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Articles selected and commented on by: **Professor John Kolbe**. Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland City Hospital, Auckland, New Zealand



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In choosing article for inclusion in this APSR Respiratory Update, I have taken a slightly different approach. I have included several mini-reviews to give a broader perspective of a topic than is possible from a single article. I have also included some “small print” topics that I hope readers will find interesting and stimulating.

John Kolbe.

Impact of azithromycin on the clinical and antimicrobial effectiveness of tobramycin in the treatment of cystic fibrosis.

Authors: Nichols DP et al.

Reference: Journal of Cystic Fibrosis 2017; 16: 358 – 66

URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5492972/>

Individually inhaled tobramycin and oral azithromycin demonstrate clear benefit in cystic fibrosis and up to half of United States cystic fibrosis patients use these agents concomitantly. Previous post-hoc analysis of clinical trials has suggested the possibility of tobramycin-specific interaction with oral azithromycin and in vitro studies have provided support and biological plausibility.

In this study, investigators have analysed clinical trial data and showed that in cystic fibrosis patients with chronic PA infection on azithromycin, there was a much greater increase in FEV1 with nebulised aztreonam than with nebulised tobramycin (6.4 vs 0.8%, $p < 0.005$). This was paralleled by changes in quality of life. Such a discrepancy did not occur in patients not taking azithromycin. In in vitro studies, they demonstrated that azithromycin reduced the bactericidal effects of tobramycin in cultures of clinical stains of PA, possibly through up-regulation of antibiotic resistance through Mex XY efflux.

Most previous studies of CF therapies have examined the effects “in relative isolation”. In clinical practice a number of “proven” therapies are used together, generally with scant regard as to whether the treatments are additive, multiplicative or indeed antagonistic. While we probably do not have sufficient evidence based on retrospective analyses to avoid the combination of inhaled tobramycin and oral azithromycin, the possibility of clinically significant antagonistic effects needs to be borne in mind. This possibility of interactions between cystic fibrosis therapies requires greater consideration in future studies; both the benefits and the potential liabilities of treatment combinations need to be considered.

Acquired resistance to macrolides in *Pseudomonas aeruginosa* from cystic fibrosis patients.

Authors: Mustafa M-H et al.

Reference: European Respiratory Journal 2017; 49: 160 1847

URL: <http://erj.ersjournals.com/content/49/5/1601847.long>

The long term use of macrolides for their anti-virulence and anti-inflammatory properties is common in CF patients, particularly in those chronically infected by *Pseudomonas aeruginosa* (PA). This treatment has been shown to improve lung function and reduce exacerbations. In conventional culture media, macrolides are intrinsically inactive against *Pseudomonas aeruginosa*; this resistance due to the efflux of macrolides via multidrug efflux systems.

However in physiological conditions similar to those that exist in the airways, macrolides may kill *Pseudomonas aeruginosa* as a result of increased cell wall permeability. In this study the macrolide activity against 333 *Pseudomonas aeruginosa* isolates from 155 cystic fibrosis patients from four European centres, and 48 *Pseudomonas aeruginosa* isolates from patients with hospital acquired pneumonia (HAP), was tested in eukaryotic cell culture medium. Cystic fibrosis isolates were significantly less susceptible to macrolides than HAP isolates. This was due to specific mutations in the ribosomal target of macrolides, and was associated with the mucoid, biofilm forming, phenotype. Such mutations were common in the cystic fibrosis isolates from those chronically treated with macrolides.

Thus while macrolides are not used for their anti-bacterial properties against *Pseudomonas aeruginosa*, the organism can acquire mutations that render it non-susceptible to macrolides. As in vivo macrolide effectiveness may be partly dependent on *Pseudomonas aeruginosa* killing in vivo, the effectiveness of these agents may decline over time; a phenomenon for which there is emerging evidence.

It is not clear whether these mutations may also affect the anti-virulence and anti-inflammatory properties of macrolides. However, these findings are relevant to the use of long term macrolide therapy for other airway conditions and remind us of our role in antibiotic stewardship generally. Further research on the long term risk/benefit ratio associated with long term macrolide use is certainly warranted.

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Clostridium difficile carriage in adult cystic fibrosis (CF): implications for patients with CF and the potential for transmission of nosocomial infection.

Authors: Burke DG et al.

Reference: Journal of Cystic Fibrosis 2017; 16: 291 – 298

URL: <https://doi.org/10.1016/j.jcf.2016.09.008>

Clostridium difficile is an anaerobic gram-positive, spore-forming, toxin-producing bacillus transmitted among humans through the faecal-oral route. This paper describes the high prevalence of *C. difficile* culture (50%; of whom 63% were toxin-producing) in a cohort of 60 adult CF patients who were pre-transplant, and who had no acute gastrointestinal symptoms. Acquisition of *C. difficile* did not seem to relate to antibiotic therapy.

As the title of the article suggests, this finding raises concerns about potential for such patients to be a source of nosocomial transmission of *C. difficile*. While it also highlights the importance of isolation of inpatients with CF and strict hand hygiene policy, it needs to be remembered that there is a lack of sporicidal efficacy of alcohol-based hand washes compared to hand hygiene with soap and water.


Patients with CF who are post-transplant, and occasionally pre-transplant, have a risk of developing life-threatening complications of *C. difficile* infection, the presentation of which can be atypical. There is a lack of information on whether we should be screening patients for *C. difficile* and whether (and how) eradication should be undertaken in CF patients who remain asymptomatic despite the presence of toxigenic, virulent *C. difficile* in the gut.

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The impact of a national population cancer screening programme on cystic fibrosis birth rate and age at diagnosis: Implications for newborn screening.

Authors: Stephen P et al.
Reference: Journal of Cystic Fibrosis 2016; 15: 460 – 466
URL: <https://doi.org/10.1016/j.jcf.2015.08.007>

In this paper from Israel, the authors describe the impact of a national, fully subsidised by government, population carrier screening (PCS) programme for CF based on a standard CF mutation panel. This programme was associated with a reduction in CF birth rate from 14.5 per 100,000 live births in 1990 to six in 2011. There was also a shift to milder disease with 40% of CF children being pancreatic sufficient.

The accompanying editorial (<https://doi.org/10.1016/j.jcf.2016.05.006>) makes the valid point that new-born screening, cascade carrier testing and PCS are a continuum that could form parts of a single national programme: “two ends of the same rope”.

The cumulative effects of intravenous antibiotic treatments on hearing in patients with cystic fibrosis.

Authors: Jarinis Al et al
Reference: Journal of Cystic Fibrosis 2017; 16: 401 – 409
URL: <https://doi.org/10.1016/j.jcf.2017.01.006>

A number of publications have highlighted the long term adverse effects of aminoglycoside therapy in CF patients. This publication from the US showed that cumulative lifetime IV antibiotic dosing had a negative effect on high frequency hearing loss. While the prevalence of sensory-neural hearing loss has varied considerably in other studies, in this study 56% had this complication. While these effects are generally attributed to aminoglycosides, the impact of co-administered drugs is not clear.

However vestibular system dysfunction may be even more common in CF patients; occurring in 79%, compared to 23% with hearing loss. Of those with normal hearing, 61% had vestibular dysfunction. (Paediatric Pulmonology 2017; 52: 1157 – 1162).

Thus while monitoring of auditory function particularly for higher frequencies is recommend-

ed, alone it is an insufficient way to examine for ototoxicity in an individual CF patient. Perhaps greater attention should be paid to the assessment of vestibular function. However vestibular dysfunction can present in different ways, may be masked by compensatory adjustments, and is more challenging to formally test. Simple questions on whether the patient experiences unsteadiness when standing or walking, particularly in the dark, may be a good start.

Optimal correction of distinct CFTR folding mutants in rectal cystic fibrosis organoids.

Authors: Dekkers J F et al.

Reference: European Respiratory Journal 2016; 48: 451 – 458

URL: <http://erj.ersjournals.com/content/48/2/451.long>

Rectal organoids can be grown from intestinal stem cells obtained via rectal biopsy. The cells self-organise into multi-cellular, three-dimensional structures consisting of a single epithelial layer with the apical membrane facing a closed central lumen (organoids). Forskolin-induced swelling of the organoid, reflecting ion and water transport into the lumen, can be used to quantitate CFTR function in a subject-specific manner. This technique allows in vitro testing of the ability of agents to influence CFTR activity in cells derived from an individual. This development is particularly important in an era of new drugs developed to target mutation specific CFTR defects.

In this particular paper the investigators demonstrated that the CFTR corrector efficacy selectively depended on the type of folding and trafficking defect, and highlighted the potential of this technique for the development and in vitro testing of mutation-specific corrector strategies that are optimal for the distinct CFTR mutations. Such techniques would allow for the testing of multiple drugs in organoids developed from patients with rare mutations, that have not, and could not, be tested in randomised clinical trials because of lack of sufficient subjects.

Intestinal organoids also provide a mechanism for pre-clinical testing and selection of CFTR modulators and can be used for pharmacologic studies of such agents. While much is said about the prospect of personalised medicine, this technology does hold the potential for true personalisation in the treatment of CF by CFTR modulators. (Curr Opin Pulm Med. 2016; 22: 610 – 616).

Consequences of expiratory flow limitation at rest in subjects with cystic fibrosis.

Authors: Vilozni D, et al.
 Reference: Ann Am Thr Soc 2016: 13: 835 – 832
 URL: <https://doi.org/10.1513/AnnalsATS.201508-485OC>

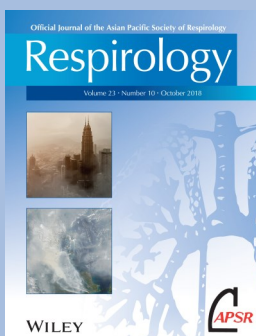
This longitudinal study examined the “best spirometry” each year for at least 10 consecutive years in 108 patients with cystic fibrosis; median age at last year of data collection of 17 years, and mean FEV1 of 76% predicted. The year in which expiratory flow limitation during tidal breathing (EFLTV) first occurred was determined; EFLTV was defined as “FEV25-75 (l/s) equal to tidal peak expiratory flow (l/s)”.

EFLTV occurred in 51% of subjects at age 23±6 years and at FEV1, of 62±10% predicted. In the two years following the development of EFLTV, FEV1 fell to 48±11% predicted and 63% of subjects reported shortness of breath at rest.

There are other, and potentially more valid, assessments of expiratory flow limitation than the one used in this study and most clinicians would recognise the presence of flow limitation during tidal breathing by the superimposition of the tidal expiratory loop on the maximum expiratory loop. This is often associated with a change in the configuration of the tidal loop to comply with that of the maximal loop. The development of EFLTV is likely reflection of the progression of airway disease in CF; most likely the increase in airway resistance of small airways upstream of the equal pressure point.

Whether or not the development of EFLTV heralds a change in the trajectory of the disease as suggested by the authors is not entirely clear. However this study did show that EFLTV first occurred in early adulthood and when the FEV1 was only moderately impaired. This study also causes us to reflect on the abnormal pulmonary mechanics in CF and how this relates to the development of dyspnoea, the patterns of breathing at rest and on exercise, and on the mechanics of reduced exercise capacity.

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Age-related survival disparity associated with lung transplantation in cystic fibrosis: An analysis of the registry of the International Society for Heart and Lung Transplantation.

Authors: Hayes D, et al.

Reference: Journal of Heart Lung Transplant 2016; 35: 1108 – 1115

URL: <https://doi.org/10.1016/j.healun.2016.04.015>

Lung transplantation is a well established treatment option for CF patients with advanced lung disease, and there is clear evidence of positive long term outcomes in this population with transplantation conferring a survival advantage.

The above is but one of a number of articles on lung transplantation in cystic fibrosis in an issue of the journal devoted to this subject. Most articles were based on the analysis of data from large registries.

The above article showed that mortality associated with lung transplantation in cystic fibrosis was associated with age at transplant of <18 years, and an earlier era of transplantation (1998 – 2005). The age related survival disparity is still present in the contemporary era.

A further study (J Heart Lung Transplant 2016; 35: 1237 – 1244) showed that CF as the indication for lung transplantation fell from >17% to <13% from 1999 to 2013. This is in the context of a markedly increased number of patients undergoing transplant over this period, and for conditions numerically much greater than CF eg COPD. In the paediatric cohort, CF was the indication for transplantation in about half; falling from 60% to 47%. Adults now constitute about 90% of all patients with CF undergoing transplantation. The overall trend was that lung transplantation is now performed in sicker and older patients with CF. Despite this the post-transplant survival has not changed.

In a further study (Journal Heart Lung Transplant 2016; 35: 1487 – 1496) of CF patients >18 years who underwent transplant, survival post-transplantation and time to the development of bronchiolitis obliterans syndrome (median of 5.2 years) did not differ based on gender or donor-recipient gender combination. However women with CF have a poorer overall life expectancy as their pre-transplant disadvantage (in the order of 2.7 years) was not overcome by transplantation. Median survival after transplant was 8.9 years and there was no difference between male and female recipients. However the sobering fact is that the mean age of death for female lung transplant recipients was 30.4 ±9.7 years while that for males was 32.9 ±9.8 years.

The lower airway microbiota in early cystic fibrosis lung disease: a longitudinal analysis.

Authors: Frayman et al.
Reference: Thorax 2017; 72: 72: 1104 – 1112
URL: <https://thorax.bmj.com/content/72/12/1104.long>

Advances in sequencing technology have expanded our knowledge of the lower airway microbiome in health and disease, with numerous publications on microbial diversity; a measure of the number of different bacterial taxa and the relative amount of each taxa detected.

This paper describes the retrospective analysis of stored broncho-alveolar lavage fluid (BALF) samples obtained from infants newly diagnosed with cystic fibrosis at a single centre. 95 samples were analysed (using 16S RNA gene sequencing) from 48 subjects aged 1.2 – 78.3 months, including longitudinal samples from 27 subjects and 13 samples obtained before the age of six months, making this the largest longitudinal study of BALF microbiota in infants and young children.

The BALF microbiota was notably diverse in newly diagnosed infants, but *Staphylococcus* was the most prevalent genus. Detection of recognised CF bacterial pathogens was associated with reduced microbial diversity and greater lower airway inflammation. This reduction of diversity and emergence of CF pathogens is consistent with the results of longitudinal studies of older patients with advanced lung disease. This study indicated that this change from a diverse bacterial community to one of reduced diversity and dominated by CF pathogens, occurred early in life. However there was no association between microbial diversity and lung function at the age of six years. The documentation of fluctuations in bacterial diversity may suggest that an initial loss of diversity is not irreversible and it may be susceptible to modulation.

Thus the lower airway microbiota in young CF patients was varied and dynamic. There is much still to learn about the airway microbiota in CF including longitudinal changes, whether the microbiota itself alters disease trajectory, the effect of intermittent and long term antibiotics, the relationship with gut microbiota, the effect of probiotics and the role of faecal transplantation to name but a few.

The quantitative link of lung clearance index to bronchial segments affected by bronchiectasis.

Authors: Verbanck S et al.
Reference: Thorax 2018; 73: 72: 82 – 84
URL: <https://thorax.bmj.com/content/73/1/82.long>

Structural abnormalities demonstrated on CT scans occur early in CF; certainly before important changes in lung function occur. CT scan assessment of the lungs has been an important component of the study of early lung disease and is regarded as the most sensitive modality.

In this study of adult 63 CF patients, there was an (almost linear) association between the lung clearance index (LCI) and the severity of bronchiectasis based simply on the number of involved broncho-pulmonary segments. This finding was strengthened by an association between the LCI and a specific index of convection-dependant ventilation heterogeneity (Scond, derived from the multiple breath wash-out). This result is consistent with the view that bronchiectasis of an airway impairs convective gas flow into the subtended lung.

While there are calls for the standardisation of CT techniques to be used for CF children and adolescents because technical differences can lead to differences in the estimates of structural abnormalities (Eur Respir J 2016; 47: 1706 – 17), other have suggested fundamental changes to how structural abnormalities should be defined. It has been suggested that the outer diameter of the airway (rather than the luminal diameter) should be used to compare with the adjacent branch of the pulmonary artery in order to define the presence of bronchiectasis in young children with CF (Pediatric Pulmonology 2017; 52: 1414 – 23). The outer diameter incorporates airway wall thickening in the measure, may be less influenced by lung volume and mucus impaction, and may thus be more reliable and more sensitive in defining abnormality.

Bronchiectasis is only one component of the structural lung disease in CF. Mosaic attenuation of the lung parenchyma on expiratory scans (often referred to as “air trapping”) is generally considered to be due to the heterogeneous emptying during expiration of pulmonary lobules (or groups of lobules). This is as a result of differing time constants of emptying, in turn likely reflecting heterogeneous narrowing of small airways. However in a study of children less than 7 years from the AREST CF team (Pediatric Pulmonology 2017; 52: 1150 – 6), while the percentage of “trapped air” was associated with severity of disease and the LCI, it was not associated with a conventional physiologic measure of global gas trapping (FRC/TLC). Amongst other things, this result raises questions about the basis of mosaic attenuation; specifically the

contribution of perfusion changes to this appearance and the fact that the description of “air trapping” may be a misnomer or at least an over-simplification. .

There are still a number of unanswered questions regarding structure/function relationships in CF but studies such as these are advancing our understanding in this important area.

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