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.
OVER THE PAST TWO DECADES, OUR THERAPEUTIC ARMAMEN-
tarium has been greatly expanded with agents that pro-
vide excellent antimicrobial activity combined with improved
pharmacokinetic features and improved adverse effect pro-
files. 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 intrave-
nous therapy and oral therapy using agents that do not com-
promise therapeutic efficacy.

This paper reviews some of the economic issues associ-
ated 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 dur-
ing 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 Can-
da. 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 strate-
gies have been developed and implemented and may be
classified as ‘educative and persuasive’, ‘facilitative’ and ‘r-
estrictive’ strategies (3). The following list includes most of
these:

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

It is beyond the scope of this article to deal with all these
cost containment strategies; our purpose is to focus specifi-
cally 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 dem-

strated the efficacy and safety of initial treatment with par-
enteral antibiotics followed by conversion to oral agents as
soon as the acute signs and symptoms of infection were con-
trolled (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 combina-
tion 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 intra-
muscular 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’, ‘switc-
ing’ 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 dif-
ferent drugs (12,13). Streamlining has also been used to de-
ote the change from combination therapy to monotherapy
(14). It might, therefore, avoid confusion by establishing a
common terminology for describing conversion from intrave-
nous 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 intrave-
nous 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 con-
version from intravenous to oral antimicrobials. Some physi-
cians 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 intrave-
nous drugs. This reluctance has, unfortunately, fostered the
unnecessarily prolonged use of intravenous medications in
the hospital setting for treatment of infections that could bene-
fit 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, re-
ferred to as the acquisition cost, and the secondary costs re-
lated 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*

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

*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 waste; 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 3 x 10^6 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 from converting 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>
<thead>
<tr>
<th>Author (reference), Number of participants</th>
<th>Mean age (years)</th>
<th>Type of infection</th>
<th>Regimen and dosages</th>
<th>Duration of therapy (days)</th>
<th>Overall efficacy Clinical (%)</th>
<th>Bacterial eradication (%)</th>
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<tbody>
<tr>
<td>Kaloger et al (39), n=281</td>
<td>61</td>
<td>Septicemia, LRTI, UTI, GI</td>
<td>Ciprofloxacin IV 200-400 mg q12h → Ciprofloxacin oral 750 mg bid</td>
<td>5.8 IV → 6.4 oral</td>
<td>84</td>
<td>61</td>
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<td>Dominguez et al (40), n=39</td>
<td>49.9</td>
<td>Skin, soft tissue</td>
<td>Ciprofloxacin IV 200 mg q12h vs Ceftazidime/tobramycin IV 1.5 g q8h based on levels</td>
<td>9.5 IV</td>
<td>84</td>
<td>66</td>
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<tr>
<td>Gaut et al (43), n=32</td>
<td>65</td>
<td>Bone &amp; joint, intra-abdominal, RTI, UTI, SST, wound, bacteremia</td>
<td>Ciprofloxacin IV 200-300 mg q12h → Ciprofloxacin oral 500-750 mg q12h vs Ceftazidime IV 1-1.5 g q8-12h</td>
<td>Minimum 2 days IV</td>
<td>82</td>
<td>53.8</td>
</tr>
<tr>
<td>Fass et al (44), n=52</td>
<td>46</td>
<td>LRTI, UTI, SST, endocarditis, sepsis, mastoiditis</td>
<td>Ciprofloxacin IV 200-300 mg q12h vs Ceftazidime IV 1-2 g q8-12h</td>
<td>3-6 IV → 13-16 oral</td>
<td>81</td>
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</tr>
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<td>Cox (41), n=77</td>
<td>61</td>
<td>Complicated UTI</td>
<td>Ciprofloxacin IV 200 mg q12h vs Ceftazidime IV 500 mg q8h</td>
<td>13.5 IV</td>
<td>71</td>
<td></td>
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<td>Hirata-Dulas et al (47), n=50</td>
<td>68</td>
<td>Nursing home acquired LRTI</td>
<td>Ciprofloxacin IV 200-400 mg q12h vs Ceftriaxone IV 2 g</td>
<td>4 IV → 6 oral</td>
<td>100</td>
<td>100</td>
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<td>Khan and Basir (48), n=122</td>
<td>79.3</td>
<td>Lower RTI 58 overall (not differentiated by treatment arm)</td>
<td>Ciprofloxacin IV 200-300 mg q12h vs Ceftazidime IV 1-2 g q12h</td>
<td>7.4 IV → 17.1 oral</td>
<td>76</td>
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</tr>
<tr>
<td>Menon et al (49), n=37</td>
<td>32</td>
<td>Pneumonia</td>
<td>Ciprofloxacin IV 200 mg q12h vs Ceftazidime IV 1-2 g q8h</td>
<td>9 IV → 10.6 oral</td>
<td>97</td>
<td>87</td>
</tr>
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<td>Peacock et al (50), n=39</td>
<td>58</td>
<td>UTI, LRTI, bone, joint, skin, soft tissue, gall bladder, bacteremia</td>
<td>Ciprofloxacin IV 200 mg q12h vs Ceftazidime IV 1-2 g q8h</td>
<td>9.9 IV → 12.1 oral</td>
<td>91</td>
<td></td>
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<tr>
<td>Gangji et al (42), n=65</td>
<td>66</td>
<td>Gram-negative septicemia</td>
<td>Ciprofloxacin IV 200 mg q12h vs Amoxicillin/clavulanic IV 2.2 g bid</td>
<td>3 IV → 7-11 oral</td>
<td>97.2</td>
<td>94</td>
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<td>Feist (51), n=92</td>
<td>62</td>
<td>LRTI</td>
<td>Ciprofloxacin IV 200 mg q12h vs Amoxicillin/clavulanic IV 2.2 g bid</td>
<td>7-11 IV</td>
<td>93.1</td>
<td>96</td>
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<td>Khajotia et al (52), n=92</td>
<td>63</td>
<td>LRTI</td>
<td>Ofloxacin IV 200 mg bid vs Amoxicillin/clavulanic IV 2.2 g bid</td>
<td>Minimum → 4-7 oral</td>
<td>100</td>
<td>95</td>
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<td>Johnson et al (53), n=85</td>
<td>25</td>
<td>Pyelonephritis</td>
<td>Ciprofloxacin IV 200 mg bid vs Amoxicillin + gentamicin IV 1 g q8h/IV 68h</td>
<td>Minimum → 11 days</td>
<td>98</td>
<td>89</td>
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<tr>
<td>Author (reference), Number of participants</td>
<td>Type of infection</td>
<td>Mean age (years)</td>
<td>Regimen and dosages</td>
<td>Duration of therapy (days)</td>
<td>Clinical* (%)</td>
<td>Overall efficacy (%)</td>
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<td>Daly et al (12), n=32</td>
<td>SST, osteomyelitis, pneumonia, UTI, peritonitis, bacteremia</td>
<td>61</td>
<td>Ciprofloxacin IV 200-400 mg q8-12h → Ciprofloxacin oral 500-1000 mg q12h</td>
<td>5 IV → 17.5 oral</td>
<td>94</td>
<td>77</td>
</tr>
<tr>
<td>Chrysanthopoulos et al (52), n=169</td>
<td>Pneumonia, biliary sepsis, complicated UTI</td>
<td>62</td>
<td>Ciprofloxacin IV 200 mg q8-12h → Ciprofloxacin oral 500-750 mg q12h</td>
<td>3.7 IV → 5.5 oral</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>Bouza et al (55), n=68</td>
<td>UTI, RTI, intra-abdominal, SST, bone or joint, bacteremia</td>
<td>53.5</td>
<td>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</td>
<td>13.3 IV → 11.8 oral overall</td>
<td>94</td>
<td>93</td>
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<td>Chayakul et al (56), n=19</td>
<td>1° bacteremia, meningitis, intra-abdominal abscess, peritonitis, pneumonia, UTI</td>
<td>32</td>
<td>Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 500 mg q12h</td>
<td>6 IV → 7.5 oral</td>
<td>85</td>
<td>90</td>
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<td>Dworkin et al (57), n=10</td>
<td>Right-sided Staphylococcus aureus endocarditis in IV drug users</td>
<td></td>
<td>Ciprofloxacin 300 mg q12h → Ciprofloxacin oral 750 mg q12h</td>
<td>7 IV → 21 oral</td>
<td>100</td>
<td>100</td>
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<td>Neu et al (58), n=60</td>
<td>Endocarditis, osteomyelitis, RTI, UTI, SST</td>
<td></td>
<td>Ciprofloxacin IV 200-300 mg q12h</td>
<td>18 IV → 80 oral overall</td>
<td>85</td>
<td>70</td>
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<tr>
<td>Scully et al (59), n=28</td>
<td>Osteomyelitis, septic arthritis, SST, pneumonia, UTI</td>
<td>55</td>
<td>Ciprofloxacin IV 200-300 mg q12h → Ciprofloxacin oral 750 mg q12h</td>
<td>19 IV → 37 oral overall</td>
<td>87</td>
<td>70</td>
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<tr>
<td>Giamarelou et al (60), n=54</td>
<td>Pneumonia, intra-abdominal abscess, liver abscess, SST, UTI, osteomyelitis, malignant otitis externa</td>
<td>53.2</td>
<td>Ciprofloxacin IV 200 mg q12h → Ciprofloxacin oral 750 mg q12h</td>
<td>IV only: 14.9 oral 10.6</td>
<td>91</td>
<td>61.1</td>
</tr>
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<td>Gentry et al (61), n=100</td>
<td>Pneumonia</td>
<td>57</td>
<td>Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h</td>
<td>5.7 IV → 6.9 oral</td>
<td>95</td>
<td>95</td>
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<tr>
<td>Auten et al (62), n=32</td>
<td>Skin, soft tissue</td>
<td>59</td>
<td>Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h</td>
<td>3.9 IV → 8.1 oral</td>
<td>94</td>
<td>94</td>
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<tr>
<td>Soper et al (63), n=36</td>
<td>Salpingitis</td>
<td>25</td>
<td>Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h</td>
<td>Minimum 3 days IV 7-11 days oral</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Hepp et al (64), n=61</td>
<td>Otitis externa and otitis media</td>
<td>43</td>
<td>Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h</td>
<td>1 IV → 7 oral</td>
<td>82</td>
<td>80</td>
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<tr>
<td>Lento et al (65), n=21</td>
<td>Skin, soft tissue</td>
<td>65</td>
<td>Ofloxacin IV 400 mg q12h → Ofloxacin oral 400 mg q12h</td>
<td>Minimum 3 days IV 5-14 oral</td>
<td>86</td>
<td>86</td>
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<tr>
<td>Gelfand et al (66), n=32</td>
<td>Complicated UTI</td>
<td>68</td>
<td>Fleroxacin IV 400 mg q24h → Fleroxacin oral 400 mg q24h</td>
<td>3.2 IV → 5.3 oral</td>
<td>91</td>
<td>81</td>
</tr>
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<td>Tetzlaif et al (6), n=30</td>
<td>Osteomyelitis, septic arthritis</td>
<td></td>
<td>Pediatric age group IV: methicillin 200 mg/kg q6h, cefazolin 60 mg/kg q6h, chloramphenicol 100 mg/kg q6h, ampicillin 100 mg/kg q6h</td>
<td>Osteomyelitis: 7.3 IV → 19.8 oral</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Fleenor et al (67), n=2</td>
<td>Skin, soft tissue</td>
<td></td>
<td></td>
<td>Septic arthritis: 1.9 IV → 17.9 oral</td>
<td></td>
<td>81</td>
</tr>
</tbody>
</table>
dos ing, 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 (i.e., 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 (cefazidime 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.
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 leg-work 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


