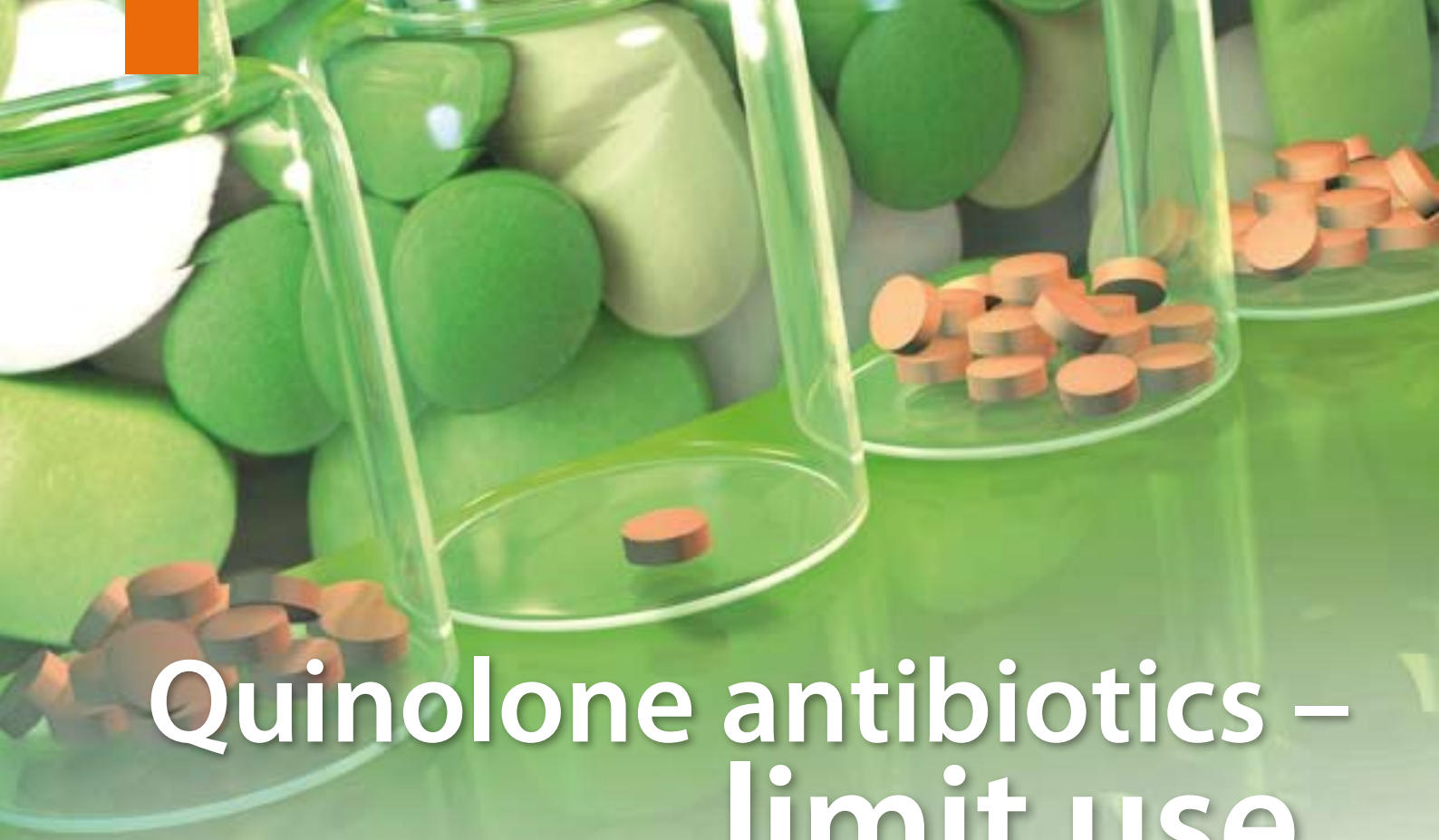

Quinolone antibiotics – limit use

Key concepts

- There are very few situations in general practice where quinolones are considered first line treatment
- Ciprofloxacin may be used for acute pyelonephritis, severe travellers' diarrhoea, severe cases of salmonellosis and for gonorrhoea (if known to be sensitive)
- Ciprofloxacin should not be used in pneumococcal pneumonia as it does not cover *Streptococcus pneumoniae* adequately
- Norfloxacin can be considered as a second-line treatment in urinary tract infections, if other antibiotic treatment has failed or is not suitable
- Elderly people are at increased risk of experiencing adverse effects to quinolones. Adverse effects of the central nervous system, such as anxiety, restlessness and insomnia, are of particular concern
- Rare but serious adverse effects of quinolones include tendinitis, QT prolongation and photosensitivity

There are few indications for quinolones in General Practice

Fluoroquinolones (commonly referred to as quinolones) are a class of broad-spectrum antibiotics, often implicated in antimicrobial resistance. Quinolones available in New Zealand include:

- Ciprofloxacin (tablets and eye drops)
- Norfloxacin
- Moxifloxacin (specialist use only)

Indications in general practice

Quinolones should be reserved for serious bacterial infections, and used only when there is no practical alternative.

There are very few situations in general practice where a quinolone would be considered first-line treatment. Ciprofloxacin may be considered for the treatment of patients with pyelonephritis, travellers' diarrhoea, gonorrhoea (if sensitive) and severe cases of salmonella. Norfloxacin may be considered as a second-line option (after trimethoprim or nitrofurantoin) for recurrent UTI

or for people who have failed to respond to a first-line antibiotic treatment for UTI. N.B. quinolones should not be used in pregnant women.

Pharmaceutical dispensing data in New Zealand indicates that the use of ciprofloxacin is continuing to increase, along with consistently high levels of norfloxacin. This is of concern as community prescribing of quinolones significantly contributes to antimicrobial resistance.

See Quinolone Prescribing Report, bpac[nz] April 2011 and July 2010.

Ciprofloxacin should be used only when there is no alternative[1, 2, 3, 4, 5,]

Spectrum	Ciprofloxacin is active against Gram-negative bacteria including *Salmonella spp.*, *Shigella spp.*, *Campylobacter spp.*, *Neisseria spp.* and *Pseudomonas aeruginosa*. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as *Streptococcus pneumoniae* and *Enterococcus faecalis.* Most anaerobic organisms are not susceptible.
Resistance	*Neisseria gonorrhoeae* resistance to quinolones increased from 6% in 2002 to almost 30% in 2009. Methicillin-resistant staphylococci are typically resistant to quinolones.
Uses in general practice	Acute pyelonephritis Travellers' diarrhoea – in moderate to severe cases. Gonorrhoea – only if isolate is known to be sensitive. Salmonellosis – antibiotics are not routinely required therefore only use for invasive or severe infection and in immunocompromised patients. Other indications include acute prostatitis, invasive pseudomonas infections, bone and joint infections and prophylaxis of meningococcal disease, when no alternative is available. Antibiotics are not routinely required for campylobacteriosis, but ciprofloxacin can be considered second-line if treatment with erythromycin has failed.
Inappropriate use	Should not be used for pneumococcal pneumonia. Repeated courses should be avoided in chronic prostatitis if bacterial involvement has not been confirmed, as chronic prostate pain is frequently not due to infection. Contraindicated during pregnancy and lactation.

Norfloxacin is a second-line treatment for urinary tract infections[1, 2, 3, 6]

Spectrum	Mainly active against Gram-negative pathogens
Resistance	Urinary isolates of *E. coli* resistant to quinolones have increased from 1.9% in 2002 to 7.7% in 2009. This varies with geographical location.
Uses in general practice	Norfloxacin may be considered for the treatment of urinary tract infections (UTI) in recurrent infections or where treatment with a first-line antibiotic has failed.
Inappropriate use	Not recommended as first-line treatment for urinary tract infections. It is not appropriate to use norfloxacin for upper urinary tract infections including pyelonephritis. Contraindicated during pregnancy and lactation.
Comments	Some DHBs have excluded norfloxacin from their formularies as it is no longer considered appropriate. Ciprofloxacin is more appropriate to use than norfloxacin if there is any suggestion of upper urinary tract involvement. The most appropriate antibiotic for the empiric treatment of uncomplicated UTI is either nitrofurantoin or trimethoprim.

Moxifloxacin is for specialist use only[1, 3, 4, 7]

Spectrum	Improved activity against Gram-positive and atypical pathogens, as well as anaerobes. Enterococci are likely to be intrinsically resistant.
Resistance	Moxifloxacin is a newer quinolone, developed due to resistance associated with other quinonlones. There is no current data on resistance.
Use	Many drug resistant *Streptococcus pneumoniae* isolates are susceptible to moxifloxacin.
Comments	Special authority criteria apply. QT interval prolongation may be more of a concern than with other commonly used quinolones. Moxifloxacin should not be considered active against *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*.

Adverse effects associated with quinolones

Common adverse effects include dyspepsia, dizziness and rash

The most common adverse effects associated with quinolones include gastrointestinal and central nervous system (CNS) toxicity such as nausea, diarrhoea, abdominal pain, dyspepsia, dizziness, headache and insomnia. Rash is also a common adverse effect. Rare but clinically important adverse effects include QT interval prolongation, tendinitis and tendon rupture (see Page 36), disrupted glucose metabolism, seizures and photosensitivity.[3, 7]

Patients should be well informed so that they can prevent or minimise the impact of any adverse effects if they occur.

Advise patients to:

- Increase fluid intake to reduce the risk of crystalluria
- Apply sunscreen when outdoors to avoid a photosensitivity reaction
- Cease taking the quinolone if tendon pain or swelling occurs

Use quinolones with caution in older people and people with epilepsy

Many of the adverse effects associated with quinolones occur more frequently in people with pre-existing risk factors, or in certain at risk groups, including older people and those with epilepsy.

Older people

Quinolones should be used at the lowest effective dose in older people. Renal function declines consistently with age and quinolone doses need to be reduced accordingly to avoid adverse effects. For example, an appropriate dose for ciprofloxacin in renal impairment is 250–500 mg, twice daily, if eGFR is 30–60 mL/minute/1.73 m^2 or once daily, if eGFR is less than 30 mL/minute/1.73 m^2.[4]

Quinolones are most active against Gram-negative bacteria

Quinolones are very active against aerobic Gram-negative bacilli and cocci including *Enterobacteriaceae*, *Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria gonorrhoeae* and are also active against *Pseudomonas aeruginosa*. They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as *Streptococcus pneumoniae*.[1] Quinolones are not effective against anaerobic organisms.

Adverse CNS effects are of particular concern in older people and may include anxiety, restlessness, nervousness, confusion, weakness, insomnia, euphoria, nightmares, hallucinations, psychosis and seizures.[3] Some of these signs and symptoms may be attributed to "old age", so it is important to consider quinolone use when such symptoms are reported.[3] Factors that increase the risk of these adverse effects include the dose not being reduced in renal insufficiency, electrolyte imbalance and a history of seizures.[3]

People with epilepsy or a history of CNS disorders

As CNS effects may occur with quinolone use, they should be used with caution in people at increased risk of seizures, with CNS disorders or in those concurrently using medicines which may lower the seizure threshold, e.g. bupropion. The potential for seizures, although very rare, may be increased with concomitant NSAID treatment.[3, 4]

Other at risk groups

Care is also required with quinolone use in people with:[4]

- Diabetes - glucose levels may be altered
- Myasthenia gravis – symptoms may be exacerbated
- G6PD deficiency – increased risk of haemolytic anaemia

Quinolones are generally not used in children

Quinolones are not recommended for use in children and adolescents aged under 18 years as they are associated with adverse effects on cartilage and tendons.[3] There are some specific circumstances, such as pseudomonal infections associated with cystic fibrosis, where the short term use of ciprofloxacin may be justified in children.[4]

Tendinitis and tendon ruptures are a rare adverse effect

A number of toxicological studies have confirmed that quinolones damage cartilage fibres, which on rare occasions can result in tenditinits and tendon rupture. This can occur even after a single dose of quinolone and the effect can persist for months.[3, 7] Tendon rupture has been reported within 48 hours of starting treatment, however, cases have also been reported several months after stopping treatment.

The risk of tendonopathy is increased in people aged over 60 years, people using long-term corticosteroid treatment and people with chronic kidney disease.[3]

Although this adverse effect is rare (estimated incidence rate 0.14% to 0.4%),[7] it is important to remember that:[4]

- Quinolones are contraindicated in patients with a history of tendon disorders related to previous quinolone use
- If tendinitis is suspected, the quinolone should be discontinued immediately.

The future for quinolones

Despite increasing resistance and adverse effects, quinolones are still an important antimicrobial medicine. Research and development goals include identifying new quinolones with expanded coverage to bacterial pathogens such as MRSA and multi drug resistant tuberculosis, as well as improved pharmacokinetic and safety profiles.[1]

A restrictive approach to the use of quinolones is recommended. Ideally they should be reserved for serious, life-threatening or difficult-to-treat infections, when other antibiotics cannot be used due to allergy or intolerance, or when the pathogen is resistant to alternative antimicrobial agents.

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Increasing resistance to quinolones is concerning

Antimicrobial resistance to quinolones is prevalent in many geographic locations in New Zealand, and includes both Gram-negative and Gram-positive strains.[1]

Urinary tract infections: community prescribing impacts on resistance patterns

Acute uncomplicated cystitis is one of the most common indications for prescribing antibiotics in otherwise healthy women.[6] Antimicrobial resistance to uropathogens causing uncomplicated cystitis has increased over time.[4]

Uncomplicated cystitis and pyelonephritis is mainly caused by *E. coli* (75 to 95%), with occasional involvement of *Enterobacteriaceae*, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus*. Local antimicrobial susceptibility patterns of *E. coli* should be considered in empirical antibiotic selection.[6]

While quinolones are an effective treatment for acute cystitis, the pattern of increasing antimicrobial resistance threatens their long-term usefulness. The resistance level of urinary *E. coli* infections to quinolones is approaching 8% (Table 1).[2] There is also concern about the association between quinolone use and increased rates of MRSA infections.[6]

Although local antimicrobial resistance rates are often skewed by data obtained from infections treated in the hospital setting, which are more likely to be complicated infections, quinolone resistance is also linked to community prescribing practices and therefore restrictive use is important.

Gonorrhoea – ciprofloxacin resistance greater than for penicillin

Penicillin was originally used to treat gonorrhoea but increasing penicillin resistance meant that empiric treatment with ciprofloxacin became more favoured. Data collected by ESR in 2009 reveals that resistance levels of *N. Gonorrhoeae* to quinolones is approaching 30%.[2] This far exceeds the acceptable 5% resistance threshold for first-line therapy. The rate of penicillin resistance for the same time period was approximately 12%.[2] Ciprofloxacin resistance is now more prevalent than penicillin resistance in most areas of New Zealand, but local variations do occur. Ceftriaxone injection is advised for treating suspected gonorrhoea, unless susceptibility data is available.

See "Treatment of sexually transmitted and other genital infections, BPJ 20 (April, 2009).

Table 1: Antimicrobial resistance to urinary *E. Coli*: data from hospital and community laboratories (ESR, 2002, 2008, 2009)[2]

	Trimethoprim	Fluoroquinolone	Nitrofurantoin
2002	21.7%	1.9%	1.5%
2008	22.5%	4.2%	1.6%
2009	24.1%	7.7%	1.6%