
Life in Limbo: Medical Management of Cystic Fibrosis Patients Awaiting Lung Transplantation

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Outline

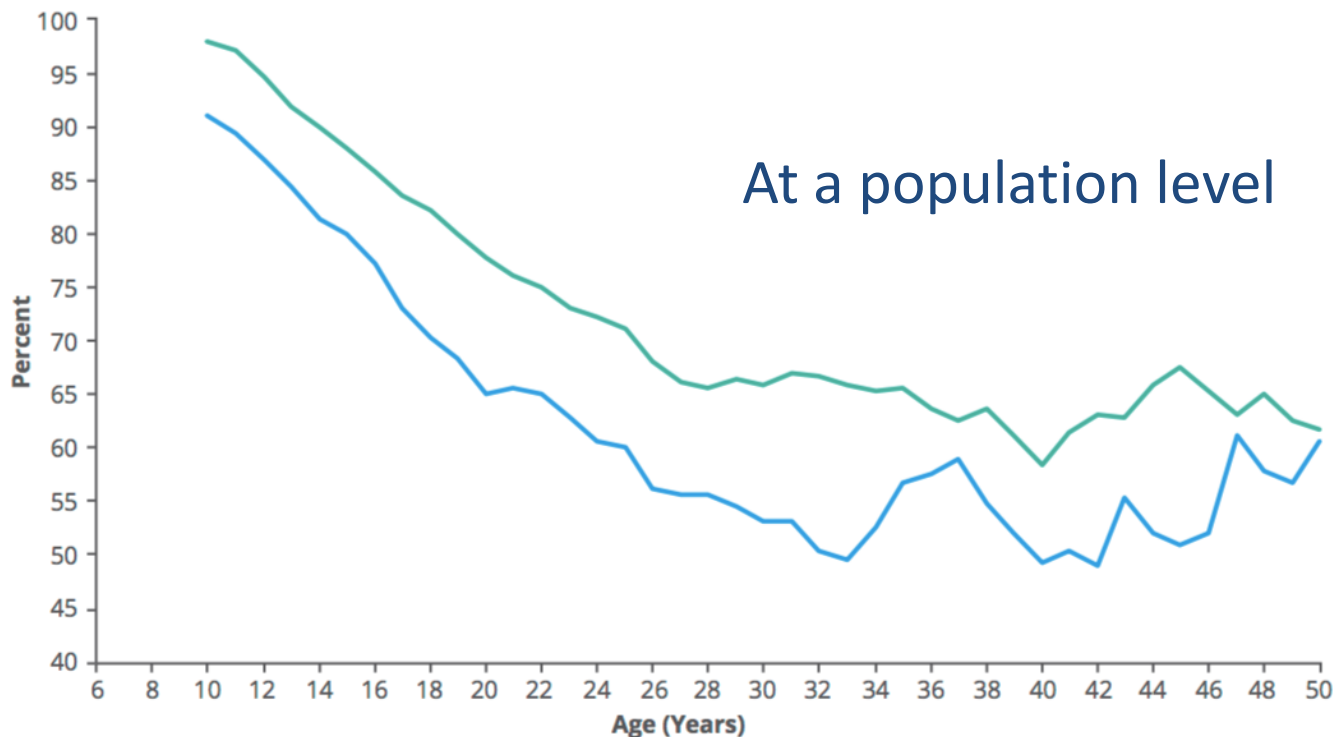
- Medical management of patients on transplant list
 - Improve factors that increase life expectancy while waiting & post transplant
 - Management of CF exacerbations
 - Role of NIV
 - Role of pulmonary rehabilitation
 - Management of dyspnea and anxiety
- Preparation for post transplant challenges
 - Diabetes
 - DIOS
 - GI cancer
- Optimize communication between CF and transplant team



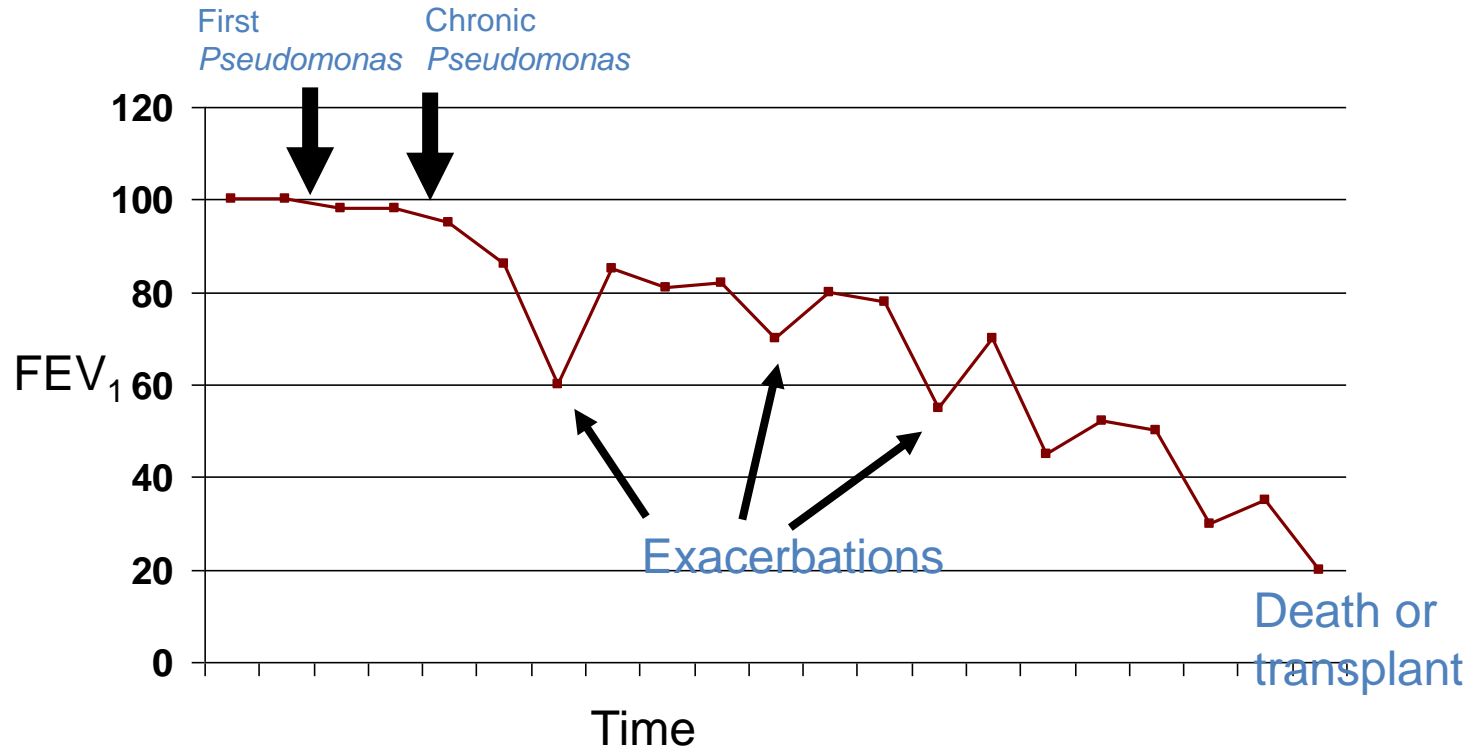
CF is a progressive disease

Median FEV₁, percent predicted vs. age (in a 5-year moving window), 1995 and 2015*

— 1995 — 2015



And at an individual level



Lung transplant indicated when no other options

Challenges and approach to:

- Selection
- Timing of listing
- Outcomes
- Complications
- Management post transplant



Medical management of CF patients awaiting transplant

- Evidence-based practice ¹
- Practice-based evidence ²

Our approach to caring for patients with CF awaiting transplant



All CF patients listed for transplant re locate to Toronto area and have care at Toronto Adult CF Centre

One CF team managing all listed patients

Canada does not have a national priority score (like LAS in USA) so centre-specific medical priority status drives transplant allocation

Lower wait list mortality: 2.1% (12/245) from 2006-2016

Infection with *Burkholderia cepacia* complex (even *B. cenocepacia*) not a contraindication for transplant

85/402 (23%) of patients transplanted from 1988-2016 had BCC
Genotyping for 67/85 (82%), with 64 (96%) having *B. cenocepacia*
BCC +ve patients had 46% 5-year survival. (vs 76% in BCC-ve patients)



Risk factors for increased mortality for CF patients

Pre transplant mortality

- ~~Burkholderia cepacia complex~~
- ~~Female gender~~
- Pulmonary exacerbations
- Low BMI
- ~~CFR~~
- FEV₁

BMI tends to decrease CF standard care decisions, inhaled antibiotics, improved BMI, CFR, dehydrates

Post transplant mortality

- ~~Burkholderia cepacia complex~~
- ~~Age at transplant~~
- ~~Pancreatic sufficiency~~



The typical highway of CF



Not again!

Good FEV₁

Time for more antibiotics

Aurghh....sick again

Off antibiotics

Good FEV₁

On antibiotics

Sick

Doing well

Not a good road if you are waiting for lung transplant



The road to transplant



Eliminate peaks and troughs



Call promptly if not feeling well

Maintain stable clinical condition



CF clinic visits q1-4 weeks

Never get really sick



Low threshold to start antibiotics

Minimize bacterial density



Longer duration of therapy



Pre transplant management of infection

- Frequent clinic visits
- Quicker response to suspicion of pulmonary exacerbation (increased symptoms, drop in FEV₁ or ex tolerance, increasing O₂ requirements)
- Longer duration of antibiotic therapy
- More aggressive strategies to prevent exacerbation – use of oral or IV antibiotics, in addition to inhaled a/b, with weekly Home IV clinic
- Suggestions of antibiotic therapy for early post transplant period



Non-invasive ventilation in CF

6 weeks of nocturnal BiPAP in 8 CF pts with daytime hypercapnea improved:

- nocturnal hypoventilation (reduction in difference in $P_{tc}CO_2$ from non-REM to REM sleep and reduction in maximal $P_{tc}CO_2$)
- chest symptoms & exertional dyspnea

Cochrane Review 2017

- 10 trials (only 3 longer than 2 weeks) in 191 patients
- Non-invasive ventilation, used in addition to O_2 , may improve gas exchange during sleep to a greater extent than O_2 alone in moderate to severe disease.
- Other outcomes not consistent
- Some benefits with airway clearance

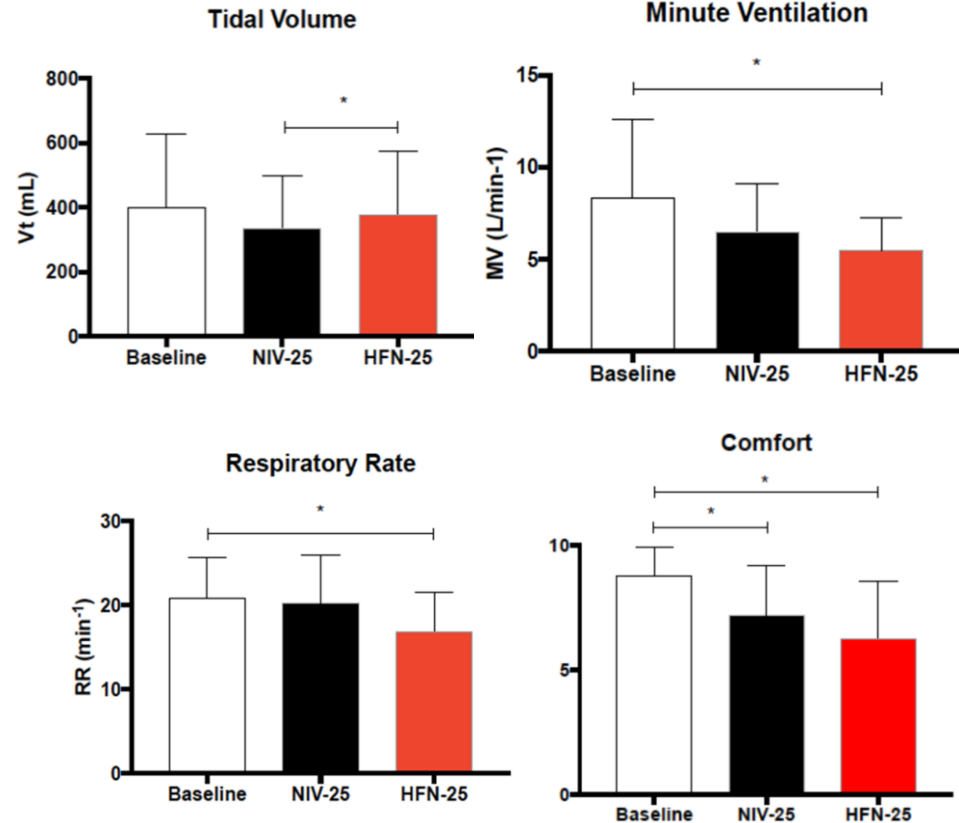
Our practice

- Initiate nocturnal BiPAP early to acclimatize pts before needed as ventilatory support



BiPAP vs high flow nasal oxygen

- Cross over study of 15 CF pts with low lung function of HFNC vs. NIV on inspiratory work of breathing
- Thickening fraction of the diaphragm (TFdi), hemodynamics, dyspnea and comfort
- HFNC was not inferior to NIV with respect to diaphragmatic work (Tfdi).
- RR was reduced with HFNC vs BL
- Vt was higher with HFNC vs NIV
- Comfort scores lower for both devices vs BL
- No significant differences between SpO₂, PtcCO₂, HR or dyspnea scores
- HFNC an alternative to BiPAP



Pulmonary rehabilitation in CF

- Persistent impairments in exercise capacity and skeletal muscle function despite improvement in lung function after transplant
- Peripheral muscle weakness is major factor for reduced exercise capacity
- Low levels of physical activity pre transplant predict:
 - worse survival to transplant (HR – 9.12, $p = 0.04$)
 - poor early post-op outcomes (duration of mechanical ventilation)
 - N = 33 CF patients (total N = 146)
 - Physical activity level defined as total energy expenditure in 24 hrs/basal metabolic rate



Does pulmonary rehabilitation improve survival pre-transplant and outcomes post transplant?

- Systematic review of 6 studies with 1305 participants
 - 5 studies showed improvement in QOL using the Short Form 36
 - 5/6 studies showed improvements in exercise capacity (6MWT)
- No trials have shown survival advantages of pulmonary rehabilitation or improvements in post operative measures



Pulmonary rehab in CF pre lung transplant in Toronto

Pre-transplant

Exercise sessions

Outpatient:

Exercise training

Using FITT-P: Aerobic, resistance, flexibility

Oxygen titration

to support exercise/activity

Inpatient:

Modified exercise

and mobility program on ward/ICU as tolerated¹

Oxygen titration

to support exercise activity

- 3 times per week during entire time on waitlist.
- Individualized training including resistance and aerobic exercise, with treadmill walking and cycle ergometry.
 - Target duration 20 minutes each.
 - Aerobic training intensity increased as tolerated to keep $O_2\text{sat} > 88\%$, modified Borg dyspnea score of 3-4/10 and $HR < 85\%$ age-pred.
- Strength and flexibility exercises for upper and lower extremities



Management of anxiety and depression

Anxiety and depression common in CF

- Screening study of 6,088 pts over age 12 in 9 countries
- Anxiety reported in 32% of adults and 22% of adolescents
- Depressive symptoms in 19% of adults and 10% of adolescents
- Rates of anxiety & depression 2-3 times higher than general popⁿ

What we do:

- Annual screening with PHQ-9 and GAD-7
- Involvement of social work and CF psychiatrist
- CBT and pharmacotherapy (SSRIs)
- Link with transplant team psychiatrist



Role of CF team in palliation

- Increasing numbers of CF patients now die in ICU
- Advanced directives and planning for end of life and treatment preferences is the responsibility of the CF team
 - Timing of when terminal – especially hard if on mechanical ventilation
 - Participation in family meetings
- Management of pain, dyspnea, anxiety important
- Change terminology from “palliation” to ”symptom control”



To summarize

- Treat aggressively to **reduce exacerbations** and **optimize FEV₁** to reduce deaths prior to transplant
- Recognise that **low BMI** may be very challenging to treat and is not a post transplant predictor of mortality in CF
- Transplantation is not yet a scheduled surgery – must be **ready to transplant** at all times
- **Pulmonary rehabilitation** improves QOL and exercise capacity
- **NIV** improves symptoms so early institution when awaiting transplant
- Management of pain, dyspnea
- Screening and treatment of anxiety and depression



Preparation for post-transplant challenges in CF

- Development of CFRD post transplant
- Development of more severe DIOS (distal intestinal obstruction syn)
- Higher risk for GI cancers (especially colon cancer)



Increased prevalence of CFRD after lung transplant

Toronto

- N = 77
- 22 (28.6%) had CFRD before transplant
- 38 (49.4%) had CFRD after transplant
- 16/55 (29.1%) of PI pts without CFRD developed diabetes post transplant

UK

- N = 176
- 71 (40%) had CFRD pre transplant
- 106 (60%) had CFRD after transplant
- 35/105 (33%) of pts without CFRD developed diabetes post transplant

Canada

- N = 580
- 278 (47.90%) had CFRD pre-transplant



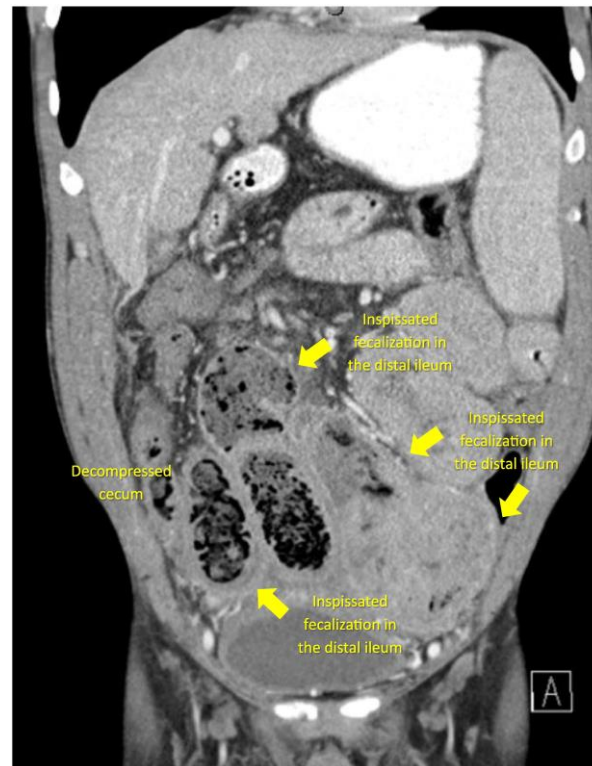
How to prepare patients for CFRD post transplant

- CFRD common, especially post transplant
- About 1/3 of patients will develop diabetes post lung transplant
- Yet another disease to manage at time when a lot of new information
- Trouble with blood glucose control post transplant
- Preparation by CF team helpful with:
 - education
 - glucose monitoring
 - CHO counting



More problematic DIOS post transplant

- Severity of DIOS worse post transplant
- 10 - 20% prevalence post lung transplant
- Factors causing increased risk include:
 - hx of MI, previous bowel surgery
 - post-operative ileus
 - bowel dysmotility 2° to narcotic pain med
 - prolonged immobility/deconditioning
- Response to therapy not as good and ~10% of pts with DIOS may require surgery
- Can be fatal



How to prepare patients for higher risk of DIOS

- Discuss risk so patients aware
- Identify high risk pts with prior DIOS, MI or abdominal surgery
- Optimize enzyme adherence and adjustment with fat intake
- Regular use of PEG3350 to try and normalize intestinal fluid status
- Prophylactic Peglyte (daily or weekly)
- CF team to stay involved with post transplant GI management
- Early recognition and prompt therapy
- Therapy may require hyperosmolar contrast enemas and endoscopic instillation of hyperosmolar contract into terminal ileum



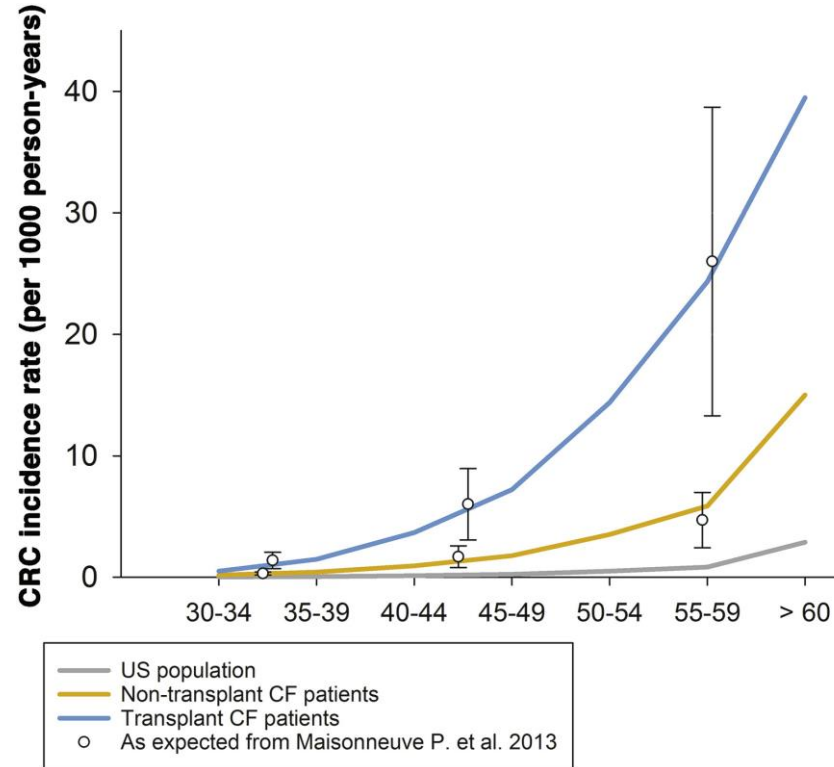
CF is a hereditary colon cancer syndrome

- Increased risk of GI malignancies in CF first recognised in retrospective publication in 1995 from USA and Canada
- Confirmed in USA CF population from 1990- 2009
- Increased risk of digestive tract cancer with SIR of 3.5 (95% CI, 2.6–4.7)
- SIR for colon cancer was 6.2 (95% CI, 4.2–9)
- Risk for colorectal cancer was associated with male sex, severe functional CF genotype, F508del homozygosity, and age >30 years.
- Reasons: uncertain but possibly increased gut inflammation, abn in intestinal microbiome, mucin and bile acids, CFTR oncogene



Increased incidence of cancer post transplant

- US transplant and 16 cancer registries.
- 10,179 lung transplant pts (1,681 with CF)
- Standardized incidence ratios (SIRs) compared cancer incidence to gen popⁿ
- Greater risk in CF lung transplant recipients than non-CF for:
 - overall cancer (SIR 9.9 vs. 2.7)
 - colorectal cancer (24.2 vs. 1.7)
 - esophageal cancer (56.3 vs. 1.3)
 - non-Hodgkin lymphoma (61.8 vs. 9.4)



CRC screening and lung transplant

Cystic Fibrosis Foundation recommends:

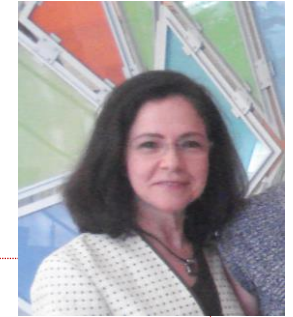
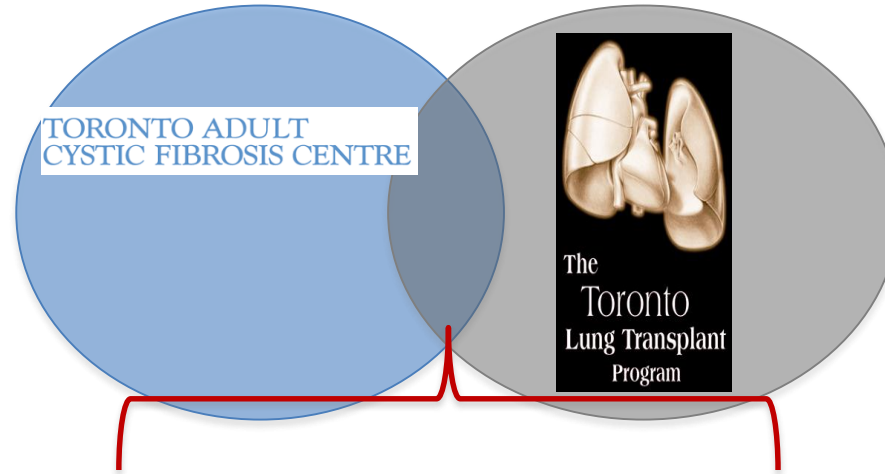
- CRC screening starting within 2 yrs of transplant for pts > 30 yrs except if -ve colonoscopy in the past 5 yrs.
- CRC rescreening every 5 yrs post solid organ transplant. If polyps seen then re-screen every 3 yrs.
- Role of FIT for CRC screening in CF not known

What we do:

- Screening colonoscopy in pts doing transplant assessment
- FIT if patient not well enough to do colonoscopy



Interaction between CF & Lung Transplant teams



- Physician overlapping both teams (Dr Cecilia Chaparro)
- CF GI consultant at transplant centre
- CF team attends transplant assessment meetings in person
- Email communications between team members
- Joint QI initiative



CF team as patient advocate & resource



- provides information about the pt and honest assessment of risk of problems post transplant
- helps with CF-related complications (eg. DIOS, CFRD, CRC screening)
- provides emotional support for pt during wait time
- keeps pts clinically stable and medically ready for transplant
- helps identify changes in clinical condition which can impact priority



A tricky balance

Hope for
transplant

Aggressive
management



Compassionate
end of life care

Freedom from
pain & dyspnea



Questions ?



St. Michael's

Inspired Care. Inspiring Science.

