

Commentary

# Are the new quinolones appropriate treatment for community-acquired methicillin-resistant *Staphylococcus aureus*?

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## Abstract

The use of quinolones in the treatment of non-serious community-acquired methicillin-resistant *Staphylococcus aureus* is discussed. The new C8-modified quinolones may be suitable for such treatment but controlled trials should be carried out to ensure that the pharmacokinetics are such that there is little risk of resistance developing.

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## 1. Introduction

Newly developed C8-modified quinolones, such as garenoxacin and moxifloxacin, exhibit enhanced activity against *Staphylococcus aureus*. The arrival of these compounds coincides with the recent description of community-acquired, methicillin-resistant *S. aureus* (CA-MRSA), strains that appear to be uniformly susceptible to fluoroquinolones. The effectiveness of new quinolones against skin and soft tissue infections [1,2] suggests they should be carefully considered as an alternative to the intravenous use of vancomycin for treatment of non-serious CA-MRSA infection. However, resistance may threaten the long-term efficacy of these compounds. Below we review considerations underlying the potential use of the quinolones for treatment of *S. aureus*.

Traditionally, methicillin-resistant *S. aureus* infections that appear to be community-acquired have, on investigation, been associated with risk factors that link individuals to the health care system, implying infection with health-care-associated methicillin-resistant *S. aureus* (HA-MRSA) [3]. HA-MRSA usually has a multi-drug resistant phenotype that often includes ciprofloxacin resistance. Fortunately, HA-MRSA strains are not ubiquitous in the healthy community [4]. In contrast, strains causing

genuine CA-MRSA infections are usually unlinked to the health care environment [3], and they are frequently resistant only to  $\beta$ -lactams. The staphylococcal chromosomal *mec* DNA element, which encodes methicillin resistance among CA-MRSA, differs from that of most hospital strains [5], and it is associated with diverse *S. aureus* chromosomal backgrounds that differ from those of HA-MRSA populations [6,7].

CA-MRSA infections commonly involve the skin and soft tissue, resembling those caused by methicillin-susceptible community-acquired *S. aureus* [8,9]. Outside endemic regions [10–12], CA-MRSA infections are associated with a variety of populations, including children [13–17], men who have sex with men [18], prison inmates [18–21] and athletes [22,23]. Several treatment options are available for non-serious CA-MRSA infection, suggesting that the use of vancomycin is often unnecessary [24].

The susceptibility of CA-MRSA to quinolones encourages consideration of these agents as treatment. However, the rapid development of resistance to ciprofloxacin by *S. aureus* [25] serves as a warning. At issue is whether the new quinolones are active enough to prevent the development of resistance. We recently introduced a new activity measurement, the mutant prevention concentration (MPC), that may eventually help make that decision [26]. The MPC is the concentration of drug required to block growth of the least susceptible, single-step mutant (mutant MIC). Compounds that can be maintained at concentrations above their MPC at the site of infection are expected to rarely enrich

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resistant mutants because such an event would require the acquisition of two concurrent resistance mutations, which is itself a rare event [27]. When drug concentrations fall between the MIC and the MPC, i.e., inside the mutant selection window, resistant mutants are expected to be selectively enriched [28]. This expectation has been supported experimentally by Firsov and associates using an in vitro pharmacodynamic model with *S. aureus* and *Streptococcus pneumoniae* [29,30].

As predicted by the selection window hypothesis, serum concentrations of ciprofloxacin, a compound that readily selects *S. aureus* resistance [25,31], fall inside the window. In contrast, concentrations for newer quinolones, such as garenoxacin and moxifloxacin, are above MPC for 24 h with recommended doses [30,32]. Thus, by this in vitro assay garenoxacin and moxifloxacin show promise as anti-staphylococcal agents for strains, such as CA-MRSA, which are fully susceptible to ciprofloxacin.

With ciprofloxacin-resistant HA-MRSA, garenoxacin exhibits a low MIC, which has led to guarded optimism about its use against these organisms [33–36]. However, serum concentrations fall between MIC and MPC, just as was seen for ciprofloxacin with fully susceptible *S. aureus*. Thus use of garenoxacin for HA-MRSA is likely to lead rapidly to fluoroquinolone resistance. We expect a similar outcome with moxifloxacin.

Since MPC has not been measured in vivo for any organism, we do not know how well this in vitro measurement predicts success and failure in a clinical setting. For example, drug concentrations and mutation rates in the laboratory may differ from those at sites of colonisation and infection [37], and in vitro estimates cannot address transmission dynamics of pathogens and determinants responsible for maintenance of resistance alleles in a population. A further complication is bacterial load and total number of patients treated, since increases in either will increase the frequency at which new mutants are enriched. However, neither factor has been described well enough to predict the rate at which resistant strains will emerge. Thus clinical tests with both efficacy and resistance as outcomes are important before quinolones should be advocated for CA-MRSA.

A new agent, linezolid, is an alternative to the new fluoroquinolones for the treatment of CA-MRSA infections. An advantage of linezolid is that it can be used to treat children, a potential reservoir of CA-MRSA. To minimise the development of resistance to linezolid, we favour restricting its use to the treatment of serious and difficult-to-treat hospital infections. Hospital use is supported by the high cost of linezolid and by mathematical modelling [38]. The latter suggests that use of compounds for which resistance is not yet present may reduce the prevalence of resistant bacteria through an indirect effect on host colonisation status. In contrast, the use of antibiotics to which resistance is widespread is likely to promote resistance. Consistent with this hypothesis, fluoroquinolone use tends to increase the occurrence and persistence of multi-resistant staphylococci

[39], but not methicillin-susceptible strains [40]. Thus, the new fluoroquinolones may be most beneficial when used for community infections, provided that community-based resistance remains rare.

In conclusion, C8-modified quinolones are promising agents for treatment of CA-MRSA infection, but experience demands clinical studies that include a measure of resistance. In addition to guiding therapy, such trials would also provide a test of the selection window hypothesis. Complications are likely to arise from collateral damage, because *S. aureus* is a colonising and commensal organism that causes disease only in a minority of hosts. Ubiquitous use of older quinolones for other organisms may lead to CA-MRSA becoming resistant. The development of resistance in some geographical localities suggests that the window of opportunity for the quinolones may already be closing [41]. Increased community use of quinolones [42] and reports of health care-associated CA-MRSA infection and transmission [21,43] suggest that this trend will continue. More generally, prudence demands restraint on all quinolone use until it is known that selection of incidental resistance will not eliminate these agents as treatment options for a variety of bacterial diseases. Thus, while immediate patient cure is necessary, it may be an insufficient endpoint for quinolone use.

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