The pharmacological management of patients with cystic fibrosis largely focuses on maintaining lung function; however, other aspects of care, such as managing pancreatic insufficiency, are also important.

Cystic fibrosis pharmacological management

By Sarah Smyth, DipClinPharm

Maintenance of respiratory function is the most important aspect of cystic fibrosis (CF) treatment. Interventions to prevent respiratory deterioration include segregation of patient cohorts to reduce the risk of cross-infection, physiotherapy-assisted mucus clearance and prevention and prompt treatment of infection. Despite these measures, some patients' lung function may deteriorate to such an extent that lung transplantation needs to be considered; this is outside the scope of this article (see Clinical Pharmacist 2010;2:41).

Bacterial infection
Antibiotics are used to prevent, eradicate and control respiratory bacterial infections. Antibiotics commonly selected for patients with CF are summarised in Box 1 (p248). Additional information (including recommended doses) can be found in a Cystic Fibrosis Trust consensus document, accessible at www.cftrust.org.uk.

Prophylaxis Infections of the lower respiratory tract begin in the first few weeks of life for CF patients. At the time of diagnosis, CF patients are started on long-term oral antibiotics to prevent *Staphylococcus aureus* infection. Flucloxacillin is the most commonly used, but the suspensions that are currently available are often not acceptable to children because of their unpleasant taste; alternative antistaphylococcal antibiotics may need to be considered. When patients become chronically colonised with other pathogens, prophylaxis will need to change to cover for these organisms.

Treatment If a patient with CF acquires an acute respiratory tract infection (particularly common during the winter months), oral prophylactic antibiotic treatment can be stepped up to cover other common respiratory pathogens (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*). If patients are chronically colonised with *Pseudomonas aeruginosa*, ciprofloxacin might be prescribed to prevent pseudomonas-associated deterioration.

Typically, treatments for acute infections last for 14 days, after which patients will restart prophylaxis. Patients may keep a supply of oral antibiotics at home as “back-up” to take as directed by their clinician if they are showing signs of infection.

Second-line treatment When patients have episodes of acute infection that have failed to respond to oral antibiotics, intravenous treatment may be required.

Antibiotic selection is based on a patient’s recent microbiological profile and clinical symptoms. It is important to note that, in chronic infection, bacteria can develop resistance to various antibiotics and can have different antibiotic sensitivities from those causing acute infection. Accordingly, the antibiotic sensitivities for an organism isolated in the laboratory will not necessarily match those of the organism causing the acute infection, and therefore will not always correlate with antibiotic selection.

Usually therapy will include a combination of at least two intravenous (IV) antibiotics as an attempt to avoid antibiotic resistance (research comparing combination...
Now you can give previously untreated follicular lymphoma patients MabThera maintenance therapy (375mg/m² every 2 months for 2 years in responders to R-chemo induction). Continuing MabThera after induction almost halves the risk of relapse at 3 years compared with observation. So wouldn’t anything else seem like half measures?
Half measures in follicular lymphoma increase the risk

MabThera first-line maintenance almost halves the risk of relapse.

Why risk anything else?

www.MabThera-support.co.uk
treatment with monotherapy is under way). Treatment is usually continued for 10–14 days, extending to 21 days if required.

Oral candidiasis often occurs in patients on long courses of IV antibiotics and oropharyngeal antifungals (e.g., nystatin) can be given to prevent this. Information on medicines commonly used to treat pseudomonal infections can be found in Box 2 (p249). Pharmacokinetic considerations for antibiotic therapy are outlined in Box 3 (p250).

**Eradication** Despite long-term antibiotic prophylaxis, some patients will intermittently grow *P. aeruginosa* in their sputum cultures. These intermittent infections are managed using eradication protocols, which usually include a combination of nebulised aminoglycosides and systemic antibiotics. Eradication is successful in about 80–90% of cases. Despite this, most patients will eventually become chronically colonised with *P. aeruginosa*.

When patients have become chronically colonised with one or more of the common respiratory pathogens (*P. aeruginosa, S. aureus, H. influenzae*) aims of treatment are to:

- Reduce bacterial load
- Reduce inflammation
- Treat infective exacerbations promptly
- Reduce hospital admissions

Chronic *P. aeruginosa* infection is seldom, if ever, eradicated. Regular use of nebulised antibiotics is common for patients with chronic *P. aeruginosa* infection to reduce the rate of deterioration. Nebulised delivery of antibiotics allows around 10% deposition in the lungs (depending on the device used) and, although the concentration of the antibiotic in airway secretions may not always achieve bactericidal levels, it is thought that levels are sufficient to weaken bacterial virulence.

Authors of a recent Cochrane review concluded that the use of nebulised antibiotics for patients with CF reduces the number of hospital admissions and improves lung function. Nebulised antibiotics, alone or in combination with oral antibiotics, were better than no treatment for early infection with *P. aeruginosa*.

In another review, nebulised antibiotics did not enhance the clinical effect of IV antibacterial therapy for acute exacerbations. Therefore, nebulised antibiotics are usually temporarily stopped during acute exacerbations while patients receive IV antibiotics.

Nebulised antibiotics should be used after physiotherapy and bronchodilators to ensure maximum deposition in the lungs. Using bronchodilators before nebulised antibiotics also offers protection from bronchoconstriction that can occur during nebulisation. Colistin, tobramycin and gentamicin are the most commonly prescribed nebulised antibacterials.

In some centres patients who are chronically colonised with *P. aeruginosa* will elect to have routine IV treatment every three to four months to prevent deterioration and improve health status.

**Fungal infections**

*Aspergillus fumigatus* is a fungus that often colonises the airways of adolescents and young adults with CF. About 2–11% of CF patients will develop an allergic reaction to *A. fumigatus*, which is known as “allergic bronchopulmonary aspergillosis” (ABPA). ABPA causes lung inflammation, deterioration in respiratory function and, if untreated, further scarring and fibrosis. The symptoms of ABPA are similar to those of CF and, therefore, diagnosis can be difficult, involving chest imaging and measurement of immunoglobulins (IgE/IgG) and eosinophils.

Management of ABPA involves preventing acute exacerbations and treatment of acute episodes. The inflammatory response is treated with oral corticosteroids (usually a six-week course of prednisolone 0.5–1mg/kg daily, up to 60mg daily depending on severity of symptoms and inflammatory markers). Fungal colonisation is treated with itraconazole (see Box 4, p251, for practical considerations). Although there is little evidence that antifungals are useful for treating ABPA flares in CF patients, reducing the fungal burden in the respiratory tract may reduce the long-term risk of disease progression. For patients who have problems with recurrent ABPA, long-term prophylaxis with itraconazole may be considered.

Recently there has been interest in the use of omalizumab (a monoclonal antibody against IgE) to improve symptoms of ABPA, following success in case
reports. Further studies are needed before this therapy can be recommended.\textsuperscript{13}

\textbf{Mucus clearance}

Patients and parents are taught physiotherapy techniques that aid mucus clearance from the lungs. Inhaled bronchodilators (eg, salbutamol or salmeterol) can be used before physiotherapy. Mucolytics are useful adjuvants to physical therapies: dornase alfa nebules are used once daily (often before bed for patients who have physiotherapy in the morning); hypertonic saline nebules can be used immediately before physiotherapy.

\textbf{Inflammation}

Airway inflammation can be controlled using inhaled corticosteroids, ideally after physiotherapy to ensure optimal deposition in the lungs after mucus clearance.

Azithromycin is believed to reduce airway inflammation, which can improve lung function and prevent deterioration; the mechanism for this is unknown. Azithromycin is also sometimes used, along with other medicines, to manage \textit{Ps aeruginosa} — it does not kill the organism but can help reduce its growth in the lungs (it is thought to do this by interfering with adherence of the bacteria to epithelial cells and also with bacterial synthesis).\textsuperscript{13} Azithromycin is usually given once daily, three times a week. Generally, patients will take this in addition to their long-term prophylactic antibiotics.

\textbf{Nasal problems}

At one time or another, most patients with CF will experience chronic sinusitis or other nasal problems (eg, polyps). Management is difficult and treatment options are limited. Corticosteroid nasal sprays, such as fluticasone or mometasone, can help with pain and inflammation associated with sinusitis. Oral or nasal decongestants can provide some relief from symptoms. Underlying infections should be treated using appropriate antibiotics. Nasal irrigation or surgery may be required.

\textbf{Vaccination}

There are no differences in the routine childhood vaccinations recommended for newborns diagnosed with CF. Patients with CF should receive pneumococcal and annual influenza immunisations in line with Department of Health recommendations.\textsuperscript{16} H1N1 influenza vaccination was combined with the trivalent seasonal influenza vaccine in the 2010/11 season and is likely to be included in the seasonal vaccine in subsequent years.

\textbf{Gastrointestinal complications}

\textbf{Pancreatic insufficiency} Approximately 85\% of patients with CF will be affected by pancreatic insufficiency at some time in their lives.\textsuperscript{17} Patients usually present with symptoms of malabsorption (eg, poor growth or steatorrhoea). Enzymes are replaced by taking capsules containing pancreatic enzymes formulated in gastro-resistant granules (eg, Creon or Pancrease). These supplements are taken with all meals, feeds and snacks, and symptoms should resolve within a few days of starting treatment. An alkaline environment is thought to aid absorption of these enzymes, so ranitidine or omeprazole are often co-prescribed.\textsuperscript{18} The dose of enzymes is based on symptoms, dietary intake and weight gain. Generally, the dose should not exceed 10,000 units of lipase per kilogram of body weight, since higher doses can precipitate bowel obstruction.

\textbf{Box 2: Antipseudomonal antibiotics}

The decision to use one antipseudomonal medicine over another will depend on patient and drug factors. The most commonly used antipseudomonal drugs are the aminoglycosides, quinolones and various \textit{beta-lactams}. An aminoglycoside with an extended-spectrum \textit{beta-lactam} is usually considered for first-line treatment. No trial has shown significant clinical advantage of any particular combination over another.

\textbf{Quinolones} Ciprofloxacin has an advantage over other agents in that an oral preparation is available. However, long-term use as prophylaxis is not recommended because of a steady increase over time in its minimum inhibitory concentration for \textit{Pseudomonas aeruginosa}, which can lead to resistance. Ciprofloxacin is often the only oral antibiotic effective for CF patients with pseudomonal respiratory infections; it is twice as active against \textit{Ps aeruginosa} as levofloxacin and four times as active as ofloxacin.\textsuperscript{6}

\textbf{Beta-lactams} The \textit{beta-lactam} antibiotics that can be used as part of combination therapy include the carabepenem imipenem and meropenem, and the monobactam aztreonam (which has good activity against Gram-negative organisms such as \textit{Ps aeruginosa} but no activity against Gram-positive bacteria). Ceftazidime has generally good activity \textit{in vitro} and advantages include ease of parenteral administration, no requirement for monitoring drug concentrations and a flexible dosing schedule (two or three times daily).

\textbf{Aminoglycosides} The aminoglycosides gentamicin, tobramycin and amikacin inhibit bacterial protein synthesis and, for patients with CF, tend to be administered once daily. Aminoglycosides demonstrate a post-antibiotic effect, which means that bacteria that survive drug exposure will not metabolise normally for up to eight hours afterwards, despite undetectable drug concentrations.\textsuperscript{6} Although studies have demonstrated reduced toxicity with once-daily aminoglycoside regimens, serum monitoring of trough levels is still necessary (however, there is no consensus on interpretation of results). Patients starting aminoglycosides for the first time will usually have baseline auditory and renal function tests and at least annual assessment thereafter. There is a higher potential for nephrotoxicity with ill patients, who may be dehydrated, and those who are exposed to other nephrotoxic drugs such as loop diuretics and cephalosporins.
**Gastro-oesophageal reflux disease** In infants, gastro-oesophageal reflux disease (GORD) is usually treated with a prokinetic drug (eg, domperidone or erythromycin) combined with an antacid (usually Gaviscon Infant). GORD may be exacerbated in CF because gastrointestinal secretions tend to be more acidic. Drugs that reduce acidity (such as proton pump inhibitors or H2 antagonists) may be helpful and will also aid pancreatic enzyme absorption. Occasionally surgery may be required for GORD if an underlying structural abnormality is identified.

**Distal intestinal obstruction syndrome** Distal intestinal obstruction syndrome (DIOS), described in the accompanying article (p.239), is usually treated with lactulose or oral acetylcysteine. Acetylcysteine can be used prophylactically in patients who have recurrent episodes of DIOS. There is no preparation of acetylcysteine that is licensed for oral administration. The solution for injection can be diluted and administered orally or sachets can be obtained from special manufacturers.

When other treatments have failed, the contrast solution Gastrografin can be used orally or rectally to treat DIOS, although it is not licensed for this indication. Fluid intake should be encouraged for three hours following administration of Gastrografin and IV fluid replacement should be considered for neonates. If rectal instillation is necessary this should be under radiological supervision to ensure the required site is reached.

**Constipation** Because of the risk of DIOS it is important to treat signs of constipation promptly. Routine laxatives can be given in combination with dietary advice to treat symptoms.

**Rectal prolapse** Rectal prolapse occurs in about 20% of CF patients aged from six months to three years and is thought to be related to malnutrition due to pancreatic insufficiency. Prolapse usually resolves with pancreatic enzymes, and surgery is rarely required.

**Liver disease** It has been suggested that ursodeoxycholic acid may have beneficial effects in CF-associated liver disease through a number of mechanisms, including: an improvement in bile flow; displacement of toxic hydrophobic bile acids; and stimulation of biliary bicarbonate secretion. Several clinical trials involving paediatric patients with CF-related liver disease have demonstrated that treatment with ursodeoxycholic acid is associated with an improvement in serum liver enzyme levels, hepatic function and nutritional status.

Vitamin K is usually only administered if there is evidence of hepatosplenomegaly or abnormal clotting. For oral administration it is important that the water-soluble formulation menadiol is selected rather than fat-soluble phytomenadione, which is not well absorbed by CF patients.

**Nutrition** Patients with CF are at risk of deficiency of fat-soluble vitamins because of fat maldigestion and malabsorption. Low vitamin levels have been associated with compromised clinical status and reduced lung function. Routine supplementation of vitamins A, D and E should help prevent these problems. These vitamins should be taken with enzyme supplements to maximise absorption.
digestion and absorption. There are various multivitamin preparations available which contain vitamins A and D. Vitamin E is usually given separately as alpha-tocopherol acetate; chewable tablets, capsules and suspensions are available from special manufacturers. Doses of vitamin E can be expressed in terms of international units or milligrams depending on the preparation (75iu is equivalent to 50mg). More information, including recommended doses, can be found in the Cystic Fibrosis Trust consensus documents (www.cftrust.org.uk).

CF patients are also at risk of sodium chloride depletion, particularly during the first year of life and, for older patients, during the warmer months when they are perspiring more. Fluids and salty snacks should be encouraged, and sodium chloride supplements are usually taken in divided doses throughout the day.16

Patients receiving IV antibiotics, especially aminoglycosides, are occasionally found to have low serum magnesium levels.1 This is because nephrotoxic drugs can cause renal tubal damage resulting in loss of magnesium from the kidneys. The condition improves when IV antibiotics are stopped.1

ACKNOWLEDGEMENT Thanks to Catrin Barker, acting deputy chief pharmacist, and Octavio Aragon Cuevas, lead medical clinical pharmacist, both at Alder Hey Children’s NHS Foundation Trust.

References
4 Plummer A, Wildman M. Duration of IV antibiotic therapy in people with cystic fibrosis. Cochrane Database of Systematic Reviews 2011; issue 1.