

Cystic fibrosis

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ABSTRACT There are now more adult than paediatric cystic fibrosis (CF) patients and their life expectancy continues to improve. This means that CF patients will be more commonly encountered in a variety of hospital settings including fertility services, gastrointestinal (GI) clinics, diabetes clinics, surgical wards, and acute admissions. Cystic fibrosis units welcome early contact when patients are admitted to other units and it is important to have a structured approach to their assessment and management.

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INTRODUCTION

Cystic fibrosis (CF) is the commonest autosomal recessive disease associated with decreased longevity within the Caucasian population.^{1,2} The European population carrier frequency of 1:25 and disease incidence of 1:2,500 are familiar figures, but the changing composition of the CF population is perhaps not quite so widely appreciated. There are now more CF patients in adult than in paediatric clinics and advances in management have meant that patients not only live longer but also experience less early morbidity.^{1,2} The aim of this paper is to provide some background information and practical management advice with regard to CF for the non-specialist as it is increasingly likely that these patients will be encountered in diverse clinical settings.

Patients with CF are usually reviewed at regional or national CF units but may present acutely to their local hospital with a variety of complaints. Additionally, they may be referred for specialist assessment and management of (usually extrapulmonary) manifestations of the disease. Cystic fibrosis is a multi-system disease but the prominent respiratory component, bronchiectasis, is responsible for most of the morbidity and, ultimately, the mortality. Optimal management of the respiratory system is only achieved by adopting a multi-system approach and arguably the greatest impact on morbidity and mortality has been achieved with this understanding.

Translation of gene therapy to the clinic awaits the development of a reliable gene delivery system but small molecule agents are showing promise.^{3,4} Lung transplantation is an important intervention when respiratory function declines and patients become functionally limited. The preparation of patients for transplant and their post-operative management are significant challenges for all CF specialists and an excellent

relationship with the transplant centre is important. An appreciation of the information summarised below should provide an approach to some common CF presentations and enable good communication with regional/national CF units.

SCREENING AND DIAGNOSIS: DISEASE IDENTIFICATION IN A CHANGING POPULATION

The gene responsible for the manifestations of CF is called the cystic fibrosis transmembrane regulator (CFTR) and was identified on the long arm of chromosome 7 in 1989.⁵ Over 1,500 different mutations have been identified since and many more phenotypes are now diagnosed. There isn't a strict relationship between genotype and phenotype in CF but some relationships are apparent. The fact that there isn't a direct relationship is probably partly explained by the existence of modifier genes, the identification of which ought to provide new opportunities for therapeutic intervention.^{6,7} Environment, accessibility of healthcare, and psychosocial factors such as compliance, contribute significantly to disease manifestation. Screening for CF is possible pre-conceptually, antenatally, or postnatally. Pre-conceptual screening is useful where there is a family history of CF or if one of the couple has CF, where partners may be genotyped to give an indication of the risk of a child having the disease.

It is important to appreciate that genetics services will provide a variety of different screens depending on the clinical situation (the most common genotype, deltaF508, is always included and usually the most common 30 mutations geographically). More comprehensive genetic screening can be requested, particularly in the setting of a possible new adult diagnosis where the phenotype is suggestive but only one mutation is identified on a basic screen. Population screening has moved from antenatal

to newborn screening because experience has shown that termination of pregnancy as a result of a positive screen is a rare event, presumably because of the increasing life expectancy. Regardless of the results of screening tests, CF remains a clinical diagnosis and in the future there is likely to be debate as to the legitimacy of applying the CF label to genetically identified patients with very mild phenotypes.¹

THE CYSTIC FIBROSIS POPULATION

Most CF patients are diagnosed during infancy. Late diagnosis is, however, increasingly encountered. Patients must meet most of the following criteria in order to be diagnosed with CF:⁸

1. Genetic profile consistent with CF.
2. Clinical symptoms of frequent chest infections and/or malabsorption and/or failure to thrive (Table 1).
3. Abnormality of salt/chloride exchange as detected by raised skin salt or impaired nasal potential difference.

Unsurprisingly, respiratory physicians occasionally make new diagnoses in general respiratory clinics or in specialised bronchiectasis clinics. These patients usually combine bronchiectasis with a new (or recently appreciated) abdominal complaint such as diarrhoea, malabsorption, or pancreatitis, leading the astute clinician to request genetic testing. Another common route of referral is from fertility services, where the male partner is found to be azoospermic with congenital bilateral absence of the vas deferens (CBAVD). A subset of the CF population may have this finding as their only apparent manifestation of disease. Gastrointestinal physicians/surgeons will occasionally make the diagnosis in patients with recurrent pancreatitis or malabsorption.

It is important to be aware that a significant change in predicted median survival has occurred, from age 27 years in 1986 to 40.1 in 2013.^{2,3} This reflects better multi-system management of CF and a wider range of phenotypes due to the identification of more CF gene abnormalities. A further important shift in the CF population has been the increase in mean age at which *Pseudomonas aeruginosa* is first isolated.

CYSTIC FIBROSIS BRONCHIECTASIS: MONITORING, MICROBIOLOGY AND MANAGEMENT

Microbiology is of paramount importance in CF as evidence suggests that patients colonised with pathogens such as *P. aeruginosa* and *Burkholderia cepacia* have increased exacerbation rates, a more rapid decline in lung function, and ultimately earlier mortality, compared with patients colonised with *Staphylococcus aureus*.⁹ The majority of CF clinics are now segregated on a

Complication	Frequency
Infertility	98% male patients 20% female patients
Bronchiectasis	90% of patients surviving neonatal period
Pancreatic insufficiency	85% of patients with cystic fibrosis
Cystic fibrosis-related diabetes (CFRD)	50% by age 30 years
Cystic fibrosis liver disease	25% have chronic liver disease, 10% develop cirrhosis
Sinonasal polyps	10–25%
Distal intestinal obstruction syndrome (DIOS)	20% patients
Arthropathy	10% of adults with cystic fibrosis
Meconium ileus	10–20% of infants with cystic fibrosis
Low bone mineral density	10–25%
Pneumothorax	4–20%
Allergic broncho-pulmonary aspergillosis (ABPA)	7%

TABLE 1 Frequency of different cystic fibrosis (CF) complications.

microbiological basis with separate clinics for *P. aeruginosa*-colonised patients, *B. cepacia*-colonised patients, and patients with a milder microbiological profile (*S. aureus*, *Haemophilus influenzae* and arguably *Stenotrophomonas maltophilia*). Some units are more rigid than this and will run separate clinics for methicillin-resistant *Staphylococcus* (MRSA)-colonised patients, patients with potentially transmissible *P. aeruginosa*, and patients with multi-drug-resistant *P. aeruginosa*. Regardless of the clinic make-up, environmental cleaning procedures and strict hand-hygiene are essential. It is increasingly the norm that the patient stays in one room throughout a clinic session and the various members of the multi-disciplinary team (MDT) visit each patient in turn.

Pseudomonas aeruginosa

Eradication

P. aeruginosa was previously present in most patients (80%) transitioning from child to adult CF services (ages 14–16).^{10–13} It is generally a marker of significant bronchiectasis and is accepted to have negative implications from a morbidity and mortality perspective, compared to those patients colonised with *S. aureus*. The mean age at which patients acquire *P. aeruginosa* has increased (to age 25 years) in the last decade.^{10–13} This is a welcome development that reflects the widespread adoption of *P. aeruginosa*-eradication protocols.¹⁴ Usually a combination of nebulised and oral antipseudomonals are administered after a first isolation of pseudomonas and sputum is re-cultured after a defined course. If *P.*

aeruginosa is grown again then further eradication attempts may be made but at some point repeated eradication attempts will fail, and the patient is regarded as chronically colonised with Pa.

Long-term treatment

When chronic *P. aeruginosa* colonisation occurs there are a number of options for the long-term control of this pathogen, which slow the rate of decline in lung function over time. Nebulised antibiotics (colistin for example) is widely accepted as a useful therapy in Europe though it is not used in the USA because of the main side-effect of bronchospasm; this is despite the fact that strong trial evidence is lacking presumably because of the perceived benefit and the ethical implications of a placebo-controlled trial. A 28-day course of nebulised preservative-free tobramycin is usually used as a second-line agent in this setting although it has been shown to have a high eradication rate.¹⁵ Oral azithromycin (usually a long-acting preparation given three times per week) also has positive trial evidence and has the added benefit of ease of administration.¹⁶

Exacerbations

In acute exacerbations associated with systemic symptoms or a drop in lung function either at home or hospital administration of intravenous antipseudomonal antibiotics may be necessary (usually a combination of an aminoglycoside and a beta-lactam antibiotic such as a second/third generation cephalosporin or a carbapenem). Mild exacerbations where lung function may be stable or slightly reduced can be treated with oral antibiotics (usually in combination e.g. co-amoxiclav and ciprofloxacin). Adherence is an extremely important consideration in CF management and the time-consuming nature of nebulised delivery of antibiotics is problematic for some patients with busy work and social schedules. The advent of smaller, faster, more efficient nebuliser devices has been beneficial in this regard and the recent introduction of tobramycin delivered via an inhaler device is likely to prove even more popular.¹⁷

BURKHOLDERIA CEPACIA

The Burkholderia complex was first identified in CF clinic populations in the 1980s and rose to prominence when both patient-to-patient spread of the organism and rapid decline and death in a subset of colonised patients was demonstrated.¹⁸ This was a main driver of the clinic segregation and patient isolation policies described above and led to the abandonment of many patient-group social activities (e.g. CF holiday camps). We now know that the *B. cepacia* complex consists of nine distinct genomovars with the most commonly encountered in CF being *B. cenocepacia* and *B. multivorans*. These Gram-negative organisms are extremely resistant to conventional antimicrobial therapy by *in vitro* testing though it is clear that some patients derive benefit from combination

antibiotic therapy *in vivo*.¹⁸ *B. cenocepacia* is the organism that may be associated with a sudden precipitous decline in lung function followed by sepsis and death at any stage in the disease process (the 'cepacia syndrome', responsible for the early decline in the subset of 1980s patients described above). Additionally, colonisation by *B. cenocepacia* is a contraindication to lung transplantation because of the poor outcomes experienced in these patients (patients colonised with other genomovars may still be transplanted if other parameters are optimal).

Other bacteria

Stenotrophomonas maltophilia, *Achromobacter xylosoxidans*, and various anaerobic organisms are frequently isolated from CF sputum. Whether they are markers of severe disease or may play a part in disease progression is not clear. The consensus of CF physicians is that they may cause pulmonary exacerbations of bronchiectasis though data on lung function impact over time, exacerbation frequency, and mortality are not yet available. These organisms are highly resistant to conventional antibiotic therapy and represent a significant challenge to our current therapeutic armamentarium. Studies into the importance of these organisms and the development of novel antibiotic agents are needed.

VENOUS ACCESS DEVICES

The requirement for frequent courses of intravenous antibiotics means that many patients will need a permanent venous access. This often takes the form of a totally implanted venous access device (TIVAD). Essentially this is a tunnelled central line with a subcutaneous access port which is accessible with the use of a bespoke 'gripper' needle. These make administration of antibiotics more convenient and are an important part of outpatient management of infective exacerbations of bronchiectasis. It is important that these devices are only accessed by the patient or by professionals with appropriate training. Important complications can arise including blockage (most common), infection (bacterial and fungal), and thrombosis. These may present as recurrent pyrexia (especially when associated with TIVAD use, i.e. flushing or antibiotic administration), inability to flush the TIVAD or withdraw blood from it, or as arm/face swelling (essentially as superior vena cava obstruction [SVCO]). Investigation includes blood culture (both peripheral and TIVAD), imaging by ultrasound scan, lineogram (if line accessible for administration of dye) and more definitively CT venogram.

EXTRAPULMONARY MANIFESTATIONS OF CYSTIC FIBROSIS

Cystic fibrosis-related diabetes

Cystic fibrosis-related diabetes (CFRD) is essentially an insulin deficiency due to pancreatic destruction and usually requires replacement therapy to ensure that the

patient's weight is maintained. This element of the disease is underappreciated by clinicians and patients alike, but acute presentation with diabetic ketoacidosis is very uncommon and symptoms usually occur insidiously. There is a significant additional concern in CF where declining nutritional status may seriously affect respiratory health and potentially have an impact on longevity. Screening with glucose tolerance testing and serial blood sugar monitoring helps to make the diagnosis so that insulin therapy can be established.

Liver disease

Cystic fibrosis liver disease is relatively common, affects the biliary system (cholecystectomy is often required) and may become chronic leading to portal hypertension and possibly hypersplenism and oesophageal varices. An abdominal ultrasound is an annual review screening test for all CF patients and some will require surveillance endoscopy for early detection of varices. Another important consideration is that a patient with previously undiagnosed liver disease may present with haematemesis (which may be difficult to distinguish from, or be mistaken for, massive haemoptysis) caused by undetected oesophageal varices. The mainstay of chronic disease management is ursodeoxycholic acid.

Distal intestinal obstruction syndrome

In the gastrointestinal tract, failure of CFTR-mediated chloride secretion leads to enhanced sodium absorption and relative luminal dehydration, resulting in a slower bowel transit time and a predisposition to constipation. Distal intestinal obstruction syndrome (DIOS, the adult equivalent of meconium ileus) is common in the CF population and may be precipitated by a number of different events (Figures 1A and B). Diet is important and appropriate matching of pancreatic supplements to food fat content may prevent DIOS. In patients with troublesome bowels one of the first interventions should be review by a dietitian experienced in the management of CF. Another precipitating factor is dehydration where inadequate fluid intake, increased exercise, fever, or holidays to warm climates may contribute. Great care must be taken in the prescription of even weak opioid analgesics to CF patients as the constipating effect of these drugs becomes dramatically apparent in some. Analgesia may be an important part of CF management in settings such as intercostal drain insertion for pneumothorax or following insertion of percutaneous gastrostomy, but concurrent prescription of laxative medication is almost mandatory.

Where mild DIOS develops (constipation, mild abdominal discomfort) standard laxatives such as polyethylene glycol preparations (commonly Movicol™) or senna may be appropriate. In moderate DIOS with constipation, abdominal discomfort, and fecal loading on abdominal X-ray, advice should be sought from a specialist CF unit, but Gastrografin™ 30 ml three times a day (or equivalent

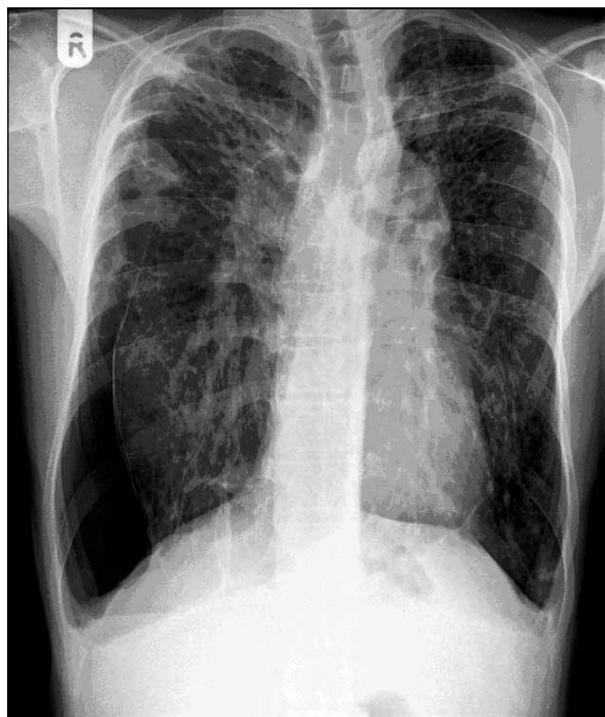


FIGURE 1A A 23-year-old patient shown at presentation with pneumothorax, which was successfully treated by intercostal drain insertion and pleurodesis.



FIGURE 1B Abdominal X-ray of the same patient (1A) two weeks later with analgesia-induced distal intestinal obstruction syndrome (DIOS) requiring nasogastric (NG) tube, suction, intravenous fluids, rectal Gastrografin™ and Klean-Prep™ via NG tube for resolution.

regimes) may be effective. In severe DIOS with abdominal pain, constipation, gaseous distension of bowel, and tinkling bowel sounds insertion of a large bore NG tube

with suction, administration of Klean-Prep™ via NG tube and Gastrografin™ by enema are often required.

Severe DIOS requires specialist management and patients should be managed in a CF unit with regular surgical advice. Surgery can usually be avoided if specialist medical management is instituted early. In our experience problems occur when CF patients present with abdominal pain out of hours, and are transferred directly to their local surgical unit, who are not experienced in managing this CF complication.

Rhinosinusitis

Nasal polyps and rhinosinusitis are very common in CF. Nasal symptoms may flare up with exacerbations of CF bronchiectasis where the only treatment required may be antibiotics appropriate to the known sputum microbiology. Nasal symptoms presenting in isolation are usually managed with oral steroids, steroid nasal drops, or nasal sprays. In more severe disease long-term macrolide therapy, nasal douching, or operative intervention by an ear, nose and throat surgeon may be required.

Infertility

Male patients with CF usually produce sperm but are infertile because they have a fibrous blockage in their vas deferens and so no means of sperm transport. They may still father children with the help of fertility services through procedures such as intra-cytoplasmic sperm injection (ICSI). Female patients with CF should all be regarded as fertile. The disease however reduces the chance of a normal pregnancy due to its effect on the fallopian tubes and on uterine secretions. Due to improvements in longevity and good general health, many female CF patients wish to have children. It is important to remember that pregnancy affects the course of CF and vice versa. There is a greater chance of the child having CF and there is a real risk that the child will become motherless. Therefore, careful assessment and counselling prior to consideration of a pregnancy are needed. The timing depends on the patient, but on the whole, this is better done during late adolescent years. Good communication between fertility services, CF units, transplant services, diabetes specialists, and the patient are absolutely essential.

LUNG TRANSPLANTATION

Lung disease is the primary cause of death for 80% of CF patients and transplantation is an important potential intervention.¹⁻³ Indeed, 14% of all lung transplants are for CF, and post-transplant survival is at the upper end of the spectrum.¹⁹ Lung transplant is usually discussed with patients when the forced expiratory volume (FEV1) falls below 30% and they are functionally limited. This may occur following a gradual decline or a sudden deterioration in health status. Recurrent pneumothoraces and recurrent, massive haemoptysis are other CF-specific

reasons for lung transplant. Multi-disciplinary care is imperative for the preparation and assessment of patients for transplantation. Optimal nutrition (body mass index [BMI] >17), bone density, control of extrapulmonary manifestations (diabetes, liver disease), and favourable microbiology are all very important to make transplant feasible. Arguably, however, it is psychological status that is the most formidable, potentially addressable barrier to transplantation. This can affect adherence to therapy and disease management strategies which prevent the physical optimisation required prior to transplant. Additionally, patients understandably struggle to come to terms with deteriorating health, and need a period of time to adjust psychologically to being referred for transplant. The transplant referral is a long process, and it can take many months from referral to active listing. Patients often wait up to two years for a transplant once actively listed and, in the UK, 50% of CF patients will die on the list before suitable lungs become available.² Thus it is important that the patient is referred in the 'window of opportunity' when they are 'bad enough to need it' (lung function is below 30% and functionally limited) but 'medically fit enough' for the procedure.

Post-transplant management is complex and requires good communication between the CF unit and transplant team should problems arise. Careful attention to lung function, other manifestations of CF, additional considerations of optimal control of blood pressure, and potential side-effects of immunosuppressant medications mean that multi-disciplinary care and frequent clinic assessments by the parent CF unit continue post-transplant. A chest X-ray of the 'new lungs' post-transplant, taken at the parent CF unit, is essential as a baseline should further respiratory complications arise at a later date (Figures 2A and B). Median survival rates post-lung transplant continues to rise and are currently above ten years.^{2,19} Drug interactions, which the non-transplant specialist may not be aware of, can cause serious consequences, thus discussion with the transplant team/CF unit is vital when a post-transplant CF patient presents acutely for emergency care.

NOVEL THERAPIES FOR THE FUTURE

The identification of a single-gene defect as causative of CF led to the hope that gene therapy might provide a cure.⁵ Unfortunately, there are significant problems with the delivery of durable, robust gene therapy and although work is ongoing there is currently no time frame for translation to the bedside. Furthermore, gene therapy is designed to treat lung disease only. However, small-molecule agents that aim to facilitate defective CFTR processing or function have now been developed. Ivacaftor has recently been investigated in patients carrying the G551D mutation (6% of all CF patients).⁴ The results were impressive. Administration of this

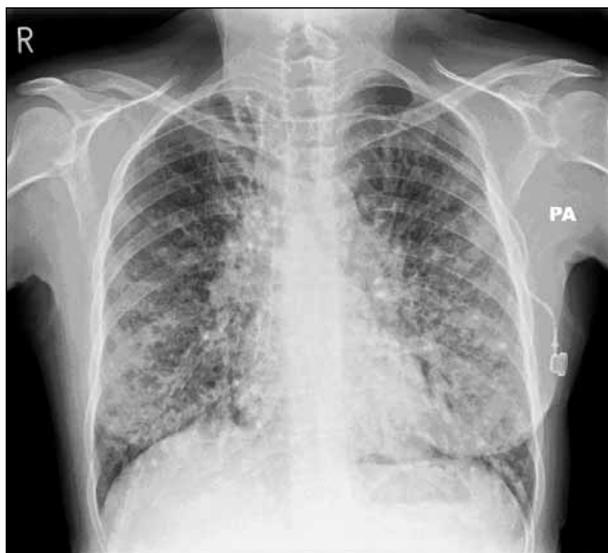


FIGURE 2A Chest X-rays of a 31-year-old female patient with CF taken when on the active lung transplant list.



FIGURE 2B Chest X-ray same patient (2A) with 'new lungs' five months post-transplant.

agent orally in two groups of patients, adults and children has resulted in an increase in lung function, body weight, and improvement of quality of life measurement that has lasted for 12 months. One of the prohibitive factors in prescribing this drug is its high cost. The fact that this high cost drug needs to be continued 'for life' in G551D patients has resulted in challenging discussions about funding of ivacaftor in the UK. Following successful lobbying by professionals and the CF Trust it is now available everywhere in the UK apart from Wales (decision expected May 2013).

CONCLUSION

There has been a significant improvement in CF patient longevity and the outlook is bright thanks to novel small molecule pharmacological treatments. CF units will continue to be the optimal setting for management of CF patients but they are likely to be more commonly encountered in alternative hospital settings, including: fertility services, GI clinics, diabetes clinics, surgical wards and acute admissions. While CF units will continue to welcome early contact when patients are managed by other teams it is important to have an appreciation of some of the unique challenges this condition presents.

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SELF-ASSESSMENT QUESTIONS

1. A 40-year-old lady has experienced increasingly frequent lower respiratory tract infections over the last year. She has had poor respiratory health all her life having started smoking age 13 years and reached a maximum habit of 40 cigarettes per day. *Pseudomonas aeruginosa* has been isolated in her sputum. High resolution CT (HRCT) reveals significant bronchiectasis with a predominantly upper zone distribution as well as some evidence of emphysema. Her sister, aged 45 years, is also a long-term smoker of 30 cigarettes per day, a regular at her GP practice and had a recent admission under the surgeons with pancreatitis.

Which ONE of the following statements is most accurate?

- A. It is likely she has CF because *Pseudomonas aeruginosa* has been isolated from her sputum and this pathogen requires defective or absent cystic fibrosis transmembrane regulator (CFTR) to achieve colonisation of the airways.
- B. If cystic fibrosis genotyping is negative or reveals heterozygosity another cause for bronchiectasis should be sought, such as primary ciliary dyskinesia.
- C. A normal sweat test would exclude cystic fibrosis.
- D. Pancreatitis is irrelevant because the pancreas is destroyed in cystic fibrosis.
- E. Cystic fibrosis should not be excluded without consulting a geneticist.

2. A known cystic fibrosis patient presents to Accident & Emergency at his local hospital with colicky abdominal pain, nausea, sluggish bowels, and a soft but tender abdomen (especially in the right upper quadrant). He has just returned from a tour of Spain with his football team and says that he sometimes feels like this when his chest is bad.

Reasonable investigation and management might include which ONE of the following?

- A. Abdominal ultrasound, abdominal X-ray and, dependent on results, oral Gastrografin™.
- B. Induced sputum, physiotherapy, and intravenous antibiotics.
- C. Intravenous fluids, nasogastric tube, and admit under surgery.

- D. Immediate blue-light transfer to regional cystic fibrosis unit.
- E. Start ursodeoxycholic acid for biliary disease.

3. A 23-year-old cystic fibrosis patient is awaiting lung transplant as she has significant bronchiectasis with an FEV1 of 26 ml/min. Her sputum is colonised by resistant *Pseudomonas aeruginosa* and she has home oxygen. Today she presents to medical receiving significantly more breathless with predominantly right-sided chest pain. Diffuse crackles are heard in the upper zones of the lungs and arterial blood gases (ABGs) on 2 litres O₂ via nasal prongs reveal PaO₂ 6.2, PaCO₂ 6, H⁺ 34, HCO₃ 28.

Which ONE of the following statements regarding management is most reasonable?

- A. Alert transplant team and blue light ambulance to cystic fibrosis unit.
- B. Chest X-ray, increase FiO₂, sputum culture and inform cystic fibrosis unit.
- C. Isolate patient, increase FiO₂ and start intravenous antipseudomonals.
- D. Start intravenous antipseudomonals and BiPaP (before patient tires) then inform cystic fibrosis unit.
- E. Chest X-ray, steroids, nebulised bronchodilators, antibiotics, and check d-dimer.

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