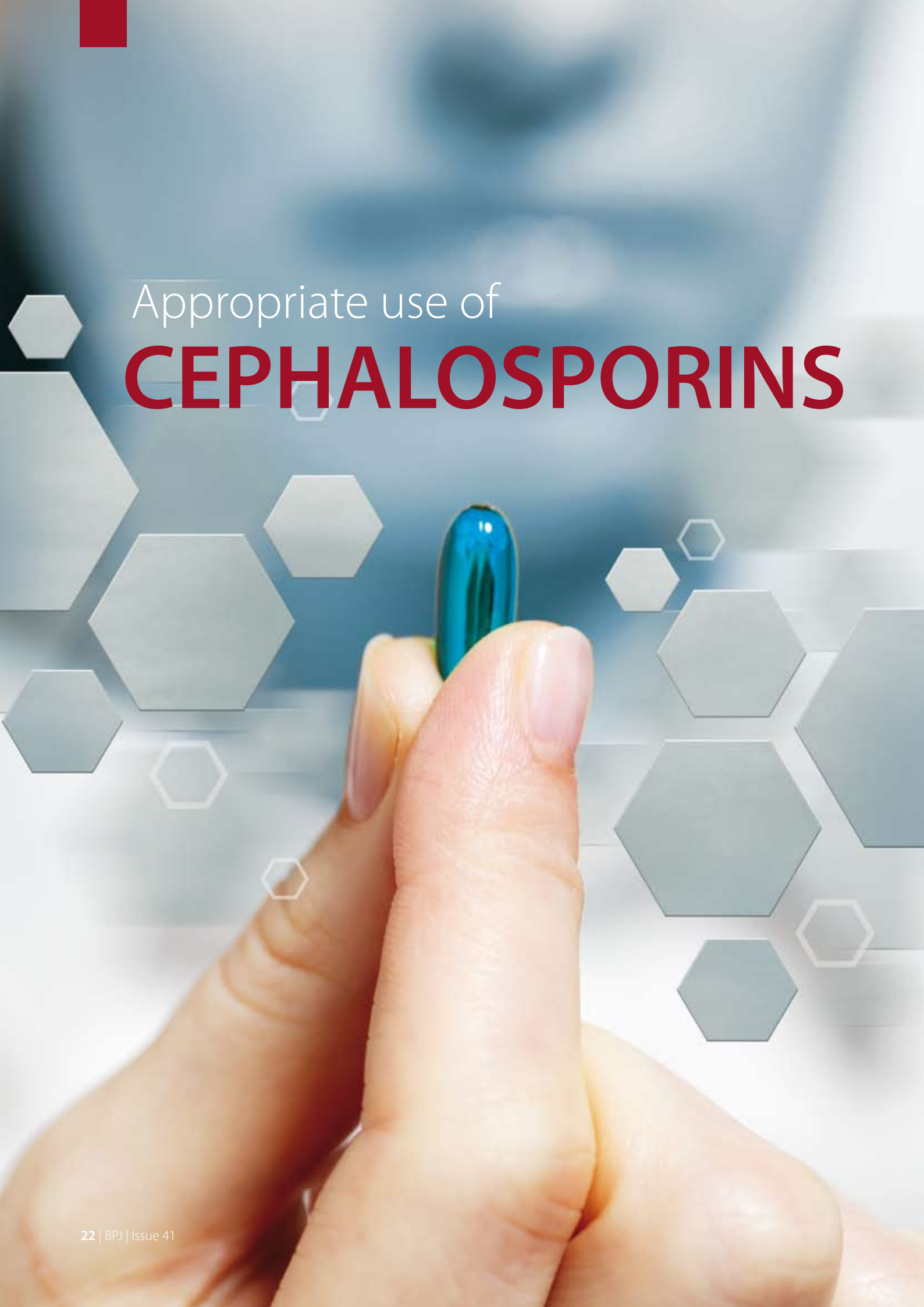

Appropriate use of CEPHALOSPORINS

Understanding cephalosporins

Cephalosporins are broad spectrum antibiotics similar to penicillins. They have a beta-lactam ring which interferes with bacterial cell wall synthesis by binding to penicillin-binding proteins, eventually leading to cell lysis and death.[1] Like amoxicillin clavulanate, cephalosporins should be avoided when a narrower spectrum antibiotic would be effective because they increase the risk of *Clostridium difficile*, MRSA and other resistant infections.

Cephalosporins mainly used in general practice are; **cefaclor**, **cephalexin** and **ceftriaxone** (injection). Other cephalosporins available on the Pharmaceutical Schedule are; cefazolin, cefoxitin and cefuroxime – these medicines are usually prescribed for patients undergoing dialysis and for patients with cystic fibrosis.

Cephalosporins are grouped based on their antibacterial properties and when they were introduced:[2]

- First generation cephalosporins include cephalexin and cefazolin. They have good activity against a wide spectrum of Gram-positive bacteria including penicillinase-producing staphylococci. However, they are not active against methicillin-resistant staphylococci (MRSA). Enterococci are resistant.[2]
- Second generation cephalosporins include cefaclor, cefuroxime and cefoxitin. They are more stable to hydrolysis by beta-lactamases produced by Gram-negative bacteria and therefore have enhanced activity against many of the Enterobacteriaceae, e.g. *Escherichia coli*, Salmonella.[2]
- Ceftriaxone is a third generation cephalosporin. They have the widest spectrum of activity compared to other generations of cephalosporins and are active against Gram-negative organisms, including many of the significant Enterobacteriaceae. They are also very active against streptococci.[2]

Key concepts

- There are few infections where cephalosporins are the antibiotics of first choice and their use should be avoided when other more narrow spectrum antibiotics remain effective
- Ceftriaxone is an appropriate first line treatment for gonorrhoea, pelvic inflammatory disease and epididymo-orchitis
- Ceftriaxone may also be used for suspected meningitis in patients allergic to penicillin (benzylpenicillin is first-line)
- Cefaclor may be considered as a second-line treatment for otitis media, sinusitis, cellulitis, diabetic foot infection and mastitis
- Cephalexin is a third-line alternative for the treatment of urinary tract infection in pregnant women (after nitrofurantoin and trimethoprim)

Indications for the use of cephalosporins

There are few infections where cephalosporins are the antibiotics of first choice (Table 1). Ceftriaxone may be used first-line for some genital tract infections such as gonorrhoea, pelvic inflammatory disease (PID) and epididymo-orchitis (if sexually transmitted pathogens are suspected). Ceftriaxone is also appropriate empiric treatment for suspected meningitis in people allergic to penicillin.

First line indications for cephalosporins

Gonorrhoea A single dose of ceftriaxone 250 mg given intramuscularly is the treatment of choice for gonorrhoea. N.B. Ceftriaxone is subsidised if prescribed for the treatment of confirmed ciprofloxacin-resistant gonorrhoea, and the prescription or MPSO is endorsed accordingly.

Research shows that ceftriaxone attains the optimal concentrations to prevent the development of step-wise

Table 1: First and second-line indications for cephalosporins

First-line indications	Second-line indications
Sexually transmitted infections Gonorrhoea – **ceftriaxone** in combination with azithromycin Pelvic inflammatory disease – **ceftriaxone** in combination with doxycycline and metronidazole Epididymo-orchitis – **ceftriaxone** in combination with doxycycline	**Respiratory tract infections** Otitis media – first-line amoxicillin, second-line erythromycin, co-trimoxazole or **cefaclor** Sinusitis – first-line amoxicillin, second-line doxycycline, co-trimoxazole or **cefaclor**
Serious infections Meningitis – **ceftriaxone** is an alternative to benzylpenicillin	**Skin infections** Cellulitis – first-line flucloxacillin, second-line erythromycin, roxithromycin, co-trimoxazole or **cefaclor** Diabetic foot infections – first-line amoxicillin clavulanate, second-line co-trimoxazole or **cefaclor** in combination with metronidazole Mastitis – first-line flucloxacillin, second-line erythromycin or **cefaclor**
	Urinary tract infections in pregnancy First-line nitrofurantoin, second-line trimethoprim, third-line **cephalexin**

For further information see "Antibiotics choices for common infections", bpac^{nz} (Apr, 2011).

mutations and resistance in Neisseria gonorrhoea.[3] Standard treatment with ceftriaxone has been shown to be greater than 95% effective.[4] Therefore a repeat test to ensure cure is not usually required as long as the patient is asymptomatic after treatment. Azithromycin (oral) is also routinely given when treating gonorrhoea, because co-infection with chlamydia is common.

Ciprofloxacin (500 g stat) is an alternative to ceftriaxone if cephalosporins are contraindicated (most often due to a documented allergy to beta-lactam antibiotics) or if the isolate is known to be sensitive to ciprofloxacin. Ciprofloxacin resistance is becoming increasingly common, with a prevalence of approximately 30% across New Zealand, varying by location.[5]

Pelvic inflammatory disease Broad-spectrum treatment is justified in pelvic inflammatory disease (PID) because the consequences of untreated infection can be serious, e.g. infertility, ectopic pregnancy. The recommended treatment which covers *N. gonorrhoea*, *Chlamydia trachomatis* and anaerobes is ceftriaxone 250 mg IM stat **and** doxycycline 100 mg, twice daily, **and** metronidazole 400 mg, twice daily, for two weeks.
Ceftriaxone is included in the regimen primarily to cover *N. gonorrhoeae.* Patients should be advised to inform sexual partners that they need to be screened and treated if positive for gonorrhoea and chlamydia.

Epididymo-orchitis if STI pathogens are suspected
Ceftriaxone 250 mg IM stat in combination with doxycycline 100 mg, twice daily, for two weeks is recommended for epididymo-orchitis if sexually transmitted infections (mostly chlamydia or gonorrhoea) are the suspected cause. Most guidelines recommend this regimen in men aged less than 35 years.[6] Other risk factors for sexually transmitted infection include urethral discharge and more than one sexual partner in the last 12 months.[7]

Ceftriaxone is an alternative to benzylpenicillin for suspected meningitis

Any patients with suspected meningitis should be immediately transferred to hospital. IV or IM benzylpenicillin should be given while transfer to hospital is being arranged. Ceftriaxone is an alternative to benzylpenicillin for people with suspected meningitis who have a history of immediate allergic reaction to penicillin. Although there is some cross-reactivity between penicillin and cephalosporin allergy, it is appropriate to use ceftriaxone given the seriousness of the infection (Page 26).

Second-line indications for cephalosporins

Cefaclor is used as a second-line alternative for some respiratory tract infections
Cefaclor is a second-line alternative to amoxicillin for suspected acute bacterial sinusitis. Other second-line alternatives are doxycycline or co-trimoxazole. However, in most cases antibiotics are not necessary at all. Eighty percent of sinusitis cases resolve in 14 days without antibiotics. In addition, antibiotics only offer marginal benefit after seven days.[8] Analgesics (e.g. paracetamol or NSAIDs) are the primary treatment for sinusitis.[9] Other treatments that may increase drainage of exudate and improve symptoms include: intranasal corticosteroids, sodium chloride 0.9% sprays and drops, steam inhalations and decongestants.[1] Purulent nasal discharge persisting for more than seven days, facial pain or maxillary tooth ache, unilateral sinus tenderness or fever suggest that bacterial infection is more likely and antibiotics may be appropriate in people with these symptoms and signs.

Cefaclor is also a second-line alternative (as are erythromycin or co-trimoxazole) to amoxicillin for acute otitis media, however, again antibiotic treatment is usually unnecessary. Most cases of acute otitis media can be treated symptomatically (e.g. with paracetamol) and arrangements for a follow-up appointment and antibiotic prescription can be made if no improvement occurs in the next 24 hours. Antibiotics can be considered earlier for those with systemic symptoms, children aged under six months or children under aged two years with severe or bilateral disease.

Serum sickness type syndrome with cefaclor

Cefaclor has been associated with serum sickness-like reactions, especially in young children, and typically after several courses. Symptoms include skin reactions, arthralgia and lymphadenopathy, which may last for six to twelve days. A full recovery usually occurs after stopping cefaclor.[1]

Probenecid increases the activity of cephalosporins

Probenecid reduces renal and gut secretion of cephalosporins (excluding ceftriaxone), increasing their half-life and prolonging their activity. Probenecid 250–500 mg can be given orally three to four times daily to increase serum and tissue antibiotic levels. Monitor for adverse effects of cephalosporins and halve doses of NSAIDs if taken concomitantly.[1, 6]

Cephalexin is appropriate as a third-line option for UTI in pregnant women

Cephalosporins are not associated with an increased risk of congenital malformations when used in pregnancy and are therefore considered safe to use.[1] However, it is recommended that cephalexin is reserved as a third-line option after nitrofurantoin (avoid at 36+ weeks) and trimethoprim (avoid during first trimester) for the treatment of UTI in pregnant women because it is a broad spectrum antibiotic and increases the risk of *C. difficile*. *C. difficile* infection can be life-threatening in pregnant women, with case reports of both maternal deaths and stillborn infants.[10]

Cefaclor may be used as a second-line option for mastitis, cellulitis and diabetic foot infections

Cefaclor has good activity against a wide spectrum of Gram-positive bacteria and also has activity against Gram-negative bacteria, particularly *Haemophilus influenzae*. This makes it suitable as a second-line option for treating mastitis (first-line flucloxacillin, other second-line option erythromycin) and cellulitis (first-line flucloxacillin, other second-line options erythromycin, roxithromycin or co-trimoxazole). It may also be used as a second-line alternative to amoxicillin clavulanate to treat diabetic foot infections (in combination with metronidazole). Co-trimoxazole plus metronidazole is another second-line option.

Issues associated with cephalosporins

Cross-reactivity with penicillin allergy is often over-estimated

Penicillin allergy is reported by up to 10% of people, however, many do not have a true (IgE mediated) allergy. True allergy is recognisable by clinical features such as urticaria, laryngeal oedema, bronchospasm, hypotension or local swelling within 72 hours of administration or a pruritic rash, developing even after 72 hours.[11]

Cross-reactivity between penicillins and cephalosporins of 10% is widely quoted, however, this is now believed to

be an overestimate. This estimation was largely based on reviews in the 1970s which included the following limitations:[11]

- Up until 1982, compounds relating to penicillin had been produced commercially using the cephalosporin mould and the cephalosporins used in these reviews were contaminated with penicillin
- The fact that people with penicillin allergy are three times more likely to have adverse reactions to other drugs was not accounted for
- The definition of allergy was imprecise and differed between studies

A more recent review suggests that the cross-reactivity between first generation cephalosporins and penicillins is closer to 0.5% than 10% and that second and third generation cephalosporins (e.g. ceftriaxone) are unlikely to be associated with cross-reactivity as they have different side chains to penicillin.[11]

It is still considered appropriate to avoid cephalosporins in patients who have a history of an immediate hypersensitivity (Type I allergy) to penicillins for mild to moderate infections when a suitable alternative antibiotic exists. However, in life-threatening cases (e.g. suspected meningitis) where a cephalosporin is essential because a suitable alternative is not available then a second or third generation cephalosporin (such as ceftriaxone, but excluding cefaclor) can be used with caution.[12]

Gonorrhoea shows potential signs of resistance to cephalosporins

Cephalosporins are now widely used for the treatment of gonorrhoea, following the development of resistance to fluoroquinolones. In New Zealand the recommended treatment is IM ceftriaxone which is the same advice given by the United States Centres for Disease Control and Prevention (CDC). United States data is now showing that the percentage of isolates with elevated mean inhibitory concentrations (the lowest concentration that will inhibit the growth of a microorganism) to cephalosporins (cefixime and ceftriaxone) has increased during the last ten years. These trends are concerning because the emergence of resistance to fluoroquinolones followed a similar pattern in the United States as what is now being seen with ceftriaxone. Cephalosporin treatment failures have also been reported in Europe and Asia.[13]

Although cephalosporins are still effective, the CDC is advising health-care providers to be vigilant for gonorrhoea treatment failures after using a cephalosporin (shown by persistent symptoms or a positive follow-up test despite treatment).[13]

Extended-spectrum beta lactamases

Extended spectrum beta lactamases (ESBLs) are produced by some bacteria and confer resistance to all penicillins and cephalosporins, including the extended spectrum cephalosporins (e.g. ceftriaxone, cefuroxime) that were originally designed to resist the action of older beta-lactamases. Many of these organisms producing ESBLs may also be resistant to other antibiotic classes, e.g., aminoglycosides, sulphonamides and fluoroquinolones, limiting treatment options for patients infected with ESBL-producing organisms.[14] ESBLs are most common in *Escherichia coli* and *Klebsiella pneumoniae*. The most typical type of infection they cause is urinary tract infections, however, they can cause serious infections in the blood stream, in which case they are likely to be resistant to many of the empirical antibiotics used for these infections.

Infections with ESBL-producers are most common amongst elderly people or those who have recently been in hospital, received antibiotic treatment or travelled overseas. The incidence of these infections has been increasing in New Zealand and globally and is of concern because these organisms are resistant to many commonly used antibiotics. As with other types of antibiotic resistance, minimising the spread of resistant organisms relies in part on only using antibiotics when necessary and at appropriate doses for the correct duration in both the community and inpatient settings.[14]

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