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# Quinolones in 2005: an update

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## ABSTRACT

Quinolones are one of the largest classes of antimicrobial agents used worldwide. This review considers the quinolones that are available currently and used widely in Europe (norfoxacin, ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin) within their historical perspective, while trying to position them in the context of recent and possible future advances based on an understanding of: (1) their chemical structures and how these impact on activity and toxicity; (2) resistance mechanisms (mutations in target genes, efflux pumps); (3) their pharmacodynamic properties (AUC/MIC and $C_{max}$/MIC ratios; mutant prevention concentration and mutant selection window); and (4) epidemiological considerations (risk of emergence of resistance, clonal spread). Their main indications are examined in relation to their advantages and drawbacks. Overall, it is concluded that these important agents should be used in an educated fashion, based on a careful balance between their ease of use and efficacy vs. the risk of emerging resistance and toxicity. However, there is now substantial evidence to support use of the most potent drug at the appropriate dose whenever this is required.

**Keywords** Ciprofloxacin, pharmacodynamics, quinolones, resistance, review, toxicity

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## INTRODUCTION

With more than 800 million patients treated, quinolones are currently one of the main classes of agent in the antimicrobial armamentarium, with therapeutic indications having evolved from urinary tract infections in the early 1970s to infections of almost all body compartments at the present time. This achievement has been made possible by a clear understanding of the structure–activity relationships for this class of molecules [1,2]. This knowledge has led to an intense effort to synthesise new derivatives with a broader spectrum, higher intrinsic activity, and an improved pharmacokinetic (PK) profile (all attributes that were meant to yield better clinical outcomes), and the ensuing publication of a very large amount of chemical, microbiological and clinical data. It has been estimated that more than 10 000 new molecules have been synthesised in this class; a PubMed search reveals *c*. 2000 primary papers and 600 reviews on the topic of quinolones for the period 1985–2005. However, these efforts were compromised by the emergence of resistance [3–7] and, for some of these molecules, unacceptable side-effects [8]. Many authors [9–15] have examined quinolones in terms of their development, susceptibility of clinical isolates, clinical efficacy in specific indications, positioning in guidelines, or the profile of specific molecules. While these drugs originally appeared almost as a panacea, and promised a bright future [16,17], the scientific community now tends to call for cautious, or even restricted, use of these agents [18–21] for ecological reasons, to avoid the dissemination of resistance, and to control antibiotic overuse and misuse (see [22,23] for two practical approaches in Europe). Together with considerations based on local costs and the availability of generic agents, this has resulted in large variations in quinolone sales among countries, especially in Europe [24].

This review presents an historical perspective of the quinolones, and attempts to reposition

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them in the context of recent and possible future advances based on an understanding of resistance mechanisms, pharmacodynamic (PD) concepts, and a critical appraisal of the advantages and drawbacks of these compounds when used for their main therapeutic indications.

## ORIGIN AND STRUCTURE–ACTIVITY RELATIONSHIPS

Discovered in 1962 as a by-product of antimalarial research [25], nalidixic acid is the parent compound of the quinolone class of antibiotics. The use of nalidixic acid was originally limited because of its narrow spectrum, low serum levels, and toxicity issues, but it regained attention in the 1980s for the treatment of diarrhoea and urinary tract infections following the development of resistance in *Shigella* and *Escherichia coli* to other classes of antibiotics used at that time. This marked the beginning of an active campaign of chemical synthesis to refine structure–activity relationships, with the aim of improving activity while optimising pharmacokinetics and reducing toxicity and drug interactions (Fig. 1; see [1,2,26] for reviews on structure–activity and structure–toxicity relationships). Accordingly, many quinolone molecules have been patented (key examples are shown in Fig. 2), but only a few have been commercialised and reached the clinic; indeed, the attrition rate of > 999/1000 molecules created illustrates clearly the unpredictable and risky nature of pharmaceutical research.

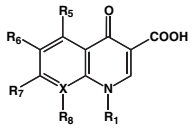
Quinolones available for clinical use have been classified into four generations, mainly on the basis of their spectrum of activity [27]. Following the lead of flumequine, the second generation of quinolones had the major feature of a fluorine substituent (F) at position 6 (hence the name of fluoroquinolones often given to the whole class), which increased activity markedly. These early compounds were most potent against Gram-negative organisms; thus their activity against *Streptococcus pneumoniae* was too marginal to warrant clear indications for use in the treatment of respiratory tract infections, and the emergence of resistance soon reduced their potential against *Staphylococcus aureus*. Of these compounds, ciprofloxacin and ofloxacin are the most widely used today, with ciprofloxacin still being the most active against *Pseudomonas aeruginosa*. Ofloxacin is a chiral molecule with only the S-(–) isomer as an active component. The latter has been commercialised as levofloxacin, which is, by its nature, twice as active as ofloxacin per unit of mass, but with no intrinsic change in its spectrum. The other members of the second generation, sparfloxacin and grepafloxacin, must be considered separately, since their substituent at position 5 and the bulkiness of their substituent at position 7 improved their activity significantly against *Strep. pneumoniae*. However, both of these agents were soon withdrawn or restricted for toxicological reasons.

Further improvement in activity against Gram-positive bacteria, together with significant anti-anaerobe activity, was seen with the third-generation molecules, caused by the presence of an alkyl-substituted piperazine or pyrrolidine at position 7, and of a methoxy at position 8. In this class, trovafloxacin (a naphthyridone), although not an 8-methoxyquinolone, was one of the most active compounds, and had the broadest spectrum when registered, but was soon restricted to the treatment of severe infections in the USA, and was withdrawn in Europe, because of rare cases of hepatotoxicity. The most recent available member of this group is gemifloxacin (also a naphthyridone), which possesses a very large spectrum of activity, including some anaerobes, but gemifloxacin is currently approved only in Korea, New Zealand, the USA and Canada.

These extensive research efforts have enabled a better definition of the structural moieties or elements around the basic pharmacophore that offer the best combination of clinical efficacy, reduced resistance selection, and safety. These elements include a cyclopropyl at position 1, a methoxy at position 8, a (substituted) pyrrolidine or substituted piperazine at position 7, and a fluor substituent at position 6. Optimising all other substituents has permitted the removal of the fluorine atom at position 6 (which has been claimed to be involved in genotoxicity and central nervous system defects [2] possibly involved in genotoxicity), giving rise to the fourth generation of quinolones, termed des-fluoroquinolones, with garenoxacin as its first representative. The future of this molecule is, however, uncertain.

## MECHANISM OF ACTION AND SPECTRUM OF ACTIVITY

Fig. 3 shows the cumulative distribution of susceptibilities of the five fluoroquinolones with



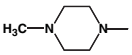
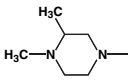
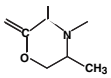
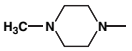
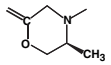
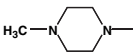
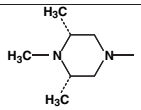
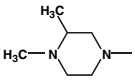
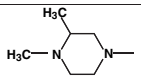
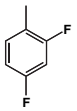
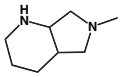
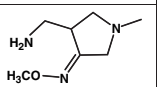
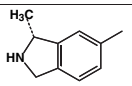

| generation | drug [orig. ref./patent]] | X | $R_8$ | $R_1$ | $R_5$ | $R_6$ | $R_7$ |
|---|---|---|---|---|---|---|---|
| 1 | nalidixic acid [283;284] | N | | $-CH_2-CH_3$ | H | H | $-CH_3$ |
| 2a | **norfloxacin** [285-287 | C | H | $-CH_2-CH_3$ | H | F |  |
| | pefloxacin [288;289] | C | H | $-CH_2-CH_3$ | H | F |  |
| | lomefloxacin [290;291] | C | F | $-CH_2-CH_3$ | H | F |  |
| | **ciprofloxacin** [292-294] | C | H |  | H | F |  |
| | **ofloxacin** [295;296] | |  | | H | F |  |
| | **levofloxacin** [297;298] | |  | | H | F |  |
| 2b | *sparfloxacin* [299;300] | C | F |  | $-NH_2$ | F |  |
| | *grepafloxacin* [301;302] | C | H |  | $-CH_3$ | F |  |
| 3a | gatifloxacin [303;304] | C | $-O-CH_3$ |  | H | F |  |
| | *trovafloxacin* [305;306] | N | |  | H | F |  |
| | **moxifloxacin** [307;308] | C | $-O-CH_3$ |  | H | F |  |
| 3b | gemifloxacin [309;310] | N | |  | H | F |  |
| 4 | garenoxacin [311;312] | C | $-O-CHF_2$ |  | H | H |  |

**Fig. 1.** Pharmacophore and structures of the main quinolones that have been approved for human use. Names in bold refer to compounds in large-scale clinical use in Europe. Names in italic refer to compounds for which commercialisation has been suspended or severely reduced because of side-effects and/or a decision of their registration holders (the development of garenoxacin in Europe and North America is at present uncertain).

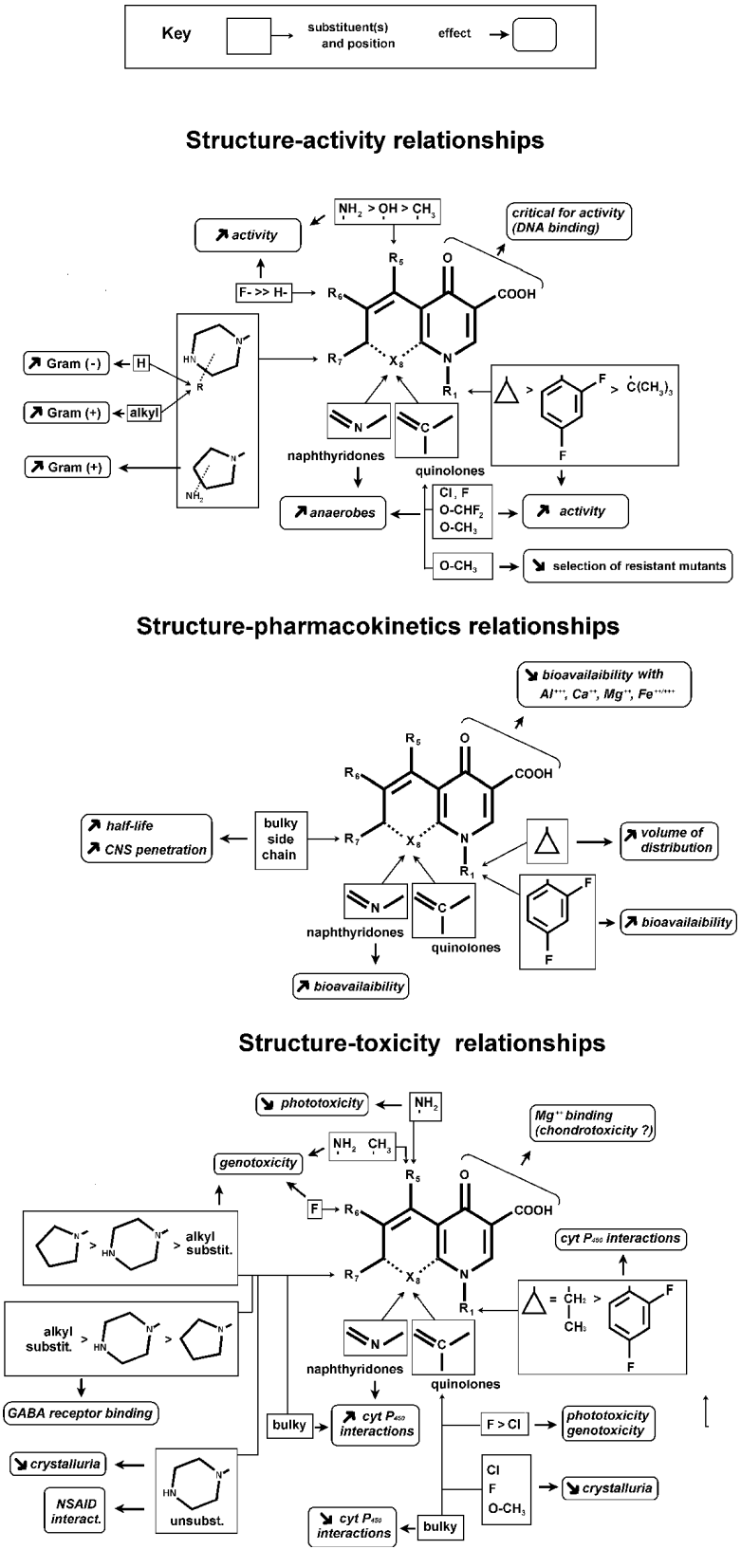



**Fig. 2.** Structure–property relationships in quinolones. The central part of the molecule refers to the pharmacophore shown in Fig. 1.

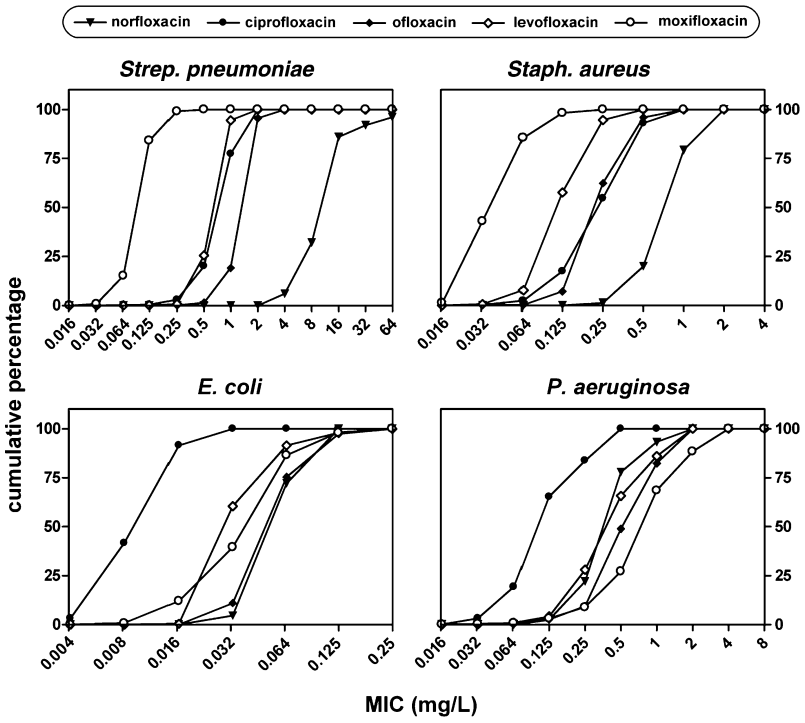



**Fig. 3.** Cumulative MIC distributions for wild-type populations of four major pathogens (redrawn from data obtained and made publicly available by the European Committee on Antimicrobial Susceptibility Testing (EUCAST); see http://www.eucast.org). Each reference distribution is the result of aggregated MIC data obtained from publications in international journals, national breakpoint committees, reference laboratories, international antimicrobial surveillance systems, such as EARSS (http://www.earss.rivm.nl) or those sponsored by pharmaceutical companies, and antimicrobial susceptibility testing device manufacturers. As such, the data are meant to represent the natural variability in the susceptibility of organisms without specific, acquired resistance mechanisms to the corresponding drugs.

the current largest clinical usage in Europe with respect to wild-type populations of four major pathogens, i.e., in the absence of acquired resistance. These data support the structure–activity relationships discussed above, and confirm that ciprofloxacin is the most active agent against Gram-negative organisms, that moxifloxacin is preferentially active against Gram-positive organisms, that ofloxacin and levofloxacin show intermediate activity (with the two-fold difference in intrinsic activity for levofloxacin mentioned above), and that norfloxacin is an intrinsically weak fluoroquinolone against Gram-positive organisms.

As described previously [28–31], the activity of quinolones stems primarily from the formation of ternary complexes between DNA and type II topoisomerases, namely DNA gyrase and topoisomerase IV, two enzymes that play a critical role in the supercoiling of DNA [32–34]. The rapid bactericidal effect of fluoroquinolones is thought to result from the release of DNA ends, which are thought to induce bacterial apoptosis [35].

Both topoisomerase enzymes are essential for bacterial growth, but they cannot complement one another. Several studies have highlighted substantial variations in the in-vitro inhibitory concentrations for DNA gyrase and topoisomerase IV, depending on both the bacterial species and the molecule being studied (Table 1). These data, which are roughly consistent with MIC

**Table 1.** Range of inhibitory concentrations of 5-fluoroquinolones for DNA gyrase and topoisomerase IV isolated from different bacterial species [36,52,236–249]

| | $IC_{50}$ (mg/L) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Streptococcus pneumoniae* | | *Staphylococcus aureus* | | *Escherichia coli* | | *Pseudomonas aeruginosa* | |
| Drug | DNA gyrase | Topo IV | DNA gyrase | Topo IV | DNA gyrase | Topo IV | DNA gyrase | Topo IV |
| Norfloxacin | 582 | 35 | 55.5 to > 100 | 10–12 | 1.5 | 7 | | |
| Ciprofloxacin | 80–138 | 5–7 | 13.5–25 | 4–6 | < 0.75 | 2 | 0.5 | 4 |
| Ofloxacin[a] | 88 | 10 | 12–19 | 10–23 | < 0.75 | 12 | 1.5 | 9.5 |
| Moxifloxacin | 22 | 6 | 3.5 | 8 | | | | |
| Gemifloxacin | 5–10 | 2–5 | | | | | | |

[a]Values for levofloxacin (active isomer of ofloxacin) are half of these values.
Topo IV, topoisomerase IV.

values and data obtained from analysis of resistant mutants, confirm that DNA gyrase is the preferred target of fluoroquinolones in Gram-negative bacteria. The situation is more complex in Gram-positive bacteria. For example, the $IC_{50}$ ratio in *Strep. pneumoniae* is significantly different between ciprofloxacin and ofloxacin (or sparfloxacin) and moxifloxacin (or gemifloxacin). Taking into account the fact that equivalence in target preference is denoted by an $IC_{50}$ ratio of 2–3, and the fact that inhibition of DNA gyrase is probably more lethal to the cell than inhibition of topoisomerase IV, this could explain the observation that gyrase becomes the preferred target in clinical isolates with resistance mutations.

Although the structural features responsible for the interaction of fluoroquinolones with the binding sites on DNA gyrase or topoisomerase IV are not yet unravelled fully, the design of derivatives that target both enzymes selectively has been proposed [36–39]. A useful development in that direction has been the introduction of a methoxy group (such as in moxifloxacin and gatifloxacin [40], where this group actually replaced a chlorine that had similar properties with respect to activity, but caused phototoxicity).

## RESISTANCE

Bacterial resistance to quinolones can essentially develop through two main mechanisms, namely a decrease in the intrabacterial concentration of a drug, or alterations in a drug's target enzymes. While the former mechanism permits immediate survival and is largely inducible, the second is stable and is disseminated more easily. It will therefore be discussed first.

Target site alteration results from mutations in the chromosomal genes encoding the DNA gyrase and topoisomerase IV. These genes are commonly called *gyrA* and *gyrB*, and *parC* and *parE*, respectively (*grlA* and *grlB* in *Staph. aureus*). Such mutations probably result from transcription errors during chromosome replication, and occur at rates as high as 1 in $10^6$ to 1 in $10^9$ in wild-type bacteria [41]. In *Strep. pneumoniae*, another mechanism that might also lead to fluoroquinolone resistance mutations is horizontal gene transfer [42,43] from viridans group streptoccoci. Mutations tend to cluster in a region called the 'quinolone resistance-determining region' which, in the resulting GyrA protein, corresponds to the domain that is bound to DNA during enzyme activity [44]. These mutations result in reduced drug affinity [45,46].

Phenotypic resistance arises in a stepwise fashion as a result of accumulating mutations. First-step mutations occur commonly in the primary or preferred drug target enzyme (thus more often in *gyrA* for Gram-negative, and more often in *parC* for Gram-positive organisms; mutations in *parE* mutations are uncommon). However, in *Strep. pneumoniae*, first-step mutants selected with ciprofloxacin tend to be *parC* mutants, whereas those selected with moxifloxacin (or gatifloxacin and sparfloxacin) tend to be *gyrA* mutants, reflecting a different preferred target of these fluoroquinolones for this species [35,47–49]. Mutation of *gyrA* has been described for *Chlamydia pneumoniae* following serial cultures with increasing moxifloxacin concentrations [50]. Second-step resistance mutations may then accumulate in the secondary drug target enzymes and will further affect quinolone resistance [51].

The precise effect of mutations in the gyrase and topoisomerase IV genes on the resistance phenotype may differ between bacterial species [52], but depends also on the precise gene involved and which specific quinolone is used. While some mutations in the primary target might be sufficient for acquisition of detectable resistance, this is not always the case. Thus, first-step *parC* mutations in *Staph. aureus* are associated with low-level resistance, and highly resistant clinical isolates usually possess several mutations [53–55]. In studies involving well-defined single-step mutants, each mutation in the quinolone resistance-determining region of gyrase or topoisomerase genes usually decreased susceptibility 4–8-fold [56–58]. Although second-step mutations in the secondary targets tend, in general, to have less impact on the resistance phenotype, they increase the resistance level further, but the effect of each mutation on the resistance level to different quinolones may vary. Thus, a pattern of cross-resistance between different molecules may develop, whereby parallel, simultaneous increases in MICs are observed. Conversely, dissociated resistance may occur in which there is no significant change in MIC values for some molecules, but significant increases for others [41,51,59] (Fig. 4). These observations are obviously important in that they may favour the use of compounds that display this type of dissociated

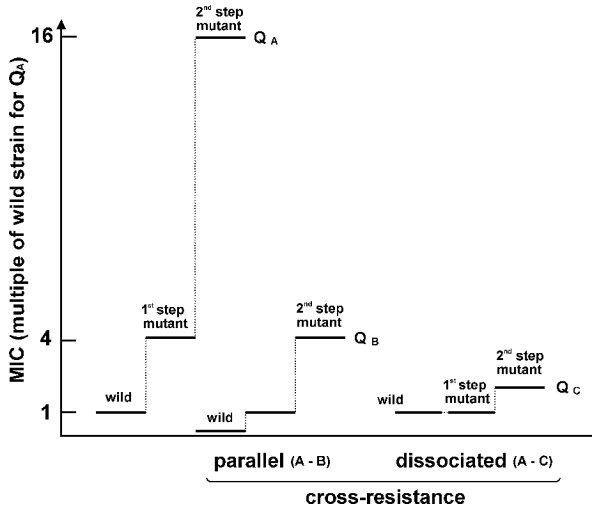



**Fig. 4.** Cross-resistance and dissociated resistance in quinolones. $Q_{A \text{ and } B}$ illustrate a situation of cross-resistance: although the initial susceptibility of the strain may be different for molecules A and B, mutations in the target enzymes lead to similar changes in the susceptibility to both drugs. $Q_C$ illustrates a situation of dissociated resistance: the susceptibility to molecule C does not change in spite of the acquisition of a first mutation, and will increase only upon acquisition of a second mutation.

resistance, select mutants with less impact on MIC values, or display lower frequencies of selection of resistance mutations. In this respect, a methoxy in position 8 could also be important, since it has been shown to reduce the probability of selection of resistant mutants [60–62].

The second main mechanism leading to quinolone resistance is associated with a decrease in their intrabacterial concentrations. Changes in the outer-membrane, including altered outer-membrane porins (OmpF) leading to reduced entry of antibiotics, have been reported previously with Gram-negative bacteria [63,64]. The resulting changes in quinolone susceptibility were often accompanied by reduced susceptibility to other classes of antibiotics (mainly carbapenems). Resistance in such mutants is usually of a relatively low level, as entry is not prevented completely; so clinically significant resistance often occurs in combination with other resistance mechanisms. However, because the mutations identified in these strains cause pleiotropic alterations, the possibility that resistance in these mutants is actually caused by increased efflux, which was only recognised in the mid-1980s [65], cannot be excluded. An increasingly large number of reports have now implicated efflux as a major mechanism of antibiotic resistance [66]. Efflux pumps appear to be ubiquitous, and are probably essential in the general physiology of bacteria [67]. They can be encoded either by chromosomal genes or by genes associated with mobile elements. When expressed constitutively, these genes are probably responsible for many cases of so-called 'intrinsic resistance', and bacteria lacking efflux pumps have even been proposed as ideal organisms to screen for new antibiotics because of their hypersensitivity to a large number of antimicrobial agents [68]. When induced or activated, they usually cause low-to-moderate levels of phenotypic resistance to fluoroquinolones [46], which can become clinically relevant when combined with mutations in the target enzymes. In some cases, however, efflux-pump systems can themselves be responsible for clinically relevant resistance [69–72]. Perhaps more importantly, efflux favours the emergence of resistant mutants because it enables bacteria to survive in the presence of sub-optimal concentrations of antibiotics [73]. Increasing the bulkiness of the substituent at position 7 contributes to a reduction in the transport of quinolones by efflux proteins of bacteria [74], which explains the low efflux rate of moxifloxacin and garenoxacin in *Strep. pneumoniae* [74–77]. Efflux-mediated resistance has now been described in pneumococci (PmrA) [78,79], staphylococci (NorA) [80,81], anaerobes [82] and Gram-negative bacteria [73,83,84]. In the last of these groups, efflux systems usually have broad substrate specificity, recognising several classes of chemically unrelated molecules and yielding a multiresistance phenotype.

Finally, plasmid-mediated resistance to quinolones has been reported in *Klebsiella pneumoniae* and in *E. coli* [85,86]. The plasmid encodes a *qnr* gene product (218 amino-acids) that lowers gyrase binding to DNA [87,88], but bacteria carrying the plasmid still need additional deficiencies in outer-membrane proteins to display clinically meaningful resistance [87,89]. So far, the prevalence of the *qnr* gene is rare, although reports from China suggest that a high local prevalence is possible [86]. The *qnr* gene has been observed recently in a single isolate of *E. coli* from Europe, carried on a conjugative plasmid conferring resistance to quinolones, most β-lactams

except carbapenems, most aminoglycosides, sulphonamides, rifampicin, trimethoprim and chloramphenicol [90].

## PHARMACOKINETICS AND PHARMACODYNAMICS

Most quinolones show excellent bioavailability, which makes them ideal for ambulatory patients and for intravenous-to-oral antibiotic switches in hospitalised patients [91]. They are also characterised by excellent penetration into most tissues and body fluids (consistent with a distribution volume of *c*. 1–4 L/kg), but their serum levels are usually low, especially when fractionated dosing schedules are used. Although barely greater than the breakpoints of 2 mg/L proposed originally [92], these levels were nevertheless considered to be sufficient at the time of registration of the second-generation quinolones. Early studies showed that quinolones, like aminoglycosides but in contrast to β-lactams, work mainly in a concentration-dependent manner [93] and exert a marked post-antibiotic effect [94], although this is not consistent across all species. Studies in neutropenic animals reinforced this conclusion by demonstrating that unfractionated schedules produced a better survival rate [95], provided that a $C_{max}$/MIC ratio of > 10 could be reached (see [96] for a definition of the various PK and PD parameters of antimicrobial agents and their meaning). At lower values, the $AUC_{24\ h}$/MIC ratio became more predictive, perhaps because of the decreased rate of bacterial killing.

At about the same time, clinicians noticed unacceptable rates of failure and emergence of resistance to ciprofloxacin when treating infections caused by organisms with an MIC close to the breakpoints with the commonly used low dosages (2 × 200 mg) [97–99]. This led to the first, large-scale clinical study aimed at defining the PD parameters which were predictors of efficacy [100]. Univariate analysis showed that the $AUC_{24\ h}$/MIC ratio (> 125) linked best with both the clinical and microbiological outcomes, and that a $C_{max}$/MIC ratio of < 4 was associated significantly with a sub-optimal outcome. However, the use of twice- and three-times-daily dosing schedules did not allow analysis of the benefits of high peak concentrations, since these were infrequent. A subsequent clinical study of levofloxacin with community-acquired pneumonia [101] stressed the importance of the $C_{max}$/MIC ratio (if > 12.2). However, in this study, as in that of Forrest *et al.* [100] and most other clinical studies, the lack of variability in dosing schedules made $C_{max}$ and AUC covariates, so that their relative roles could not be distinguished. Taking into account this limitation, and realising that high $C_{max}$/MIC ratios are difficult to obtain with second-generation quinolones and organisms with elevated MICs, most investigators and drug companies have now adopted the $AUC_{24\ h}$/MIC ratio (using preferably free levels) as a practical predictive parameter for efficacy. Indeed, in limited trials this parameter appeared to be linked strongly to clinical outcome and, in experimental studies, was largely independent of the dosing interval, the fluoroquinolone used, the animal species and the site of infection [102–104]. The question remaining unanswered is the minimal value of this parameter, with a value of 25 appearing sufficient for less severe infections and/or immunocompetent hosts, but with a value of ≥ 100 appearing necessary for severe infections and/or immunocompromised hosts [105].

Perhaps the true picture comes from a close examination of both the experimental studies and the clinical data. The former show that required levels of drug exposure depend critically upon the desired effect [106]. For instance, moving from an $EC_{50}$ to an $EC_{99}$ effect with in-vitro dynamic models requires an increase of about ten-fold in AUC/MIC ratios [107]. In animals, this ratio must be increased up to five-fold to move from a static effect and a $2 \times \log_{10}$ kill in immunocompetent animals, and up to about three-fold for a static effect between neutropenic and non-neutropenic animals [108]. The clinical data actually point to the same conclusion by showing that an $AUC_{24\ h}$/MIC ratio of 125 will yield efficacy by day 7, but that higher values (> 250) will produce faster bacterial eradication [109]. Therefore, time-related events must also be taken into consideration. The available data can therefore be interpreted as meaning that aiming at minimal values may be quite dangerous, given the possibility of large variability in individual PK parameters [110], the often imprecise character of the MIC determinations [111], and the uncertain immunological status of many patients. Table 2 proposes conservative $AUC_{24\ h}$/MIC-based limits of sensitivities (free drug concentrations have been used, since bound fluoroquinolones do not participate

**Table 2.** Pharmacokinetic parameters used for proposing PK/PD based limits of sensitivity and conditions favouring the prevention of emergence of resistance for most common organisms and systemic infections, together with the breakpoints set by European and American ad-hoc organisations

| | | Typical PK values | | Proposed PK/PD upper limit | | Breakpoints (mg/L)[d] | |
|---|---|---|---|---|---|---|---|
| Drug | Typical daily dosage[a] | $C_{max}$ in mg/L total/free (dose) | $AUC_{24\ h}$ (mg × h/L) total/free | Efficacy[b] | Prevention of resistance[c] | EUCAST (S-R) | NCCLS (S-I-R) |
| Norfloxacin | 800 mg | 1.4/1.1 (400 mg PO) | 14/11 | 0.1–0.4 | 0.1 | ≤ 0.5 to > 1[e] | ≤ 4–8 > 16[j] |
| Ciprofloxacin | 1000 mg | 2.5/1.75 (500 mg PO) | 24/18 | 0.2–0.8 | 0.2 | ≤ 0.5 to > 1[f] (≤ 0.125 to > 2)[g] | ≤ 2–2 > 4[k] |
| Ofloxacin | 400 mg | 4/3 (400 mg PO) | 40/30 | 0.3–0.9 | 0.4 | ≤ 0.5 to > 1[f] (≤ 0.125 to > 4)[g] | ≤ 2–4 > 8[l] |
| Levofloxacin | 500 mg | 4/2.8 (500 mg PO) | 40/28 | 0.3–0.9 | 0.3 | ≤ 1 to > 2[f] (≤ 2 to > 2)[h] | ≤ 2–4 > 8[l] |
| Moxifloxacin | 400 mg | 3.1/1.8 (400 mg PO) | 35/21 | 0.2–0.7 | 0.2 | ≤ 0.5 to > 1)[e] (≤ 5 to > 0.5)[i] | ≤ 1–4 > 4[m] |

EUCAST, European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org) [241].
NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.nccls.org).
S, susceptible; I, intermediately resistant; R, resistant.
[a]In patients with no gross abnormality of the excretory functions, and for most common tissue-based infections (thus excluding simple cystitis); based on recent typical 'Summary of Product Characteristics' (SPC, or 'labelling' in Europe). Recent guidelines, and SPC in some countries, suggest higher dosages for ciprofloxacin (up to 1200 mg/day), ofloxacin (up to 800 mg/day), and levofloxacin (750–1000 mg/day). Because the pharmacokinetics of registered quinolones are linear with respect to doses (within the limits of the agents registered), adaptation of the figures of $C_{max}$ and $AUC_{24\ h}$ for doses other than those shown here can be done by simple extra- or intrapolation.
[b]Based on a free $AUC_{24\ h}$/MIC ratio ranging from 30 (pneumococcocal infection/immunocompetent host) to 100 (Gram-negative infection/immunoimpaired host); see discussion in text in support of these values as average means for free concentrations.
[c]Based on a minimal $C_{max}$/MIC ratio of 10, considered to encompass the 'mutant prevention concentration' of most susceptible isolates (see text for discussion). Application of this criterion will also meet the requirement for larger $AUC_{24\ h}$/MIC ratios than needed for efficacy.
[d]For organisms within the main indications.
[e]Enterobacteriaceae only (*Pseudomonas* is considered to be non-susceptible).
[f]For most Gram-negative organisms, including *Pseudomonas*; 1 for *Staph. aureus* with high-dose therapy.
[g]Values in parentheses refer to *Streptococcus pneumoniae*, where the wild-type population is not considered susceptible to ciprofloxacin or ofloxacin, and is therefore categorised globally as 'intermediate'.
[h]For *Strep. pneumoniae* and levofloxacin, the breakpoint was increased to 2 to avoid dividing the wild-type population (see [242] for a typical example from France), but this breakpoint relates to high dose therapy.
[i]For *Strep. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.
[j]Enterobacteriaceae and *P. aeruginosa*.
[k]*Staphylococcus aureus*, Enterobacteriaceae and *P. aeruginosa*.
[l]*Strep. pneumoniae*, *Staph. aureus*, Enterobacteriaceae and *P. aeruginosa*.
[m]*Strep. pneumoniae*.

directly in activity [112,113]). However, the $C_{max}$/MIC ratio may be critical in preventing the emergence of resistance (see below), and quinolones with a higher $C_{max}$ are probably desirable in this context.

## IMPLICATIONS OF PK/PD FOR THE PREVENTION OF RESISTANCE

The recognition of the relatively fast emergence of resistance to quinolones has only recently triggered PK/PD research aimed at reducing this risk. Yet in-vitro studies and animal models, and, to some extent, clinical investigations concur in indicating that low $AUC_{24\ h}$/MIC ratios, even if clinically effective, will be conducive to the selection of resistant mutants [114–119]. A more fundamental approach has probably been taken by developing a novel in-vitro measure of quinolone potency called the 'mutant prevention concentration' (MPC). Described originally for *Mycobacterium bovis* [60], the MPC is the concentration that prevents the growth of the next-step mutant of a bacterial strain. It essentially defines the concentration threshold that would require a bacterium to simultaneously acquire two resistance mutations for growth in the presence of that specific drug. Determination is made by plating at least $10^{10}$ bacteria in the presence of increasing concentrations of a quinolone, and determining the concentration at which no growth occurs [120]. A concentration of $10^{10}$ CFU was chosen to detect mutations occurring at frequencies of $10^{-7}$–$10^{-9}$, as well as to mimic the typical bacterial load and population heterogeneity at the site of infection. This method has now been applied to several bacterial species and different quinolones [121–128]. The MPC provides a numerical threshold that might be used to severely restrict, if not prevent, the selection of resistance during therapy [129], and can thereby suggest minimum serum concentrations to be attained [130]. Third-generation fluoroquinolones (gatifloxacin, gemifloxacin,

moxifloxacin) usually display lower MPC values for isolates of *Strep. pneumoniae* than do older fluoroquinolones, although the situation may be less favourable with organisms already carrying one mutation [131–133]. For *P. aeruginosa*, ciprofloxacin has a lower MPC than levofloxacin [134]. These observations are concurrent with the observed stepwise 4–8-fold increase in MICs that results from accumulating mutations in the topoisomerase genes, and the observation that the higher the ratio of $C_{max}$ over MIC, the better the outcome [135]. Studies on the MPC have led to the development of the concept of the 'mutant selection window', which states that resistant mutants are best selected at antibiotic concentrations above the MIC (a selection pressure being necessary), but below the MPC [129]. This concept has now been demonstrated *in vitro* for *Staph. aureus* [124] and *Strep. pneumoniae* [116].

Two practical difficulties face the clinician wishing to use the MPC as a useful target concentration. First, apart from a natural variation in MPC values between genetically different strains from the same species, the unknown status of resistance mutations in the strain makes predictions difficult, as outlined above. Second, little is known about the time during which the bacteria must be exposed to concentrations above the MPC to effectively prevent the selection of resistant mutants. Experimental studies show that selection will occur when the quinolone concentration remains inside the mutant selection window for > 20% of the dosing interval, which will most often be the case for patients with an $AUC_{24\ h}$/MIC ratio of 30–60 [116]. Therefore, the available data can be interpreted as meaning that quinolones should be chosen, and their dosages and schedules selected, to reach at least a $C_{max}$/MIC ratio of 10. This will increase the probability of maintaining the concentration above the mutant selection window for a large proportion of the dosing interval. This concept has been included in Table 2 (prevention of resistance).

## EPIDEMIOLOGY OF RESISTANCE DEVELOPMENT

The notoriously fast development of resistance to second-generation quinolones has quickly removed the effectiveness of compounds such as pefloxacin against both Gram-negative and Gram-positive organisms. The situation has been more mixed for ciprofloxacin and ofloxacin with respect to Gram-negative organisms. While both of these quinolones still remain as first choices in many therapeutic guidelines, quite alarming levels of resistance in *P. aeruginosa* are now reported worldwide and in specific settings [6,7,136–143]. However, large variations in resistance levels exist that are not explained easily (see [144] for a typical example in Europe), although the volume and type of fluoroquinolone used, both in the hospital and the surrounding community, are among the determinants [145–147]. The correct approach probably requires close surveillance of susceptibilities at the local level, and the formulation of appropriate antibiotic policies that should restrict unnecessary use, in combination with appropriate PK/PD-based dosing when needed, and more systematic MIC measurements. Collecting MIC data appears essential; indeed Table 2 illustrates that resistance breakpoints are set at values which are not supported by recent PK/PD data, not to mention optimal efficacy. In apparent contrast, there are optimistic global reports concerning *E. coli* [139,148–151], albeit with local observations that often point to much higher rates of resistance, perhaps related to the site of infection and the status of the patient. Here also, the answer may lie in closer surveillance and application of PK/PD principles in all cases for which the outcome might become uncertain.

The picture is quite different for levofloxacin (and third-generation quinolones) against *Strep. pneumoniae*. Resistance has remained low [152] and increases only slowly [153,154]. In this context, the alarming increase in ciprofloxacin resistance observed between 1988 and 1997 in Canada [155] should be considered atypical, as it results from inappropriate use of ciprofloxacin for the treatment of community-acquired respiratory tract infections in this country. There is also one well-known exception in Hong Kong [156], which retrospective analysis suggests was associated with the pan-regional dissemination of a specific fluoroquinolone-resistant variant, Hong Kong (23F)-1, perhaps triggered by low doses used in the treated population of patients with chronic obstructive pulmonary disease [157]. This is of interest when considering the extensive use worldwide of older quinolones for indications other than respiratory tract infections, since, because of the weak anti-streptococcal activity of these agents, exposure of commensal streptococci

to insufficient concentrations for a lengthy period of time might be anticipated. However, in contrast to macrolides and penicillin, for which the rates of resistance and/or decreased susceptibilities are much higher, quinolones have not been used in children, who may constitute a major reservoir for resistant streptococci, as they are prescribed a large proportion of the total human antibiotic consumption. Recent data suggesting decreased susceptibility of *Strep. pneumoniae* to levofloxacin in the USA in relation to its local use [158], coupled with reports of clinical failures [159] and recent trends towards decreased susceptibility of European isolates to ciprofloxacin [160], indicate a need for close surveillance and the formulation of global restrictive prescribing policies.

There is also considerable evidence for clonal spread [161], although polyclonal spread has been seen in Japan [162]. Since resistance to quinolones is the result of the accumulation of spontaneous mutations that can occur rapidly in treated patients [159], it seems logical that resistant mutants would belong to many different genotypes. If this were indeed the principal driving force for resistance, a gradual increase in resistance rates following the gradual emergence and selection of resistant mutants in a wide range of different genotypes would be expected, more or less concurrent with the total use of quinolones. However, recent data support an important role for a small number of highly epidemic bacterial clones in the spread and overall rate of quinolone resistance [163]. This has also been observed for fluoroquinolone-resistant methicillin-resistant *Staph. aureus* [164] and gonococci [164].

Finally, target mutations and overexpression of efflux mechanisms have often been associated with significant fitness cost, resulting in a reduced growth rate and/or virulence in the absence of antibiotic challenge. However, compensatory mutations may partly or fully restore the function impaired by the resistance mutation [165]; indeed, evidence for an enhanced in-vivo fitness of resistant strains in the absence of antibiotic pressure has been presented for *Campylobacter jejuni* [166]. The biological price that bacteria pay for quinolone resistance appears therefore to be limited [51], and, as a consequence, the emergence of resistant strains could be easy, leading to a rapid increase in resistance rates that will depend not solely on total quinolone use, but also on all the other factors that drive the spread of epidemic clones. For *Strep. pneumoniae* in particular, there are fears that use of quinolones for indications that carry a higher risk of multiresistant epidemic clones (e.g., infections in children, and chronic respiratory infections in elderly patients) could impact significantly on resistance rates. A first case of failure of oral levofloxacin treatment for community-acquired pneumonia caused by *Haemophilus influenzae* has been reported, with step-by-step mutations in DNA gyrase and topoisomerase IV [167]; this type of mutant can be obtained easily in the laboratory with ciprofloxacin by stepwise selection [128]. Again, these concerns can be addressed by the implementation of closer and improved surveillance methods (including not only serotyping and MIC determination, but also surveillance of specific mutations and efflux mechanisms), a decrease in the non-justifiable use of quinolones, and closer attention to PK/PD considerations when the use of an antibiotic is deemed essential. This is probably critical, as current breakpoints fail to identify most *Strep. pneumoniae* isolates with only first-step mutations [168] or with efflux mechanisms.

## TISSUE ACCUMULATION/DISTRIBUTION AND ITS MEANING

Much has been reported regarding the presence of fluoroquinolones in epithelial lining fluid and pulmonary tissues [19,169] in support of the use of fluoroquinolones for treating respiratory tract infections. However, the key question, unanswered so far, is whether tissue accumulation is necessary in such a highly vascularised tissue as lung, where most common pathogens are probably extracellular. Penetration in other less accessible tissues, such as bone or prostate, is probably more important and beneficial [170,171]. Penetration in cerebrospinal fluid is certainly critical, and explains the appropriateness of quinolones for the treatment of meningitis [172]. A key feature of quinolones is their ability to accumulate in polymorphonuclear leukocytes and macrophages, with cellular concentrations at equilibrium being 5–20-fold higher than extracellular concentrations [173,174]. Influx probably occurs by simple passive diffusion, although active transport has also been suggested [175,176]. However, neither the mechanism of accumulation nor the subcellular localisation are known with certainty; the bulk of cell-associated quinolone is found in the soluble

fraction of cell homogenates [174,177], but part of the drug could have access to other organelles [178].

Quinolones show activity in a large series of models of cells infected by bacteria sojourning in different subcellular compartments [179], such as *Listeria monocytogenes* (cytosol) [180], *Salmonella* spp. (phagosomes) [181], *Legionella pneumophila* (endoplasmic reticulum; phagolysosomes) [182], *Chlamydia* spp. (inclusions) [183,184], *Mycobacterium* spp. (endosomes) [185], or opportunistic intracellular species such as *Staph. aureus* [186] or *H. influenzae* [187]. The efficacy of quinolones against intracellular pathogens has been confirmed in the corresponding animal models of infection [188–192]. Clinical studies demonstrating their efficacy in human infections, such as in atypical pneumonia [193–195] or tuberculosis, are now being published, [196–198]. However, in-vitro models show that the intracellular activity of quinolones is markedly lower than would be anticipated from their level of accumulation [179].

Cell-associated quinolones are also subject to active efflux, mainly because of the activity of ABC transporters known to confer multiresistance, such as P-glycoprotein and 'multiple resistant protein'. This active efflux will cause reduced accumulation of antibiotic in phagocytic cells, and hence a reduction in intracellular activity [177]. The polarised location of the ABC transporters, organic cation transporter and the organic anion transporter [199] at the surface of epithelial cells bordering the intestine, liver, kidney and blood–brain barrier means that they can modulate the resorption, distribution and elimination of quinolones [200–202]. In some cases, transporters can also act in a concerted fashion and cooperate with the detoxification metabolism [203,204]. Efflux also plays a major role in the protection of the central nervous system, since an inverse relationship has been observed between the propensity of fluoroquinolones to induce seizures [205] and their rate of efflux from the central nervous system [206].

## TOXICITY AND DRUG INTERACTIONS

Quinolone use is limited by a series of unwanted or adverse effects, most of which are mild but frequent, whereas others are rare but severe, and have caused the withdrawal of several class members (Table 3). Among these unwanted effects, some are class-related, meaning that they are not associated with any particular structural feature other than the general pharmacophore of the quinolones (Fig. 1). These effects are reported for all the molecules in the class, albeit with differences in incidence (e.g., gastrointestinal discomfort or arthralgia). Similarly, the ability of quinolones to form complexes with divalent and trivalent metal ions is linked intrinsically to the presence of the carboxylate function, and is therefore unavoidable. Oral bioavailability of quinolones can be retained by separating and delaying the administration of medications containing divalent and trivalent metal ions. Most of the other unwanted effects of quinolones are dependent on their substituents (Fig. 2), and are therefore specific to particular agents (Table 3).

The safety profile of quinolones is being updated constantly, since some of the adverse effects, such as cardiotoxicity, have recently attracted additional attention (see [207] for a review of current knowledge and an outline of strategies for early prediction during drug development), and use in large populations has revealed rare but severe toxicities, such as those observed with temafloxacin [208] and trovafloxacin [209], leading to a reassessment of registered compounds and a better appreciation of the true cost/benefit ratios. The introduction of new compounds will certainly be made more difficult because of these unforeseen events, and may lead to higher hurdles that must be passed before regulatory approvals are issued. One consequence for the commercialisation of new derivatives could be the initial restriction of new agents for indications or infections in those populations where the possible anticipated benefits are high (e.g., severe infections caused by organisms resistant to other classes of antibiotics), with broader use only when safety has been assessed satisfactorily. In parallel, proactive post-marketing surveillance studies [210] should be encouraged, since it is well-known that spontaneous reporting does not necessarily reveal the true impact of important unwanted side-effects.

## CLINICAL USAGE: THE PROS AND THE CONS

Table 4 presents a summary of the main indications for the use of quinolones, together with the arguments for and against such use. Considering

**Table 3.** Main side-effects of quinolones that contribute to the limitation of their use, the frequency observed, and the populations at risk

| Side-effect | Quinolone | Frequency | Population at risk |
|---|---|---|---|
| Genotoxicity | | | Pregnant women |
| Gastrointestinal effects | Fleroxacin, sparfloxacin, grepafloxacin[a] | > 10% | |
| (nausea, vomiting > diarrhea) | Others | 2–8% [243] | |
| Skin reaction: phototoxicity | Sparfloxacin[a], fleroxacin[a], lomefloxacin[a], Bay 3118[a] | > 10% [244] | |
| | Others | < 2.5% | Cystic fibrosis [245] |
| Skin reactions: rash | Clinafloxacin[a] | 4% [243] | |
| | Gemifloxacin | 2.8% [246] | Young women |
| Chondrotoxicity | Pefloxacin[a] | 14% [247] | Children, pregnant women |
| | Others | 1.5% in children (ciprofloxacin [248]) | |
| Tendinitis | Pefloxacin[a] | 2.7% [249] | Elderly, especially if on corticosteroid therapy [250] |
| | > Levofloxacin/ofloxacin ≥ ciprofloxacin > Others [252,253] | 0.4% | Athletes in training [251] |
| Minor CNS effects | Trovafloxacin | 2–11% dizziness | Elderly [254] |
| Major CNS effects | Levofloxacin | 0.026% confusion, alteration in mentation and affect [243] | Co-administration of NSAID or of inhibitors of CYP 450 [255] |
| | Fleroxacin[a] [256] | 8% insomnia [257] | |
| Cardiovascular effects | Sparfloxacin[a] (9–28 ms) | 2.9% | Female gender |
| | Grepafloxacin[a] (10 ms) | | Co-administration of other drugs (prolonging QTc interval or inhibiting CYP 450 metabolism) |
| | Moxifloxacin (6 ms) | | |
| | Levofloxacin (3 ms)[b] | | |
| | Gatifloxacin (2.9 ms) | | |
| | Gemifloxacin (2.6 ms) [246,258–260] | | Heart disease [254] |
| Minor hepatic effects (transaminase elevation) | Grepafloxacin | 12–16% transaminase elevation [243] | |
| | Others | < 3% [261] | |
| Major hepatic effects | Trovafloxacin[a] | 0.006% [243] | Treatment duration > 14 days [262] |
| Hypoglycaemia | Clinafloxacin[a] | | Co-administration of oral hypoglycemic agents [264] |
| | Gatifloxacin | | |
| | Levofloxacin (one fatal case [263] | | |
| Haematological toxicity | Temofloxacin[a] | 0.02% haemolysis, thrombocytopenia, renal failure [256] | |
| CYP 450 inhibition | Enoxacin[a], clinafloxacin[a] [256] > ciprofloxacin > lomefloxacin, ofloxacin > levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin [262] | | |

[a]Side-effects have contributed to the withdrawal or limitation in use.
[b]Further studies have been requested from the manufacturer, as recent pharmacovigilance reports document a significant increase of the QTc interval, mainly in patients with concurrent medical conditions or other medications [243,265]; see also [266] for a recent study in the province of Varese, Italy, using prescription data on all incident users of several antibacterial and anti-arrhythmic drugs during the period July 1997 to December 1999.
NSAID, non-steroidal anti-inflammatory drug; CNS, central nervous system.

the general negative aspects, the argument presented most frequently is the risk for selection of resistance. As discussed above, acquisition of resistance to quinolones seems to be a relatively easy process, which is at variance with β-lactams, at least in pneumococci, where the process of acquisition of resistance has taken decades [211]. This is well-illustrated for *E. coli* [212,213], but, as described above, the dynamics of the phenomenon may differ from one species to another [144]. The fact that certain quinolones are orientated towards either Gram-positive or Gram-negative bacteria, rather than having a narrow spectrum, may actually trigger resistance in less susceptible organisms. Another consideration is that the absence of precise aetiological diagnostic tests for a number of common infections contributes, indirectly, to the overuse of quinolones as empirical drugs. As for other broad-spectrum antibiotics, the correct approach probably involves a more prudent use, based on a correct assessment of the necessity and knowledge of how to prescribe an antibiotic correctly in the first place [214–216].

The second, and less disputed, argument stems from known or suspected toxicities in specific populations, such as pregnant or breast-feeding women, children, or elderly patients with co-morbidities. Although children are an important target population with respect to infections that respond well to quinolones, such as diarrhoea or Gram-negative meningitis, the combined risks of toxicity and the rapid spread of resistance should contraindicate treating children with quinolones, with the possible exception of children with cystic fibrosis (for whom close monitoring of bacterial susceptibilities is essential) or life-threatening infections with organisms resistant to

**Table 4.** Use of quinolones in the clinics: pros and cons

| Indication | Pros | Cons | References |
|---|---|---|---|
| All | PK/PD profile<br>Once-daily administration (as compared to β-lactams) | Not recommended for children, or breast-feeding and pregnant women<br>Prudent use in elderly because of increased risk of side-effects (co-morbidities, concurrent therapies)<br>Risk of development of resistance | [233,267–269] |
| Respiratory tract infections | | | |
| Acute exacerbation of chronic bronchitis | Higher potency against *Haemophilus influenzae* than macrolides and ketolides | | [14,19] |
| Community-acquired pneumonia | Easy switch to oral therapy<br>Coverage of intracellular pathogens<br>Polymicrobial infection | | [14,19,270,271] |
| Cystic fibrosis | Oral administration | Joint complications more frequent in cystic fibrosis patients | [268] |
| Intensive care infections | High activity against Gram-negative bacteria, including *Pseudomonas aeruginosa*<br>Lack of (or reduced) association with *Clostridium difficile* colitis<br>No promotion of vancomycin resistance in enterococci | Increasing resistance in nosocomial pathogens | [272] |
| Skin and soft tissue infections | Concentration in skin and blister fluid equivalent to serum levels<br>Coverage of Gram-positive and Gram-negative bacteria useful in polymicrobial infections | Too broad a spectrum for uncomplicated infections<br>Resistance increasing in *Staphylococcus aureus*, including MRSA<br>Combination with anti-anaerobic agent sometimes needed | [273,274] |
| Osteomyelitis | Oral route shortens hospital stay<br>Penetration into bone | Combination with anti-anaerobic agent sometimes needed (e.g., for diabetics)<br>Association with rifampicin for staphylococci | [275] |
| Abdominal infections | Adequate penetration in infected territories | Insufficient coverage of anaerobes | [276] |
| Intestinal infections | Good absorption, even in cases of diarrhoea, and high concentrations in stool | High resistance in *Campylobacter* and increasing resistance in *Salmonella*<br>Limited use in children, who are at greatest risk of infection<br>High cost in developing countries | [277] |
| Urinary tract infections | Elevated concentration in the urinary tract (including in the urine and in obstructed tractus) and in the prostate<br>Little dosage adaptation if renal function impaired<br>Easy switch to oral therapy | Increasing resistance | [278,279] |
| Sexually transmitted diseases | Intracellular penetration | Less effective than macrolides against *Chlamydia*<br>Resistance widespread in *Neisseria gonorrhoeae* (with the possible exception of gemifloxacin) | [280,281] |
| Meningitis | Unique dose efficient in prophylaxis<br>Penetration in CSF | Concentrations lower than in serum in non-inflamed meninges; use limited to very susceptible organisms (Gram-negative bacteria)<br>Use restricted in the population most at risk (children) | [282] |

MRSA, methicillin-resistant *Staphylococcus aureus*; CSF, cerebrospinal fluid.

other antibiotics. The situation may be more complex for elderly patients, for whom co-morbidities or co-medications clearly increase the risks (Table 4). However, these considerations should be weighed against the necessity to treat in the most effective way what are often recurrent polymicrobial infections, possibly involving organisms resistant to first-line antibiotics. Future studies should address these issues more carefully in order to better demonstrate the real

usefulness of quinolones in these populations [217].

The main advantages of quinolones are related to their PD (bactericidal activity) and PK properties. Their ease of use (oral route, once-a-day administration for some agents) is helpful, but compliance should not be the main issue for seriously ill patients. The easy switch to an oral therapeutic route can contribute to a reduction in the length of hospital stay, and has proven cost-effective in various settings and countries [218–223]. The latter argument might be quite compelling, since it can probably be applied for almost all types of infection in view of the wide distribution of quinolones in the body.

With regard to specific indications, the role of quinolones in urinary and digestive tract infections is not disputed [224,225]. Conversely, much debate exists in relation to their use in the treatment of abdominal and respiratory tract infections. The latter accounts for a variable extent of all quinolone usage among different countries (from almost no use to *c*. 50% of all quinolone consumption in the community), and the divergent guidelines published by scientific societies or national authorities [226] illustrate the difficulty of finding a consensus position in this area [21,227]. The advantages put forward concern the better activity of quinolones compared with macrolides against *H. influenzae* strains causing acute exacerbations of chronic bronchitis, the activity of a single drug against extracellular and intracellular pathogens, the quicker switch to the oral route, and the potential lower mortality for moxifloxacin in comparison with β-lactams for community-acquired pneumonia [228], although the registered dose of comparator used in this latter study may have been sub-optimal. However, most European guidelines have placed the so-called respiratory quinolones as second-line antibiotics only, with high-dose amoxycillin as the first choice (combined with clavulanic acid for a β-lactamase-producing organism). Such a recommendation is based on the assumption that early coverage of the so-called atypical organisms is not a priority, and that true resistance of pneumococci to β-lactams will remain low, despite continuous use [229]. The downside of the recommendation is the subsequent large-scale use of amoxycillin–clavulanic acid combinations (as seen from records of antibiotic prescriptions for respiratory tract infections), based on the premise that missing a β-lactamase-producing organism may put the patient at risk.

With respect to abdominal infections, the main reason for limiting the use of quinolones is the level of resistance, which, as explained above, has become alarmingly high in certain settings. For instance, in addition to *E. coli*, *Bacteroides fragilis* has a more than doubled mean MIC of levofloxacin and moxifloxacin in the USA in the last 3 years, so that monotherapy with fluoroquinolones in intra-abdominal infections may become unwise in the absence of appropriate surveillance and aetiological diagnosis [230]. This may be a consequence of the previous widespread use of quinolones, which may have enriched first-step mutants in the intestinal tract [231], although efflux pump systems also contribute to resistance [232].

Besides the still-open question of whether or not to use a quinolone for a given indication, the other question of importance concerns the selection of a specific compound within the class. The answer here is not disputable, based on the PK/PD concepts and resistance mechanisms discussed above. The best advice would undoubtedly be to use the most potent drug at the appropriate dose [233] for the right infection, based on likely aetiology, with ciprofloxacin preferred for Enterobacteriaceae and *P. aeruginosa*, and moxifloxacin (or gemifloxacin where available) for streptococci.

## CONCLUDING REMARKS

Fluoroquinolones were introduced with a fanfare in the mid-1980s as ciprofloxacin became the answer to many physicians' prayers for the treatment of Gram-negative infections, and as the spectre of multiresistant pneumococci made new agents more and more desirable. As long as these agents are used to treat the appropriate types of patients, and are not regarded by prescribers as the magic bullet, the effectiveness of the class will survive long into the present century. However, if they are dispensed with a lack of concern, then their day will conclude prematurely. As always, bacteria are smarter than humans, and both fundamental and very practical approaches are required to conserve antibiotics as useful agents and not as discoveries of the past [234,235]. Quinolones are no exception to this rule, which makes it essential that they are used in an educated fashion.

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