suspect not, as neither measure is related to the blood eosinophil count or to the effects of ICS on the long-term outcomes in COPD (1). There is some evidence that the bronchodilator response is related to the increase in FEV₁ after treatment with ICS (1) and that allergy is related to a more complete suppression of symptoms with ICS (4). However, neither lung function improvement nor symptom control is a major goal of ICS treatment in patients with COPD. For measures that figure so highly in our current criteria to stratify airways disease, it is remarkable how little useful prognostic and theragnostic information these measures provide.

It is interesting that of the 135 patients with at least one asthma-like feature, the majority had only one feature (71%), and very few had all (5%). This lack of segregation, and the very different relationship with ICS treatment response, suggests that these markers represent discrete, mechanistically distinct disease pathways. This is an important consideration, given that all are potential qualifying measures for a diagnosis of ACOS. The difficulty is that once this label is applied, there will be an assumption of homogeneity. We believe that this assumption, which also occurs in patients labeled as having asthma or COPD, is becoming an important barrier to progress against key outcomes in airways disease. For example, it was the main reason the beneficial effects of oral corticosteroids (14) and anti-IL-5 in eosinophilic airways disease (15, 16) were missed initially. We suspect that the time has come to move beyond arbitrary labels and toward a position where the goal of assessment is to identify treatable pathways causally linked to important clinical outcomes (17). At a time when we are moving toward precision medicine, it seems a retrograde step to create a new diagnosis that does not have one underlying targetable molecular pathway. ■

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References

- Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015;3:435–442.
- Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax* 2015;70:683–691.
- Suzuki M, Makita H, Konno S, Shimizu K, Kimura H, Kimura H, Nishimura M; Hokkaido COPD Cohort Study Investigators. Asthma-like features and clinical course of chronic obstructive pulmonary disease: an analysis from the Hokkaido COPD cohort study. *Am J Respir Crit Care Med* 2016;194:1358–1365.
- Fattahi F, ten Hacken NHT, Löfdahl C-G, Hylkema MN, Timens W, Postma DS, Vork JM. Atopy is a risk factor for respiratory symptoms in COPD patients: results from the EUROSCOP study. *Respir Res* 2013;14:10.
- Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;192:523–525.
- ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med* 2001;164:744–748.
- Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715–1721.
- Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J* 2016;47:1374–1382.
- Hospers JJ, Schouten JP, Weiss ST, Rijcken B, Postma DS. Asthma attacks with eosinophilia predict mortality from chronic obstructive pulmonary disease in a general population sample. *Am J Respir Crit Care Med* 1999;160:1869–1874.
- Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, Barnes NC. Blood eosinophils and inhaled corticosteroid/long-acting β -2 agonist efficacy in COPD. *Thorax* 2016;71:118–125.
- Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, Vogelmeier C, Fabbri LM, Chanez P, Dahl R, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016;4:390–398.
- Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. *Eur Respir J* 2014;44:789–791.
- Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;186:48–55.
- Brown HM. Treatment of chronic asthma with prednisolone: significance of eosinophils in the sputum. *Lancet* 1958;2:1245–1247.
- Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973–984.
- Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985–993.
- Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410–419.

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Hospital-acquired Pneumonia: A Host of Factors

Extensive clinical data show that community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) are different clinical entities: they are characterized by different patient populations, comorbidity profiles, pathogens, and outcomes (1, 2).

However, although mere exposure to the hospital can factor in developing different types of pneumonia (healthcare-associated pneumonia), HAP does not appear to be simply a bad case of CAP with a different bug. One hypothesis is that the immune system of

the hospitalized patient is disrupted by the index illness and that this immune disruption may contribute to both susceptibility to infection and a dysregulated host response (3). It has been shown that after severe injury, rather than consecutive proinflammatory and then antiinflammatory states, the innate immune system undergoes simultaneous activation and suppression, leading to severe and persistent dysregulation (4). Further literature from the trauma community has shown that some patients experience progressive immunosuppression after this initial insult (5). Although severe blunt traumatic injury may be an extreme case, it seems likely that many acute severe illnesses for which patients are hospitalized may similarly lead to immune dysregulation of varying degrees.

In this issue of the *Journal*, van Vught and colleagues (pp. 1366–1374) sought to characterize whether and how the immune system is dysregulated at the time of diagnosis of HAP, as opposed to CAP (6). They measured several plasma protein biomarkers, as well as genome-wide expression using microarrays, to characterize the two conditions. However, a simple comparison of the host response in CAP and HAP may yield large differences solely because of different patient characteristics or pathogen types. Thus, van Vught and colleagues also performed several subgroup analyses, matching patients for clinical characteristics (chronic obstructive pulmonary disease) or pathogen type, or both (6). Their results showed, primarily, that there are few differences in the host response between CAP and HAP. Most plasma biomarkers were similarly perturbed by both conditions, as compared with healthy control subjects. Similarly, in the overall (nonmatched) analysis, the gene expression changes induced by CAP and HAP shared greater than 75% similarity, whereas in the closest-matched comparison there were no significant differences between the CAP and HAP groups (although this was largely owing to a dramatically reduced sample size in this subanalysis). Still, some persistent findings came through in other sensitivity analyses (including comparisons of only patients without chronic obstructive pulmonary disease and only patients with bacterial infections), including down-regulation of type I IFN response genes and up-regulation of cell–cell junction and cell mobility pathways. The authors speculate that a reduced expression of genes in the type I IFN pathway may lead to increased susceptibility to bacterial infections, perhaps thus predisposing these patients to HAP. On the other hand, such an association may be true of all patients several days into their hospitalization.

Perhaps the most surprising finding from this study is the similarity of the host response measured in CAP and HAP. Even with a reasonably large sample size in the unmatched group (CAP, $n = 110$; HAP, $n = 111$), most genes were not significantly differentially expressed between the two groups. Furthermore, PCA of the entire gene expression profile mostly showed a large degree of overlap between the two groups. Several papers have demonstrated conserved differential host responses to severe infections versus noninfectious critical illness (7–9) and to bacterial versus viral infections (10–12). In fact, in two separate analyses of the same cohort studied here (with some overlapping patients), this group has demonstrated differential gene expression in response in patients with CAP versus non-CAP admissions or associated with thrombocytopenia (13, 14). Thus, the current finding of few differences between the host response in CAP and HAP suggest not absence of evidence, but evidence of absence.

The study does have some weaknesses; one, in particular, is that the fully matched subgroup analysis had a drastically reduced

sample size in the gene expression comparison (CAP, $n = 49$; HAP, $n = 39$). The lack of difference between HAP and CAP in this group may thus simply reflect low power. In addition, the relatively limited number of genes above the set level of significance (false discovery rate $< 5\%$) means that the pathway analyses had relatively few data points to consider. This is an unfortunate limitation of many single-cohort omics analyses (despite the relatively large cohort used here); we hope that as more data are published, more robust conclusions can be drawn.

In broader context, the present work invites two questions: the first is how the host response in HAP is linked to the infection. The standard model for infection pathogenesis suggests that the host is invaded by an external infectious pathogen. However, some evidence suggests that, especially in the hospitalized patient (or in late-onset sepsis), host factors may contribute both to the loss of a healthy microbiome and to the pathogenicity of existing commensal bacteria (15–17). The changes described by van Vught and colleagues may thus be part of a complex interplay between host defenses, “pathogenized” commensal bacteria, and external “healthcare-associated” pathogens (6).

The second question this work raises is how this heterogeneity (CAP vs. HAP) relates to other sources of heterogeneity in the septic host response. Several groups have begun to investigate whether patients with sepsis can be classified into subpopulations (also known as endotypes) on the basis of profiling of the host response (18, 19). Better definitions of sepsis subpopulations may allow for a “precision medicine” approach to the patient with sepsis. These prior studies have been able to take seemingly similar groups of patients with sepsis and identify distinct differences in host response; it is thus perhaps surprising that here, examining two groups that are clinically distinct (CAP and HAP), major gene expression differences are not evident.

Overall, van Vught and colleagues have contributed valuable insight to a complex issue (6). Although the immune response profiles between HAP and CAP were largely similar, some consistent differences in cell-signaling genes were observed. Further work should focus on (1) confirming these findings (2), investigating the causative relation in host response and late-onset infection, and (3) investigating whether other sources of heterogeneity may account for the clinical differences that distinguish CAP from HAP. ■

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References

1. Marik PE. The bacterial pneumonias: a new treatment paradigm. *Hosp Pract* (1995) 2015;43:46–55.
2. Eccles S, Pincus C, Higgins B, Woodhead M, Group GD; Guideline Development Group. Diagnosis and management of community and

- hospital acquired pneumonia in adults: summary of NICE guidance. *BMJ* 2014;349:g6722.
3. Wunderink RG. Nosocomial pneumonia, including ventilator-associated pneumonia. *Proc Am Thorac Soc* 2005;2:440–444.
 4. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL, Hennessy L, Moore EE, Minei JP, *et al.*; Inflammation and Host Response to Injury Large-Scale Collaborative Research Program. A genomic storm in critically injured humans. *J Exp Med* 2011;208:2581–2590.
 5. Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, Ungaro R, Davis R, Cuenca AG, Gentile LF, Nacionales DC, Cuenca AL, Bihorac A, *et al.* Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. *J Trauma Acute Care Surg* 2014;76:21–29. [Discussion, pp. 29–30.]
 6. van Vught LA, Scicluna BP, Wiewel MA, Hoogendijk AJ, Klein Klouwenberg PM, Frantz M, Toliat MR, Nürnberg P, Cremer OL, Horn J, *et al.* Comparative analysis of the host response to community-acquired and hospital-acquired pneumonia in critically ill patients. *Am J Respir Crit Care Med* 2016;194:1366–1374.
 7. Sweeney TE, Shidham A, Wong HR, Khatri P. A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set. *Sci Transl Med* 2015;7:287ra71.
 8. Pena OM, Hancock DG, Lyle NH, Linder A, Russell JA, Xia J, Fjell CD, Boyd JH, Hancock RE. An endotoxin tolerance signature predicts sepsis and organ dysfunction at initial clinical presentation. *EBioMedicine* 2014;1:64–71.
 9. McHugh L, Seldon TA, Brandon RA, Kirk JT, Rapisarda A, Sutherland AJ, Presneill JJ, Venter DJ, Lipman J, Thomas MR, *et al.* A molecular host response assay to discriminate between sepsis and infection-negative systemic inflammation in critically ill patients: discovery and validation in independent cohorts. *Plos Med* 2015;12:e1001916.
 10. Ramilo O, Allman W, Chung W, Mejias A, Ardura M, Glaser C, Wittkowski KM, Piqueras B, Banchereau J, Palucka AK, *et al.* Gene expression patterns in blood leukocytes discriminate patients with acute infections. *Blood* 2007;109:2066–2077.
 11. Suarez NM, Bunsow E, Falsey AR, Walsh EE, Mejias A, Ramilo O. Superiority of transcriptional profiling over procalcitonin for distinguishing bacterial from viral lower respiratory tract infections in hospitalized adults. *J Infect Dis* 2015;212:213–222.
 12. Andres-Terre M, McGuire HM, Pouliot Y, Bongen E, Sweeney TE, Tato CM, Khatri P. Integrated, multi-cohort analysis identifies conserved transcriptional signatures across multiple respiratory viruses. *Immunity* 2015;43:1199–1211.
 13. Scicluna BP, Klein Klouwenberg PM, van Vught LA, Wiewel MA, Ong DS, Zwinderman AH, Frantz M, Toliat MR, Nürnberg P, Hoogendijk AJ, *et al.* A molecular biomarker to diagnose community-acquired pneumonia on intensive care unit admission. *Am J Respir Crit Care Med* 2015;192:826–835.
 14. Claushuis TA, van Vught LA, Scicluna BP, Wiewel MA, Klein Klouwenberg PM, Hoogendijk AJ, Ong DS, Cremer OL, Horn J, Frantz M, *et al.*; Molecular Diagnosis and Risk Stratification of Sepsis Consortium. Thrombocytopenia is associated with a dysregulated host response in critically ill sepsis patients. *Blood* 2016;127:3062–3072.
 15. Hayakawa M, Asahara T, Henzan N, Murakami H, Yamamoto H, Mukai N, Minami Y, Sugano M, Kubota N, Uegaki S, *et al.* Dramatic changes of the gut flora immediately after severe and sudden insults. *Dig Dis Sci* 2011;56:2361–2365.
 16. Babrowski T, Holbrook C, Moss J, Gottlieb L, Valuckaite V, Zaborin A, Poroyko V, Liu DC, Zaborina O, Alverdy JC. *Pseudomonas aeruginosa* virulence expression is directly activated by morphine and is capable of causing lethal gut-derived sepsis in mice during chronic morphine administration. *Ann Surg* 2012;255:386–393.
 17. Krezalek MA, DeFazio J, Zaborina O, Zaborin A, Alverdy JC. The shift of an intestinal “microbiome” to a “pathobiome” governs the course and outcome of sepsis following surgical injury. *Shock* 2016;45:475–482.
 18. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald J, Checchia PA, Meyer K, *et al.* Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med* 2015;191:309–315.
 19. Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, Rautanen A, Gordon AC, Garrard C, Hill AV, *et al.* Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* 2016;4:259–271.

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Sweat Chloride: The Critical Biomarker for Cystic Fibrosis Trials

Sweat chloride determinations have long been the diagnostic gold standard for cystic fibrosis (CF); however, it is only recently that sweat chloride has also been considered a biomarker to assess the impact of new therapies (1, 2). In this issue of the *Journal*, Collaco and colleagues (pp. 1375–1382) report on the sources of variation in sweat chloride among individuals diagnosed with CF and propose its future use as a valuable biomarker for assessing response to therapy (3). The conclusion of Collaco and colleagues regarding waiting to call sweat chloride a biomarker contradicts the strong body of evidence that irrefutably defines sweat chloride as a biomarker for CF clinical trials (3).

Post-therapy change in sweat chloride has been used to demonstrate the effect of new cystic fibrosis transmembrane conductance regulator (CFTR) modulators (2, 4–6). Some argue that the lack of correlation between sweat chloride and clinical outcomes weakens the conclusions, and these changes fall short of the desired clinical changes, such as improvements in FEV₁ (6). Others postulate that it is time to promote biomarkers such as sweat chloride and nasal potential difference to the level of

surrogate markers for clinical efficacy (7). Both of these arguments distract from the underlying physiologic processes that are being uncovered through the interplay between the biomarkers and surrogate outcomes. Sweat chloride is a direct measurement of sweat gland dysfunction, a result of the defective CFTR protein, and unlikely to be influenced by external factors (Figure 1). Other clinical surrogates are the best measures we have to assess malnutrition, poor growth, and pulmonary function but are distant markers from the underlying biologic process. Furthermore, each of these is influenced by a host of factors. Collaco and colleagues demonstrated that the primary source of variation in sweat chloride can be traced to CFTR mutations (3). In addition to its proximal relationship to sweat gland dysfunction, sweat chloride is not prone to extrinsic influences, further strengthening its role as a key biomarker (8). Variability in both FEV₁ and body mass index is much harder to quantify, given the true surrogate nature of the measurements and additional variability stemming from genetic modifiers and environmental factors (9–11). Furthermore, the variability in changes in