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HIGHLIGHTS FROM ERS/NACF 2016

This issue of CARE Perspectives explores relevant abstracts and research presented at both the European Respiratory Society (ERS) & North American Cystic Fibrosis (NACF) conferences within the fields of cystic fibrosis, chronic obstructive pulmonary disease, non-CF bronchiectasis, asthma, chronic cough, and pneumonia. Content is further contextualized and framed from a Canadian perspective.

We hope you find this valuable and stay tuned for more respiratory medicine updates in 2017!

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The content that follows is written in the language in which it was presented. The following content is drawn from the abstracts at the ERS/NACF 2016 meetings, and is augmented with content and perspectives from the CARE Respirology Faculty.
CYSTIC FIBROSIS

ERS 2016. LBA PA1268: Aerobic exercise capacity in cystic fibrosis – Does CFTR genotype matter?
Thomas Radtke et al.

Results: 513 patients (45% females) from 10 CF centers in North America and Europe had both valid maximal CPET and complete CFTR genotype data and were included in the analysis. Overall, patients had reduced VO2peak (means SD, 81.5 ± 19.2% predicted), but values were comparable among different CFTR classes. Using multilevel mixed-effects models adjusted for study center and relevant confounders, lung function and body mass index were the main predictors of VO2peak, independent of CFTR genotype.

Conclusions: Lung disease severity and reduced nutritional status rather than CFTR genotype are the major determinants of maximal exercise capacity in CF patients.

NACF 2016. Abstract 188. Discovery and Biological Profile of Next-Generation CFTR Correctors
Amy Sturges et al.

Results: VX-152 and VX-440 are CFTR correctors, as they facilitated the processing and trafficking of CFTR in F508del/F508del-HBE to increase the amount of CFTR at the cell surface. Addition of a first-generation CFTR corrector in combination with VX-152 or VX-440 further facilitated the processing and trafficking of CFTR, indicating that the combination delivered more CFTR to the cell surface than either corrector alone. In Ussing chamber studies using F508del/F508del-HBE, 24-hour treatment with VX-152 or VX-440 alone enhanced chloride transport from a baseline of 6% normal to 19% and 16% normal, respectively. Compared with lumacaftor plus ivacaftor, which increased chloride transport to 27% of normal, the triple combination of VX-661, ivacaftor and VX-152 or VX-440 increased chloride transport to 75% and 68% normal, respectively. These levels were higher than the level of chloride transport in G551D/F508del-HBE treated with ivacaftor (48% normal). For all conditions tested, the response in F508del/G542X- or F508del/3905InsT-HBE was approximately half of that observed in F508del/F508del-HBE, consistent with a gene dose effect. In addition to improving chloride transport, the triple combination with VX-152 or VX-440 improved fluid transport and ciliary beat frequency more than lumacaftor and ivacaftor in F508del homozygous and heterozygous HBE. In addition to these results, further progress on the identification and optimization of next-generation correctors were discussed.

Conclusions: These in vitro data support the clinical evaluation of VX-152 or VX-440 in combination with first-generation CFTR correctors and ivacaftor to evaluate clinical benefit in patients with CF who have F508del on one or both CFTR alleles.

ERS 2016. PA1257. Ivacaftor-as effective in clinical practice?
A. Aziz et al.

Results: 15 patients with CF were started on ivacaftor, mean age of 32 years (range 18-69). The mean predicted FEV1 was 59.6% (range 20-94%) at baseline. There was a significant increase in percentage points in predicted FEV1 (11.3% at 6 months, 7.5% at 1 year, 9.7% at 18 months and 11.8% at 2 years (p<0.0001), in BMI (7.2% at 6 months, 9.4% at 1 year, 8.4% at 18 months and 8.1% at 2 years (p=0.0083) and a decrease in sweat chloride from baseline (-47.2mmol/l at 1 year and -55mmol/l at 2 years (p<0.0001) There was a reduction in pulmonary exacerbations of 40.6% at 1 year and of 39.3% at 2 years. Only 3/15 patients showed a temporary derangement in LFTs. For 3/15 patients bone density measurements were available at baseline and 2 years later which showed an improvement irrespective of vitamin D levels. There was one successful pregnancy whilst on treatment in this cohort.

Conclusions: In practice, ivacaftor therapy has realised clinically relevant improvements in FEV1, BMI, pulmonary exacerbation rate and bone density in CF patients.

CARE FACULTY PERSPECTIVE: In clinical trials, Ivacaftor has demonstrated consistent efficacy and safety data for patients with cystic fibrosis. This study aimed to look at whether the efficacy results differed at all when used in clinical practice. Based on this retrospective analysis over the course of 2 years, results suggest ivacaftor does in fact treat CF effectively (demonstrated by improvements in FEV1, BMI, pulmonary exacerbation rate, and bone density).

"RESULTS SUGGEST IVACAFTOR DOES IN FACT TREAT CF EFFECTIVELY"

Ivacaftor has also been investigated in combination with Lumacaftor. The combination (Orkambi*) therapy has recently been approved by FDA and Health Canada for CF patients homozygous for the most common CFTR mutation (F508del/F508del).

Better access to appropriate CF therapy could help to improve the quality and length of their lives. Cystic Fibrosis Canada has made a submission to the Canadian Drug Expert Committee (CDEC) of the Canadian Agency for Drugs and Technologies in Health (CADTH). They have requested that Orkambi be reconsidered at the next CDEC meeting in September 2016. Moreover, they have requested that the CDEC consider the recommendations made by a panel of Cystic Fibrosis specialists across Canada regarding its clinical use.

Venkateshwar Mutyam et al.

Results: GLPG1837 and VX-770 showed dose-dependent increases in CFTR activity (Gt) in all the three FRT CFTR PTC cell lines compared to vehicle control (P<0.05), but only when RT was induced by G418 pre-treatment. In FRT W1282X and R1162X, GLPG1837 CFTR activity was significantly greater than VX-770 (P<0.05). In a triple-combination approach, correctors alone (C1 or C2) or combined (C1+C2) did not significantly enhance CFTR-dependent Gt compared to G418 alone, indicating the synergy of CFTR modulators with RT agents. In HRP assay, CFTR expression levels were significantly higher in combination of C1+C2 and GLPG1837 pre-treatment (Gt: 6.5± 0.3 mS/cm2) as compared to VX-809+GP-5 (Gt: 1.8± 0.1 mS/cm2). In contrast to FRT G542X, in FRT W1282X cells, C1+C2 were significantly efficacious, both alone and in combination with RT agents. In addition, GLPG1837-induced response was significantly higher in the FRT-W1282X mutation compared to G542X and R1162X mutations. Evaluation of CFTR activity in primary cells is in progress.

Conclusions: The combination of novel correctors and a potentiator show significant synergy with RT agents. Further, the combination of correctors (C1+C2) exhibited a significant benefit for the W1282X mutation as corrector therapy was efficacious on its own (without RT), especially when combined with GLPG1837. Combination therapy (CFTR modulators + RT agents) may be a useful approach to augment repair of CFTR nonsense mutations.

ERS 2016. PA4869. Ataluren in nonsense mutation cystic fibrosis patients not receiving chronic inhaled tobramycin: Evaluation of exacerbations and lung function

Isabelle Sermet-Gaudelus et al.

Results: Patients not receiving chronic inhaled tobramycin (non-TOBI; n=146), showed a 5.7% difference in relative ppFEV1 between ataluren and placebo (−0.7% vs −6.4%; p=0.0082) and 40% fewer exacerbations (1.42 vs 2.18; p=0.0061). Non-TOBI patients ≥6 to <18 years old (n=42) showed an 8.2% difference in relative ppFEV1 between ataluren and placebo (4.9% vs −3.3%; p=0.026) and a 60% lower exacerbation rate favoring ataluren (p=0.030). In all intent-to-treat patients (N=232) at week 48, including tobramycin patients, neither relative change from baseline in ppFEV1 (<2.5% vs −5.5%; p=0.12), nor number of exacerbations (1.42 vs 1.78; p=0.099) significantly differed between ataluren and placebo.

Conclusions: Ataluren significantly reduced exacerbations and improved lung function (LF) in nmCF patients not receiving chronic inhaled tobramycin, with markedly improved treatment effect in children and adolescents. Ataluren thus shows promise as a disease-modifying therapy in nmCF.

CARE FACULTY PERSPECTIVE: In patients with CFTR nonsense mutation, ataluren appears to be a promising agent with an efficacy similar to CFTR-targeting therapies currently used in patients with class II or class III mutations.

"COMBINATION THERAPY (CFTR MODULATORS + RT AGENTS) MAY BE A USEFUL APPROACH TO AUGMENT REPAIR OF CFTR NONSENSE MUTATIONS."
NON-CF BRONCHIECTASIS

ERS 2016. LBA OA272: RESPIRE 1: Ciprofloxacin DPI 32.5mg b.d. administered 14 day on/off or 28 day on/off vs placebo for 48 weeks in subjects with non-cystic fibrosis bronchiectasis (NCFB)
Anthony De Soyza et al.

Results: Overall 416 patients were randomised. Primary endpoints: Ciprofloxacin DPI 14 day on/off regimen significantly prolonged time to first exacerbation vs pooled placebo (p=0.0005) and significantly reduced frequency of exacerbation vs matched placebo (p=0.0061). The 28 day on/off regimen had no significant effect for either endpoint. The frequency of treatment emergent adverse events was similar across groups.

Conclusions: Ciprofloxacin DPI 14 day on/off regimen for 48 weeks significantly prolonged time to first exacerbation, reduced exacerbation frequency in NCFB patients and was well tolerated.

CARE FACULTY PERSPECTIVE: While treatment regimens for NCFB are not often evidence-based, this randomized controlled trial provides positive results for use of ciprofloxacin dry-powder inhaler (DPI). There may be potential for its inclusion/use in the Canadian landscape, given its potential to prolong the time to first exacerbation, as well as reduce exacerbation frequency when used in the 14 day on/off regimen.

ERS 2016. OA276. Long term prognosis of non-cystic fibrosis bronchiectasis
Amparo Sanz Cabrera et al.

Results: 170 patients (58.2% male, mean age 64.4 ± 14.6) were included. Mortality at the end of the follow-up was 36.5%. First year, 5th year and 9th year survival was 86%, 63% and 56%, respectively. In univariate analysis mortality were related to age, comorbidities, COPD, FEV1 <50%, volume of sputum, greater degree of dyspnoea (mMRC), type of bronchiectasis (cylindrical vs cystic), radiographic changes, respiratory insufficiency, total proteins level and higher number of exacerbations after discharge. In the multivariate analysis, the following showed a statistically significant association with mortality: degree of dyspnoea > 3 (OR: 3.2, CI 95%: 1.7 to 5.8), extension> 4 lobes (OR: 2.5; CI95%: 1.3-5), radiological evidence of pulmonar hypertension (OR: 2.8; CI95%: 1.5 to 5.3), residual fibrosis (OR: 1.6, CI 95%: 0.9 to 3), total proteins level (OR:0.4 CI 95%: 0.3-0.7) and age> 70 years (OR: 2.8; CI 95%: 1.5-5).

Conclusions: 1. We found high mortality in patients with non-CF BQ after hospitalization (36.5%). 2. Mortality was associated with age, radiographic extension, functional impairment and nutritional status.

CARE FACULTY PERSPECTIVE: Non-cystic fibrosis bronchiectasis (NCFB) imposes a significant burden on affected individuals and the health care system. This study provides insight into specific risk factors contributing to morbidity and mortality of NCFB patients. Canadian respiratory medicine specialists should consider paying close attention to monitoring patients that fall into these risk factor groups.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ERS 2016. PA727. Information exchange between primary care (PC) and secondary care (SC): What is considered important in COPD?
Edmée van den Akker (Zeist, Netherlands)

Results: SC requests information from PC only about respiratory complaints and anxiety/depression. In contrast, at referral back, PC considered important to receive detailed description of physiologic impairment (12 of 17 items were rated important) including detailed lung function and radiology, as well as in-depth information about symptoms (4/7), limitations (4/4) and QoL (2/2).

Conclusions: SC requires only little information from PC at referral, probably because they would repeat the assessment anyway. In contrast, PC expects information on all four domains of health status. This suggests great awareness of the importance of health status indicators with implications for further treatment in primary care. It also implies that PC judges SC as the expert to deliver this information.

CARE FACULTY PERSPECTIVE: In many disease categories, there can be breakdown in communication between primary care (PC) and secondary care (SC) physicians. This study looked at the relationship between PC and SC and provides insight for both specialties. This study observed that SC physicians do not need as much information from PC, however PC expects more in depth information on the patient from SC, as they are the experts. The study does not, however, did not look at the outcomes of these consultations and is therefore unable to validate if the exchange of information leads to better health outcomes for patients.

Nevertheless, the implication of this data supports an open dialogue between SC and PC in order to satisfy PC’s need for information to ultimately help better manage patients.

"DATA SUPPORTS AN OPEN DIALOGUE BETWEEN SECONDARY AND PRIMARY CARE."
Effect of indacaterol/glycopyrronium (IND/GLY) vs salmeterol/fluticasone (SFC) on moderate or severe COPD exacerbations and lung function based on baseline blood eosinophil counts: Results from the FLAME study

Kenneth R. Chapman et al.

Results: 3362 patients were randomised to IND/GLY (n=1680) or SFC (n=1682). The annualised rate of moderate or severe exacerbations was significantly lower in IND/GLY-treated vs SFC-treated patients at all eosinophil counts, although not significant for small number of patients with ≥300 cells/µL. The lung function was significantly improved at all the visits with IND/GLY vs SFC irrespective of eosinophil count (Table 1).

Table 1. Annualized rate of moderate or severe exacerbations and lung function improvement in IND/GLY vs SFC.

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<th>Subgroups by blood eosinophil counts</th>
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<td>&lt;2%, n=1279</td>
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<td>≥2%, n=2019</td>
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<td>&lt;150 cells/µL, n=1277</td>
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Change from baseline in pre-dose trough FEV₁ (L) at post-baseline visit

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Conclusions: In patients with high risk of exacerbations, IND/GLY was superior in reducing moderate or severe exacerbations and showed significant improvement in lung function vs SFC independent of blood eosinophil counts.

CARE FACULTY PERSPECTIVE: Guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with COPD and a high risk of exacerbations.

This large 52-week multicentre study (3362 patients) compared the effect of IND/GLY (LABA-LAMA) vs SFC in patients with moderate to severe COPD. Results showed a better outcome for patients given IND/GLY vs SFC, in terms of rate of reduction of moderate or severe exacerbations and lung function independent of blood eosinophil counts. This could be misleading as there were not many patients with very high blood eosinophils and there is good evidence that patients with airway eosinophils (sputum) do well on corticosteroids. Therefore, we need more studies to see if these conclusions would be true if treatment was guided by raised sputum eosinophils rather than by blood eosinophils.

The once-daily LABA-LAMA combination regimen used in this study is approved in Canada and Europe (Ultibro™ Breezhaler®).

ERS 2016. LBA OA249: Effect of fluticasone furoate (FF)/vilanterol (VI) on the rate of COPD exacerbations in everyday clinical practice: Results of the COPD Salford lung study (SLS)

Jørgen Vestbo et al.

Results: Based on 2799 ITT patients; baseline exacerbation rate was 2.01; pre-bronchodilator FEV₁ predicted was 56%. 177 patients experienced an SAE of pneumonia 94 initiated on FF/VI; 83 on usual maintenance therapy (UC) (Incidence ratio 1.1, 95% CI 0.9–1.5). The SAE profile was similar across the groups.

Conclusions: In an everyday clinical practice setting, treatment initiated with FF/VI significantly reduced the rate of exacerbations compared with UC. FF/VI was non-inferior to UC for incidence of pneumonia. Clinical Trial: NCT01551758.

CARE FACULTY PERSPECTIVE: This was a year-long, open-label comparative effectiveness real world trial, conducted in a population of patients undergoing treatment at 75 general practices in the U.K. Thus, in an unselected primary care population, on average, an easy regimen of a low dose corticosteroid and an ultra long-acting beta-agonist bronchodilator as a single inhaler was very effective in reducing exacerbations. However, it should not deter physicians from considering higher doses of corticosteroids in those small proportion of patients with COPD who may have high blood or sputum eosinophils.

ERS 2016. PA296. Effect of indacaterol/glycopyrronium (IND/GLY) vs salmeterol/fluticasone (SFC) on moderate or severe COPD exacerbations and lung function based on baseline blood eosinophil counts: Results from the FLAME study

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ERS 2016. PA305. Mepolizumab in COPD with eosinophilic bronchitis: A randomized clinical trial
Angira Dasgupta et al.

Results: 18 patients were randomised (8 in active-arm, 10 in placebo). Mepolizumab reduced sputum eosinophils (baseline 11% to 0.5% at 6 months in active arm vs 7.35% to 2.2% in placebo arm, p<0.05) and blood eosinophils (0.69 at baseline to 0.03 at 6 months in active-arm vs 0.33 to 0.26 in placebo-arm, p<0.05). There were no significant changes with treatment in the secondary outcomes: lung function (FEV₁, FVC, SVC, FEV₁/SVC, FEV₁/FVC, TLC, RV, RV/TLC and DLCO), exacerbation rates, patient-related outcomes, sputum markers (hyaluron and versican) and CT assessments of remodelling (airway-wall, lumen area, parametric response maps or relative areas of the CT density-histograms).

Conclusions: Mepolizumab did not improve lung function and exacerbation rates in COPD with eosinophilia. This suggests that although eosinophils are a predictor of response to treatment with corticosteroids, unlike in asthma, they may not directly contribute to luminal obstruction in COPD.

CARE FACULTY PERSPECTIVE: This study questions the role of eosinophils in the pathobiology of COPD and would suggest that monoclonals directed specifically at reducing eosinophils may have limited role in the treatment of COPD. The study also suggests that that steroids (ie. prednisone) may be acting on inflammatory cells, cytokines or a pathway not directly linked to eosinophils. This opens up a new avenue of research to treat COPD.

ERS 2016. LBA OA1976. Tackling the burden of chronic cough: A dose escalation study of AF-219
Jaclyn Smith et al.

Results: 30 patients (12 naïve, 18 previously treated at higher doses) at 10 US sites were randomized; mean age 60yrs, median cough duration 13yrs, 80% female. AF-219 30 and 50mg BID produced equivalent, marked reductions in awake cough vs. placebo (p<0.05). Awake cough frequency also reduced with 7.5 and 15 mg BID (p>0.05). Patient perception of improvements in cough severity lagged the objective measure. Separation between efficacy and tolerability was seen, with few patients reporting taste AEs at 7.5 and 15mg (none in naïve group).

Conclusions: Lower doses of AF-219 produced marked reductions in cough frequency; fewer patients noted reduced taste, portending promising efficacy and tolerability in studies of longer duration.

CARE FACULTY PERSPECTIVE: This is the first new effective treatment for chronic cough in a very long time. This study, demonstrated, that a lower dose of this compound than the previous reports in the Lancet 2016 is effective without causing the adverse effect of loss of taste sensation.

"AF-219 IS THE FIRST NEW EFFECTIVE TREATMENT FOR CHRONIC COUGH IN A VERY LONG TIME."
ASTHMA

INADEQUATELY CONTROLLED ASTHMA

ATS 2016. OA1797. Reslizumab (RES) in patients (pts) with inadequately controlled asthma and elevated blood eosinophils (EOS): Analysis of two phase 3, placebo-controlled trials

Johann Christian Virchow et al.

Results: Of 953 randomised pts, 306 (32%) had inadequately controlled asthma (PBO=161; RES=145). Efficacy results in this asthma patient subset consistently favored RES compared with PBO across measures of CAE (rate ratio 0.41 [95% CI: 0.28, 0.60]), lung function (FEV1, difference [diff] 158mL [-76, 240]), and pt-reported asthma control (ACQ-7 diff -0.295 [-0.471, -0.119]; ASUI diff 0.07 [0.038, 0.102]; AQLQ diff 0.432 [0.233, 0.632]). The magnitude of effects in this patient subset for FEV1, AQLQ and ASUI were greater than that observed in the overall population (Castro et al. Lancet Resp Med 2015).

Conclusions: RES was highly effective at reducing the frequency of CAE and in improving lung function and pt-reported asthma control and quality of life in this subset of pts.

CARE FACULTY PERSPECTIVE: Previous studies have confirmed that reslizumab is able to reduce exacerbation frequency and improve lung function and asthma control in patients with inadequately controlled asthma and elevated blood EOS.

This study confirmed these findings, reporting reslizumab as a highly effective agent at reducing the frequency of clinical asthma exacerbations.

UNCONTROLLED ASTHMA

ERS 2016. LBA OA4832. Benralizumab provides significant improvements for patients with severe, uncontrolled asthma: SIROCCO Phase III results

Eugene Bleecker et al.

Results: For the primary analysis, pts receiving benralizumab achieved significantly greater decreases in the annual exacerbation rate vs. PBO (table), and lung function and asthma symptom improvement at Week 48. Adverse events were similar between the benralizumab-treated groups and PBO.

Conclusions: Benralizumab significantly reduced annual exacerbation rates, improved lung function, and reduced asthma symptoms, in patients with severe, eosinophilic asthma.

CARE FACULTY PERSPECTIVE:

These replicate studies confirm the following:

1. In patients with eosinophilic asthma, blocking IL-5 signalling by blocking the receptor is also as effective as blocking IL5 directly.
2. A convenient 8-weekly sub-cutaneous injection is effective in reducing exacerbation in patients with moderate to severe asthma. The effect is more obvious in patients with higher blood eosinophil count.
3. Patients in the CALIMA trial (Fitzgerald et al) were generally milder than those in the SIROCCO trial (Bleecker et al) and they had less clinical benefits. It is unclear from the clinical trials why a 8-weekly dosing was better than the 4-weekly dosing.
4. Since this molecule has the potential to cause tissue eosinophil depletion, long term safety data are necessary as to the consequences of eosinophil depletion.
ERS 2016. LBA OA1969. Benralizumab reduces exacerbations in severe, uncontrolled asthma: Results of the phase III CALIMA trial

J. Mark FitzGerald et al.

Results: Annual asthma exacerbation rates (primary endpoint) were reduced significantly, with improvements in lung function and asthma symptoms in pts receiving either regimen of benralizumab compared with PBO at Week 56. Adverse events were similar between the benralizumab-treated groups and PBO.

Conclusions: Benralizumab significantly reduced annual exacerbation rates, improved lung function, and reduced asthma symptoms, in patients with severe, eosinophilic asthma.

ERS 2016. LBA OA 1975. LAVOLTA I and II. Results of 2 phase III studies to assess the efficacy and safety of lebrikizumab in patients with uncontrolled asthma

Nicola Hanania et al.

Results: 1081 and 1067 patients were randomized and treated in LAVOLTA I and II. Over 52 weeks, lebrikizumab treatment reduced exacerbation rates in biomarker-high patients by 51% for the 37.5 mg dose (p<0.0001) and 30% for the 125 mg dose (p<0.05) in LAVOLTA I and 26% for both doses in LAVOLTA II (not-significant) vs placebo. FEV1 improved vs placebo (p<0.05) in biomarker-high patients in LAVOLTA I (103 and 113 mL) and LAVOLTA II (88 and 82 mL). There were no improvements in ACQ-5 vs placebo. Proportion of patients with treatment-emergent AEs, SAEs and AEs leading to discontinuation were balanced between groups.

Conclusions: In these replicate Phase III trials, LAVOLTA I met its primary endpoint and LAVOLTA II did not. Further work is ongoing to understand the trial results in more detail.

CARE FACULTY PERSPECTIVE: This large study demonstrated that the effect of blocking IL-13 alone, although biologically makes a lot of sense, may have only a limited role in the treatment of majority of patients with severe asthma.

ERS 2016. P4112. Vitamin D for the management of asthma: Cochrane systematic review and meta-analysis

Adrian R. Martineau et al.

Results: Seven trials involving a total of 435 children and two trials involving a total of 658 adults were included in the primary analysis. Administration of vitamin D reduced the rate of exacerbations requiring systemic corticosteroids (Rate Ratio 0.63, 95% CI 0.45 to 0.88; 680 participants; 3 studies), and decreased the risk of having at least one exacerbation requiring an emergency department visit and/or hospitalisation (Odds Ratio [OR] 0.39, 95% CI 0.19 to 0.78; 963 participants; 7 studies). Sub-group analysis to determine whether the effect of vitamin D on risk of severe exacerbation was modified by baseline vitamin D status was not performed, due to unavailability of suitably disaggregated data.

Conclusions: Vitamin D is likely to prevent severe asthma exacerbation and reduce health care use by people with asthma. It is not yet clear whether these effects are confined to people with lower baseline vitamin D status. Further research is needed before definitive clinical recommendations can be made.

CARE FACULTY PERSPECTIVE: While there is fairly convincing evidence that asthma severity is associated with low levels of Vitamin D levels (25 (OH)D), these small clinical trials where majority of patients had mild to moderate asthma do not provide conclusive evidence that Vitamin D supplementation is effective or which patients are likely to benefit. Vitamin D levels were not measured in these studies, and the reductions of severe exacerbation was modest, 6% reduced to 3%. Lung function or day-day symptoms were not improved. Larger clinical trials are necessary to know if Vitamin D (as well as dosage and formulation) is effective in improving asthma outcomes. Meanwhile, physicians should continue to recommend Vitamin D if patients have osteopenia from the adverse effects of corticosteroids, used to treat asthma.

IN THESE REPLICATE PHASE III TRIALS, LAVOLTA I MET ITS PRIMARY ENDPOINT AND LAVOLTA II DID NOT.
**ERS 2016. PA 613.** Evolutionary trend of invasive pneumococcal disease according to serotypes

*Maria Jose Galvez Medina et al.*

**Results:** Comorbidities of patients with IPD caused by PCV13 serotypes and evolutionary trend of IPD by serotypes. No statistically significant differences found with other serotypes or with age, type of comorbidities or clinical presentation. 36% of the patients with IPD by serotypes included in PCV13 had received the 23V polysaccharide vaccine (PPSV23) which also includes these serotypes.

Table 2: Comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>No</th>
<th>Yes</th>
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<tbody>
<tr>
<td>Active smoker</td>
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<tr>
<td>Cardiovascular dis.</td>
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<td>Hematology</td>
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<td>CKD</td>
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<tr>
<td>Autoimmune dis.</td>
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<td>Asplenia</td>
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<tr>
<td>IBD, COPD, CLD</td>
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<td>HIV Infection</td>
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<tr>
<td>Asthma</td>
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<td>Immunosuppression</td>
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<td>DM</td>
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<tr>
<td>Alcoholism</td>
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<td>Chemotherapy or chemotherapy</td>
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<td>DM</td>
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<tr>
<td>Immunosuppression</td>
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</table>

**Conclusions:** Almost half of IPD cases were caused by serotypes included in PCV13. No differences between groups for age, type of comorbidity or clinical presentation. The vaccination coverage in our setting is low, the effectiveness of PPSV23 has been limited. There was a decrease in the incidence rate in both groups from 2011 to 2014. However, there has been a striking increase in the rate of IPD caused by serotypes not included in the PCV13.

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**ERS 2016. OA3330.** Non-steroidal anti-inflammatory drugs may worsen the course of community-acquired pneumonia: A cohort study

*Damien Basille et al.*

**Results:** Of the 224 included patients, 43 (19.2%) had developed a pleuropulmonary complication. NSAIDs intake prior to admission was reported for 25 patients (11.2%) who were younger (51.3 ± 18.5 vs. 66.5 ± 16.3 years; p=0.001), had less comorbidities (60% vs. 25.1%; p=0.001), had a longer duration between the first symptoms of CAP and the start of an antibiotic therapy (6.1 ± 7.6 vs. 2.8 ± 3.8 days; p=0.001), and more frequently developed pleuropulmonary complications (36% vs. 17.1%; p=0.032). In multivariate analyses, two factors were independently associated with development of pleuroparenchymal complications: NSAID intake (OR=2.68 [1.06–6.76]; p=0.037) and alcohol abuse (OR=3.20 [1.55–6.60]; p=0.002).

**Conclusions:** Our findings suggest that NSAIDs, often taken by young and healthy patients, may worsen the course of CAP with delayed therapy and a higher rate of pleuropulmonary complications.

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**ERS 2016. LBA OA3323.** Intravenous infusion of Chinese medicine xuebijing significantly improved clinical outcome in severe pneumonia patients in a multiple center randomized controlled clinical trials

*Yuanlin Song et al.*

**Results:** Results showed Xuebijing infusion significantly reduced mortality (24.63% vs 15.87% in control and treatment group separately, P<0.05) and number of patients who got improved pneumonia severity index (PSI) were 46.33% in control and 60.78% in treatment group respectively (P<0.001). There was similar results for MODS and lung injury score changes.

**Conclusions:** Take together, Xuebijing infusion combined with standardized treatment could be a potential and promising therapy against severe pneumonia.

**CARE FACULTY PERSPECTIVE:** Xuebijing is a Chinese medicine herbal extract preparation of five Chinese herbs (Radix Salviae Miltiorrhiae, Rhizoma Chuanxiong, Flos Carthami, Angelica Sinensis and Radix Paeoniae Rubra), delivered via infusion formula. It has been used since 2004 for sepsis treatment. It has anti-inflammatory effects with demonstrated cytokine reduction, anti-coagulation, and neutralization of cytotoxins released by bacteria in various infectious disease including pneumonia.
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