Sequential antibiotic therapy: Effective cost management and patient care

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LA MANDELL, MG BERGERON, MJ GRIBBLE, et al. Sequential antibiotic therapy: Effective cost management and patient care. Can J Infect Dis 1995;6(6):306-315. The escalating costs associated with antimicrobial chemotherapy have become of increasing concern to physicians, pharmacists and patients alike. A number of strategies have been developed to address this problem. This article focuses specifically on sequential antibiotic therapy (SAT), which is the strategy of converting patients from intravenous to oral medication regardless of whether the same or a different class of drug is used. Advantages of SAT include economic benefits, patient benefits and benefits to the health care provider. Potential disadvantages are cost to the consumer and the risk of therapeutic failure. A critical review of the published literature shows that evidence from randomized controlled trials supports the role of SAT. However, it is also clear that further studies are necessary to determine the optimal time for intravenous to oral changeover and to identify the variables that may interfere with the use of oral drugs. Procedures necessary for the implementation of a SAT program in the hospital setting are also discussed.

Key Words: *Cost effectiveness, Intravenous antibiotic therapy, Oral antibiotic therapy, Quality of life, Sequential antibiotic therapy*

Antibiothérapie séquentielle : rentabilité et soins

RÉSUMÉ : Les coûts sans cesse croissants associés à l'antibiothérapie inquiètent de plus en plus les médecins, les pharmaciens et les patients. Certaines stratégies ont été mises au point pour répondre à ce problème. Le présent article s'attarde plus précisément au traitement antibiotique séquentiel, une stratégie par laquelle les patients passent de la forme intraveineuse à la forme orale d'un médicament, qu'il s'agisse ou non de produits d'une même classe. Parmi les avantages de l'antibiothérapie séquentielle, notons l'aspect économique et la commodité pour le patient et pour le personnel soignant. Les désavantages potentiels sont les coûts assumés par le consommateur et le risque d'échec thérapeutique. Une analyse critique de la littérature publiée révèle que les données tirées d'essais contrôlés randomisés appuient l'antibiothérapie séquentielle. Toutefois, il faut de toute évidence poursuivre les études afin de déterminer le moment idéal du passage de la forme intraveineuse à la forme orale et d'identifier les variables qui peuvent interférer avec l'emploi des médicaments par voie orale. Les étapes nécessaires à l'application d'un programme d'antibiothérapie séquentielle dans le contexte hospitalier sont également décrites.

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OVER THE PAST TWO DECADES, OUR THERAPEUTIC ARMAMENTARIUM has been greatly expanded with agents that provide excellent antimicrobial activity combined with improved pharmacokinetic features and improved adverse effect profiles. At the same time, however, economic constraints and hospital bed closures have forced us to consider approaches other than traditional in-hospital intravenous antibiotic use. We now have a number of options that facilitate and simplify patient care and reduce costs. These include home intravenous therapy and oral therapy using agents that do not compromise therapeutic efficacy.

This paper reviews some of the economic issues associated with antimicrobial therapy and examines the treatment of infections with intravenous antimicrobials and the subsequent use of oral agents. This practice is referred to as sequential antibiotic therapy (SAT); simply stated, it is the practice of changing from intravenous to oral dosage forms as early during a course of antibiotic treatment of infection as is clinically possible.

COST CONTAINMENT ISSUES

Antibiotics are among the most commonly prescribed drugs in Canada. According to the Fifth Annual Report of the Patented Medicine Prices Review Board (1), total Canadian patented prescription drug revenue was over $2 billion in 1992. Anti-infective agents, costing $354 million, accounted for the largest number of patented drug products sold in Canada. The cost of injectable antibiotics alone was $110 million (2). In any Canadian hospital, antibiotics often represent the single largest component of the hospital pharmacy budget, accounting for 20 to 40% of total drug costs.

In an attempt to cope with increasing costs, several strategies have been developed and implemented and may be classified as 'educative and persuasive', 'facilitative' and 'restrictive' strategies (3). The following list includes most of these:

- prescriber education
- formulary restriction and reserved antimicrobial program
- selective reporting of susceptibility testing
- automatic stop policies
- therapeutic interchange programs
- antimicrobial order forms
- required consultation and physician or service restriction
- SAT (3).

It is beyond the scope of this article to deal with all these cost containment strategies; our purpose is to focus specifically on SAT.

SEQUENTIAL ANTIBIOTIC THERAPY

SAT refers to the practice of limiting the use of intravenous antibiotics to the early stages of infection and then converting to oral agents for the duration of treatment.

SAT is not as new an approach to cost effective antibiotic prescribing as one might think. Studies published in the 1970s involving children with osteomyelitis and septic arthritis demonstrated the efficacy and safety of initial treatment with parenteral antibiotics followed by conversion to oral agents as soon as the acute signs and symptoms of infection were controlled (4-8).

In a 1991 survey of antibiotic decision making at a 1000-bed tertiary care hospital, Quintiliani et al (9) reported that antibiotic therapy could be 'streamlined' in approximately 75% of patients in one of three ways: first, by changing from combination therapy to monotherapy; second, by changing to another agent with a narrower antimicrobial spectrum of activity and/or to one with preferable pharmacokinetics; and third, by changing the route of administration from intravenous to intramuscular or oral.

This concept of streamlining from a more complex, often more expensive, regimen to a less complex one has also been referred to in the literature as 'stepdown therapy', 'switching' or 'sequential therapy'. However, these terms have not always been used synonymously.

For example, stepdown therapy and switching have been used to denote not only a change from intravenous to the oral form of the same drug, but also a change to a different drug once the conversion to oral therapy has been made (10,11). Likewise, sequential therapy has been used to denote a change from intravenous to oral forms of the same drug or different drugs (12,13). Streamlining has also been used to denote the change from combination therapy to monotherapy (14). It might, therefore, avoid confusion by establishing a common terminology for describing conversion from intravenous to oral medications. Not only would this make discussion of such treatment strategies easier, it would aid in cataloguing the medical literature dealing with this subject. We propose that the term 'sequencing' or 'sequential antibiotic therapy' be used to define the strategy of converting patients from intravenous to oral medications, regardless of whether the same or a different class of drug is used.

ADVANTAGES AND DISADVANTAGES OF SAT

There are sound clinical and financial reasons to pursue a therapeutic strategy that incorporates appropriate early conversion from intravenous to oral antimicrobials. Some physicians remain reluctant to do this, perhaps because of a lack of knowledge and appreciation of the efficacy and advantages of such a strategy, as well as the sense of security provided by the serum and tissue drug levels obtained using intravenous drugs. This reluctance has, unfortunately, fostered the unnecessarily prolonged use of intravenous medications in the hospital setting for treatment of infections that could benefit from a shortened course of intravenous treatment followed by oral therapy.

Advantages of SAT: Three main benefits are associated with the use of SAT: economic benefits, patient benefits and benefits to the health care provider.

Economic benefits: With any drug, there are two costs to consider: the more obvious or apparent cost of the agent, referred to as the acquisition cost, and the secondary costs related to delivery or administration of the drug. The latter include a variety of factors, such as a pharmacist's preparation

TABLE 1
Acquisition cost of one dose of commonly prescribed antibiotics*

Drug	Dose (route)	Acquisition cost ($)
Ampicillin	1-2 g (IV)	0.70-1.40
Amoxicillin	500 mg (PO)	0.08
Cefuroxime	750 mg-1.5 g (IV)	6.93-12.29
Cefuroxime axetil	500 mg (PO)	2.60
Ciprofloxacin	400 mg (IV) 250-750 mg (PO)	33.00 2.22-4.73
Clindamycin	600 mg (IV) 300-450 mg (PO)	12.86 1.58-2.38
Metronidazole	500 mg (IV) 500 mg (PO)	1.49 0.04
Trimethoprim-sulfamethoxazole	160 mg/800 mg (IV) 160 mg/800 mg (PO)	3.20 0.04

**Prices supplied by purchasing department, Henderson General Division, Hamilton Civic Hospitals, Hamilton, Ontario, December 1993. IV Intravenous; PO Oral*

and delivery time; a nurse's administration time; ancillary supplies, such as intravenous bags and tubing; loss due to wastage; and the need for laboratory monitoring of drug serum levels, as is required with aminoglycosides and vancomycin. All these factors contribute to the cost of drug therapy and should be considered when the cost of a particular drug is evaluated.

Preparation and administration costs vary among hospitals. Rush (15) reported that the cost of preparation and administration added US$7.00 to the cost of each dose of intravenous antibiotic. In Australia, such costs add between AUS$4.55 and $10.58 to the cost of each intravenous dose (16). Others have reported that, by simply replacing one intravenous antibiotic with another that is given less frequently, substantial cost savings are realized, even when the acquisition cost of the replacement drug is higher (17,18). For example, at one American hospital, the total daily administration cost of penicillin G $3x10^6$ U given intravenously every 4 h is US$29.26 (17), yet the cost of cefazolin 1 g intravenously every 8 h is only US$14.60.

Generally, acquisition costs for the intravenous form of a drug are greater than those of the oral form. Some examples of these comparative costs are given in Table 1. The use of oral agents obviates the need for most, if not all, ancillary costs.

At the Vancouver Hospital and Health Sciences Centre, an intravenous to oral antibiotic conversion program has been in place since 1987. Changing from intravenous to oral therapy using drugs such as metronidazole, clindamycin, ciprofloxacin, fluconazole, cefuroxime and cefixime has resulted in savings of at least $30,000 yearly (10,11). Hartford Hospital in Connecticut projected an annual saving of US$107,637 based on an antibiotic streamlining program (14).

Another major financial saving is realized by the earlier discharge of the patient from the hospital. This eliminates the expenses associated with housing a patient in an acute care facility solely for the purpose of administering intravenous antibiotics (19).

The magnitude of cost savings that can accrue by sequencing from intravenous to oral treatment is apparent from a multicentre study in the United States involving 766 hospitalized patients. After successful conversion to oral ciprofloxacin from a variety of parenteral antimicrobial agents, 418 patients were discharged from the hospital earlier than would have otherwise occurred. An estimated total of 2266 hospital days were saved, resulting in savings of US$793,100. Projected savings for total drug plus hospitalization costs were US$980,246 (20).

Patient benefits: Although less quantifiable than the more tangible financial gains, patient-related benefits are nevertheless real and important. In hospital, the use of oral instead of intravenous drugs increases patient comfort and mobility, the latter being a particularly important consideration in the elderly. By not using intravenous lines, there is less risk of phlebitis and line-related infections. The earlier discharge from hospital also decreases the risk of development of other nosocomial infections. An earlier return to family and, possibly, to work provides benefits in terms of enhanced quality of life as well as possible economic benefits.

Health care provider benefits: Considerable time is spent by pharmacists and nurses in preparing and administering intravenous antibiotics. Use of SAT decreases the amount of personnel time associated with drug delivery and, although the actual benefits of 'saved time' are difficult to assess, it may serve to free the individual for other tasks that may improve patient care and enhance job satisfaction for the health care provider.

Disadvantages of SAT: There are two perceived disadvantages with SAT: economic and risk of therapeutic failure.

Economic disadvantages: While receiving medication in the hospital, the patient is not responsible for any of the drug-related costs. However, once discharged, the consumer must bear the cost of therapy. It is therefore important to discuss the cost of therapy with the patient before discharge.

Risk of therapeutic failure: Patient compliance with treatment while in the hospital is taken for granted. However, once outside the hospital this becomes much more difficult to ensure. Poor compliance with the planned oral treatment regimen could result in treatment failure or relapse of infection. Readmission of the patient to the hospital would quickly offset any cost savings realized by a change to oral therapy.

Another potential problem is that incomplete or inadequate treatment of infection may contribute to the development of microbial resistance, making it necessary to use more expensive or possibly more toxic agents to treat infection.

In a study that specifically examined patient compliance with an oral regimen, Paladino et al (21) documented an 81% compliance rate in out-patients taking ciprofloxacin twice daily following initial treatment with intravenous antibiotics in hospital. Therapeutic outcomes in this group were excellent despite compliance rates of less than 100%. Compliance rates were also examined by Cramer et al (22), who showed results identical to those described by Paladino et al for twice-daily

TABLE 2
Randomized controlled trials of sequential antibiotic therapy for treatment of infection

Author (reference), Number of participants Type of infection	Mean age (years)	Regimen and dosages	Duration of therapy (days)	Overall efficacy Clinical* (%)	Overall efficacy Bacterial eradication (%)
Kalager et al (39), n=281 septicemia, LRTI, UTI, GI	61	Ciprofloxacin IV 200-400 mg q12h → Ciprofloxacin oral 750 mg bid	5.8 IV → 6.4 oral	84	61
	65	vs Ceftazidime/tobramycin IV 1.5 g q8h based on levels	9.5 IV	84	66
Dominguez et al (40), n=39 skin, soft tissue	49.9	Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 500 mg q12h	4 IV → 12 oral	95	
	53.3	vs Ceftazidime IV 1 g q8h	9 IV	80	
Gaut et al (43), n=32 bone & joint, intra-abdominal, RTI, UTI, SST, wound, bacteremia	66	Ciprofloxacin IV 200-300 mg q12h → Ciprofloxacin oral 500 mg q12h	Minimum 2 days IV	82	53.8
		vs Ceftazidime IV 1-1.5 g q8-12h	16 IV	72	55.5
Fass et al (44), n=52 LRTI, UTI, SST, endocarditis, sepsis, mastoiditis	46	Ciprofloxacin IV 200-300 mg q12h → Ciprofloxacin oral 500-750 mg q12h	3-6 IV → 13-16 oral	81	
		vs Ceftazidime IV 1-2 g q8-12h	13.5 IV	71	
Cox (41), n=77 complicated UTI	61	Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 500 mg q12h	4 IV → 6 oral	100	100
	68	vs Ceftazidime IV 500 mg q8h	9 IV	97	87
Hirata-Dulas et al (47), n=50 nursing home acquired LRTI	79.3	Ciprofloxacin IV 200-400 mg q12h → Ciprofloxacin oral 750 mg q12h	3.4 IV → 10.6 oral	50	
	79.4	vs Ceftriaxone IV 2 g → Ceftriaxone IM 1 g	3.9 IV → 10.1 IM	54	
Khan and Basir (48), n=122 lower RTI	58 overall (not differentiated by treatment arm)	Ciprofloxacin IV 200-300 mg q12h → Ciprofloxacin oral 500 mg q12h	6 IV → 5 oral	91	
		vs Ceftazidime IV 1-2 g tid → Various oral antibiotics	7 IV → ?	89	
Menon et al (49), n=37 pneumonia	32	Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 750 mg q12h	Minimum 2 days IV	100	
	38	vs Ceftazidime IV 1-2 g q8h → Appropriate oral antibiotics	Minimum 2 days IV	95	
Peacock et al (50), n=39 UTI, LRTI, bone, joint, skin, soft tissue, gall bladder, bacteremia	58	Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 500 mg q12h	7.4 IV → 17† oral	76	
	55	vs Ceftazidime IV 1-2 g q8h → Appropriate oral antibiotics	9.9 IV → 12‡ oral	82	
Gangji et al (42), n=65 Gram-negative septicemia	66	Ciprofloxacin IV 200 mg q12h → 3 IV → Ciprofloxacin oral 750 mg q12h	7-11 IV → 7-11 oral	97.2	94
	62	Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 750 mg q12h	7-11 IV → 7-11 oral	93.1	96
Feist (51), n=92 LRTI	63	Ofloxacin IV 200 mg bid → Ofloxacin oral 200 mg bid, tid or qid	Minimum 3 days IV → 4-7 oral	100 overall	95
		vs Amoxicillin/clavulin IV 2.2 g bid-tid → Amoxicillin/clavulin oral 625 mg bid-tid or qid	Minimum 3 days IV → 4-7 oral	94	82
Khajotia et al (52), n=92 LRTI	63	Ofloxacin IV 200 mg bid → Ofloxacin oral 200 mg bid, tid or qid	Minimum 3 days IV → 4-7 oral	100 overall	95
		vs Amoxicillin/clavulin IV 2.2 g bid-tid → Amoxicillin/clavulin oral 625 mg bid-tid or qid	Minimum 3 days IV → 4-7 oral	94	82
Johnson et al (53), n=85 pyelonephritis	25	Ampicillin + gentamicin IV 1 g q6h/IV q8h → Ampicillin oral 500 mg qid	Minimum 3 days IV → 11 days oral	98	89
		vs TMP/SMX IV 160 mg/800 mg q12h + gentamicin IV q8h → TMP-SMX oral 160 mg/800 mg bid	Minimum 3 days IV → 11 days oral	100	91

**Includes cured and improved; †63% of ciprofloxacin patients given additional 17 days oral ciprofloxacin; ‡55% of ceftazidime patients given additional 12 days oral antibiotics. GI Gastrointestinal; IM Intramuscular; IV Intravenous; LRTI Lower respiratory tract infection; RTI Respiratory tract infection; SST Skin and soft tissue; TMP-SMX Trimethoprim/sulfamethoxazole; UTI Urinary tract infection*

TABLE 3
Nonrandomized studies of sequential antibiotic therapy for treatment of infection

Author (reference), Number of participants Type of infection	Mean age (years)	Regimen and dosages	Duration of therapy (days)	Overall efficacy Clinical* (%)	Overall efficacy Bacterial eradication (%)
Daly et al (12), n=32 SST, osteomyelitis, pneumonia, UTI, peritonitis, bacteremia	61	Ciprofloxacin IV 200-400 mg q8-12h → Ciprofloxacin oral 500-1000 mg q12h	5 IV → 17.5 oral	94	77
Chrysanthopoulos et al (52), n=169 pneumonia, biliary sepsis, complicated UTI	62	Ciprofloxacin IV 200 mg q8-12h → Ciprofloxacin oral 500-750 mg q12h	3.7 IV → 5.5 oral	96	
Bouza et al (55), n=68 UTI, RTI, intra-abdominal, SST, bone or joint, bacteremia	53.5	Ciprofloxacin IV 100-200 mg q12h or Ciprofloxacin oral 500-750 mg q12h or Ciprofloxacin IV 100-200 mg q12h → Oral 500-700 mg q12h	13.3 IV 11.8 oral 11.9 IV → 10.4 oral	94 overall	93
Chayakul et al (56), n=19 1° bacteremia, meningitis, intra-abdominal abscess, peritonitis, pneumonia, UTI	32	Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 500 mg q12h	6 IV → 7.5 oral	85	90
Dworkin et al (57), n=10 right-sided *Staphylococcus aureus* endocarditis in IV drug users	–	Ciprofloxacin 300 mg q12h → Ciprofloxacin oral 750 mg q12h	7 IV → 21 oral	100	100
Neu et al (58), n=60 endocarditis, osteomyelitis, RTI, UTI, SST	–	Ciprofloxacin IV 200-300 mg q12h → Ciprofloxacin IV 200-300 mg q12h / Ciprofloxacin oral 750 mg q12h	10 IV → 18 IV / 80 oral	85 overall	70 overall
Scully et al (59), n=28 osteomyelitis, septic arthritis, SST, pneumonia, UTI	55	Ciprofloxacin IV 200 -300 mg q12h → Ciprofloxacin IV 200-300 mg q12h / Ciprofloxacin oral 750 mg q12h	10 IV → 19 IV / 37 oral	87 overall	70 overall
Giamarellou et al (60), n=54 pneumonia, intra-abdominal abscess, liver abscess, SST, UTI, osteomyelitis, malignant otitis externa	53.2	Ciprofloxacin IV 200 mg q12h → Ciprofloxacin IV 200 mg q12h / Ciprofloxacin oral 750 mg q12h	IV only: 14.9 oral:10.6	91 overall	61.1
Gentry et al (61), n=100 pneumonia	57	Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h	5.7 IV → 6.9 oral	95	
Auten et al (62), n=32 skin, soft tissue	59	Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h	3.9 IV → 8.1 oral	94	
Soper et al (63), n=36 salpingitis	25	Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h	Minimum 3 days IV → 7-11 days oral	100	
Heppt et al (64), n=61 otitis externa and otitis media	43	Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h	1 IV → 7 oral	82	80
Lentino et al (65), n=21 skin, soft tissue	65	Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h	Minimum 3 IV → 5-14 oral	86	
Gelfand et al (66), n=32 complicated UTI	68	Fleroxacin IV 400 mg q24h → Fleroxacin oral 400 mg q24h	3.2 IV → 5.3 oral	91	81
Tetzlaff et al (6), n=30 osteomyelitis, septic arthritis	Pediatric age group	IV: methicillin 200 mg/kg q6h, cefazolin 60 mg/kg q6h, chloramphenicol 100 mg/kg q6h, ampicillin 100 mg/kg q6h Oral: cephalexin 100 mg/kg, penicillin V 100 mg/kg, ampicillin 100 mg/kg, cloxacillin 50 mg/kg	Osteomyelitis: 7.3 IV → 19.8 oral Septic arthritis: 1.9 IV → 17.9 oral	93	

TABLE 3 (cont'd)

Author (reference) Number of participants Type of infection	Mean age years)	Regimen and dosages	Duration of therapy (days)	Overall efficacy Clinical* (%)	Bacterial eradication (%)
Nelson et al (13), n=75 suppurative skeletal infections	? pediatric age group	Cefamandole 25 mg/kg q6h IV or Cefuroxime 25 mg/kg q8h IV → Cefaclor 150 mg/kg/day oral or Cephalexin 100 mg/kg/day oral	5.8 → 14 oral	?	?
Aronoff et al (67), n=9 osteomyelitis, septic arthritis	7.7	Ampicillin IV/sulbactam IV 50 mg/kg q6h/12.5 mg/kg q6h → Ampicillin/sulbactam 25 mg/kg q6h oral	7.1 IV → 25.9 oral	100	
Schaad et al (68), n=71 peritonsillar abscess, RTI, mastoiditis, SST, UTI	Pediatric age group	Amoxicillin/clavulanic acid 110-220 mg/kg/day divided into 4 doses IV → Amoxicillin/clavulanic acid 50-100 mg/kg/day divided into 3 doses oral	4.6 IV → 7.2 oral	100	
Buchi et al (69), n=24 RTI, SST, UTI, PID, bacteremia	–	Amoxicillin/clavulanic acid 1.2-2.2 g IV tid-qid → Amoxicillin/clavulanic acid 375-625 mg oral tid-qid	? IV / 7.9 IV 7.8 oral	97	94

IV Intravenous; PID Pelvic inflammatory disease; RTI Respiratory tract infection; SST Skin and soft tissue; UTI Urinary tract infection

dosing, while slightly higher compliance rates were seen when medication was given once daily (87%). When dosage frequency was increased to four times a day, compliance rates dropped dramatically, ie, from 87% to 39%.

Even if the patient is compliant, therapeutic failures may still occur because of drug interactions that decrease the bioavailability of oral antibiotics. It is important that all prescription medications be reviewed with the patient at the time of discharge from hospital to ensure that no untoward drug interactions occur while the antibiotics are being taken at home. It is also important to review the use of any nonprescription agents. For example, antacids have been shown to reduce the absorption of oral quinolones, tetracycline, metronidazole and cefpodoxime proxetil; thus, patients should be advised to separate antacid use from ingestion of these antibiotics by at least 2 h (23). The use of oral iron preparations should also be avoided in patients being treated with quinolones and tetracyclines because iron decreases the absorption of these drugs (24). Ingestion of milk and other dairy products can also interfere with the absorption of oral tetracycline and, to a lesser extent, of quinolones (25).

CRITERIA FOR SELECTION OF PATIENTS AND DRUGS FOR SAT

Physicians have always been more comfortable using parenteral rather than oral drugs when treating serious infection, owing to concerns about drug absorption, bioavailability, and serum and tissue levels when oral agents are used. In the selection of patients for conversion to oral therapy, several criteria should be fulfilled: the patient should be hemodynamically stable, able to ingest and swallow oral drugs and should have a functioning gastrointestinal tract. Yet, although oral antimicrobial activity can often be considered as early as three days after initiation of intravenous therapy in stable patients, some individuals are not given oral therapy until they are discharged, ie, usually after at least seven days of intravenous treatment.

There are numerous reports in the literature of the successful use of intravenous followed by oral antibiotics for treatment of serious infections. Many involve intravenous to oral sequencing within the same class of drugs, while some involve a change in drug class. Among the conditions treated with SAT are pneumonia (both community and hospital acquired), pyelonephritis, septic arthritis, osteomyelitis, and skin and skin structure infections.

If the above criteria are fulfilled, the next step is to select the antimicrobial that is most appropriate. The main therapeutic objective in changing from intravenous to oral therapy is to obtain serum and tissue antimicrobial activity that is comparable with that obtained with the intravenous formulation (26,27). Many oral agents have bioavailabilities that are similar to those of their parenteral forms. These include such drugs as metronidazole, clindamycin, chloramphenicol, fluconazole and ciprofloxacin (10,28-32). Several of these drugs have virtually equivalent bioavailability whether given intravenously or orally.

Use of these drugs as part of a sequential therapy regimen

can help to alleviate the physician's concerns about suboptimal drug concentrations when the switch to oral therapy is made, because it is generally accepted that these oral agents provide adequate therapeutic efficacy (10,11,27). Some antibiotics with oral bioavailabilities lower than those of their intravenous formulations have nevertheless been useful in sequential therapy. Such is the case for trimethoprim-sulfamethoxazole, ampicillin and cefuroxime axetil (9,10, 33).

Much has been written about the pharmacokinetics of intravenous and oral ciprofloxacin supporting the use of the oral form in intravenous to oral sequencing (30,31,34,35). For example, with an average unimpeded bioavailability of 75% (in the absence of substances that interfere with absorption), an oral dose of 500 mg ciprofloxacin provides an amount of drug equivalent (ie, statistically similar to the area under the curve) to that obtained with a 400 mg intravenous dose (36).

Other quinolones, such as ofloxacin (not available parenterally in Canada), also have nearly identical pharmacokinetic characteristics when given intravenously and orally, and all quinolones appear to have high volumes of distribution and relatively low protein binding (31). Most quinolones attain tissue concentrations that exceed the minimal inhibitory concentration values of the common aerobic pathogens (37).

When selecting an oral agent, the physician should take into account a number of factors including bioavailability, clinical efficacy, tolerability and cost.

EVIDENCE SUPPORTING SAT

Rules of scientific evidence that can be used to assess published data have been developed and published as part of a series of clinical epidemiology rounds (38). Six criteria are used to assess articles and to determine the validity and applicability of the results. These are:

1. Was the assignment of patients to treatment truly randomized?
2. Were all clinically relevant outcomes reported?
3. Were the study patients recognizably 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 at its conclusion?

A literature search revealed 32 published studies of infections treated using SAT. Of these, 13 were randomized controlled trials and 19 were nonrandomized. These studies are summarized in Tables 2 and 3, respectively.

The rules of evidence "constitute applied common sense and are designed to maximize the efficiency as well as the accuracy" of one's journal reading (38). With this in mind, the articles were first stratified into those that would be subjected to the rules of evidence and those that would not. Since the critical issue is whether SAT would perform as well as standard therapy, the standard, or control arm of a comparative study, ideally should consist of intravenous therapy. If both the experimental and control arms use SAT, the issue is confounded. Also, since the random assignment of patients minimizes much of the bias associated with nonrandomized clinical trials, use of a randomized control design is essential. Of the 32 papers, only six meet these criteria (Table 4). The rest are either randomized controlled trials, but with inappropriate control arms, or are nonrandomized trials.

For the purposes of this paper, clinically relevant outcomes were success versus failure of clinical response. Success included both cure and improvement. Bacteriological response per se was not considered as important and was viewed as a surrogate marker. Statistical significance has no bearing on whether the result is important, but simply refers to the likelihood that a particular result was obtained by chance. Consideration of statistical issues took into account whether statistical tests were done and, if so, whether a difference was found that was associated with $P<0.05$ or, if not statistically significant, whether the sample size was large enough to rule out a type II error.

Clinical significance, on the other hand, does relate to the importance of a particular finding. A difference in outcomes between treated and control patients "becomes clinically significant when it leads to changes in clinical behavior" (38). In the case of SAT versus conventional therapy, either a difference in favour of SAT or no difference between them is relevant since, in the latter instance, the implication is that by using intravenous to oral switchover money is saved, there is improvement in the quality of life for the patient, or both.

Among these six papers, the main flaws are in the statistical considerations. From the point of view of experimental design, the best study was that of Kalager et al (39). The control arm consisted of two drugs – both effective against most aerobic Gram-negative bacillary pathogens. The sample size was the largest, and the statistical analysis was the most rigorous. Only three of the six studies (40-42) examined patients with only one type of infection, while the other three (39,42,43) studied patients with a variety of infections, eg, lower respiratory tract, urinary tract, and skin and soft tissue infections.

In one trial (not included in any of the tables) both comparative and noncomparative study arms were used (45). The comparative arm randomized patients to either ofloxacin or a third-generation cephalosporin (ceftazidime or ceftriaxone) for treatment of pneumonia, urinary tract infection, or skin and soft tissue infection. However, of the 22 patients randomized to receive ofloxacin, only eight were given sequential intravenous to oral treatment. It is not clear from the paper whether a direct comparison was made between this small group of eight patients and those receiving intravenous therapy alone with a third-generation cephalosporin. The authors do, however, state that "none of the eight subjects who were randomized to ofloxacin and who received initial parenteral therapy deteriorated when switched to oral ofloxacin therapy." In the noncomparative study arm, patients were treated with oral ofloxacin only.

TABLE 4
Clinical trials complying with rules of scientific evidence

Author (reference)	Randomized controlled trial	Study patients similar to your own	Consideration of issues		Manoeuvre feasible in your practice	All patients accounted for
			Statistical	Clinical		
Kalager et al (37)	Yes	Yes	Yes	Yes	Yes	Yes
Dominguez et al (38)	Yes	Yes	No	Yes	Yes	Yes
Gaut et al (41)	Yes	Yes	No	Yes	Yes	Yes
Fass et al (42)	Yes	Yes	No	Yes	Yes	Yes
Cox (39)	Yes	Yes	No	Yes	Yes	Yes
Gangji et al (40)	Yes	Yes	No	Yes	Yes	Yes

IMPLEMENTATION OF SAT

In hospitals where SAT programs are particularly successful, they are usually developed jointly by the infectious disease and pharmacy departments working in conjunction with the Pharmacy and Therapeutics Committee. To facilitate the introduction of SAT into a particular hospital, the appropriate infrastructure must first be created. To do this, the collaborative efforts of members of the pharmacy, microbiology, infectious disease, nursing and administration departments are required. The multidisciplinary perspective provided by these groups allows the successful implementation of recommendations made by the Pharmacy and Therapeutics Committee.

Integral to this program is the use of 'sequential therapy reminders'. These educational tools, developed at the Vancouver Hospital and Health Sciences Centre, are highly visible printed forms with the necessary information on them (46). At the Henderson General Division of the Hamilton Civic Hospitals, for example, when a patient is started on a drug intravenously for which an oral preparation is also available, the pharmacist sends the sequential therapy reminder, printed on bright yellow paper, to the ward together with the intravenous drug. The ward nurse then attaches this yellow sheet to the front of the patient's chart, where it remains until the intravenous drug is either discontinued or changed to an oral form. An example of such a form is provided in Figure 1. Information relevant to SAT is printed on the form, thereby providing an educational service as well as a reminder to the physician that oral therapy should be considered.

Some of the challenges in the implementation of SAT are resistance to change on the part of medical colleagues; a perceived increase in workload by those involved in managing the SAT program; and physician reluctance because of medical and/or legal concerns. Experience with SAT programs has shown that they are, in fact, relatively easy to implement and are readily accepted by physicians and other health care personnel provided that the appropriate legwork is done and the necessary infrastructure is first created. To help implement SAT, it is imperative that colleagues be educated concerning antimicrobial costs, support of chiefs of services as well as colleagues be enlisted, and continuous surveillance and feedback to colleagues regarding the success of the program be assured.

CONCLUSIONS

Since the 1970s, medical literature has documented the clinical efficacy of converting patients from intravenous antibiotic therapy to oral antibiotic therapy as early as three days after initiation of intravenous therapy in stable patients. Yet, such patients traditionally have not been given oral therapy until hospital discharge, ie, usually after at least seven days of intravenous treatment. The use of drugs that have virtually equivalent bioavailability in intravenous and oral forms, such as metronidazole, clindamycin, fluconazole and ciprofloxacin, can help alleviate physician concerns about suboptimal drug concentrations when converting to oral therapy, and can perhaps increase the acceptance of SAT. A critical review of the medical literature supports the role of SAT. What is also clear, however, is that further studies are necessary to determine the ideal time for intravenous to oral conversion and factors that may limit or impede the use of oral therapy.

We conclude that SAT is not only an important tool for realizing substantial cost savings in the treatment of patients with serious infections, but can greatly add to patient comfort and

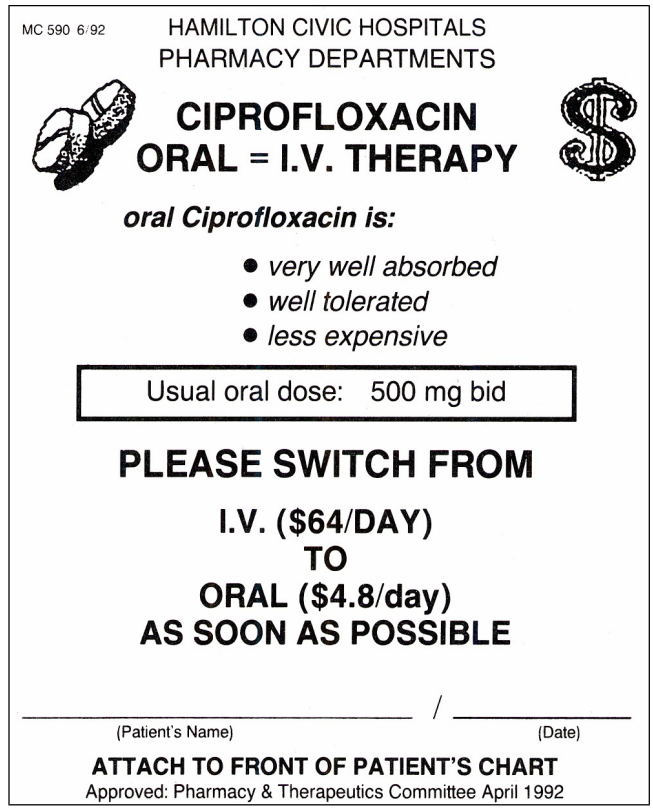

Figure 1) *An example of sequential therapy reminders (reference 46)*

productivity. Hospitals must play a proactive educational role in implementing SAT programs if this important therapeutic strategy is to become the future standard of care.

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