Prophylactic Use of the New Quinolones for Prevention of Nosocomial Infection in the Intensive Care Unit

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Summary

The new quinolone antimicrobial agents, particularly those with less activity against anaerobes, selectively prevent colonisation of the alimentary tract by Gram-negative bacilli and staphylococci without substantially affecting the normal anaerobic flora, which preserve the colonisation resistance of the gut. These properties ideally position this class of antibacterial agent for selective decontamination of the digestive tract (SDD) in the prevention of nosocomial infection. The rationale for this procedure is based on the presumption that a significant proportion of infections in compromised patients are endogenous in origin, arising from the host's own microbial flora. If this colonisation by potentially pathogenic microflora within the normal flora can be significantly reduced without being replaced by other more pathogenic microorganisms, the risk of endogenous infection should be minimised.

The quinolones have proved to be ideal agents for use in preventing infection in bone marrow transplant and other neutropenic patients. They have been used for SDD in the general intensive care unit population, although the technique has not received widespread acceptance. There have been only 4 reported randomised studies using quinolones as part of SDD regimens and only 301 patients have been evaluated. Although the incidence of ventilator-associated pneumonia has been significantly reduced from 36 to 15%, no effect has been shown on mortality. The cost of using SDD is significantly less with the quinolones than with other regimens, and induction of resistance has not been noted.

The new quinolones, and in particular the more recently developed agents with extended Gram-positive activity, appear to be ideally suited for SDD, and their careful evaluation in further large, well designed trials is warranted.

The use of prophylactic antibacterials, especially when required for a prolonged period, always causes concern regarding the induction of resistance. This particularly applies in the intensive

care and burns units, which are usually regarded as 'sumps' of multiresistant microorganisms. This fear of antibacterial prophylaxis in the intensive care unit (ICU) was fuelled by the early studies of

Klick et al.,^[1] who used aerosolised endotracheal polymixin in ventilated patients. Their promising initial results showed that the incidence of nosocomial pneumonia was reduced from 40 to 10%; however, within a year, a second paper by the same group reported problems with infections caused by polymixin-resistant organisms and other unusual pathogens, with a higher patient mortality than previously, and it was concluded that this was a 'dangerous' practice.^[2]

With the increasing complexity of the diseases being treated in the ICU and more aggressive therapy being used for patients with haematological malignancies, nosocomial infections have become increasingly prevalent and significantly contribute to mortality. While exogenous infections could be largely controlled by handwashing and aseptic techniques, it became apparent that most of these infections were endogenous rather than exogenous in origin, and thus would lend themselves to being controlled by prophylactic antibacterial therapy.^[3,4] This led to early attempts at total decontamination, with complete control of the environment, including the use of laminar flow nursing rooms as well as sterile foods in bone marrow transplant patients, with some initial success.^[5] It soon became obvious, however, that the 'normal' host flora played an important role in preventing colonisation by other, more pathogenic, microorganisms; thus, the antibacterial regimens were modified, with the aim of leaving this largely anaerobic flora intact.^[6] Antibacterials such as polymixin, cotrimoxazole (trimethoprim-sulfamethoxazole) and the new quinolones, which exert their main activity against the aerobic Gram-negative microorganisms and therefore have minimal effect on this 'colonisation resistance' flora, have all proved useful in this setting. The use of these drugs is termed selective decontamination (SD).^[7]

The success of SD in this group of patients soon led to its introduction in the ICU, where the technique is known as selective decontamination of the digestive tract (SDD) and has received wide acceptance. Nevertheless, there is controversy surrounding its lack of effect on mortality, although it de-

creases the incidence of ventilator-associated pneumonia.^[8]

1. Rationale for SDD

In ICUs where exogenous infection has largely been eliminated by usual infection control measures, the incidence of nosocomial infection is 15 to 50%, depending on the population. This infection is usually of direct endogenous origin, although the microorganisms are frequently acquired in hospital and are not necessarily the patient's own normal flora. These microorganisms first colonise the alimentary tract and, in intubated patients, this subsequently leads to bronchial acquisition and colonisation, often within 24 to 48 hours of admission. Given time, a large inoculum of pathogenic microbes and depressed humoral defences, this colonisation will frequently lead first to bronchial infection and then spread to the lung parenchyma.^[4,9,10] While normal nursing procedures such as mouth and endotracheal tube and cuff care combined with limited sedation, gastric acid maintenance and mobilisation with physiotherapy will help to prevent the onset of pneumonia, elimination of Gram-negative and other highly pathogenic colonisers of the alimentary tract should go a long way towards providing complete protection.^[11,12]

2. Antibacterial Regimens in SDD

The properties of the antimicrobial agents used for SDD are of vital importance for the success of this technique. Ideally, they should eliminate the potentially pathogenic microorganisms from the alimentary tract without influencing the largely anaerobic normal flora, which provide colonisation resistance against other microorganisms that may be unaffected by the SDD regimen and more dangerous than the original microorganisms. In addition, the SDD regimen should not induce resistance, as it is often required for a prolonged period and infections with resistant organisms may then develop.

The quinolones, particularly norfloxacin, have been widely used for SD in patients with

Table I. Influence of orally administered norfloxacin on intestinal microflora in healthy volunteers^[16-18] and patients being treated for urinary tract infections^[19]

Reference no.	No. of volunteers/ patients	Dose (mg/day)	Test day ^a	Norfloxacin concentrations		Effects on faecal microorganisms		
				serum (peak, mg/L)	faeces (mg/kg)	Enterobacteriaceae	enterococci	anaerobes
18	10	200 × 2	7	0.75 ± 0.15	303-1906	+++	NC	NC
16	10	400 × 2	8	1.58 ± 0.37		+++	NC	NC
17	6	200 × 2	5	1.0 ± 0.3	2271 ± 859	+++	NC	NC
17	6	400 × 2	6	1.9 ± 0.9		+++	+	NC
19	8	400 × 2	90	ND	1756	+++	+	NC

a Duration of administration of norfloxacin prior to microbiological sampling.

Abbreviations and symbols: CFU = colony-forming units; NC = no significant change; ND = not done; +++ = very strong suppression (>4 log₁₀ CFU/g faeces); + = mild suppression (~2 log₁₀ CFU/g faeces).

Table II. Spectrum of *in vitro* activity of ofloxacin, ciprofloxacin and sparfloxacin

Organism	MIC ₉₀ (mg/L)		
	sparfloxacin	ciprofloxacin	ofloxacin
<i>Streptococcus pneumoniae</i>	0.25-1	0.5-4	2-8
<i>Staphylococcus aureus</i>	0.06-0.25	0.25-2	0.5-1
<i>Enterococcus faecalis</i>	0.5-2	1-4	2-4
<i>E. faecium</i>	0.39-1	2-4	6.25
<i>Klebsiella pneumoniae</i>	0.06-0.5	0.03-1	0.25-1
<i>Proteus</i> spp.	0.25-1	0.01-0.5	0.12-1.56
<i>Acinetobacter</i> spp.	0.01-0.12	0.12-1	
<i>Pseudomonas aeruginosa</i>	1-8	0.25-4	4-16
<i>Bacteroides fragilis</i>	1-2	4-32	8-12.5
<i>Prevotella</i> spp.	8-16	16	8

haematological disease and all have been shown to be effective. They have ideal properties in terms of their spectrum of activity, which covers most Gram-negative microorganisms and leaves the Gram-positive microorganisms, particularly the anaerobes, untouched.^[13,14] Numerous studies have evaluated these effects, as well as antibacterial concentrations in the faeces, and these results are summarised in table I.^[7,15-17] Interestingly, at higher doses there may be a greater effect on problematic organisms such as the enterococci and it may be possible to use this property to good effect with SDD regimens.^[14,17] The newer agents (such as sparfloxacin) with better Gram-positive coverage may have a role in this area, but this extended spectrum of activity usually includes the anaerobes (table II).

The quinolones have the additional advantage of being much cheaper than other regimens used for SDD and, in addition, they provide the systemic effect needed for rapid action. They are also much more easily administered than the standard topical oropharyngeal paste and enteral regimens. The most commonly used regimen popularised by Van Saene and Stoutenbeek consists of tobramycin, polymixin E and amphotericin B, which is given both enterally by nasogastric tube and by oropharyngeal paste every 6 hours, with intravenous cefotaxime every 8 hours for the first 5 days.^[20] This regimen also provides very specific cover against Gram-negative and yeast species, and numerous studies have demonstrated the efficiency with which it decontaminates the alimentary tract. Although there has been concern about the develop-

ment of resistance to the agents used, this has been demonstrated in only a small number of studies: in one, increasing resistance to tobramycin occurred among *Staphylococcus aureus* isolates and, in another, an increasing number of isolates of *Acinetobacter* spp. was found.^[21,22] As these potent agents are not absorbed they can be used in dosages far exceeding the minimum inhibitory concentrations of resistant microorganisms, and cover against *Proteus* and *Morganella* spp. is provided by the tobramycin. However, some investigators have reported increasing colonisation by staphylococci and enterococci, which has not resulted in infection but is of concern.^[23,24]

Cotrimoxazole has been used either alone (mostly in patients with haematological disease), or as part of SDD regimens, where it has been shown to be effective.^[25] It has the additional advantage of providing systemic effects, as well as prophylaxis against *Pneumocystis carinii*, but is most likely to lead to resistance if used alone.^[7]

Vancomycin has also been combined in a regimen with polymixin E and amphotericin B, effectively broadening the cover against staphylococci and enterococci.^[26] The influence of this regimen on the anaerobic flora may well limit colonisation resistance; however, the effect of this has not been adequately explored.

Thus, it would appear that there is no ideal agent or combination of agents for SDD at present; any new agent that has largely Gram-negative cover with some activity against staphylococci and en-

terococci and minimal effect on the anaerobes should be considered for use in this setting.

3. Efficacy of SDD

The efficacy of SDD is possibly one of the most contentious areas in critical care at present; despite more than 3 major meta-analyses of data from over 3000 randomised patients no consensus exists, and its role is still debatable.^[8,27,28] There is some agreement on its effect in decreasing the incidence of lower respiratory tract infections. It would appear that between 5 and 9 (mean 6) patients need to be treated to prevent one respiratory infection, and the higher the background incidence of infection, the easier it is to show a positive effect of SDD. The influence on mortality is inexplicably less clear, and it would seem that 13 to 139 (mean 23) patients need to be treated to prevent one death.^[8] A criticism of these meta-analyses is that there are many discrepancies in diagnostic and other clinical criteria between the reported studies, most of which are poorly designed. Perhaps one of the most important factors is that the various antibacterial regimens may differ significantly in efficacy, but this is not taken into account.

4. Role of Quinolones in SDD

The quinolones have firmly established their place in SD in severely immunocompromised patients with haematological disease, from the perspective of both efficacy in reducing mortality and of the cost of the regimen. Unfortunately, their role

Table III. Results of clinical trials of selective decontamination of the digestive tract (SDD) using quinolones in the decontamination regimen

Study population	No. of patients (SDD/control)	SDD regimen	Methodology score ^a	Rate of infection (%)		Mortality (%)	
				SDD	control	SDD	control
T, S, M ^[29]	28/60	P, NOR, AMB, C	12	4	48	14	20
T, S, M ^[30]	193/185	OFL, AMB	11	11	22	24	22
T, S, M ^[31]	55/57	P, NOR, AMB	12	13	46	40	58
S ^[32]	25/23	NOR, NY	15	56	100	52	43
Total	301/325		12.5	15	36	29	29

a Heyland et al.^[28]
Abbreviations: AMB = amphotericin B; C = cefotaxime; M = medical; NOR = norfloxacin; NY = nystatin; OFL = ofloxacin; P = polymixin E; S = surgical; T = trauma.

in the ICU has been inadequately investigated and only 4 controlled studies have been reported.^[29-32] These studies, which were of adequate scientific standard as described by Heyland et al.,^[28] reported on the use of quinolones, usually as part of multiple drug regimens. All 4 studies (3 with norfloxacin and 1 with ofloxacin) demonstrated a significant reduction in the incidence of infection that was possibly greater than that of the other regimens (table III). Increased antibacterial resistance was not detected. As in previous studies, the effects on mortality were equivocal. In a further noncomparative study using norfloxacin, sulfamethoxypyrazine, and amphotericin B over three 6-month periods, the incidence of infection was reduced from 75 to 30%. This was largely related to a decrease in respiratory infections and septicæmia caused by Enterobacteriaceae and *Pseudomonas* spp. Again, no effect on mortality was observed over the period of SD.^[33]

The major difference between SD for patients with haematological disease and SDD in the ICU is that the patients in the ICU frequently require prophylaxis for a much longer period. The effectiveness of a quinolone regimen in this area may therefore be limited by the potential of these agents to induce antimicrobial resistance after prolonged use. A recent study examining the risk factors in 68 patients who had developed infection with quinolone-resistant microorganisms found that prior quinolone therapy was an independent risk factor.^[34] When norfloxacin was used prophylactically in a group of 31 hospitalised alcoholic cirrhotic patients in an attempt to decrease the risk of spontaneous bacterial peritonitis, no selection of resistant organisms occurred in 15 patients; however, in the remaining 16, resistant faecal organisms were detected from the second week of treatment. These included *S. aureus* (4), coagulase-negative staphylococci (6), *Citrobacter freundii* (4), *Enterobacter* spp. (3), *Klebsiella oxytoca* (2), *Providencia rettgeri* (1) and untypeable streptococci (6).^[33] Other studies have suggested that ciprofloxacin may in fact increase the incidence of candidal colonisation and infection.^[14]

5. Conclusions

The quinolone antibacterials, including norfloxacin, ofloxacin, ciprofloxacin and pefloxacin, are all useful agents for SD in severely compromised agranulocytopenic patients. Their use in SDD in ICU patients has been inadequately investigated, and although these 'older' new quinolones show much promise in this area the newer agents with enhanced Gram-positive cover may be even better, provided that they have only a minimal effect on colonisation resistance. These agents warrant further evaluation in large, well designed trials.

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