The Growing Problem of Nosocomial Bacterial Resistance
An Epidemiological Perspective with Emphasis on the Fluoroquinolones

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Summary

Today’s nosocomial microbiological environment is characterised by increasing numbers of drug-resistant bacteria, notably methicillin-resistant staphylococci, glycopeptide-resistant enterococci, extended-spectrum β-lactamase-producing Enterobacteriaceae and hyperproducers (or stably derepressed mutants) of AmpC β-lactamases. Although the precise prevalence of these pathogens varies between institutions and between countries, they are now sufficiently widespread to pose a major clinical and therapeutic problem.

Treatment options for these pathogens, especially multidrug-resistant Gram-positive bacteria, are limited. However, the new broad-spectrum fluoroquinolone agents may have some potential against these and other pathogens. An important factor likely to influence the efficacy of these agents is the degree of fluoroquinolone resistance in the nosocomial setting. Infection control measures and the rational use of the fluoroquinolones as a class must be encouraged to ensure that the full potential of these valuable agents is realised.
or topoisomerase IV, resulting in decreased affinity for the quinolones.
2. Decreased accumulation in the cell as a result of mutations to regulatory genes controlling bacterial permeability (seen in Gram-negative bacteria only).
3. Decreased accumulation in the cell as a result of efflux mechanisms. This mechanism of resistance can affect multiple classes of antibiotics, for example as in \textit{P. aeruginosa}.\cite{6}

All mechanisms of resistance decrease bacterial susceptibility to the fluoroquinolones by about 4-fold.\cite{7} Usually 2, or even 3, mechanisms need to be expressed simultaneously in order to achieve high levels of resistance (e.g. increased efflux coupled with \textit{gyrA} mutation, or 2 mutations in \textit{gyrA}) \cite{fig. 1}.

2. Resistance Patterns in the Nosocomial Environment

2.1 Gram-Positive Pathogens

\textbf{2.1.1 Current Status}

\textbf{Staphylococci}

Methicillin-resistant staphylococci and, more recently, vancomycin-resistant enterococci have emerged worldwide as a major clinical and therapeutic problem in today’s nosocomial environment. The first strain of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) was detected in Europe in 1961, only 2 years after the introduction of the semisynthetic penicillins (methicillin and oxacillin). These penicillins were introduced to overcome the problem of penicillin resistance already observed in \textit{S. aureus}.\cite{8} Reported frequencies of MRSA now range from 1 to 2% in northern Europe to 29% in the US and to more than 30% in Spain, France and Italy.\cite{9} MRSA are present not only in large hospitals, but also in smaller hospitals and community nursing homes.\cite{10} For some time, it has been known that high-level vancomycin resistance can be transferred from enterococci to \textit{S. aureus in vitro};\cite{11} the first clinical isolates of MRSA with intermediate resistance to vancomycin (MIC of 8 mg/L) have recently been reported in Japan (\textit{n} = 1)\cite{12} and the US (\textit{n} = 2).\cite{13}

Coagulase-negative staphylococci, in particular \textit{S. haemolyticus}, have also emerged as major nosocomial pathogens,\cite{14} and the incidence of methicillin resistance among these bacteria can exceed that observed in \textit{S. aureus}.\cite{15} It has been suggested that coagulase-negative staphylococci may act as a reservoir of resistance genes that can be readily transferred to \textit{S. aureus}.\cite{14}

Glycopeptides are the mainstay of treatment for infections caused by methicillin-resistant staphylococci, as these strains, in addition to being resistant to most \textit{β}-lactam agents, are often co-resistant to the aminoglycosides, macrolides and fluoroquinolones. Some drug combinations (e.g. vancomycin with rifampicin, fusidic acid or fosfomycin, cefotaxime with fosfomycin, and amoxicillin with clavulanic acid) may have activity in MRSA infections; however, this has yet to be demonstrated in controlled clinical trials.\cite{8}

\textbf{Enterococci}

Predictably, the increasing prevalence of MRSA was accompanied by an increase in the use of vancomycin.\cite{14,15} At about the same time, oral vancomycin was being used for the treatment of pseudomembranous colitis, and a second glycopeptide, teicoplanin, was introduced into clinical practice.\cite{16} This marked increase in glycopeptide use was followed by the emergence of glycopeptide resistance in enterococci.

Vancomycin-resistant enterococci (VRE) were first documented in Europe in 1988. This had been preceded by reports of infections caused by commensal bacteria, such as \textit{Leuconostoc} and \textit{Lactobacillus} spp., which were naturally vancomycin resistant.\cite{15} By the end of 1994, VRE made up almost 14% of intensive care isolates and 9% of non-intensive care enterococci in the US.\cite{17} VRE are rarer in Europe (0.7 to 1% of enterococcal isolates).\cite{8}

Both intrinsic and acquired mechanisms of resistance have equipped enterococci to adapt well to the hospital environment, where antibiotic selection pressure is heavy.\cite{18} Enterococci are now the second most common nosocomial infectious agents in the US.\cite{19} There is also evidence to