Perioperative care for the Cystic Fibrosis patient.

January 2020.
Dr Claire Dunstan,
Dr Christopher Francis,
Dr Kathryn Simpson.

Background

This project aims to provide a background knowledge of Cystic Fibrosis [CF] for the anaesthetist and give guidance and best practice for the perioperative anaesthetic management of the patient with CF presenting for surgery.

CF affects multiple organ systems. However, the impact of CF on the respiratory and gastrointestinal systems account for the majority of morbidity and mortality. Therefore CF patients are generally considered a high risk group for anaesthesia, particularly given their potential for postoperative respiratory complications[1].

The UK Cystic Fibrosis Registry reports 10,509 patients in the UK living with CF. It is the most common inherited life limiting condition in caucasians[3]. It is often diagnosed in the newborn and is one of the conditions screened for by the newborn heel prick screening program. Life expectancy for patients diagnosed with CF is increasing and the predicted median survival for those born in 2018 is now 51 years for Males and 44 years for females[12].

There are, at the time of writing; 301 patients registered with the ‘All Wales Adult Cystic Fibrosis Centre’ based at University Hospital Llandough (UHL). Transfer of care from paediatric services begins at 17, with the oldest patient registered at the Centre being 84 years old.

Whilst the All Wales Adult Cystic Fibrosis Centre is based at UHL. Patients with CF present for both elective and emergency surgery requiring surgical and anaesthetic care across Wales and at both sites within the Cardiff and Vales University Health Board. However, those with severe disease or requiring complex or major surgery should ideally be managed in a tertiary centre where specialist MDT input can be provided[1].

Current practice within Cardiff and Vale UHB

Over a 5 year period (2014-2018) 315 surgical procedures were performed on patients with cystic fibrosis (CF) in Cardiff and Vale - on average 63 surgical cases per year (these figures do not include cases performed elsewhere in Wales).

Of the 315 cases performed; 33 (10.45%) were admitted to either the PACU/HDU/ ITU post operatively. The most common destination was for ward care, particularly;

the CF ward at UHL. Day surgery has been successfully achieved for selected patients having minor procedures.

Over this time the most common surgical procedures performed in Cardiff were for; Vascular access (portacath insertion); Urological and renal surgery; Insertion of PEG and jejunostomy for feeding; ENT cases particularly sinus surgery and nasal polypectomy.

It is reasonable to think that with improving survival, the requirements for adult surgical services are and will continue to increase[3]. This will lead to both an increased workload and increasing complexity of the cases being performed.

As part of this project and with great thanks to the All Wales Adult Cystic Fibrosis Centre we have recorded all surgical cases performed on CF patients retrospectively over the last 5 years. We have then performed a pilot review to examine existing anaesthetic practice. 37 surgical care episodes have been reviewed to include paper notes review, review of anaesthetic record and review of electronic records relating to the individual cases. The findings of this pilot review are found below:

- Recorded ASA grade:

ASA grade:	ASA 1	ASA 2	ASA 3	ASA 4
No. of patients	0	16	16	5

- Urgency of surgery

Category of surgery	elective	emergency/urgent
No. of patients	21	16

- Only 13 of 37 were seen in pre op clinic or had any input from an anaesthetist pre op.

- Anaesthetic technique

Technique	GA	Neuraxia/RA	Sedation	unrecorded
No. of patients	31	2 (spinals with sedation)	2 (pure sedation	2

- Airway management for GA

Airway used	ETT	SGA	Unknown
No. of patients	14	16	1

- Perioperative complications
    - One passive aspiration under GA with LMA required suction, change to Ett and bronchoscopy - patient extubated post surgery and went back to the ward. No immediate complications following this.
    - One had a recorded desaturation and developed a T2RF after return to the ward - managed with nebulisers, chest physio and titration of oxygen - stayed on ward

- Post op destination

Destination post op	Day surgery	Ward	ITU/HDU/PACU	unknown
No. of patients	10	21 (CFU 11)	4	2

    - No unanticipated higher care admissions
        - 1 ITU admission - major head and neck
        - 1 HDU (planned) at UHL following reversal of stoma
        - 2 PACU cases (planned) at UHW
    - CF Unit was the commonest ward destination

- Pre op pulmonary function

Severity of lung disease (% predicted FEV1)	Mild >80%	Mod <79% >50%	Severe <49%, >30%	V. Severe <30%
No. of patients	19	11	4	3

    - 4 patients were included who had previous lung transplant 3 had mild disease predicted from their pulmonary function tests, 1 had moderate disease.
    - There was 1 patient actively on transplant waiting list. They had very severe lung disease.

- Domiciliary/Long term oxygen therapy (LTOT) or NIV
    - 1 patient on LTOT

- 28 of the 37 patients looked at had pancreatic insufficiency and were receiving enzyme replacement.

- 12 of the 37 patients had CF related diabetes mellitus (9 were inuslin dependent)

- BMI

BMI at time of surgery	<17	>17.1 <20	>20.1<25	>25.1<30	>30.1
No. of patients	6	8	16	3	4

- Day of surgery cancellations
    - 3 DOS cancellation -
        - an acute lower respiratory tract infection requiring admission to the CF ward at UHL.
        - A DVT and anticoagulation shortly pre op - delayed surgery
        - 1 cancellation for no bed being available.

- Average duration of surgery was 65mins

- 30 day survival
    - All survived at least 30 days,

- 1 year survival
    - 3 deaths occurred within the year post op.
        - At 5,6 and 8 months post op respectively
        - All had severe or very severe lung disease.
        - All ASA 4 at time of surgery
        - 1 died whilst on lung transplant list, 2 were not suitable for transplant due to low BMI
        - All died from respiratory complications of their disease.

Cystic Fibrosis -

- CF is a common genetic condition inherited in an autosomal recessive manner.
- CF affects 1/2500 live caucasian births. Carrier rate 1/25 in UK[2]
- Mutations in the CF transmembrane conductance regulator (CFTR) gene. Various mutations are described with variable genotypic and phenotypic manifestations[3].
- CFTR is a chloride channel expressed in a variety of epithelial cells in organs such as lung, sinuses, pancreas, liver, sweat glands, intestines and vas deferens[4].
- CF is therefore a multi-systemic disease
- Lung disease accounts for 90% of morbidity and mortality from CF[3]. Liver disease and diabetes are also important causes of morbidity and mortality.
- Therapy is primarily aimed at slowing progression of lung disease, preventing malnutrition and managing complications including CF related diabetes mellitus (CFRD).

Pathophysiology in CF

CF is a multisystem condition. The main systems affected which may impact on an anaesthetic are considered below

Respiratory system.

Mucus is thickened and mucociliary clearance is reduced. Mucus plugging occurs together with small airway collapse and air trapping. A cycle of airway inflammation, airway hyperreactivity, chronic bacterial colonisation and infection leads to airway destruction and bronchiectasis. There is typically an obstructive pattern of respiratory disease ultimately leading to hypoxia, hypercarbia and cor pulmonale[4].

Chronic bacterial colonisation is described with the following pathogens; pseudomonas aeruginosa, staphylococcus aureus, haemophilus influenzae, stenotrophomonas maltophilia, burkholderia cepacia, aspergillus, nontuberculosis mycobacterium (NTM) and MRSA[12]. Management of these pulmonary complications is complex yet important to maintain respiratory function.

As part of their annual CF review respiratory function results will be recorded. A target FEV_1 >85% is the target for those with CF and the aim is to preserve this for as long as possible. Helped by the patient, their family support unit, and a broad MDT including physicians, pharmacists, physiotherapists, and dietitians (maintenance of a BMI>22 for women and >23 for men is thought to be protective and preserve lung health)[2018 CF registry annual data report].

Patients with declining respiratory function may be considered for lung transplant;particularly those with severe disease (usually for those with a predicted 5 year expected survival <30%) In 2018; 58 Bilateral sequential lung (double lung) transplants were carried out[12].

Upper airway and nasal sinuses.

- Chronic sinusitis and nasal polyps are common.
- Nasal intubation should be undertaken therefore with caution[3]
- At Cardiff 29 ENT cases were performed in 5 years including nasal polypectomy and sinus surgery.

Upper GI pathology.

- Vitamins A,D,E and K are commonly deficient

- There is a decrease in volume and pH of pancreatic secretions[8]. This, together with the blockage of ducts leads to retention of pancreatic enzymes leading to fibrosis and destruction of glands. These patients are at risk of acute and chronic pancreatitis and often develop CF related Diabetes (CFRD)[8]
- Incidence of CFRD increases with age [8]. It is also associated with a deterioration of pulmonary function[11]
- Those with pancreatic insufficiency will be prescribed Creon (enzyme replacement) and this should be continued in the perioperative period, it is given 4-hourly.
- The liver can also be affected by the blockage and obstruction of biliary ducts. Cirrhosis and portal hypertension can occur. Liver transplants are sometimes considered and performed in this patient group
- There is an increased fat excretion and steatorrhea due to viscid duodenal fluid
- There is a higher incidence of gastroesophageal reflux in CF patients and so history of reflux should be directly asked[9]. In selected patients with no significant history of reflux supraglottic airways have been used successfully.

Lower GI

- Neonates with CF can have a first presentation of the disease with meconium ileus (up to 20% of infants with CF)[1]
- Distal intestinal obstruction syndrome (DIOS)– an obstruction within the intestinal lumen caused by thick tenacious stool[5] can be a cause of recurrent abdominal pain.
- Slowing of gastric motility with opiates may increase the likelihood of DIOS. As may dehydration and missed doses of creon. Multimodal analgesia with a consideration of regional techniques may help avoid DIOS in the postoperative period, together with reduced fasting times and continuing pancreatic enzyme replacement.

Low Bone Mineral Density

Impaired vitamin D and calcium absorption with increased bone catabolism through altered activity of osteoclasts and osteoblasts[7].

Psychological

CF is a lifelong, and life limiting disease. Patients with CF are often diagnosed at a young age, they have frequent interactions with healthcare professionals and the care they require can cause a huge burden on both the patient and their family. They may as a result have complex psychological needs. As with any chronic disease depression and anxiety can exist. This can lead to issues with concordance and refusal of treatment and ultimately progression of disease.

The patient and their family are often very well informed and involved in their decision making and the care they receive. Patients may have advanced directives and strong feelings about how they should be looked after in case of them becoming critically ill or dying. It would be appropriate to discuss their wishes with the surgeon and anaesthetist particularly when presenting for major or emergency surgery. Being seen in the POAC clinic would give an excellent opportunity for these discussions to occur.

Treatment aims

Management of CF is supportive and utilises a MDT. Patients and their families will often be experts in the condition. The aim of treatment is to maintain respiratory function as long as possible, optimise nutritional status, manage complications and ease symptoms [8].

Respiratory

- Regular physiotherapy (including airway clearance techniques; percussion and postural drainage) at least twice daily
- Mucolytic agents, including DNA-ase a nebulised mucolytic for those with CF, nebulised hypertonic saline and mannitol are also used[8]. These can reduce the frequency of exacerbations.
- Inhaled/nebulised bronchodilators
- Inhaled/systemic corticosteroids/anti-inflammatories
- Antibiotics – inhaled, oral or IV preparations all used in short or long term/ suppressive or prophylactic courses.

- 6.5% were using Long term oxygen therapy and 2.2% using domiciliary NIV (non-invasive ventilation)[12]
- Bilateral sequential lung transplantation was considered for 247 patients in 2018 with 104 accepted and 58 patients received lung transplants [12]

Nutrition

Nutritional requirements may be hard to achieve in CF patients. Many require enteral or parenteral supplementation.
The use of supplemental enteral feeding occurs most commonly via nasogastric and PEG (or button) routes. Occasionally jejunal feeding and rarely TPN may be required. However even with feeding support, nutritional targets may not always be met. Especially during illnesses.
Minimising the perioperative starvation time is therefore important.

The use of enzyme replacement (CREON) should be continued 4 hourly as normal pre and post op.

Glycaemic control should be monitored for all those with CFRD. Even those not yet on insulin therapy may require exogenous insulin in the perioperative period. Early recognition and starting insulin replacement therapy can be important to improve health outcomes.

Anaesthetic considerations

Pre-operative

These are complex patients whose pre-optimisation and MDT input is important prior to elective surgery[1].

- Pre-op planning should begin at the time of booking for surgery, the CF team should be informed of any patient being booked for theatre at the time of booking.
- All CF Patients should be seen in the Preoperative Anaesthetic clinic (POAC). For a discussion of anaesthetic risk, consent and for pre optimisation if possible.
- A date for surgery should be provided as early as possible to allow for logistical planning.
- Pre optimisation should involve the CF team and will include a medical and medication review. Pre optimisation in these patients will likely involve intense daily physiotherapy, and where appropriate a preoperative admission to the CF centre.

- The patient's CF annual review will be available via the 'Welsh Clinical Portal'. This will have lots of valuable information, including complete past medical history, current medications, weight, and recent investigations which should include at least yearly spirometry and in some cases CPET, echo and shuttle walk test results.

- For emergency surgery work-up should include a thorough history and examination, CXR, ECG, baseline capillary/arterial blood gas analysis, and spirometry where time permits.

- In those with CF related diabetes, the usual anaesthetic considerations apply. Including; Placing first on the list whenever possible, adjusting anti-diabetic medications as per local guidance and the use of variable rate intravenous insulin infusion if necessary (ie. missing more than one meal, emergency surgery, poorly controlled type 1 DM, HbA1c >69mmol/mol) [AAGBI guidelines on perioperative management of diabetes]

- Minimise starvation times and continue pancreatic enzyme supplementation. Creon should be continued 4hrly through any fasting period.

- Consider use of PPI pre-operatively as CF patients have an increased incidence of GORD [9].

- Patients receiving systemic steroids may require supplementation perioperatively. As per the usual steroid cover guidance.

- Those who are immunosuppressed due to transplant surgery should have care taken to ensure appropriate continuation of their anti-rejection medications. If unable to tolerate oral immunosuppressants these can be given IV but must be prescribed by trade name. For these patients it may be necessary to seek advice from the CF &/or the transplant team.

- CF patients should have provision for pre op, intra op and post op administration of nebulisers.

- Arrangements should be made for chest physio pre and immediately post op where required.

- ~10% of CF patients operated on are admitted to the PACU/HDU/ITU post operatively. Post op destination should be considered particularly higher risk patients or those having major surgery. The most common post op destination is back to the CF ward at UHL. Day surgery has been successful for selected patients having minor procedures.

The risks of pulmonary complications are high in this patient group. Those at highest risk are those with;

- Prolonged duration of surgery/ventilation

- Surgical site; upper abdominal, thoracic incisions carry the highest risk
- NGT insertion is an independent risk factor for postoperative respiratory complications.
- Emergency surgery

History:

Usual PMH, DH and anaesthetic history, plus include

- Recent admissions
- Evidence of current active chest infection, chronic airway colonisation or infection and antibiotic history.
- Assessment of functional and performance status.
- Presence of pancreatic insufficiency, diabetes mellitus, and GORD.
- Presence of a TIVAD (totally implantable venous access devices)
- Transplant plus any related steroids/immunotherapy

Investigations;

- FBC
- U&E
- LFT
- Coagulation study
- Blood glucose
- CXR
- ABG/Capillary BG (baseline)
- Spirometry – in CF patients an obstructive pattern is typically seen.
    - A decrease in FEV<1L especially in hypoxaemic patients may indicate need for postoperative ventilation[3].
    - FEV1<61%, PaO2 <9.3KPa, PaCO2 >6.6KPa may also predict an increased risk of respiratory complications post op[3,1].
    - ECG, ECHO – Presence of right ventricular hypertrophy and cor-pulmonale are sinister signs – indicating advanced, decompensated disease.
    - CPET may be useful in situations where time allows.

Intra operative

Monitoring

- Full AAGBI monitoring is mandatory.
- Arterial line insertion facilitates frequent blood gas analysis and maintaining baseline blood gas results should be a target particularly those presenting as an emergency, advanced disease or for major surgery.
- Use of cardiac output monitoring may be useful in those with cor-pulmonale or those undergoing major surgery.

Anaesthetic technique

- Consideration of regional techniques may avoid the need for general anaesthetic and provide good pain relief post op in those who still require a GA.

- Nasal intubation should be avoided where possible.

- TIVA or volatile are appropriate choices.
    - Of the volatile anaesthetic agents; sevoflurane is preferred due to its tendency to produce bronchodilation.
    - Avoid N_2O due to effects on pulmonary vascular resistance.

- Where appropriate a spontaneously breathing patient through a supraglottic airway could minimise the detrimental respiratory effects of general anaesthetics. However, an ETT does allow for tracheal suctioning of what can be copious purulent secretions intraoperatively.

- Where invasive positive pressure ventilation is required lung protective ventilation strategies should be used i.e.
    - Minimising pressures (increased risk of pneumothorax)
    - Adjustment of inspiratory: expiratory ratios should be considered.
    - Tidal volumes 6-8ml/kg
    - PEEP 5-10cmH_2O
    - Avoid aggressive ventilation to restore a ‘normal’ $PaCO_2$ - maintain baseline values avoiding hypoxia.
    - The shortest period of ventilation possible.

- Avoidance of hypothermia, hypoxia, hypercarbia, and acidosis to avoid increasing pulmonary vascular resistance which can precipitate acute right ventricular failure

- Gases should be humidified (including pre and post operatively).

- There should be provision for giving nebs pre, intra and post op.
    - Giving a dose of nebulised DNAse - dornase alpha 2500
        - Dosage one 2.5mg vial.
        - DNAse is kept in the fridge,
        - Available on formulary. However, patients will usually be prescribed this pre op by the CF team. Either the patient or the Physiotherapist who will ideally accompany the patient to the theatre will bring this with them.
        - Hypertonic saline pre extubation would be an alternative in the event DNAse was unavailable for whatever reason.
    - Bronchodilator nebs may be required

    - Chest physio in recovery where possible (Usual practice for Physiotherapist to accompany patient to theatre.)

- Clean emergence with avoidance of long acting sedatives, full reversal of NMBDs
- Multimodal analgesia, including consideration of regional techniques to reduce opioid use with an aim to avoid respiratory complications and the risk of DIOS (Distal intestinal obstruction syndrome.)
- Caution with positioning as often cachectic and malnourished.
- Ensure optimal reversal of neuromuscular blockade and avoidance of long acting sedatives.

Post-operative

- Goal is to minimise the risk of respiratory tract infection.
- Chest physiotherapy as soon as possible post op.
- Early use of positive expiratory pressure devices to aid clearance of secretions in those patients who normally use these.
- Post op nebs, humidified oxygen, and incentive spirometry.
- Multimodal analgesia to reduce opioid use, particularly bearing in mind these patients are at risk of DIOS. Prescribe additional laxatives alongside any opioids to minimise this risk.
- Early mobilisation.
- High care bed/PACU would be appropriate for those with advanced respiratory disease or those having major surgery.
- Those with FEV1<1L, PaO2<9.3KPa, PaCO2>6.6KPa may require an elective period of postoperative ventilation[1,3]. Those with worse baseline respiratory function who are anticipated to have respiratory issues should be discussed with CF centre and HDU/ITU prior to anaesthesia.

Special considerations;

The CF patient with failing RV

It is difficult to quantify how many patients with CF presenting for surgery will have cor pulmonale or pulmonary hypertension. It is reasonable to suggest that those with more severe lung disease will be most at risk[1].

In these patients RV failure could be precipitated preop, intraop or post op by an acute rise in afterload or ischaemia (beware hypotension). Priority for managing this scenario is to reduce afterload and preserve coronary perfusion.

Acidosis, hypoxia, hypercarbia and hypothermia will all increase pulmonary vascular resistance. Avoidance of these together with maintaining coronary perfusion pressure are clear goals in anaesthetising these patients.

Inotropes such as milrinone, or enoximone will produce pulmonary (and systemic) vasodilation, they may need to be combined with alpha-adrenoreceptor agonists to maintain SVR and therefore coronary perfusion.

Inhaled nitric oxide or nebulised prostaglandins may also be of some help reducing PVR (although may worsen shunt) and can be used in these situations.

Notes on those with previous lung transplant

CF patients who present post lung transplant will have undergone bilateral sequential single lung transplants (ie a double lung transplant with separate bronchial anastomosis for each lung). This is advantageous because of improved pulmonary mechanics and compliance, this also avoids exposure of the donor lung to infection from the native.

Gaining advice from the transplant team will prove helpful prior to theatre for advice on managing immunosuppression, as the plasma levels and the effectiveness of immunosuppressants in the perioperative period can be altered by surgical stress response/acute illness, and disruption of the usual regimen[17].

Immunosuppression, whilst necessary in this patient group, can cause a number of problems including; hypertension; diabetes; renal and hepatic toxicity; it is also linked to malignancy; there is significant potential for drug-drug interactions; and the risk of overwhelming systemic infection - which may not exhibit typical signs of infection[13,14,15].

Unfortunately there is little data available on the interactions between anaesthetic drugs and immunosuppressants[15]. Therefore discussion with the transplant service will be of use as they have the most clinical experience managing these patients.

It is thought that:

- Induction agents propofol, thiopentone as well as volatiles such as sevoflurane are safe to use and well tolerated[15].
- Opiates and benzodiazepines may have increased effects and dosing adjustments may need to be made[16, 18, 19].
- Some muscle relaxants may have prolonged action (Rocuronium and Vecuronium)[15].

- Antibiotics and antimicrobials may affect plasma concentration of immunosuppressants such as cyclosporine and tacrolimus[15,16,18].
- NSAIDs have an increased risk of side effects (renal and GI especially) and can increase the plasma conc. Of the immunosuppressants[15,20].
- Bupivacaine and ropivacaine can be safely used. Although lignocaine can cause prolonged QTc - and affect cyclosporine, tacrolimus levels[17,20].
- Drugs altering the QTc - such as ondansetron, droperidol, haloperidol may have an exaggerated effect in this regard[15].

Anaesthetic management of the patient with previous bilateral sequential single lung transplant:

- Aim here is to avoid ventilator associated graft/lung injury
- FiO_2 should be aggressively weaned
- Minimise ventilation time
- Tidal volumes not to exceed 6-8ml/kg
- Keep peak inspiratory pressures below 30cmH_2O
- Gentle volume resuscitation only. Excessive fluid should be avoided as the graft will be susceptible to low pressure pulmonary oedema - due to interrupted lymphatic clearance [14,15,20]
- May be useful to use bronchoscope to identify any strictures present - smaller endotracheal tubes should be available.
- Cough reflex is lost below the anastomosis (cough reflex of the carina should remain intact)
- Mucociliary clearance will be poor and chest physio will be necessary post op.
- PVR and hypoxic pulmonary vasoconstriction is expected to be preserved
- Bronchomotor tone is preserved
- Normal regulation of breathing (chest wall efferents) is observed

References

1. Fitzgerald, M. and Ryan, D. 2011, Cystic Fibrosis and Anaesthesia. *Continuing Education in Anaesthesia Critical Care and Pain.* 11(6), pp. 204-209.
2. https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/what-causes-cystic-fibrosis
3. Huffmyer, J.L., Littlewood, K.E. and Nemergut, E.C. 2009. Perioperative management of the adult with cystic fibrosis. *Anaesthesia and Analgesia.* 109 (2009), pp. 1949-1961.

4. Davies, J.C., Alton, E.W.F.W. and Bush, A. 2007. Cystic Fibrosis. *BMJ*. 335:1255 https://doi.org/10.1136/bmj.39391.713229.AD
5. Sabharwal, S. 2016. Gastrointestinal Manifestations of Cystic Fibrosis. *Gastroenterology and Hepatology*. 12(1), pp. 43–47
6. Laguna, T.A. 2012. 'To Sweat or Not to Sweat', Is That Enough to Diagnose Cystic Fibrosis? *American Journal of Respiratory and Critical Care Medicine*. 186(8) pp700-701 https://doi.org/10.1164/rccm.201208-1510ED
7. Aris, R.M., Merkel, P.A., Bachrach, L.K., Borowitz, D.S., Boyle, M.P., Elkin, S.L., Guise, T.A., Hardin, D.S., Haworth, C.S., Holick, M.F., Joseph, P.M., O'Brien, K., Tullis, E., Watts, N.B. and White, T.B. 2005. Guide to Bone Health and Disease in Cystic Fibrosis, *The Journal of Clinical Endocrinology & Metabolism*, 90(3), pp 1888–1896, https://doi.org/10.1210/jc.2004-1629
8. Smyth RL. 2005. Diagnosis and management of cystic fibrosis. *Archives of Disease in Childhood - Education and Practice.* 90. pp1-6 http://dx.doi.org/10.1136/adc.2005.074021
9. Weeks, A.M. and Buckland, M.R. 1995. Anaesthesia for adults with cystic fibrosis. *Anaesthesia and Intensive Care*. 23, pp. 332-338.
10. G Della Rocca. 2002. **Anaesthesia in patients with cystic fibrosis** *Current Opinion in Anaesthesiology*, 15, pp. 95-101
11. Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, Brunzell C, Campbell PW 3rd, Chesrown SE, Duchow C, Fink RJ, Fitzsimmons SC, Hamilton N, Hirsch I, Howenstine MS, Klein DJ, Madhun Z, Pencharz PB, Quittner AL, Robbins MK, Schindler T, Schissel K, Schwarzenberg SJ, Stallings VA, Zipf WB. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. Diabetes Res Clin Pract 1999;45:61–73
12. 2018 Cystic Fibrosis Registry Annual Data Report
13. Wekerle T, Klepetko W, Wisser W, Senbaklavaci O, Artemiou O, Zuckermann A, Wolner E. Incidence and outcome of major non-pulmonary surgical procedures in lung transplant recipients. European Journal of Cardio-Thoracic Surgery. 1997;12:718-723. PMID: 9458142
14. Haddow GR. Anaesthesia for patients after lung transplantation. Canadian Journal of Anaesthesia. 1997;44:182-197. PMID: 9043732. DOI: 10.1007/BF03013008
15. Tomulić Brusich K, Acan I. Anesthetic Considerations in Transplant Recipients for Nontransplant Surgery. Organ donation and transplantation. July 25th 2018. DOI: 10.5772/intechopen.74329
16. Campana C, Regazzi MB, Buggia I, Molinaro M. Clinically significant drug interactions with cyclosporin. An update. Clinical Pharmacokinetics 1996;30:141-179. PMID: 8906896
17. Zeyneloglu P, Pirat A, Sulemanji D, Torgay A, Karakayali H, Arslan G. Perioperative anesthetic management for recipients of orthotopic liver transplant undergoing nontransplant surgery. Experimental and Clinical Transplantation 2007;5(2):690-692. PMID: 18194123

18. Rancic N, Vavic NN, Kovacevic AM, Mikov MM, Drgojevic-Simic VM. Drug-drug interactions of tacrolimus. Hospital Pharmacology. 2015;2:291-296
19. Cirella VN, Pantuck CB, Lee YJ, Pantuck EJ. Effects of cyclosporine on anesthetic action. Anesthesia and Analgesia. 1987;66(8):703-706. PMID: 3605689
20. Herborn J, Parulkar S. Anesthetic considerations in transplant recipients for nontransplant surgery. Anesthesiology Clinics. 2017;35(3):539-553. DOI: 10.1016/j.anclin.2017.04.009