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Publication Date

2023-05-01

DOI

10.1016/j.clim.2023.109324

Peer reviewed

HHS Public Access

Author manuscript

Clin Immunol. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

Clin Immunol. 2023 May ; 250: 109324. doi:10.1016/j.clim.2023.109324.

Reduced quantity and function of pneumococcal antibodies are associated with exacerbations of COPD in SPIROMICS

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Disclosure Statement: The University of Alabama at Birmingham (UAB) has intellectual property rights to several multiplexed opsonophagocytosis assay (MOPA) reagents developed in MHN's laboratory, and several authors (DCL, MHN, MTD) are UAB employees. DCL reports grants from Merck Corp. and Jeffrey Modell Foundation, outside the submitted work. MHN is a co-founder of Sunfire Biotechnologies. IB reports grants/contracts from Amgen, GE Healthcare, Theravance, and Mylan; consulting for Grifols, Theravance, Viatris, GE Healthcare, Verona Pharma, Aerogen, Inhibrx, GSK, and AstraZeneca outside the submitted work. JLC reports grants/contracts from NHLBI, NIAID, Department of Veterans Affairs, and Department of Defense, and consulting for AstraZeneca and CLS Behring outside the submitted work. MTD reports grants/contracts from American Lung Association and Department of Defense, and consulting for AstraZeneca, GSK, Pulmonx, and Teva outside the submitted work. PGW reports grants/contracts from Genentech, and consulting for Glenmark Pharmaceuticals, University of Wisconsin, NGM Pharma, GSK, Theravance, Sanofi, and Astra Zeneca outside the submitted work.

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Abstract

While hypogammaglobulinemia is associated with COPD exacerbations, it is unknown whether frequent exacerbators have specific defects in antibody production/function. We hypothesized that reduced quantity/function of serum pneumococcal antibodies correlate with exacerbation risk in the SPIROMICS cohort.

We measured total pneumococcal IgG in n=764 previously vaccinated participants with COPD. In a propensity-matched subset of n=200 with vaccination within five years (n=50 without exacerbations in the previous year; n=75 with one, n=75 with ≥2), we measured pneumococcal IgG for 23 individual serotypes, and pneumococcal antibody function for 4 serotypes.

Higher total pneumococcal IgG, serotype-specific IgG (17/23 serotypes), and antibody function (3/4 serotypes) were independently associated with fewer prior exacerbations. Higher pneumococcal IgG (5/23 serotypes) predicted lower exacerbation risk in the following year. Pneumococcal antibodies are inversely associated with exacerbations, supporting the presence of immune defects in frequent exacerbators. With further study, pneumococcal antibodies may be useful biomarkers for immune dysfunction in COPD.

Keywords

immunity; antibodies; immunoglobulin G; opsonization; *Streptococcus pneumoniae*

1. Introduction:

Exacerbations of chronic obstructive pulmonary disease (ECOPD) are highly significant events in the natural history of COPD, and are associated with lung function decline, morbidity, mortality, and healthcare costs(1-3). Although certain individuals with COPD experience frequent exacerbations (defined as ≥2 treated ECOPD in one year) and have a particularly poor prognosis(3), risk factors for recurrent exacerbations are not well understood. Defining such risk factors could facilitate therapeutic interventions to mitigate associated morbidity and mortality.

There is growing evidence that frequent exacerbators have reduced adaptive immune function(4). Reduced concentrations of total immunoglobulin A (IgA), immunoglobulin G (IgG), and IgG subclasses are associated with increased ECOPD risk(5-9), and frequent exacerbators have blood gene expression profiles indicating reduced lymphocyte

function(10). ECOPD are commonly caused by bacterial respiratory pathogens such as *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*, which are also the most common cause of respiratory infections in primary immunodeficiency diseases (PIDs). Case series have indicated that some patients with frequent exacerbations meet criteria for PIDs(11). However, it is unknown whether defects in the production of antibodies to bacterial respiratory pathogens are common in individuals with recurrent ECOPD, and current guidelines for their evaluation do not include investigation for immune deficiencies.

In evaluating suspected PIDs, measurement of IgG antibodies to multiple capsule types (serotypes) of *S. pneumoniae* is widely utilized as an indicator of adaptive immune response(12). However, the presence of serum anti-pneumococcal IgG (PnIgG) antibodies does not necessarily indicate their ability to opsonize and kill bacteria in vivo(13). This point is particularly significant among older adults, who experience age-related decline in antibody function(14), accompanied by greatly increased risk for pneumococcal pneumonia. The multiplexed opsonophagocytosis assay (MOPA) measures pneumococcal antibody function (PnAF; reported as Opsonic Index or OI) via killing of pneumococci by serum antibodies in vitro(15) (see Figure E1 in the Supplementary material). PnIgG levels were initially used to evaluate pneumococcal vaccines and remain in use by clinical immunologists for PID diagnosis. However, a key study in infants showed that some pneumococcal antibodies generated by vaccination were not functional in opsonizing and killing bacteria(13). Because PnAF is a better indicator of in vivo protection from infections, it is now a requisite endpoint in clinical trials of pneumococcal vaccines and was the primary outcome in studies resulting in the approval of the 13-valent pneumococcal conjugate vaccine (PCV13) in older adults(16). Due to impaired PnAF, older adults are highly susceptible to pneumococcal infections despite normal antibody levels(14). We recently developed approaches to standardize MOPA results using pneumococcal reference serum, allowing comparison of measurements performed by different laboratories(17). We have also created novel analytical models to interpret PnAF responses(18). Collectively, these improvements make MOPA an attractive option to investigate adaptive immune function in COPD. However, pneumococcal antibodies have not been studied as predictors of ECOPD risk.

Our objective was to investigate the hypothesis that lower baseline pneumococcal IgG levels and lower PnAF are associated with increased ECOPD risk in a cohort from the SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS).

Some of these results were reported in a poster discussion session at the American Thoracic Society 2020 virtual conference(19).

2. Materials and methods:

2.1 SPIROMICS design and data collection

SPIROMICS is an ongoing prospective cohort study that enrolled 2,981 participants across four strata (Stratum 1: Never smokers, Stratum 2: Smokers without COPD, Stratum 3:Mild/Moderate COPD, and Stratum 4: Severe COPD) with the goal of identifying new COPD subgroups and intermediate markers of disease progression(20, 21).

SPIROMICS participants underwent a baseline study visit that included spirometry, biospecimen collection, chest CT imaging, and standardized questionnaires. At the baseline visit, participants self-reported number of ECOPD in the previous year, if they had ever received a pneumococcal vaccine, and whether that vaccine had been received in the previous 5 years. Type of pneumococcal vaccine was not specified in the baseline visit questionnaire. However, the questionnaire data and sera included in the current study were collected prior to use of PCVs in older adults and those with chronic lung disease, therefore most (if not all) previously vaccinated participants would have received PPV23.

Longitudinal follow-up consisted of up to three annual visits and quarterly telephone calls to assess for ECOPD. Prospective total ECOPD in the first year of follow-up were defined as the number of exacerbations that received any treatment in the 365 days after enrollment, and severe ECOPD were those that required emergency department evaluation or hospital admission.

Written consent for participation in SPIROMICS was provided by all participants, and the study was reviewed and approved by the institutional review board at each participating institution. The laboratory activities specific to this study were approved by the institutional review board at the University of Alabama at Birmingham.

2.2 Total pneumococcal IgG levels

With the objective of primarily evaluating pneumococcal antibodies produced in response to vaccination (as opposed to those naturally acquired via colonization and/or infection), we restricted this analysis to n=764 SPIROMICS participants with COPD (strata 3-4) who self-reported having previously received a pneumococcal vaccine (see Figure E2 in the Supplementary material). Total PnIgG levels (combined IgG levels for the 23 serotypes included in PPV23) were measured in baseline sera. Total PnIgG measurement was performed by the Johns Hopkins University Institute for Clinical and Translational Research core lab using the 23vELISA pneumococcal vaccine response assay (VaccZyme™,the Binding Site, UK) according to the manufacturer's instructions.

2.3 Serotype-specific pneumococcal IgG

From this group, we selected n=200 participants for serotype-specific analyses who specified having received a pneumococcal vaccine within the preceding 5 years. Propensity score matching was used to select three subsets based on frequency of self-reported ECOPD in the year before enrollment: n=50 with none, n=75 participants with one, and n=75 with ≥2. To select these participants, a propensity score model was created to model the probability of having had no ECOPD in the previous year at baseline, using age, sex, race, and FEV_1 (% predicted) as predictors. Propensity score matching was used to match 75 subjects with ≥2 ECOPD to 75 with 1 ECOPD. Average propensity scores from each exacerbation pair were then used to select 50 controls without ECOPD (See Figure E2 in the Supplementary material). PnIgG antibody concentrations for each of the 23 individual serotypes present in the pneumococcal polysaccharide vaccine (PPV23) were measured at ARUP Laboratories (Salt Lake City, Utah) with a multiplex bead array assay that utilized pneumococcal capsular polysaccharide conjugated to Luminex microspheres(22, 23).

2.4 Pneumococcal antibody function

In the same n=200 participants we used MOPA to determine OI for 4 pneumococcal serotypes (3, 19F, 9V, 11A) previously identified as common causes of pneumonia and exacerbations in COPD(24, 25). The killing-type OPA was performed as previously described at the UAB MOPA Core Laboratory in accordance with uniform protocols, available at www.vaccine.uab.edu(15)(see Figure E1 in the Supplementary material). To enhance generalizability, MOPA results were standardized using reference values from pneumococcal reference serum 007sp(17). Results are reported as standardized OI, the serum dilution that results in 50% bacterial killing (i.e., higher OI indicating higher PnAF).

2.5 Statistical analysis

Statistical analysis was performed using SPSS version 27 (IBM) and Prism version 9 (GraphPad). Raw PnIgG data (in μg/mL) and OI were non-normally distributed, and log transformation was performed prior to analysis. We compared mean log-transformed PnIgG levels and OI between ECOPD groups (0, 1, and ≥2 ECOPD in the previous year) using one-way ANOVA with Bonferroni correction for the three pairwise comparisons. For the four serotypes in which both PnIgG and OI were measured, we compared results using Spearman's correlation.

To investigate associations between log transformed PnIgG and ECOPD reported in the year before enrollment, we performed unconditional logistic regression, first unadjusted and then adjusted for age, baseline FEV_1 (% predicted; post-bronchodilator), sex, race, maximal educational attainment (greater than high school vs all others), current smoking, and inhaled corticosteroid (ICS) use at baseline. The same approach was then used to investigate associations between OI and ECOPD in the year before enrollment. For total PnIgG analysis, the multivariable model also included adjustment for time since vaccination (within the past 5 years vs 5 or more years ago) and oral corticosteroid use at baseline.

To investigate associations between either PnIgG or OI and prospective risk of total and severe ECOPD over the first year of follow-up, we used negative binomial models, unadjusted and adjusted for the same covariates used in retrospective analyses. P-values <0.05 were considered statistically significant. Odds ratios (OR) and incidence rate ratios (IRR) indicate the odds (or risk) of greater number/rate of ECOPD with increasing pneumococcal IgG or OI.

3. Results:

3.1 Baseline Characteristics of Participants

Baseline characteristics of study participants are shown in Table I. Mean age of the total PnIgG cohort (n=764) was 67.0±7.6 years; 55% were male, and 85% were white. Mean baseline FEV_1 (% predicted; postbronchodilator) was 60.2±23.2%. Among the 200 participants included for serotype-specific analyses, mean age was 64.5±7.7 years, 54% were male, 83% were white, and mean FEV_1 was 46.5±19.1%.

3.2 Total pneumococcal IgG

Total PnIgG concentrations were significantly higher among participants without ECOPD compared to those with ≥2 ECOPD in the year before enrollment (mean log(PnIgG) 1.96 vs 1.81, P<0.001) and for 1 vs ≥2 ECOPD (mean log(PnIgG) 1.95 vs 1.81, P=0.010)(Figure 1A; see Table E1 in the Supplementary material).

There was a significant association between higher total PnIgG and having had 0 (as compared to ≥2) ECOPD in the previous year in both unadjusted (OR 0.31, 95% CI[0.17-0.56]; P<0.001) and adjusted (OR 0.45, 95% CI[0.0.24-0.88]; P=0.018) analyses (Figure 1B). There was also a significant association between higher total PnIgG and 1 (as compared to ≥2) ECOPD in the adjusted model (OR 0.38, 95% CI[0.18-0.82]; P=0.014)(see Table E2 in the Supplementary material).

Higher baseline total PnIgG was predictive of fewer total (IRR 0.59, 95% CI [0.42-0.83], P=0.003) and severe (IRR 0.44, 95% CI [0.25-0.80], P=0.007) ECOPD in the first year of follow-up in unadjusted analysis. However in the multivariable models, baseline total PnIgG was not a significant predictor of total or severe ECOPD risk in the first year of follow-up (Figure 1C/D; see Table E3 in the Supplementary material).

3.3 Serotype-specific pneumococcal IgG levels

Among 23 serotypes tested, PnIgG levels for 13 serotypes were significantly higher among participants with 0 (vs ≥2) ECOPD in the year before enrollment. PnIgG for 5 serotypes was higher among those with 1 (vs ≥2) ECOPD. For serotype 9N, PnIgG was higher for those with 0 (vs 1) ECOPD (Figure 2A; see Table E4 in the Supplementary material).

In multivariable logistic regression models, higher serotype-specific PnIgG levels for 16 of 23 serotypes was associated with having 0 (vs ≥2) ECOPD in the year before enrollment with adjustment for age, sex, race, FEV_1, educational attainment, smoking, ICS use (Figure 2B; see Table E5 in the Supplementary material). For eight serotypes, higher PnIgG was associated with having 1 (vs ≥2) ECOPD. Higher PnIgG for serotypes 5 and 9N were associated with having 0 (vs 1) ECOPD (see Table E5 in the Supplementary material).

Five serotypes (5, 19F, 10A, 15B, and 19A) were significant predictors of future total ECOPD in the adjusted negative binomial model (Figure 3C; see Table E6 in the Supplementary material). In the multivariable model, higher PnIgG predicted lower risk for severe ECOPD in the first year of follow-up for serotypes 19A (IRR 0.42, 95% CI 0.20-0.92, P=0.029) and 20 (IRR 0.52, 95% CI [0.28-0.99], P=0.047) (Figure 2D; see Table E6 in the Supplementary material).

3.4 Pneumococcal antibody function

OI, measured by MOPA, was higher in those with 0 (vs ≥2) ECOPD in the year before enrollment for three of four serotypes (serotype 3: Log(OI) 1.68 vs 1.22; P<0.001, serotype 9V: 2.42 vs 1.94; P= 0.021, serotype 11A: 2.43 vs 1.97; P=0.035), and higher in 0 (vs 1) ECOPD for serotype 3 (1.68 vs 1.31; P=0.006) (Figure 3A; see Table E7 in the Supplementary material).

In the multivariable logistic regression model, higher OI was associated with 0 (vs ≥2) ECOPD in the year before enrollment for 3 of 4 serotypes, (serotype 3: OR 0.33, 95% CI[0.18-0.61]; P<0.001, serotype 9V: OR 0.55, 95% CI[0.36-0.84]; P=0.006, serotype 11A: OR 0.60, 95% CI[0.41-0.90]; P=0.013) (Figure 3B; see Table E8 in the Supplementary material). For serotypes 3 and 11A, higher OI was associated with 0 (vs 1) ECOPD.

However, baseline OI was not a significant predictor of prospective total or severe ECOPD risk over the following year (Figure 3C/D; see Table E9 in the Supplementary material). PnIgG positively correlated with OI for all four serotypes in which both parameters were measured (3: r=0.591, 19F: r=0.582, 9V: r=0.329, 11A: r=0.414; P<0.001 for all four serotypes).

4. Discussion:

This analysis of 764 previously vaccinated participants in the SPIROMICS cohort demonstrated significant inverse associations between total concentrations of anti-pneumococcal IgG antibodies at baseline and participant-reported ECOPD in the previous year. We confirmed these results using serotype-specific PnIgG levels in a subset of n=200 participants from this group. Using MOPA, we also demonstrated impaired function of pneumococcal antibodies in those with more frequent ECOPD.

Our study, the first to our knowledge that has demonstrated such associations, provides further support for adaptive immune dysfunction among frequent exacerbators. With further studies in COPD and non-COPD populations, polysaccharide antibody deficiency could be confirmed as an important, potentially treatable underlying risk factor for recurrent ECOPD, a large proportion of which are caused by bacterial infections. Current therapeutic approaches to prevent and treat ECOPD are applied without consideration of infectious vs non-infectious etiology, nor the patient's immune status. Characterization of immune defects in ECOPD could facilitate more targeted use of antimicrobials and/or corticosteroids, and the development of treatment strategies to augment antibody levels and/or function in susceptible individuals.

Previous studied have demonstrated associations between ECOPD and hypogammaglobulinemia, however ours is the first to demonstrate associations with reduced quantity and/or function of specific antibodies. Leitao-Filho and colleagues associated low total IgG levels with ECOPD frequency(6), COPD hospitalization(5, 6), and 1-year mortality(26). They found that low total IgG and IgG subclass concentrations were common in two clinical trials that enrolled participants with moderate-severe COPD at increased exacerbation risk(6, 7). In a case series, many frequent exacerbators referred to a specialty clinic for immunologic evaluation met diagnostic criteria for PIDs(11). However, these studies could not demonstrate whether underlying defects in antibody production and/or function (similar to PIDs) accounted for increased ECOPD risk.

Among IgG subclasses, ECOPD have been specifically associated with reduced IgG2(7). IgG2 is the primary subclass involved in immune responses to polysaccharide antigens, including pneumococcal capsular polysaccharide(27), the key virulence factor and antigenic

target for S. *pneumoniae*. Polysaccharide-specific antibody responses in COPD are not well studied. The PNEUMO study used OI and serotype-specific PnIgG to compare immune responses between PPV23 and the 7-valent pneumococcal conjugate vaccine (PCV7) in COPD(28). It found no association between pneumococcal antibodies and ECOPD but was underpowered to investigate exacerbations as a main outcome.

Our finding of independent associations between total PnIgG levels and ECOPD, supplemented by results from serotype-specific PnIgG and OI, suggest that defects in polysaccharide antibody production could account for reduced IgG2 levels in frequent exacerbators.

Measurement of serotype-specific (in addition to total) PnIgG is an important feature in our study design. Since low total PnIgG following PPV23 would strongly suggest impaired polysaccharide antibody response, 23vELISA has been proposed as an initial screening test for PID. However, this approach could fail to diagnose more subtle cases of immune deficiency if robust responses to one or more individual serotypes yielded an overall normal result(29). Therefore, our finding of independent associations between higher PnIgG and fewer ECOPD for 17 of 23 serotypes tested further supports the presence of deficiency of anti-polysaccharide antibodies in frequent exacerbators. It also suggests that associations with total PnIgG concentrations observed in the larger cohort were not driven by responses to one/several serotypes.

While associations between PnIgG levels and ECOPD support antibody deficiency as an ECOPD risk factor, they cannot be used to infer the functional ability of serum antibodies to kill bacteria in vivo. By investigating PnAF (OI) using MOPA, our study is the first to demonstrate a functional defect in serum antibodies resulting in impaired bacterial killing in COPD. This has important implications in the broader study of adaptive immune dysfunction in ECOPD.

Our analysis of functional (in addition to quantitative) pneumococcal antibody responses is a novel approach and a significant strength. PnAF is a better indication of in vivo responses to bacterial infections, as compared to PnIgG, and older adults have been shown to have functional antibody defects despite “adequate” IgG levels. This is likely to be particularly relevant in COPD, which increases in prevalence and often in severity with age. Via impaired opsonophagocytosis, lower PnAF may contribute to defective phagocytosis by COPD macrophages which was recently shown to be a risk factor for ECOPD(30, 31). Our finding of functionally impaired adaptive immunity to bacterial pathogens among those with more frequent ECOPD reinforces the potential in vivo implications of qualitative defects in antibody production. The strength of correlation between PnAF and PnIgG varied by serotype but was generally modest across the four serotypes in which both were measured. Since MOPA measures overall PnAF (i.e. not isotype or IgG-subclass specific response), further studies are needed to elucidate the relationship between antibody levels and function.

Importantly, the four serotypes we selected to investigate PnAF are among the most prevalent causes of pneumococcal exacerbations and pneumonia in COPD(24, 25). Our results suggest that impaired antibody-mediated immunity could account for the observation

that serotypes 9V, 19F, and 11A are among the most common serotypes isolated in recurrent pneumococcal ECOPD(24). We observed an association between higher OI and fewer ECOPD for three serotypes (3, 9V, and 11A) and with serotype-specific PnIgG for all four. Serotype 3 is unique among pneumococci, as its distinct capsular synthetic mechanism enhances virulence and resists immune-mediated clearance(32). Despite its inclusion in PCV13 (which has resulted in the near-elimination of other vaccine serotypes where implemented), serotype 3 remains a prevalent cause of pneumococcal community acquired pneumonia (CAP) and invasive pneumococcal disease in the general population(33, 34), and has been associated with CAP in COPD(24). We observed significant differences in OI between frequent exacerbators and those with fewer ECOPD for serotype 3, and its associations with prior ECOPD were the strongest we observed. These findings could have important implications for pneumococcal epidemiology, and vaccine development and implementation in COPD.

While there is rationale for underlying polysaccharide antibody deficiency as a risk factor for ECOPD, it is also possible that levels and/or function of antibodies could be affected by COPD treatments, most notably systemic corticosteroids. We found a significant association between higher total PnIgG and fewer ECOPD in the previous year in the multivariable model that included adjustment for oral corticosteroid use at baseline, suggesting that the observed associations are unlikely to be related to more prevalent use of these medications among frequent exacerbators. However, this adjustment was not performed in the cohort selected for serotype-specific analysis due to limited sample sizes, with infrequent oral corticosteroid use. Likewise, in the larger cohort we also observed significant associations between total PnIgG and ECOPD in the multivariable model that included adjustment for timing of pneumococcal vaccination. Baseline sera were obtained prior to routine use of PCVs in adults (i.e. previously vaccinated participants most likely received PPV23), and we found significant associations for serotypes unique to PPV23 in addition to those shared between PCVs and PPV23.

This indicates that the characteristics of participants' functional immune response to vaccination are more likely to account for the observed associations. However, further serotype-specific studies in larger cohorts with detailed information regarding previous pneumococcal vaccination will be helpful to confirm these findings from total PnIgG analysis. Before pneumococcal antibodies can be used as biomarkers for immune dysfunction in frequent exacerbators, several caveats must be considered. Despite widespread use of PnIgG for PID diagnosis(12), we and others have demonstrated variability between different laboratories and clinical cutoffs that may limit diagnostic use of PnIgG(35, 36). In contrast, MOPA measures PnAF via a uniform protocol that is available worldwide, and results are standardized using pneumococcal reference sera to minimize interlaboratory variability. Despite these advantages, our studies in non-COPD populations demonstrated wide variability between serotypes in baseline PnAF and vaccine response(18). PnIgG and PnAF that correspond with protection from infections have not been defined in adult populations (including those with COPD), and likely vary by serotype, age, and vaccine type. We therefore opted to analyze differences in log-transformed PnIgG between ECOPD groups, and did not apply cutoffs that are utilized clinically for diagnosis of PIDs. Further investigation is needed to determine optimal strategies to interpret results

of pneumococcal antibody assays for immune evaluation, and the values from our study should not be construed as cutoffs for clinical diagnostic use. We did not have detailed information regarding timing of vaccination, and prospective studies that analyze pre and post-vaccination sera at defined intervals are needed to interpret vaccine responses in COPD in the context of the diagnostic approaches used in PIDs. Future studies can also evaluate responses to PCVs in addition to PPV23, to investigate whether defects in antibodies also involve impaired response to protein-conjugated antigens.

Additional limitations of our study include analysis of a limited number of sera from a single cohort, and we measured pneumococcal antibody function in a relatively small number of serotypes. Future studies may consider a broader panel to further examine relationships between antibody levels and function. While our study may have been underpowered to detect differences in prospective ECOPD for the number of serotypes tested, the consistent trends between higher PnIgG and lower prospective ECOPD risk for most serotypes tested are noteworthy, and additional studies in larger cohorts are needed.

In conclusion, these independent, inverse associations between pneumococcal antibodies and ECOPD frequency strongly support the presence of adaptive immune dysfunction in frequent exacerbators and suggest that polysaccharide antibody deficiency may represent a key mechanism for recurrent bacterial infections in this high-risk group. Although there are currently no guidelines or recommendations for immune evaluation in COPD, our findings add to a growing body of evidence suggesting that measurement of functional antibody responses, including pneumococcal antibodies, could be useful. Individuals identified as having underlying immune defects could subsequently be targeted for personalized therapeutic interventions(11, 37-39) to mitigate the high morbidity and mortality that accompany further ECOPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

The authors thank the SPIROMICS participants and participating physicians, investigators, and staff for making this research possible. More information about the study and how to access SPIROMICS data is available at www.spiromics.org. The authors would like to acknowledge the University of North Carolina at Chapel Hill BioSpecimen Processing Facility for sample processing, storage, and sample disbursements (http://bsp.web.unc.edu/). We would like to acknowledge the following current and former investigators of the SPIROMICS sites and reading centers: Neil E Alexis, MD; Wayne H Anderson, PhD; Mehrdad Arjomandi, MD; Igor Barjaktarevic, MD, PhD; R Graham Barr, MD, DrPH; Patricia Basta, PhD; Lori A Bateman, MSc; Surya P Bhatt, MD; Eugene R Bleecker, MD; Richard C Boucher, MD; Russell P Bowler, MD, PhD; Stephanie A Christenson, MD; Alejandro P Comellas, MD; Christopher B Cooper, MD, PhD; David J Couper, PhD; Gerard J Criner, MD; Ronald G Crystal, MD; Jeffrey L Curtis, MD; Claire M Doerschuk, MD; Mark T Dransfield, MD; Brad Drummond, MD; Christine M Freeman, PhD; Craig Galban, PhD; MeiLan K Han, MD, MS; Nadia N Hansel, MD, MPH; Annette T Hastie, PhD; Eric A Hoffman, PhD; Yvonne Huang, MD; Robert J Kaner, MD; Richard E Kanner, MD; Eric C Kleerup, MD; Jerry A Krishnan, MD, PhD; Lisa M LaVange, PhD; Stephen C Lazarus, MD; Fernando J Martinez, MD, MS; Deborah A Meyers, PhD; Wendy C Moore, MD; John D Newell Jr, MD; Robert Paine, III, MD; Laura Paulin, MD, MHS; Stephen P Peters, MD, PhD; Cheryl Pirozzi, MD; Nirupama Putcha, MD, MHS; Elizabeth C Oelsner, MD, MPH; Wanda K O'Neal, PhD; Victor E Ortega, MD, PhD; Sanjeev Raman, MBBS, MD; Stephen I. Rennard, MD; Donald P Tashkin, MD; J Michael Wells, MD; Robert A Wise, MD; and Prescott G Woodruff, MD, MPH. The project officers from the Lung Division of the National Heart, Lung, and Blood Institute were Lisa Postow, PhD, and Lisa Viviano, BSN; SPIROMICS was supported by contracts from the NIH/NHLBI (HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C,

HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, HHSN268200900020C), grants from the NIH/NHLBI (U01 HL137880 and U24 HL141762), and supplemented by contributions made through the Foundation for the NIH and the COPD Foundation from AstraZeneca/MedImmune; Bayer; Bellerophon Therapeutics; Boehringer-Ingelheim Pharmaceuticals, Inc.; Chiesi Farmaceutici S.p.A.; Forest Research Institute, Inc.; GlaxoSmithKline; Grifols Therapeutics, Inc.; Ikaria, Inc.; Novartis Pharmaceuticals Corporation; Nycomed GmbH; ProterixBio; Regeneron Pharmaceuticals, Inc.; Sanofi; Sunovion; Takeda Pharmaceutical Company; and Theravance Biopharma and Mylan.

This publication was also made possible by the Johns Hopkins Institute for Clinical and Translational Research (ICTR) which is funded in part by Grant Number UL1 TR001079 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Johns Hopkins ICTR, NCATS or NIH.

The authors also acknowledge the contributions of the technicians of the MOPA Core Laboratory at UAB in PnAF measurement.

Sources of support:

National Institutes of Health 5T32HL105346 and K08HL157651 (DCL), 1K24HL140108 (MTD), K23HL123594 (NP). Support for total pneumococcal IgG assays was provided by CSL Behring. SPIROMICS was supported by contracts from the NIH/NHLBI(HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, HHSN268200900020C), grants from the NIH/NHLBI (U01 HL137880 and U24 HL141762), and supplemented by contributions made through the Foundation for the NIH and the COPD Foundation from AstraZeneca/MedImmune; Bayer; Bellerophon Therapeutics; Boehringer-Ingelheim Pharmaceuticals, Inc.; Chiesi Farmaceutici S.p.A.; Forest Research Institute, Inc.; GlaxoSmithKline; Grifols Therapeutics, Inc.; Ikaria, Inc.; Novartis Pharmaceuticals Corporation; Nycomed GmbH; ProterixBio; Regeneron Pharmaceuticals, Inc.; Sanofi; Sunovion; Takeda Pharmaceutical Company; and Theravance Biopharma and Mylan. Support for the present manuscript was also provided by NHLBI (IB, DC, JLC, PGW, AH), COPD Foundation (IB, DC, JLC, PGW), and Foundation for the NIH (DC, JLC, PGW, AH). The funding sources had no direct role in the collection, analysis, or interpretation of the data, nor in the preparation of the manuscript or decision to submit for publication.

Abbreviations:

(COPD)	Chronic obstructive pulmonary disease
(ECOPD)	exacerbations of COPD
(IgA)	immunoglobulin A
(IgG)	immunoglobulin G
(PIDs)	primary immunodeficiency diseases
(PnIgG)	pneumococcal IgG antibodies
(MOPA)	multiplexed opsonophagocytosis assay
(PnAF)	pneumococcal antibody function
(OI)	opsonic index
(SPIROMICS)	SubPopulations and InteRmediate Outcome Measures in COPD Study
(ELISA)	enzyme-linked immunosorbent assay
(PPV23)	pneumococcal polysaccharide vaccine

(FEV_1)	forced expiratory volume in the first second
(OR)	odds ratio
(CI)	confidence interval
(IRR)	incidence rate ratio
(ICS)	inhaled corticosteroids
(PCV7)	7-valent pneumococcal conjugate vaccine
(PCV13)	13-valent pneumococcal conjugate vaccine

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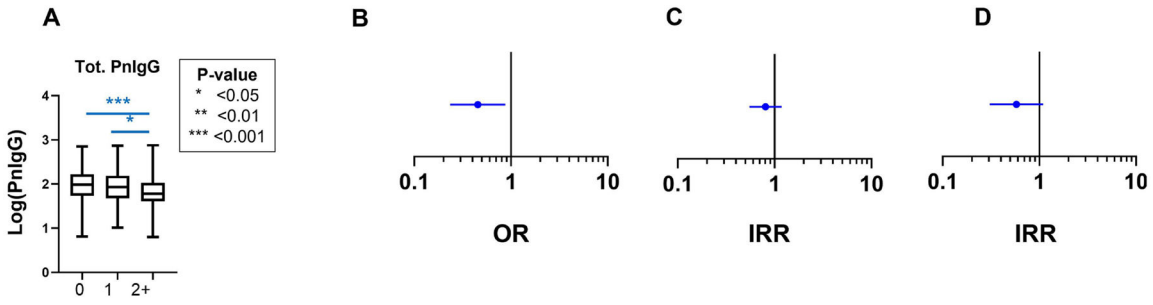

Figure 1.

A. Mean total pneumococcal IgG (PnIgG) levels were higher among SPIROMICS participants with fewer ECOPD in the previous year. P-values are from one-way ANOVA with Bonferroni correction for multiple comparisons.

B. Higher total PnIgG was associated with having 0 (vs 2+) ECOPD in the previous year in a multivariable logistic regression model that included adjustment for age, sex, race, FEV_1, maximal educational attainment, current smoking at baseline visit, inhaled corticosteroid use, oral corticosteroid use, and timing of pneumococcal vaccination within past 5 years.

C-D. Total PnIgG levels at baseline and risk for total (C.) and severe (D.) ECOPD in the first year of longitudinal follow-up, in multivariable negative binomial models that included adjustment for age, sex, race, FEV_1, maximal educational attainment, current smoking at baseline visit, inhaled corticosteroid use, oral corticosteroid use, and timing of pneumococcal vaccination within past 5 years

*Odds ratios (OR)/Incidence rate ratios (IRR) indicate the odds (or risk) of greater number of ECOPD with increasing pneumococcal IgG or OI

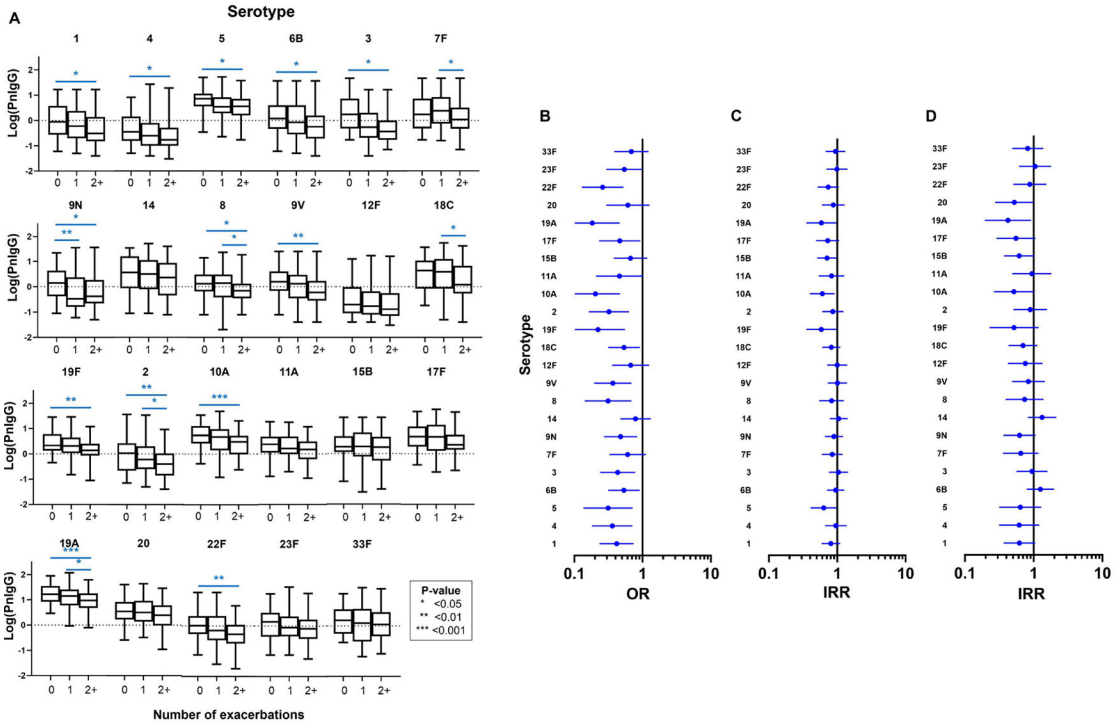

Figure 2.

A. Mean serotype-specific pneumococcal IgG (PnIgG) levels were higher among SPIROMICS participants with fewer ECOPD in the previous year across a majority of serotypes tested. P-values are from one-way ANOVA with Bonferroni correction for multiple comparisons.

B. Higher serotype-specific PnIgG levels were associated with having 0 (vs 2+) ECOPD in the previous year in multivariable logistic regression models that included adjustment for age, sex, race, FEV_1, maximal educational attainment, current smoking at baseline visit, and inhaled corticosteroid use

C-D. Serotype-specific PnIgG levels at baseline and risk for total (C.) and severe (D.) ECOPD in the first year of longitudinal follow-up, in multivariable negative binomial models that included adjustment for age, sex, race, FEV_1, maximal educational attainment, current smoking at baseline visit, and inhaled corticosteroid use

*Odds ratios (OR)/Incidence rate ratios (IRR) indicate the odds (or risk) of greater number of ECOPD with increasing pneumococcal IgG or OI

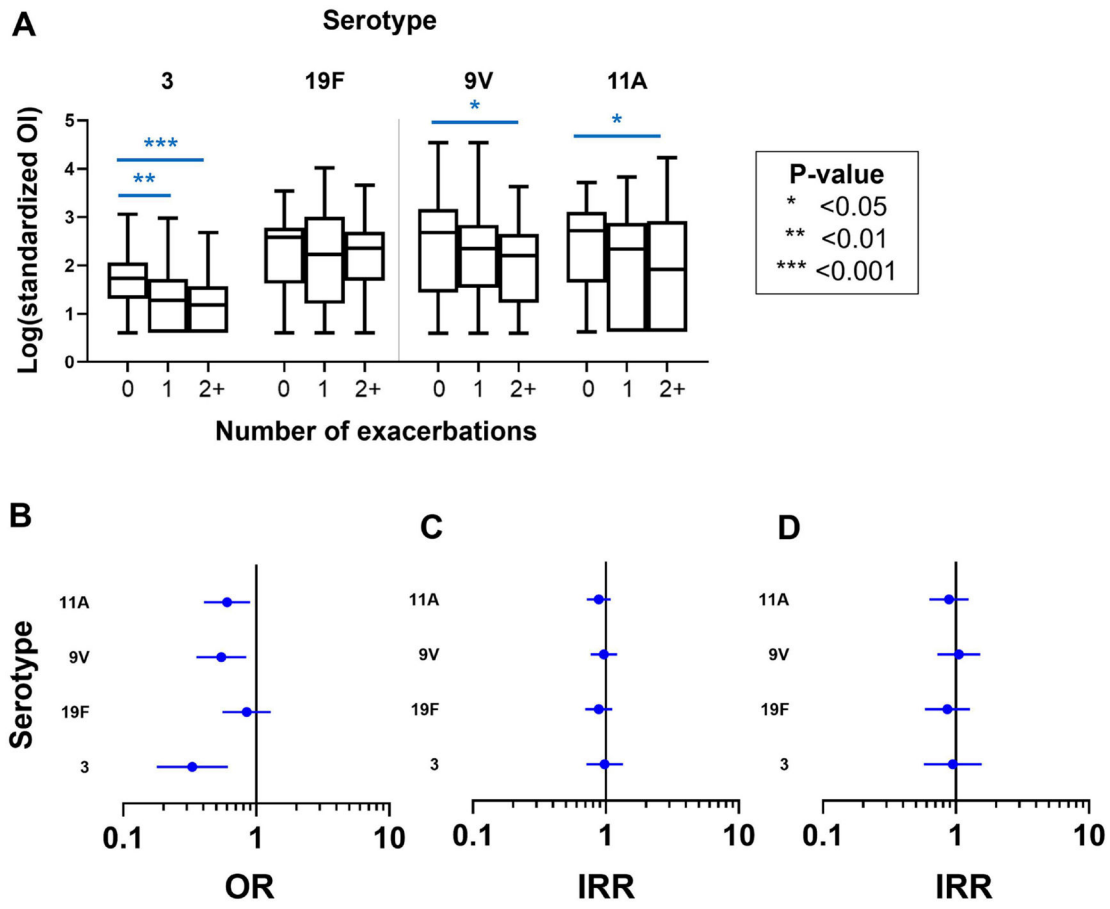

Figure 3.

A. Mean opsonic index (OI, a measure of pneumococcal antibody function) was higher among SPIROMICS participants with fewer ECOPD in the previous year in 3 of 4 serotypes tested. P-values are from one-way ANOVA with Bonferroni correction for multiple comparisons.

B. For these 3 serotypes, higher OI was associated with having 0 (vs 2+) ECOPD in the previous year in multivariable logistic regression models that included adjustment for age, sex, race, FEV_1, maximal educational attainment, current smoking at baseline visit, and inhaled corticosteroid use

C-D. Baseline OI and risk for total (**C.**) and severe (**D.**) ECOPD in the first year of longitudinal follow-up, in multivariable negative binomial models that included adjustment for age, sex, race, FEV_1, maximal educational attainment, current smoking at baseline visit, and inhaled corticosteroid use

*Odds ratios (OR)/Incidence rate ratios (IRR) indicate the odds (or risk) of greater number of ECOPD with increasing pneumococcal IgG or OI

Table I.

Characteristics of Study Participants [*]

		Serotype-specific Pneumococcal IgG (PnIgG); Opsonic index (OI)			
	Tot. PnIgG (n=764)	Overall (n=200)	Exacerbations in the previous year		
			0 (n=50)	1 (n=75)	≥2 (n=75)
Age	67.0±7.6	64.5±7.7	64.48±7.6	63.6±7.6	65.4±7.85
Male	417 (54.6)	108 (54)	30 (60.0)	39 (52.0)	39 (52.0)
White	648 (84.8)	166 (83)	40 (80.0)	65 (86.7)	61 (81.3)
Body mass index	27.5±5.3	26.9±5.4	26.17±5.47	27.7±5.4	26.61±5.30
FEV1 [†]	60.2±23.2	46.5±19.1	44.68±18.74	47.5±20.2	46.8±18.45
Eosinophils (absolute count)	0.21±0.23	0.20±0.13	0.19±0.13	0.19±0.13	0.21±0.14
Current smoking	206 (27.0)	44 (22.0)	15 (30.0)	14 (18.7)	15 (20.0)
Pack-years smoking	54.1±24.3	51.4±22.9	52.3±21.1	48.6±23.2	53.6±23.8
Inhaled steroids [‡]	369 (48.3)	131 (65.5)	25 (50.0)	50 (66.7)	56 (74.7)
Greater than high school education	476 (62.3)	117 (58.5)	28 (56.0)	46 (61.3)	43 (57.3)

[*] Values indicate n (%) and mean ± standard deviation for dichotomous and continuous variables, respectively

[†] Forced expiratory volume in the first second (post-bronchodilator; % predicted)

[‡] Self-reported use at time of baseline visit