Welcome to issue 94 of Respiratory Research Review.

Non-CF bronchiectasis is either becoming more frequent or is more frequently recognised with peak prevalence in advanced age. Certainly, bronchiectasis in patients with COPD has been shown to increase mortality. The best treatment is still a bit of a puzzle: an American group describe how microbiological respiratory flora doesn’t change at the time of an exacerbation or after treatment. After we reviewed the EMBRACE trial previously (Respiratory Research Review Issue 82), we are taking a closer look at the BLESS and BAT studies. The observation is that erythromycin is particularly effective in patients with pseudomonal infection, although it has no antimicrobial activity. Also, what is unclear is whether the risk of developing resistant organisms is worth the benefit if none of the trials showed any quality of life improvements. The ‘Concise Clinical Review: Non-Cystic Fibrosis Bronchiectasis’ (Am J Respir Crit Care Med 2013;188[6]:647–56) gives an authoritative overview.

The most readable overview about CF is the update on the ‘Cystic Fibrosis Pulmonary Guidelines’ (Am J Respir Crit Care Med 2013;187[7]:680–9), which essentially summarises 84 studies in two tables. The articles on CF report on the effect of the colistimethate dry powder inhaler, ivacaftor restoring normal chloride channel function and maintaining lung function, and a study showing that the expensive high-frequency chest wall oscillation isn’t as effective as the PEP airway clearance technique. Possibly the most exciting study comes from Perth, identifying neutrophil elastase as a risk factor for developing CF; a potential therapeutic target.

We hope you enjoy the selection, and we are happy to receive feedback and comments.

Kind regards

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Abbreviations used in this issue

- BAL = bronchoalveolar lavage
- CF = cystic fibrosis
- COPD = chronic obstructive pulmonary disease
- CT = computed tomography
- FEV1 = forced expiratory volume in 1 second
- PE = pulmonary embolism
- PEP = positive expiratory pressure
- RCT = randomised controlled trial

Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease

Authors: Martinez-Garcia M-A et al.

Summary: The prognostic value of bronchiectasis was investigated in 99, 85 and 17 patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) II, III and IV COPD, respectively; 57.2% had bronchiectasis. Of the 51 deaths during median follow-up of 48 months, 43 were in patients with bronchiectasis; the mortality risk was significantly increased in patients with bronchiectasis (adjusted hazard ratio 2.54 [95% CI 1.16, 5.56; p=0.02]).

Comment: This carefully designed Spanish study is clarifying our thinking about the relationship between COPD and bronchiectasis. The authors were vigilant not to overdiagnose bronchiectasis on the basis of a single dilated bronchus. Still, they found bronchiectasis in more than half of their GOLD stage II–IV cohort. While 10% gave a history of previous TB and 27% of pneumonia, most didn’t have classical risk factors for bronchiectasis, suggesting a possible link between inflammatory COPD with increased airway neutrophils as a contributing factor. Bottom line: bronchiectasis is common in COPD and is associated with increased all-cause mortality.


Abstract

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Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation

Authors: Tunney MM et al.

Summary: These researchers measured bacterial abundance and community composition in 40 sputum samples from patients with clinically stable bronchiectasis before and after antibiotic therapy for exacerbations. Aerobic bacteria were present in all samples, while anaerobic bacteria were present in 83%. Pseudomonas aeruginosa (n=10), Haemophilus influenzae (n=12), Prevotella (n=18) and Veillonella (n=13) were the most dominant organisms. Pyrosequencing revealed anaerobic bacteria were present in 83%.

Comment: This carefully designed study challenges our thinking of bronchiectasis. Patients with bronchiectasis develop exacerbations with fever, sputum and dyspnoea. Are these exacerbations caused by a new bacterial strain or species, a change in the bacterial community or a spread of infection to new regions of the lung? The authors investigated 40 patients with bronchiectasis during stable phases, exacerbation and post-treatment. They found a large number of organisms, including Streptococcus, Pseudomonas and Haemophilus spp. However, the bottom line: the microbiota in the lung remained stable through baseline, exacerbation and treatment making it unlikely that changed microbiota composition accounts for exacerbations.


Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis

Authors: Serisier DJ et al.

Summary: The BLESS trial randomised adult nonsmokers with non-CF bronchiectasis with a history of ≥2 infective exacerbations in the prior year to receive erythromycin 400mg (n=59) or placebo (n=58); the study completion rate was 91.5%. Compared with placebo, erythromycin was associated with: i) significant reductions in mean protocol-defined pulmonary exacerbations both overall and in those with Pseudomonas aeruginosa airway infection at baseline (1.29 and 1.32, respectively, vs. 1.97 per patient per year; p values 0.003 and 0.02); ii) median 24-hour sputum production (median difference 4.3g; p=0.01); iii) attenuation of change in postbronchodilator FEV1 (difference 2.2 percent predicted; p=0.04); and iv) a greater increase in the proportion of macrolide-resistant oropharyngeal streptococci (27.7% vs. 0.04%; p<0.001).

Comment: This is one of three studies investigating the role of long-term antibiotics in bronchiectasis. The authors noted the limited efficacy of inhaled steroids, mucolytics and prolonged oral antibiotics. They chose erythromycin because it is cheaper than other macrolides and induces less resistance. Low-dose erythromycin reduced exacerbations of bronchiectasis, particularly in patients infected with pseudomonal infection. It didn’t reduce cough, C-reactive protein level or quality of life. It did increase macrolide-resistant oropharyngeal organisms. Bottom line: long-term low-dose erythromycin reduced exacerbations, protected against lung decline and increased bacterial resistance – its place in treatment is currently unclear.


Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis

Authors: Altenburg J et al.

Summary: The BAT (Bronchiectasis and long-term Azithromycin Treatment) RCT was conducted in 14 hospitals in the Netherlands among 83 outpatients with non-CF bronchiectasis and ≥3 lower respiratory tract infections in the preceding year. Patients received either azithromycin 250 mg/day (n=43) or placebo (n=40) for 12 months. At 1 year, the median number of exacerbations was significantly lower with azithromycin than placebo (0 vs. 2; p<0.001). Thirty-two (80%) placebo-treated versus 20 (46%) azithromycin-treated individuals had ≥1 exacerbation (hazard ratio 0.29 [95% CI 0.16, 0.51]). In a mixed-model analysis, change in FEV1 (% of predicted) over time differed between groups, with an increase of 1.03% per 3 months in the azithromycin group and a decrease of 0.10% per 3 months in the placebo group (p=0.047). Gastrointestinal adverse events were reported more often by azithromycin– than placebo-treated patients (40% vs. 5%; relative risk 7.44 [95% CI 0.97, 56.88] for abdominal pain and 8.36 [1.10, 63.15] for diarrhoea), but none had to subsequently discontinue study treatment. Notably, a macrolide resistance rate of 88% was noted in azithromycin-treated individuals, compared with 26% in the placebo group.

Comment: These Dutch authors performed a study similar to the NZ Embrace study (Respiratory Research Review Issue 82); however, they offered Azithromycin 250mg once daily for 12 months, versus 500mg three times a week for 6 months. Like BLESS and EMBRACE, they also reduced exacerbations and time to first exacerbation. They demonstrated a modest improvement in FEV1, and spirometry; but also gastrointestinal side effects (40%) and increased macrolide resistant organism (88%). Stuart Elborn and Mike Tunney carefully consider these issues in their accompanying editorial (JAMA 2013;309[12]:1295–6). Bottom line: a role of long term macrolides in bronchiectasis is emerging; however, antibiotic resistance is a concern.


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Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study)

Authors: Valery PC et al.

Summary: Indigenous Australian, Māori and Pacific Island children aged 1–8 years with bronchiectasis or chronic suppurative lung disease, stratified by study site and exacerbation frequency, received azithromycin 30 mg/kg (n=45) or placebo (n=44) each week for 12–24 months (mean 20.7) in this RCT, the trial was terminated early for feasibility reasons. Compared with placebo, azithromycin was associated with a significantly lower exacerbation rate (incidence rate ratio 0.50 [95% CI 0.35, 0.71; p<0.0001]), but significantly higher carriage of azithromycin-resistant bacteria (46% vs. 11%; p=0.002). Azithromycin and placebo were respectively associated with 112 and 209 adverse events, with 71 and 132 nonpulmonary infections and 22 and 48 bronchiectasis-related events; no serious adverse events were attributed to the intervention.

Comment: Indigenous children in high-income countries have a heavy burden of bronchiectasis unrelated to CF. This combined Australian and NZ study enrolled Indigenous Australian, Māori and Pacific Island children aged 1–9 years into a trial receiving once weekly azithromycin or placebo for up to 24 months. As in the adult studies, azithromycin halved the number of exacerbations at the cost of increasing carriage of azithromycin-resistant bacteria. Bottom line: as clinicians we need to weigh up if the preservation of lung function and improvement of quality of life justifies the emergence of long-term resistant bacteria.


Abstract

Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis

Authors: Wilson R et al.

Summary: This phase II trial randomised adults with predefined potential respiratory pathogens (including Pseudomonas aeruginosa and Haemophilus influenzae) to receive dry powder inhaled ciprofloxacin 32.5mg (n=60) or placebo (n=64) twice daily for 28 days; follow-up was 56 days. Compared with placebo, dry powder ciprofloxacin was associated with a significant reduction in total sputum bacterial load at the end of treatment (–3.62 vs. –0.27 log 10 CFU/g; p<0.001), after which counts increased, and a significantly greater pathogen eradication rate at the end of treatment (35% vs. 8%; p=0.001). Safety data showed no abnormal findings, with low rates of bronchospasm.

Comment: This study explored the role of inhaled dry powder ciprofloxacin 32.5mg twice daily during a stable phase for 28 days. Participants with idiopathic or postinfective bronchiectasis were randomised to receive ciprofloxacin powder, engineered to deposit in large and small airways, or placebo. Participants in the active group had a significant reduction in bacterial load, and 35% achieved eradication of Pseudomonas spp. The effects on exacerbations, C-reactive protein level, quality of life and lung function were not significant. Ciprofloxacin was well tolerated; however, increased resistance was observed. Bottom line: ciprofloxacin dry powder achieved a reduction in bacterial load.


Abstract

Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis

Authors: Schuster A et al., for the Freedom Study Group

Summary: Patients aged ≥6 years with stable CF and chronic Pseudomonas aeruginosa lung infection (n=380) were randomised to an inhaled dry powder product containing colistimethate sodium 1662,500U per capsule (Colobreathe) twice daily or three 28-day cycles of inhaled tobramycin 300 mg/5mL twice daily for 24 weeks in this open-label study. No significant difference was seen between the colistimethate versus tobramycin arms for change in percent predicted FEV1, at week 24, with adjusted mean differences of –0.98% (95% CI –2.74, 0.86) and –0.56% (–2.71, 1.70) in the intent-to-treat (n=373) and per-protocol (n=261) analyses, respectively. Colistin-resistant isolate rates were ≤1.1% in both groups, and adverse events were similar.

Comment: This German study of 320 patients with CF investigated the role of a micronised dry powder inhalation of colistimethate. Nebulised colistimethate is effective in treatment of pseudomonal infection; however, nebulisation is rather cumbersome. The patients found the new inhaler easy to handle, and the colistimethate inhaler was as effective as tobramycin in reducing Pseudomonas burden. Only 1% colistimethate resistance was reported. At this stage, the NICE guidelines suggest the equal performance of inhaled tobramycin does not justify the higher expense. Bottom line: dry powder inhaled colistimethate is effective in reducing Pseudomonas burden.


Abstract

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START SPIRIVA** before COPD symptoms impact everyday life

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Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry

Authors: Davies J et al.

Summary: Patients with CF with ≥1 G551D-CFTR allele and FEV₁ >90% of predicted received 28 days of ivacaftor 150mg and placebo twice daily, separated by a 28-day washout period, in this phase II crossover RCT; 17/21 enrolled participants completed the trial. Compared with placebo, ivacaftor was associated with a significantly better mean improvement in baseline lung clearance index at days 15 and 29 (difference −2.16; p<0.001). No significant between-treatment difference was seen for the adverse event rate, and there were no deaths during the study period.

Comment: In the last issue of Respiratory Research Review covering bronchiectasis and CF (Issue 82), we reviewed the chloride channel enhancer, ivacaftor. This study investigated the effect of ivacaftor on 20 patients with the G551D mutation. The active treatment was associated with better FEV₁ preservation; actually the authors argued that FEV₁ may not be sensitive enough to detect early abnormalities and suggested the adoption of the lung clearance index. Burkhard Tümmler provides an insightful overview and the title of his accompanying editorial (Lancet Respir Med 2013;1[8]:591–2) is our bottom line: mutation-specific therapy in CF: the earlier, the better.


Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis

Authors: McIlwaine MP et al.

Summary: Patients with CF were randomised to receive 1 year of high-frequency chest wall oscillation (n=56) or PEP mask therapy (n=51) in this trial; 19 participants dropped out. Compared with PEP, high-frequency chest wall oscillation was associated with significantly more PEs (2.0 vs. 1.14) and shorter time to first PE (115 vs. 220 days; p=0.02), but no significant between-group difference was seen for lung function, health-related quality of life scores or patient satisfaction scores. Furthermore, PEP mask therapy was associated with a shorter treatment time.

Comment: Airway clearance is central in the management of CF. Methods include active cycle of breathing, PEP, oscillating PEP, autogenic and postural drainage, percussion and high-frequency chest wall oscillation. These Canadian physiotherapists reported a randomised trial comparing the efficacy of PEP treatment with high-frequency chest wall oscillation. The group using PEP treatment had fewer exacerbations and a longer time to the first exacerbation. Eleanor Main reflects on this well-conducted trial in her editorial (Thorax 2013;68[8]:701–2), and also wonders if one should measure lung clearance index instead of FEV₁. Bottom line: PEP masks are more effective than high-frequency chest wall oscillation for airway clearance in CF.

Reference: Thorax 2013;68(8):746–51

Risk factors for bronchiectasis in children with cystic fibrosis

Authors: Sly PD et al., for the AREST CF Investigators

Summary: These Australian researchers sought to identify risk factors for bronchiectasis onset in 127 consecutive infants diagnosed with CF after newborn screening. Data from chest CT and BAL undertaken during stable disease at aged 3 months and 1, 2 and 3 years showed that the point prevalence of bronchiectasis increased from 3.9% (age 3 months) to 61.5% (age 3 years). Multivariate analyses revealed the following significant risk factors for bronchiectasis: presentation with meconium ileus (odds ratio 3.17 [95% CI 1.51, 6.66; p=0.002]), respiratory symptoms at the time of CT and BAL (2.05 [1.17, 3.59; p=0.01]), free neutrophil elastase activity in BAL fluid (3.02 [1.70, 5.35; p<0.001]) and gas trapping on expiratory CT (2.05 [1.17, 3.59; p=0.001]), and also wonders if one should measure lung clearance index instead of FEV₁.

Comment: Neutrophil proteases, including elastase, are critical for killing engulfed bacteria. However, these proteases may overwhelm defences and accumulate in the airway impairing cilia function and degrading structural proteins, and may lead to bronchiectasis. Peter Sly and the members of the AREST-CF group report on their 127 infant cohort. They identified risk factors for developing bronchiectasis — meconium ileus at presentation, respiratory symptoms, gas trapping and neutrophil elastase activity. This paper may well become a ‘game changer’, as therapeutics targeting elastase are being explored. Bottom line: neutrophil elastase activity in BAL fluid predicts early development of bronchiectasis.


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