G.6 Pulmonary monitoring

Review question 1: What is the value of the following investigative strategies in monitoring the onset of pulmonary disease in people with CF without clinical signs or symptoms of lung disease?

- Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharangeal aspiration
- Invasive microbiological investigation- broncho-alveolar lavage
- Lung physiological function tests- Cardiopulmonary exercise testing, Spirometry and Lung Clearance Index
- Imaging techniques- Chest x-ray and CT scan

Review question 2: What is the value of the following investigative strategies in monitoring evolving pulmonary disease in people with established lung disease?

- Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharangeal aspiration
- Invasive microbiological investigation- broncho-alveolar lavage
- Lung physiological function tests- Cardiopulmonary exercise testing, Spirometry and Lung Clearance Index
- Imaging techniques- Chest x-ray and CT scan.

Review question 3: What is the added value of imaging and invasive microbiological testing in addition to non-invasive microbiological testing and lung function tests in monitoring the response to treatment following an acute exacerbation?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sanders, D. B., Li, Z., Brody, A. S., Chest computed tomography predicts the frequency of pulmonary exacerbations in children with cystic fibrosis, Annals of the American Thoracic Society, 12, 64-69, 2015 Ref Id 371914 Country/ies where the study was carried out USA Study type Follow-up registry data of the Pulmozyme Early Intervention Trial	Sample size 60 children with CF Characteristics Not reported Inclusion criteria PEIT trial enrolled: children aged 6 to 10 years FVC% predicted ≥ 85 ability to perform reproductible pulmonary function test no dornase alpha use for 6 months before enrollment no pulmonary exacerbations before enrollment Exclusion criteria Not reported	Interventions Chest CT scans, scored using the Brody scoring system. PFTs	Details Procedure Baseline data Obtained from prospective PEIT study Follow-up data 10 years of data obtained during routine care CT scans were scored independently by 2 thoracic radiologist. Data from time of the chest CT in 1999 through 2009 were obtained from the CF Foundation Patient Registry (CFFPR) and linked to the original chest CT data Pulmonary exacerbation defined as hospitalizations treated with IV AB and/ or if the “pulmonary	Results Pulmonary exacerbations (rate ratio, 95% CI)* A 1-point increase in Brody chest CT score was associated with the rate of pulmonary exacerbations during the 10-year follow-up period: Rate Ratio =1.39 (95% CI: 1.15 to 1.67) A 5-point decrease in FEV1% predicted was associated with the rate of pulmonary exacerbations during the 10-year follow-up period: Rate Ratio =1.19 (95% CI: 1.10 to 1.30) A 1-point difference in the Brody chest CT score was more strongly associated with the rate of pulmonary exacerbations between 1999 and 2009 than a 5% predicted difference in	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. UNCLEAR (follow up trial registry data) 2. Loss to follow-up is unrelated to key characteristics (that is,

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(PEIT) participants Aim of the study To determine whether chest CT scores and PFTs are associated with the rate of pulmonary exacerbations and pulmonary function over the next 10 years. Study dates 1999 to 2009 (PEIT trial 1997 to 2000) Source of funding Not reported (possible none)			exacerbation" box was checked in the CFFPR form Statistical analysis Multivariable Poisson regression models. Regression models were adjusted for important confounders Multivariable linear regression model were used to determine the association between the Brody chest CT scores in 1999 and FEV1% predicted in 2009 To compare whether chest CT scores were more strongly associated with the rate of pulmonary exacerbations than FEV1% predicted, the authors compared the magnitudes of the slopes of the chest CT score and FEV1% predicted in the multivariable Poisson regression model with a chi-square test Statistical significance was defined as a two-sided p-value ≤ 0.05	FEV1% predicted at the time of the chest CT (p=0.037 by chi-square test) Difference in FEV1% predicted (mean, 95% CI)** A 1-point increase in Brody chest CT score was associated with a reduction in FEV1% predicted at 10 years follow-up: MD=-4.76 (CI 95% -7.80 to -1.72) A 5-point decrease in FEV1% predicted was associated with a reduction in FEV1% predicted at 10 years follow-up: MD=-4.47 (CI 95% -6.48 to -2.46) No differences in the strengths of the association between the Brody chest CT score and FEV1% predicted in 1999 with FEV1% predicted in 2009 (p=0.04 by F test) * multivariate Poisson model adjusted for sex, genotype, and FEV1 and mucoid P aeruginosa status at the time of the chest CT	the study data adequately represent the sample), sufficient to limit potential bias. YES 3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. YES (CT scan is independently assessed by 2 radiologists. Measurement of FEV1% predicted is not reported) 4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. UNCLEAR (exacerbations are measured by number of hospitalizations requiring IV AB, but registry data is not always accurate. Measurement of FEV1% predicted is not reported) 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. UNCLEAR (treatment is not controlled for, although it's not an easy factor to

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				**multivariate linear regression model adjusted for sex, genotype, and FEV1 and mucoid P aeruginosa status at the time of the chest CT	control for in a long longitudinal study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES OVERALL QUALITY: MODERATE Other information (+) DOI included (+) Only study found that evaluates CT scans and PFTs as predictors of later lung disease, measured as a true outcome measure (-) Relies on registry data (-) Study published in 2015 with data from 1999 to 2009 (??) (-) Study might not be representative of more recent birth cohort of children with CF
Full citation Wainwright, C. E., Vidmar, S., Armstrong, D. S., Byrnes, C. A., Carlin, J. B., Cheney, J., Cooper, P. J., Grimwood, K., Moodie, M., Robertson, C. F.,	Sample size N=170 infants diagnosed with CF through newborn-screening programs in 8 CF centres in Australia and New Zealand. BAL directed group: n=84 Standard monitoring: n=84 Characteristics	Interventions Infants received oral flucloxicillin as antistaphylococcal prophylaxis until their first birthday. Participants were seen every 3 months from enrolment until completion at age 5	Details Pulmonary exacerbations were defined as any change in respiratory symptoms from baseline. When unwell with upper respiratory symptoms, increased cough or wheeze, an oropharyngeal	Results Lung function - FEV1 Mean z score (SD) BAL-directed therapy group:-0.56 (1.25) (n=80) Standard therapy group: -0.41 (1.23) (n=77) Mean difference (95% CI) = -0.15 (-0.58 to 0.28); p=0.49 Lung function - LCI	Limitations The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: low risk of bias (computer generated codes)

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Tiddens, H. A., Acfbal Study Investigators, Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial, JAMA, 306, 163-71, 2011 Ref Id 332248 Country/ies where the study was carried out Australia and New Zealand Study type Multicentre randomised controlled trial Aim of the study To determine if BAL directed therapy for pulmonary exacerbations during the first 5 years of life provides better	BAL Therapy Group vs Standard Therapy Group Age mean (SD), months: 3.76 (1.62) vs 3.73 (1.69) Gender (Male): 44 (52) vs 44 (52) Pancreatic insufficiency: 73 (87) vs 71 (85) Meconium ileus: 17 (20) vs 16 (19) Presence of respiratory symptoms – Cough: 36 (43) vs 37 (44) Presence of respiratory symptoms – Wheeze: 11 (13) vs 6 (7) Inclusion criteria Infants younger than 6 months of age with a confirmed diagnosis of classic CF (two of the following: 2 CF mutations, sweat chloride level >60 mEq/L, pancreatic insufficiency or meconium ileus) Exclusion criteria Not stated	years, when anthropometric assessments, BAL, high resolution chest CT scan and pulmonary function testing was performed. The child's clinical stability was assessed based on these tests which were performed within 2 weeks. Visits for illness were scheduled as necessary. Standard therapy group Treatment decisions were on the basis of oropharyngeal specimens BAL-directed therapy group Participants also received BAL: a) before 6 months of age when well b) when hospitalised for pulmonary exacerbations c) if P. aeruginosa was cultured from oropharyngeal	specimen was obtained from participants and oral nonantipseudomonal antibiotics was started. Children were hospitalised if the specimen grew P aeruginosa or if the treating physician judged that hospitalisation was warranted because of symptom severity or failure to improve after 6 weeks of ambulatory treatment. Treatment in hospital was initially with IV tobramycin and ticarcillin-clavulanate (Australia) or cefuroxime (New Zealand). Further treatment was dependant on the results of BAL culture (BAL-directed therapy group) or oropharyngeal culture (standard therapy group). If no bacterial pathogens were grown from the BAL cultures, children in the BAL-directed therapy group were discharged receiving oral nonantipseudomonas antibiotics. For children	Not included in the study Lung function - oxygen saturation Not included in the study High-resolution computed tomography (CT) appearances Not included in the study Time to next exacerbation Not included in the study Clearance of the organism from the cultures Not included in the study Inflammatory markers Not included in the study Weight Mean z score (SD) BAL-directed therapy group:-0.15 (0.88) (n=80) Standard therapy group: -0.21 (0.82) (n=77) Mean difference (95% CI) = 0.06 (-0.21 to 0.32); p=0.68 Height Mean z score (SD) BAL-directed therapy group:-0.13 (0.83) (n=80) Standard therapy group: -0.19 (0.98) (n=77) Mean difference (95% CI)	Allocation concealment: low risk of bias (only revealed after confirmed recruitment) Blinding of outcome assessment: unclear (no blinding, but it is unlikely to affect the outcomes) Incomplete outcome data: low risk of bias (All groups were followed up for an equal length of time. In the BAL-directed group (n=80) 2 refused consent for BAL and 1 refused consent for P aeruginosa eradication. In the standard therapy group (n=77) 1 excluded from group by clinician and 3 refused consent for P aeruginosa eradication) Selective reporting: low risk (All groups were followed up for an equal length of time. The groups were comparable for treatment completion. Results not available for 14 participants in each group. The groups were comparable with respect to the availability of outcome data). Other bias: low risk (The groups were comparable

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outcomes than current standard practice relying on clinical features and oropharyngeal cultures. Study dates 1 June 1999 and 31 December 2005 Source of funding National Health and Medical Research Council, the Royal Children's Hospital Foundation, Pathogenesis Corporation, Chiron Corporation, and Novartis Pharmaceuticals		specimens d) following P aeruginosa eradication therapy	in the BAL-directed therapy group, lower respiratory tract infection was diagnosed when BAL fluid cultures grew respiratory bacterial pathogens in concentrations of ≥ 103 CFUs/mL. If P aeruginosa infection was diagnosed children underwent full eradication treatment (initial 2 weeks tobramycin with either ticarcillin-clavulanate or cefazidime followed by two months of tobramycin inhalation solution and one month of oral ciprofloxacin. Children with <103 CFUs/mL of P aeruginosa in BAL fluid cultures were offered parenteral antipseudomonal antibiotics but not the full eradication course. At the end of treatment, another BAL was performed or an oropharyngeal swab was obtained to determine clearance. If P aeruginosa persisted, the eradication protocol was repeated. After the	= 0.06 (-0.23 to 0.35); p=0.69 BMI Mean z score (SD) BAL-directed therapy group:0.03 (0.93) (n=80) Standard therapy group: 0.01 (0.83) (n=77) Mean difference (95% CI) = 0.02 (-0.25 to 0.30); p=0.87 Quality of life Not included in the study Adverse events Substantial clinical deterioration during and within 24h of BAL 25/524 (4%) (During BAL: 7 children needed intervention for Hb desaturation <90% for duration>60s; 1 child had ventricular tachycardia associated with an anaesthetic protocol violation when halothane was used. Post BAL: 2 children had stridor; 6 children required supplemental O2 for>2hrs - one of whom was monitored in ICU; 2children had respiratory distress (no supplementary O2 required); 3 children were systemically unwell	at baseline, including all major confounding and prognostic. The comparison groups did not received the same care apart from the interventions studied, as the antibiotic choice varied according to best practice guidance for Australia and New Zealand, unlikely to affect relevant outcomes. The study had an appropriate length of follow-up. The study used a precise definition of outcome. The study used a valid and reliable method was used to determine the outcome) OVERALL QUALITY: LOW RISK OF BIAS Other information None.

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			second cycle, repeat testing confirmed wither successful clearance of chronic infection. Successful clearance meant that future positive cultures were treated as new isolations, whereas chronic P aeruginosa infection was treated with inhaled and oral antipseudomonas antibiotics for respiratory exacerbations no requiring hospitalisation. Statistical Analysis Power calculations were based on the primary outcome of prevalence of P aeruginosa and in evidence of structural lung damage by the total CF-CT score. After an initial calculation indicated a sample size of 240 children would be necessary, subsequent published research indicated that a sample size of 160 children would provide 80% power for a mean difference of 1.5% (% maximum score) (0.45	Unplanned hospital admission post BAL 12/524 (2.3%) (6 children had high fevers and 6 children experienced substantial clinical deterioration) Contaminated bronchoscope 2/524 (0.4%) Fever within 24h post BAL ≥38.5C 40/524 (7.6%) Fever within 24h post BAL <38.5C 40/524 (9.9%) Transient worsening of cough post BAL (151/524 (29%)	

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			SDs) and be adequate for prevalence of P aeruginosa. The study was designed as an intention to treat analysis. Continouous outcomes were compaed using t tests and corresponging confidence intervals for mean differences Weight, height and BMI z scores were calculated from the 2000 CDC Growth Reference Charts. Group comparisons are presented with 95% CIs and 2-sided p values; $p<0.05$ was used to define statistical significance.		