadroxil, co-trimoxazole, nitrofurantoin and ofloxacin for the treatment of uncomplicated cystitis.[24,25] The total costs of care are strikingly different in the 3 countries (table IV). Moreover, the rank order of each drug is also different. Ofloxacin has the lowest overall cost in the USA, whereas co-trimoxazole has the lowest costs in the UK and Germany.

5. The Impact of Resistance on Cost Effectiveness

Epidemiological studies show that infection with drug-resistant pathogens is associated with a markedly worse outcome and therefore probably reduced cost effectiveness than infection with pathogens that are sensitive to first-line therapy (table V). Therefore it seems reasonable to design decision analyses that compare the cost effectiveness of antibiotic regimens based on the prevalence of drug-resistant bacteria and the impact of drug resistance on clinical outcome.[27] However, there is little knowledge about the relative effectiveness of antibiotics against infections caused by drug-resistant bacteria because the majority of randomised clinical trials exclude such patients (table II).

There is little support for the decision analysis that assumes a response rate of 80% for community-acquired infections caused by bacteria that are sensitive to amoxicillin or ceftriaxone versus 20% for drug-resistant pathogens.[27] The authors do not specify the type of drug-resistant pathogens, nor do they provide any supporting evidence from clinical trials. Epidemiological studies certainly do not support the assumption that penicillins have a 20% success rate in respiratory infections caused by penicillin-resistant pneumococci.[28] In this study of severe pneumonia, mortality rates in patients who were treated with penicillins were 25% if the pneumococcus was resistant to penicillin versus 19% if it was sensitive.

There is so little evidence linking data about *in vitro* susceptibility tests to clinical outcomes that some have advocated use of the term 'reduced susceptibility' in preference to 'resistance'.[29,30] For example, in a randomised trial comparing amoxicillin clavulanate with amoxicillin alone for treatment of urinary tract infection in the elderly, it was clear that amoxicillin resistance dramatically reduced the effectiveness of amoxicillin treatment (table VI). However, it was also notable that amoxicillin resistance reduced the effectiveness of amoxicillin clavulanate. Moreover, amoxicillin was significantly less effective than amoxicillin clavulanate against amoxicillin 'sensitive' strains, suggesting that these strains also had a clinically significant reduction in susceptibility to amoxicillin.

Table V. The impact of drug resistance on the outcomes of serious infections. Data from epidemiological studies conducted by the Centers for Disease Control, Atlanta, Georgia, USA[26]

Outcome	Pathogen	Infection	Resistant strains		Sensitive strains		Odds ratio	95% CI
			number	%	number	%		
Death	*Salmonella* spp. (nontyphoidal)	Community-acquired salmonellosis	3/61	5	4/453	1	5.8	1.3 to 26.6
Hospitalisation	*Salmonella* spp. (nontyphoidal)	Community-acquired salmonellosis	57/100	57	158/645	24	4.1	2.6 to 6.3
Hospitalisation	*Shigella* spp.	Community-acquired shigellosis	190/1531	12	19/1304	1	9.6	5.9 to 15.4
Death	*Serratia marcescens*	Hospital-acquired bacteraemia	15/24	63	3/23	13	11.1	2.6 to 48.2
Death	*Klebsiella pneumoniae*	Bacteraemia in neonates	34/64	53	3/21	14	6.8	1.8 to 25.4

CI = confidence interval.

Table VI. Outcomes of 5 days' treatment with amoxicillin clavulanate or amoxicillin for urinary tract infection in the elderly[31]

	Amoxicillin clavulanate		Amoxicillin		Odds ratio and 95% CI amoxicillin clavulanate *vs* amoxicillin
	number		number		
Amoxicillin resistant	8/10	80	1/10	10	36.0 (2.7 to 476.3)
Amoxicillin sensitive	13/14	93	11/18	61	8.3 (0.9 to 78.0)
Odds ratio (95% CI) amoxicillin resistant *vs* sensitive	0.31 (0.02 to 3.97)		0.03 0.00 to 0.37		

CI = confidence interval.

6. Conclusions About the Cost Effectiveness of Quinolones in Community-Acquired Infections

The literature is overburdened with equivalence studies that provide little useful information about the relative effectiveness of antibiotics in representative patient populations. Thus, the available evidence does not allow firm conclusions to be drawn about the cost effectiveness of quinolone treatment for uncomplicated cystitis, despite the publication of over 100 studies. There is a need for pragmatic trials designed to emphasise the differences between drugs, not hide them.[32] In particular, inclusion of patients with infections caused by strains with reduced susceptibility to routine therapy is essential. Once evidence of differences in effectiveness of antibiotics exists, it can be used to model the cost effectiveness of treatment in different settings.

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