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Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe 508 del CFTR

Authors: Wainwright CE, et al

Reference: N Engl J Med 2015; 373:220-231; DOI: 10.1056/NEJMoa1409547

URL: <http://www.nejm.org/doi/full/10.1056/NEJMoa1409547>

After studies demonstrating the effectiveness of ivacaftor in rectifying the underlying abnormality in patients with the gating mutation, Gly 551 Asp, this study addressed the greater challenge of correcting the abnormality in the commonest and severe CF mutation, Phe 508 del. This mutation leads to incorrect folding of the CFTR protein, its destruction in the endoplasmic reticulum, reduced presence of the ion channel in the apical cell membrane, reduced channel opening and more rapid removal of the channel from the cell membrane. To address these issues associated with Phe 508 del the investigators used a combination of lumacaftor to improve processing of the CFTR (“corrector”) and ivacaftor to improve opening of the channel (“potentiator”). Previous studies had shown that neither drug alone, had clinical efficacy in patients homozygous for Phe 508 del.

The authors report two phase III, randomised, double-blind, placebo-controlled trials in patients, aged >12 years, and homozygous for the Phe 508 del mutation; the trials differed only with respect to “add-on” investigations. Patients (n=1108, mean baseline FEV₁ = 61% predicted) were randomised to receive one of 2 doses of lumacaftor (600mg/day or 400mg BD) in combination with ivacaftor (250mg BD), or placebo. Patients were continued on a variety of other CF treatments.

In both studies there were significant changes in the primary end point; the mean absolute improvement in FEV₁ at 24 weeks, which ranged from 2.6 to 4.0%. Improvements in FEV₁ were observed early (within the first month), were sustained, and were similar in all subgroups. In the lumacaftor-ivacaftor groups there was a 30-39% reduction in rate of pulmonary exacerbations, and significant reductions in hospitalisations and in the use of intravenous antibiotics. Changes in quality of life were statistically significant but of doubtful clinical significance.

While these results are important and exciting, the improvements in lung function are modest and similar to those achieved with a number of other treatments for CF. This reflects the modest changes in sweat chloride concentration indicating that this drug combination only partially addressed the underlying abnormality in ion transport, and underlines the need for continued development of CFTR modulators.

**New Topic in Focus:**

Respiratory Disease: Using Lung Function Measurements to Greater Advantage. [Click here to access](#)



A decade of healthcare improvement in cystic fibrosis: lessons for other chronic diseases

Authors: Stevens DP and Marshall BC

Reference: BMJ Qual Saf 2014; 23: i1-i2

URL: http://qualitysafety.bmj.com/content/23/Suppl_1/i1

This is the first article in a supplement of this journal devoted to CF (“Ten Years of Improvement and Innovation in Cystic Fibrosis Care”). The issue documents the improved outcome in CF consequent upon benchmarking, identification of clinical best practice, reduction of variance in clinical practice and continuous quality improvement, all facilitated by the online patient registry that is Port CF. From 2002 to 2012, the median predicted survival for people with CF increased nearly 10 years – from 31.3 to 41.1 years. One of the strengths of Port CF is the ability to adjust for a variety of factors that may influence outcome in order to reliably identify centres with outstanding outcomes. The CF Foundation then facilitates the dissemination of the subsequently identified best practices.

Another paper in the supplement describes the characteristics of a clinic which has outstanding outcomes. These include strong leadership of a well-functioning team producing consistent systematic care, high expectations by staff, patients and families, early and aggressive treatment of clinical declines, and patients/families feeling engaged, empowered and well informed on management issues. Inherent in such an approach is ongoing self-appraisal as part of a culture of continuous quality improvement.

The CF Foundation should be justifiably proud of their achievements and the fact that their approach has been recognised as a model for other chronic diseases.

Viability of *Pseudomonas aeruginosa* in cough aerosols generated by persons with cystic fibrosis

Authors: Knibbs LD, et al

Reference: Thorax 2014; 69: 740-745

URL: <http://thorax.bmj.com/content/69/8/740.long>

Infection control remains a topical, contentious and potentially divisive issue in CF care. This is in a large part due to a lack of good quality scientific information on which to base decision-making. This paper from a group of investigators from Brisbane, Australia provides data that should influence infection control recommendations for clinics.

Person to person transmission of microorganisms, including *Pseudomonas aeruginosa* (PA), has been demonstrated in CF and may be an important mechanism of acquisition. Although the precise route of transmission is not proven, it seems likely that airborne transmission is most important. Airborne transmission involves the dis-

semination of small droplets of respirable size containing viable microorganisms, over time and distance. This is in contrast to droplet transmission where larger droplets are spread directly over shorter distances to deposit directly onto mucosal surfaces.

Nineteen patients with CF and chronically infected with PA, and 10 healthy controls were studied. Subjects were asked to cough as frequently and strongly as was comfortable for 5 minutes. Using two validated cough aerosol sampling systems, viable PA in droplet nuclei were measured. CF patients produced cough aerosols that travelled up to 4 m and persisted in the air (of a clinic room) for up to 45 mins. There was marked intersubject heterogeneity in the number of viable PA cultured from cough aerosols, although the sputum PA concentration was a strong predictor of viable PA in cough aerosols. The number of PA decreased with distance, over time with a half-life of 50 mins, and with the level of room ventilation.

The results cast considerable doubt on the current recommendation to separate patients by 1-2 m to prevent cross-infection; this recommendation presumably based on transmission by direct contact or by droplets. The authors advise that after a patient with PA leaves a clinic room with the recommended 2 air changes per hour, almost an hour may be required before 90% of viable bacteria are removed from the air.

However unknowns remain: what size of inoculum is required to establish a PA chronic infection in CF patients and what microbial, environmental, patient and other factors influence this? To what extent this data applied to other organisms, including *Mycobacterium abscessus* which has now joined the list of organisms demonstrated to have patient-to-patient transmission? Hopefully we are now entering the era when all infection control recommendations will be based on sound scientific data, to protect patients while minimising stigmatisation and feelings of isolation.

Air contamination with bacteria in cystic fibrosis clinics: Implications for prevention strategies

Authors: Zuckerman JB, et al

Reference: Am J Respir Crit Care Med 2015; 191: 598-601

URL: <http://www.atsjournals.org/doi/abs/10.1164/rccm.201410-1877LE#.VIPgNE2he70>

This study determined whether mask use by CF patients reduced air contamination during clinic visits. Patients (n=303) were randomly organised to wearing or not wearing masks in the clinic room. The air contamination rate was similar between patients who wore and did not wear masks; 1.3% vs 0.7%. This low rate of contamination may relate partly to the method used to determine contamination which was not well described. Notably many who wore masks compromised any potential benefit by touching or removing the masks.

Spirometry was performed in a separate room and contamination was higher (4.0%) in this room, with a trend of greater contamination with higher cough frequency. This data, and data from the study above, highlight the potential for post-spirometry coughing to generate potentially infected aerosols.

This study calls into question the rationale for the use of masks by patients during clinic visits, particularly in view of the tolerability of wearing masks, the ill-fitting nature of many masks, that touching masks may wick respiratory secretions through mask material and the fact that in many clinics patient entry into clinic rooms is facilitated with little time in public areas. The wearing of masks is now recommended for CF patients attending clinic; a recommendation that is called into question by these results. Further studies are required to determine the effectiveness (or otherwise) of masks in reducing air contamination and person-to-person transmission of pathogenic organisms.

Origins of cystic fibrosis Lung Disease

Authors: Stolz DA, et al

Reference: NEJM 2015; 372 (4): 351-62

URL: <http://www.nejm.org/doi/full/10.1056/NEJMc1502191>

This review article provides an excellent overview of the progress that has been made in the development of animal models for CF; specifically the pig, ferret and rat. Pigs that lack CFTR have a phenotype that closely resembles the multi-organ disease of humans. Animal models have provided valuable insights into the mechanism of disease such as emphasising the importance of CFTR on the transport of bicarbonate in airway epithelial cells and the negative impact of the consequent change in the pH of airway surface liquid on bacterial killing.

Studies of these animal models have also challenged some long held views about CF. Animal models have revealed structural abnormalities in the trachea and proximal airways in new born animals thus challenging the premise that the lungs of CF infants are normal at birth, and raising the possibility that humans may also have altered airway development. In animal models, the defect in mucociliary clearance does not seem to be due to depletion of periciliary fluid volume, but due to changes in the properties of mucus – thus harking back to the early name for the disease, mucoviscidosis. On the other hand, animal models have demonstrated the importance of early lung infection and inflammation, confirming the findings of studies of human neonates.

This article will bring clinicians “up to speed” on the issue of animal models of CF and provide an excellent basis for understanding the results of animal studies being published in mainstream respiratory journals.

Medical and obstetric complications among pregnant women with cystic fibrosis

Authors: Patel EM, et al

Reference: Am J Obstet Gynecol 2015; 212: 98 e 1-9.

URL: <http://www.sciencedirect.com/science/article/pii/S0002937814007054>

Patel et al interrogated the National Inpatient Sample for pregnancy-related discharges for the years 2000-2010 and found a linear increase in the number of deliveries to women with CF, from 3.0 to 9.8 per 100,000 deliveries. Of the 1119 deliveries to CF women, multivariate logistic regression showed that CF women were more likely to die (aOR 76.0), although the absolute number of deaths was small. CF women were more likely to require mechanical ventilation (aOR 18.3), have pre-term labour (aOR 2.2) or a composite CF adverse outcome (aOR 28.1).

With advances in care, CF women are living longer and with better lung function and better nutrition. As a consequence more are able to become pregnant. Nevertheless these women are at greater risk. Co-ordination and close collaboration between the CF and obstetrics teams would seem to provide the best opportunity for a good outcome. On the other hand discussions about contraception and family planning need to take place at an appropriately early age.

Convergent evolution and adaptation of *Pseudomonas aeruginosa* within patients with cystic fibrosis

Authors: Marvig, et al

Reference: Nature Genetics 2015; 47: 57-64

URL: <http://www.nature.com/ng/journal/v47/n1/full/ng.3148.html>

Marvig et al sequenced the whole genome of 474 longitudinally collected clinical isolates of *Pseudomonas aeruginosa* (PA) from 34 children and young adults with CF. Sampling began with the initial PA isolate and serial samples provided a picture of the genetic adaptation of PA to the new in vivo environment. This analysis identified convergent molecular evolution in 52 genes. Convergent molecular evolution is the concept that, when subjected to common selective pressures, organisms proceed down similar predictable evolutionary paths. In other words, the initially diverse clonal lineages of PA adapt to patients, or more specifically to the immune pressure, oxidative and other stresses, antibiotics and other conditions existing in the airway milieu. Mutations in each lineage accumulated in a parsimonious fashion and in a highly constrained order reflecting unidirectional and parallel clonal evolution. The 52 genes involved were patho-adaptive genes with roles in host adaptation, remodelling of regulatory networks, control of metabolism, acquisition of antibiotic resistance and loss of extra-cellular virulence.

These findings are consistent with previous studies of PA showing host adaptation by loss of motility, acquisition of antibiotic resistance, loss of extra-cellular virulence factors and modifications of the cell envelope. The evolution

is towards a common beneficial phenotype includes the mutation of genes which regulate biofilm formation. The authors speculate that this improved understanding of the patho-adaptive mutations of PA may help in predicting bacterial evolution in CF patients and in the design of future intervention strategies.

Pseudomonas aeruginosa in vitro phenotypes distinguish cystic fibrosis infection stages and outcomes

Authors: Mayer-Hamblett N, et al

Reference: A J Respir Crit Care Med 2014; 190: 289 – 97

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4226041/>

This paper compliments the one above. The in vitro phenotype of *Pseudomonas aeruginosa* (PA) of a large cohort of 649 children with PA, was examined in a prospective longitudinal multi-centre study. Using multiple high throughput phenotypic assays, PA were studied from initial identification for a median period of 5.4 years. The study confirmed that PA underwent multiple phenotypic changes in response to the host airway milieu during the transition from initial culture to chronic infection. Two in vitro characteristics distinguished the three infection stages (new-onset, intermediate, chronic); pyoverdine production and reduced protease production. While the best phenotypic predictors of future pulmonary exacerbations were mucoidy and reduced motility (twitching), neither these nor other phenotypes were associated with the subsequent 2 year change in FEV1. Two additional phenotypes were associated with the emergence of mucoidy (increased growth in nitrate and B-lactamase activity), and may represent earlier prognostic markers of important CF outcomes and potentially identify patients for more intensive therapy.

This study provides further information (in terms of in vitro phenotypes) that PA undergoes adaptive changes in the airways of patients with CF during the progression from initial culture to chronic infection.

Oxidation contributes to low glutathione in the airways of children with cystic fibrosis

Authors: Kettle AJ, et al

Reference: Eur Respir J 2014; 44:122-9

URL: <http://erj.ersjournals.com/content/44/1/122.long>

Previous publications from the AREST CF studies in which neonates/children with CF have undergone serial bronchoalveolar lavages (BALs) have provided evidence that CF lung disease starts very early in life with evidence of neutrophilic pulmonary inflammation and lower respiratory tract infection, and that this infection and inflamma-

tion is associated with the early development of structural lung disease, specifically CT evidence of bronchiectasis. Another previous finding was that the presence of neutrophil elastase in BAL fluid at 3 months of age was a significant risk factor for the development of bronchiectasis at 12 months and 3 years of age.

This group now report a lower level of glutathione in the BAL fluid from children (n=167, mean age 3 years) with CF. Glutathione, which is also transported by CFTR, acts as an anti-oxidant in the epithelial lining fluid by scavenging reactive oxygen species. Neutrophils produce superoxide and hydrogen peroxide and use the enzyme myeloperoxidase to convert hydrogen peroxide to an array of reactive oxygen species including hypochlorous acid and free radicals.

Although there may be a contribution from impaired transport by CFTR, the low levels of glutathione in the BAL fluid suggest that the antioxidant defence provided by this molecule has been overwhelmed. This contention being supported by the finding of increased levels of hydrochlorous-dependant oxidation products of glutathione, the levels of which were strongly correlated with neutrophil density and levels of neutrophil elastase.

This study highlights the potential importance of neutrophil-mediated oxidation in the early development of lung damage in children with CF and identifies potential targets to slow the onset and progression of lung disease in CF. However it does need to be borne in mind that trials to augment epithelial lining fluid glutathione levels by inhalation, and trials using the oral glutathione producing N-acetylcysteine, have not produced positive results.

Early respiratory infection is associated with reduced spirometry in children with cystic fibrosis

Authors: Ramsey KA, et al

Reference: Am J Respir Crit Care Med 2014; 190: 1111 – 1116.

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201407-1277OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#.VlPh_k2he70

This study from the AREST CF group demonstrated that on multivariate analysis only the presence of pro-inflammatory bacterial pathogens (PA, Staphylococcus aureus, H. influenzae, Aspergillus species, Streptococcus pneumoniae) in the BAL fluid in the first 2 years of life with CF, was associated with reduced lung function at school age. Overall those with CF had 8.3% lower FEV_{0.75} when compared to healthy subjects.

This study further underlines the importance of early infection/inflammation in producing lung damage (lung function in this study, bronchiectasis in other reports). This damage occurs early and is likely to persist. Thus any interventions to prevent the development of a vicious cycle of infection, inflammation and lung damage will also need to occur early. Given the demonstrated importance of neutrophils and the fact that neutrophils release oxidants and proteases in a synergistic fashion, suggests either that a multi-pronged approach may be required or

one directed early in the infection/inflammation pathway. Such an aggressive approach begun early in life in the groups at highest risk of lung damage, may have long term benefits for lung health.

The authors provide the tantalising finding on univariate analysis that children who took bacterial prophylaxis in the first 2 years of life had 8.6% higher lung function than those not taking prophylaxis. While they advise caution because of the lack of information on compliance with treatment, this provides a rationale for early intervention studies such as those using macrolide therapy in CF infants identified by newborn screening, or the early use of nebulised hypertonic saline.

Pulmonary disease in cystic fibrosis: assessments with chest CT at chest radiography dose levels

Author: Ernst CW

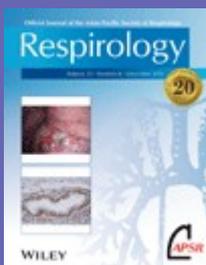
Reference: Radiology 2014; 273: 597-605

URL: <http://pubs.rsna.org/doi/pdf/10.1148/radiol.14132201>

Lung damage begins early in CF and previous studies have detected structural and other changes on CT scan before the development of symptoms or impairment of lung function. The CT scan is considerably more sensitive than plain chest radiographs in detailing structural abnormalities in CF but widespread use of CT scanning, particularly early in life, has been limited by concerns about exposure to radiation.

Ernst et al reports the use of low dose CT scans in 38 patients (age range, 6-58 years with 21 aged <18yrs). The mean effective dose for the investigative protocol was 0.04 mSv for children. This compares with 1.13 mSv for conventional CT and 0.012 mSv for conventional chest radiography. All images were regarded technically as being at least diagnostically acceptable and there was very good agreement with conventional CT scans in terms of overall Bhalla score (ICC,0.96), and severity of bronchiectasis (ICC,0.87). Less certain is the ability of the low dose CT protocols to detect centri-lobular nodules, ground glass abnormalities or gas trapping. Nevertheless the prospect of obtaining good quality CT scans to detect early structural lung disease in CF infants at a radiation dose similar to that of a plain chest radiograph is an exciting particularly if it was shown to identify those in whom early intervention was associated with long term benefit.

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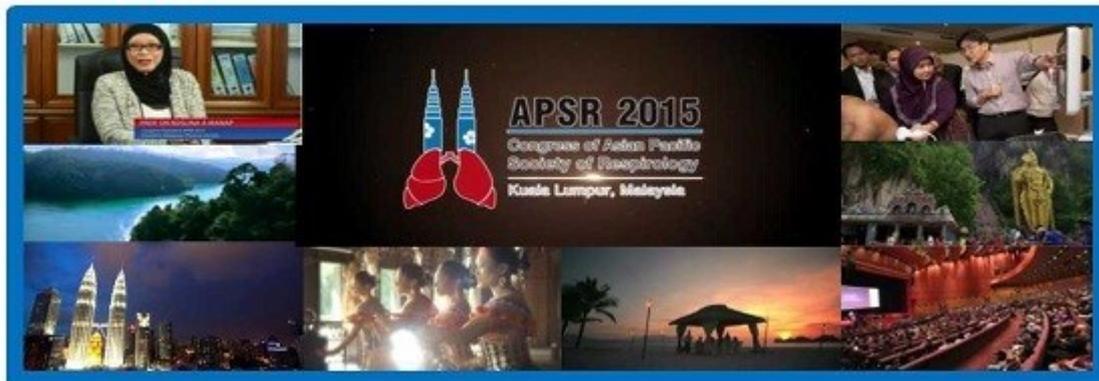
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