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FEATURE ARTICLES

Inner City Asthma – New Insights to Help Guide Future Therapy

Asthma among children in low-income urban areas is associated with high morbidity, but little is known about phenotypes that may be relevant to tailored therapy. The authors report a phenotypic analysis of asthma in inner-city children.

The study included 717 children with asthma, aged 6 to 17 years. Patients were drawn from nine inner-city asthma consortium centers; all were receiving guideline-based therapy, Data were prospectively collected at baseline and every 2 months for 1 year. Cluster analysis was performed to evaluate asthma phenotypes in 616 children with four or more follow-up visits.

Five clusters were identified. Children in cluster A had relatively low indicators of allergy and inflammation, minimal asthma and rhinitis symptoms, and pulmonary function. Those in cluster B had high asthma symptoms despite stepped-up care, but with lower allergy and inflammation and only mildly abnormal lung function. Cluster C children also had minimal symptoms and mildly impaired lung function, but with intermediate allergy and inflammation, and mildly impaired pulmonary physiology.

Children in clusters D and E had increased symptoms and allergy/inflammation. Cluster E children had a median serum IgE level of 733 kU/L with a blood eosinophil count of 400 cells/mm^3, and were sensitized to 15 of 22 allergens tested.

Cluster analysis identifies several phenotypes of inner-city childhood asthma. Some children have asthma symptoms despite low allergy/inflammation, while others have severe asthma with high allergy markers. Strategies targeting allergy and inflammation may be appropriate for most, but not all, inner-city children with asthma. • • •

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- Annals of Allergy, Asthma and Immunology
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- American Journal of Respiratory and Critical Care Medicine
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- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Journal of Asthama
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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For reasons that remain unclear, the treatment necessary to control "inner-city asthma" varies substantially. The authors sought to identify clinical factors differentiating difficult- from easy-to-control asthma in a large group of urban children.

Over a year, 619 inner-city children and adolescents with asthma received bimonthly visits including guideline-based management. Based on a requirement for at least 500 μg/d of fluticasone with or without a long-acting β-agonist, 40.9% of children were classified as having difficult-to-control asthma. Another 37.5% had easy-to-control asthma, with a fluticasone dose of 100 μg/d or less. The remaining 21.6% fell into neither group. Forty-four baseline characteristics were analyzed for their ability to differentiate the difficult- and easy-to-control groups.

The strongest indicator was FEV_1 bronchodilator responsiveness, followed by markers of rhinitis severity and atopy. Children with difficult-to-control asthma had frequent exacerbations, especially in spring and fall; increased daytime and nighttime symptoms, especially in fall and winter; and abnormal lung function results despite high-dose controller therapy.

The results lend insight into baseline factors associated with difficult-to-control asthma in inner-city children. The authors suggest a prioritized assessment to identify this group of patients, highlighting the importance of allergen sensitization and its consequences.

The Asthma Phenotypes in the Inner City (APIC) study has identified host and environmental factors contributing to asthma severity among children in low-income urban areas. The authors performed a causal network analysis of APIC data to investigate the pathways explaining asthma severity in inner-city children.

The analysis included data from 561 inner-city children and adolescents with asthma and rhinitis, evaluated every two months for one year. The conceptual model included eight risk-factor domains: allergen sensitization, allergic inflammation, pulmonary physiology, stress, obesity, vitamin D, environmental tobacco smoke (ETS), and rhinitis severity. Asthma severity was assessed by a composite measure of daytime and nighttime symptoms, exacerbations, and controller use.

The pathway analysis model explained 53.4% of the variance in asthma severity. Two different pathways significantly contributed to severity: an allergy pathway and an ETS exposure pathway. The domains with the largest standardized total effects were pulmonary physiology, -0.51; rhinitis severity, 0.48; ETS exposure, 0.30; and allergic inflammation, 0.22. Although vitamin D had indirect effects, the total effect was nonsignificant.

The pathway analysis provides new information on the relative contributions of different domains to the severity of asthma in urban, low-income children. The results may inform efforts to improve management of inner-city asthma.

COMMENT: These three lead articles from *JACI* report data from the nine US centers involved in the APIC study, with 717 children followed prospectively every 2 months for a year. Each article used a different analytic approach to characterize the children's asthma. Zoratti et al used cluster analysis differentiating five asthma phenotypes distinguished by indicators of asthma and rhinitis severity, pulmonary physiology, and allergic sensitization and inflammatory markers. Although allergy was associated with severe asthma in most phenotypes, there was a nonallergic cluster. Pongracic et al identified baseline clin- • • •

ical characteristics associated with difficult-to-control asthma. Interestingly, FEV_1 bronchodilator response, asthma control scores, rhinitis severity, and atopy were the best predictors of difficult-to-control asthma.

Liu et al used a causal network analysis model to focus on host and environmental factors that impact severity of asthma. Allergic sensitization and inflammation, exposure to ETS, pulmonary physiology, and rhinitis severity were all related to asthma severity. The take-home message is the confirmation that atopy, ETS, reduced pulmonary physiology, and rhinitis are major determinants for difficult-to-control asthma. Pathway-targeted interventions could use these parameters in helping to improve the care of our patients with asthma.

S.M.F.

Zoratti EM, Krouse RZ, Babineau DC, et al: Asthma phenotypes in inner-city children.

J Allergy Clin Immunol. 2016;138:1016-1029.

Pongracic JA, Krouse RZ, Babineau DC, et al: Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents.

J Allergy Clin Immunol 2016;138:1030-1041.

Liu AH, Babineau DC, Krouse RZ, et al: Pathways through which asthma risk factors contribute to asthma severity in inner-city children.

J Allergy Clin Immunol. 2016;138:1042-1050.

Keyword: asthma (child), inner-city, phenotypes, risk factors

Anti-CXCR2 for Asthma: Phase 2b Failure

Some patients with severe asthma have airway neutrophilic inflammation. The oral CXCR2 antagonist AZD5069 has been shown to reverse circulating neutrophil counts. This phase 2b clinical trial evaluated the safety and efficacy of AZD5069 as add-on therapy for uncontrolled severe asthma.

The multicenter trial included 640 adults, mean age 52 years, who had uncontrolled asthma despite medium- to high-dose inhaled corticosteroids plus long-acting β_2-agonists. They were randomly assigned to receive oral AZD5069, 5, 15, or 45 mg/d, or placebo. The main efficacy outcome was the number of severe asthma exacerbations over 6 months.

There was no significant reduction in exacerbations with any dose of AZD5069, compared to placebo. Nasopharyngitis was the most common adverse event with AZD5069 or placebo. Aside from the expected decreases in blood neutrophil count, there were no clinically relevant changes in laboratory measures.

Add-on anti-CXCR2 therapy with AXD5069 does not reduce the exacerbation rate in adults with uncontrolled persistent asthma. The findings question whether CXCR2-mediated neutrophil recruitment contributes to the pathophysiology of exacerbations in severe refractory asthma.

COMMENT: Some have thought the holy grail of treatment for severe asthma would be to institute therapy directed against neutrophils. This study examined the use of a CXCR2 antagonist, AZD5069. Prior studies have demonstrated that activation of CXCR2 mediates migration of neutrophils to sites of inflammation. Another CXCR2 antagonist demonstrated significant reductions in sputum neutrophils in patients with moderate to severe asthma selected on the basis of high baseline neutrophil counts in their sputum. Sadly, AZD5069 did not reduce the frequency of severe exacerbations in patients with uncontrolled severe asthma. The findings question the role of CXCR2-mediated neutrophil recruitment in the pathobiology of exacerbations in severe refractory asthma. However, before giving up on this mode of action, we should note that there is no validated marker of neutrophilic airway inflammation. Thus we must question whether this study population represents a truly "neutrophilic" asthma group.

J.J.O.

O'Byrne PM, Metev H, Puu M, et al: Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial.

Lancet Respir Med. 2016;4:797-806.

Keywords: asthma (adult), biologics, phenotypes

Anti-IL-13 for Asthma: Phase 3 Failure

In phase 2 trials, the anti-interleukin-13 (IL-13) monoclonal antibody lebrikizumab reduced exacerbations and improved lung function in patients with uncontrolled asthma. Results were especially good in patients with high type 2 biomarkers, ie, blood eosinophils and periostin. The authors present data from a pair of replicate phase 3 trials of lebrikizumab.

The LAVOLTA I and II trials included 1,081 and 1,067 patients, respectively, with uncontrolled asthma, pre-bronchodilator FEV_1 of 40% to 80% predicted, and stable background therapy. Patients were randomly assigned to lebrikizumab 37.5 mg or 125 mg sc once every 4 weeks, or placebo. The groups were stratified by serum periostin level, exacerbation history, baseline asthma medications, and country. The main efficacy outcome was asthma exacerbations over 52 weeks in biomarker-high patients: periostin level 50 ng/mL or greater or blood eosinophils 300 cells/μL or greater.

In the biomarker-high groups, lebrikizumab reduced exacerbation rate compared to placebo. In LAVOLTA I, rate ratio (RR) was 0.49 in the 37.5 mg group and 0.70 in the mg group; in LAVOLTA II, RRs were not statistically significant, but were considered "clinically meaningful." On pooled analysis, adverse events were similar with lebrikizumab and placebo. However, some serious adverse events occurred in lebrikizumab-treated patients during the placebo-controlled period, including one event of aplastic anemia and five related to elevated eosinophil concentrations.

Lebrikizumab did not consistently reduce the asthma exacerbation rate in patients with uncontrolled asthma

and high type 2 biomarkers. Despite evidence that it blocked IL-13, lebrikizumab did not provide the clinical or lung function results expected based on previous trials.

COMMENT: These replicate phase 3 studies assessed the efficacy and safety of the IL-13 antagonist lebrikizumab with uncontrolled asthma, stratified by baseline periostin level. The studies failed to meet the exacerbation rate reduction or FEV_1 improvement expected from prior phase 2 results. The biomarker strategy, which focused on patients high for either blood eosinophil counts or periostin concentrations, did not consistently identify those who benefited from lebrikizumab. Overall, these data suggest that the underlying biology of lung function and asthma exacerbations might differ, with IL-13 appearing to play a less prominent role in the latter. Likewise, targeting IL-13 alone might not be sufficient to provide meaningful improvement in exacerbations and symptoms.

J.J.O.

Hannania NA, Korenblat P, Chapman KR, et al: Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. Lancet Respir Med. 2016;4:781-796.

Keywords: asthma (adult), biologics, biomarkers

Anti-IL-5 Only Works at High Eosinophil Counts

The anti-interleukin-5 (IL-5) antibody reslizumab improves lung function and reduces exacerbations in asthma patients with high sputum eosinophils or blood eosinophil counts of 400 cells/μL or higher. This study evaluated the effects of reslizumab among asthma patients unselected for baseline blood eosinophil counts.

The study included 492 patients with poorly controlled asthma, despite medium- or high-dose inhaled corticosteroid therapy. In a 4:1 ratio, they were randomly assigned to 16 weeks of treatment with intravenous reslizumab, 3.0 mg/kg, or placebo. The main outcome of interest was change in FEV_1 at 16 weeks.

The mean change in FEV_1 was not significantly different between groups. Reslizumab improved FEV_1 only among patients with baseline eosinophils of 400 cells/μL or greater: a difference of 270 mL, compared to placebo. For this group, reslizumab was also associated with improvements in asthma control, use of short-acting β-agonists, and forced vital capacity. Overall adverse event rate was 55% with reslizumab versus 73% with placebo.

In patients with uncontrolled asthma unselected for eosinophil count, anti-IL-5 therapy with reslizumab does not improve lung function or symptom control. Although not specifically designed to test this group of patients, the results support previous findings showing an "acceptable benefit-risk profile" in patients with a baseline blood eosinophil count of 400 cells/μL or higher.

COMMENT: In this study, patients with poorly controlled asthma on medium doses of ICS were randomly assigned to the anti-IL-5 drug reslizumab or placebo, without regard to eosinophilia. Not surprisingly, this strategy did not work—as shown a decade ago for mepolizumab. Only subjects with eosinophilia of 400 cells/μL or greater showed benefits. When it comes to biologics for asthma, phenotyping is everything.

D.A.K.

Corren J, Weinstein S, Janka L, et al: Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest. 2016:150;799-810.

Keywords: asthma (adult), biologics, phenotypes

Can Yoga Improve Pulmonary Function in Asthma?

Several clinical trials have suggested benefits of yoga for patients with asthma. This study evaluated the effects of kapalabhati, a high-frequency breathing yoga technique, on lung function in adults with asthma.

The randomized study included 60 patients, aged 20 to 50 years, with nonsevere, clinician-diagnosed asthma. One group was assigned to practice kapalabhati—breathing at 1 Hz, with intentionally active inhalations—for 10 minutes. Controls practiced deep breathing with breath awareness for 10 minutes.

A 10-minute session of kapalabhati was associated with approximately a 200 mL increase in FEV_1. There were also significant effects on forced vital capacity and FEV_1/FVC ratio. No significant changes were observed in the control group.

Consistent with previous studies reporting benefits of yoga for patients with asthma, these preliminary results show immediate improvement in lung function after 10 minutes of kapalabhati practice. Kapalabhati might be a simple and cost-effective means of improving pulmonary function in asthmatic patients; further studies are needed.

COMMENT: This study supports prior evidence that yoga improved lung function in adults with asthma. After a 10-minute sessions of kapalabhati breathing, a significant increase in $FEV_1$1 was noted. Yoga appears to be both a cost-effective and easy-to-perform treatment. Further long-term studies in adults and studies in children are needed.

V.H.-T.

Raghavendra P, Shetty P, Shetty S, et al: Effect of high-frequency yoga breathing on pulmonary functions in patients with asthma: a randomized clinical trial. Ann Allergy Asthma Immunol. 2016;117:550-551.

Keywords: asthma (adult), yoga

Good Asthma Control Outcomes with Telemedicine

Many patients who could benefit most from specialized asthma care live in underserved areas. Especially in rural communities, telemedicine has the potential to improve clinical management. This study compared the outcomes of telemedicine versus in-person visits for children with asthma.

Pediatric asthma patients in two rural communities were offered the choice of in-person visits (to a clinic located 70 or 150 miles away) or telemedicine sessions at a local clinic. For the telemedicine sessions, a Remote Presence Solution (RPS)—including a digital stethoscope, otoscope, and high-resolution camera—was used to perform clinical examination. Baseline visits were followed by 30-day and 6-month follow-up visits. Tests of asthma control were compared between groups.

Of 169 children, 69 were seen via telemedicine; 40 children in the telemedicine group and 34 in the in-person group completed all three visits. Asthma control measures showed a small, statistically insignificant improvement, with no difference between groups. Most patients in the telemedicine group were satisfied with their care.

The results suggest that telemedicine is noninferior to in-person visits in terms of disease control for pediatric asthma patients. "Synchronous telemedicine" appears to be a viable alternative to traditional face-to-face care for providing specialist care to children with asthma.

COMMENT: In this study, synchronous telemedicine achieved asthma control outcomes similar to those of face-to-face care. The study is limited by small numbers and a large dropout rate, but these results support the idea of expanding telemedicine options for our asthma patients.

C.C.R.

Portnoy JM, Waller M, De Lurgio S, Dinakar C: Telemedicine is as effective as in-person visits for patients with asthma.

Ann Allergy Asthma. 2016;117:241-245.

Keywords: asthma (child), telemedicine

FOCUS ON E-CIGARETTES

E-Cigs Can (Literally) Burn You Up...

As the use of e-cigarettes continues to increase, many users do not understand the risk of fire or explosion caused by overheating of the device's internal battery. The authors report an experience of 15 patients with injuries caused by explosion of e-cigarette batteries.

The 15 patients were seen at a single medical center from October, 2015, through June, 2016. Flame burns were present in 80% of patients, chemical burns in 33%, and blast injuries in 27%. The thigh or groin was involved in 53% of cases, hands in 33%, and face in 20%. Consequences included tooth loss, tattooing, and soft tissue defects due to blast injuries and extensive wounds requiring skin grafting due to flame injuries.

Once considered isolated events, burns and blast injuries due to explosion of e-cigarette batteries appear to be increasing. This danger highlights the need for increased regulation of e-cigarettes, including design changes to reduce the risk of such injuries.

COMMENT: These authors present 15 cases of e-cigarette explosions that caused serious injuries (including flame burns, chemical burns, and blast injuries) to multiple parts of the body (the face, hands, thighs, and groin). Many patients required complex care involving emergency medicine personnel, plastic surgeons, and burn care providers.

C.D.

Brownson EG, Thompson CM, Goldsberry S, et al: Explosion injuries from e-cigarettes.

N Engl J Med. 2016;375:1400-1402.

Keywords: burns, e-cigarettes

...But Alas, Teens Consider E-Cigarettes Safe

Previous studies have identified some reasons why young people try e-cigarettes, such as curiosity, influence of friends and family, and flavors. This longitudinal survey study evaluated reasons for initial and continued e-cigarette use by minors.

An initial survey identified 340 middle and high school students who had tried e-cigarettes. Factors associated with initial e-cigarette use and with continued use at a six-month follow-up survey were analyzed.

Several reasons for initially trying e-cigarettes were also associated with continued use at follow-up, including low cost, being able to "vape" anywhere, and quitting regular cigarettes. Those who tried e-cigarettes because of low cost had more frequent use at follow-up. Other predictors of continued and more frequent use were young age and being a current smoker of regular cigarettes. Reasons related to general interest—eg, curiosity—were not associated with continued use.

Factors associated with continued and more frequent use of e-cigarettes by adolescents are identified. The findings suggest possible regulatory and educational approaches to discouraging continued use among youth who try e-cigarettes.

COMMENT: There is growing concern about the increasing adoption of e-cigarettes by youth, who consider "vaping" to be safe. There's also apprehension that this trend may incite dual use of both e-cigarettes and traditional tobacco products. This longitudinal survey study found that • • •

younger students were indeed more likely to continue using e-cigarettes.

C.D.

Bold KW, Kong G, Cavallo DA, et al: Reasons for trying e-cigarettes and risk of continued use. Pediatrics. 2016;138:e20160895.

Keywords: e-cigarettes, predictors

Health Effects of E-Cigarettes: What's the Evidence?

There is continued and contentious debate over the health effects of e-cigarettes—including their potential for "harm reduction" as an alternative to tobacco smoking and concern about unknown long-term health consequences. Current evidence on the health effects of e-cigarettes is reviewed.

Use of e-cigarettes has risen sharply in recent years, particularly among young people. These devices could potentially be an effective aid to smoking cessation, but data are limited; the available randomized trials have yielded conflicting results. Newer-generation devices have characteristics that make them more satisfying to users.

Studies of e-cigarettes liquids and aerosols have identified constituents besides the listed ingredients, including some potentially toxic substancej. In vitro studies suggest possible biologic effects on human cells, although toxicity appears lower than with tobacco smoke. Animal models have shown some in vivo effects of e-cigarette aerosols, but it is difficult to extrapolate these results to humans.

For long-term smokers, using e-cigarettes rather than tobacco might improve health outcomes, although clinical and epidemiologic data are lacking. While nicotine-free e-cigarette liquids are available, nicotine-containing solutions are much more common, with known short- and long-term effects. Limited data suggest that e-cigarette use may have lower physiologic harms than tobacco smoking. The health outcomes of long-term e-cigarette use remain unknown.

While e-cigarettes might be safer than conventional tobacco products, they may pose health risks that are not present when neither type of product is used. E-cigarettes may promote nicotine addiction in young people who might otherwise have been nonsmokers. Further research is needed to clarify both the positive and negative health effects of e-cigarettes.

COMMENT: We performed a meticulous review of the health effects of e-cigarette use. Evaluation of current evidence of the risks posed by e-cigarettes, including inhaling potentially harmful chemicals and flavorings, is balanced by appraisal of their efficacy as smoking cessation measures.

C.D.

Dinakar C, O'Connor GT: The health effects of electronic cigarettes. N Engl J Med. 2016;375:1372-1381.

Keywords: e-cigarettes, smoking

SLIT vs Medications for Allergic Rhinitis–Which Is Best?

Allergic rhinitis is a common condition that is often undertreated, despite its significant impact on daily life. The two main treatment options, medications and allergen immunotherapy, have not been directly compared. Previous data were pooled for an indirect comparison of sublingual immunotherapy (SLIT) versus pharmacotherapy for seasonal and perennial allergic rhinitis (SAR and PAR)

The analysis included nearly 19,000 subjects enrolled in 23 SAR trials and 11 PAR trials. Data were pooled to compare the effects of double-blind treatments on total nasal symptom scores (TNSSs), relative to placebo. The SLIT studies included six timothy-grass trials, two ragweed trials, and two house dust mite trials; the medication studies included seven trials of montelukast, nine of desloratadine, and eight of mometasone furoate nasal spray. Most of the SLIT studies permitted rescue medication use.

All three types of SLIT provided greater improvement in TNSSs relative to placebo—by 16.1% to 17.1%. All three medications were also associated with greater improvement, compared to placebo. In SAR studies, the improvements were 5.4% with montelukast, 8.5% with desloratadine, and 22.2% with intranasal mometasone. In PAR studies, the improvements were 3.7%, 4.8%, and 11.2%, respectively.

Within the limitations of the indirect comparisons, timothy grass and ragweed SLIT for SAR relieve nasal symptoms more than montelukast and desloratadine, and nearly as much as intranasal mometasone. For PAR, dust mite SLIT is more effective than all drug therapies.

COMMENT: Patients often ask, "What is the most effective treatment for my hay fever?" This report compared the efficacy of SLIT to medications. Since there are no head-to-head comparisons, the authors pooled data from 23 SAR and 11 PAR trials comparing treatment effect on nasal symptoms. Interestingly, improvements in TNSS for both grass and ragweed SLIT were better than antihistamine or montelukast, but not quite as good as nasal steroid for SAR. However, dust mite SLIT had greater improvements in TNSS than any treatment option for PAR. The authors suggest the complementary use of SLIT for SAR or PAR instead of pharmacotherapy alone.

S.M.F.

Durham SR, Creticos PS, Nelson HS, et al: Treatment effect of sublingual immunotherapy (SLIT) tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: pooled analyses. J Allergy Clin Immunol 2016;138:1081-1088.

Keywords: allergic rhinitis, meta-analysis, SLIT

Professionals Overestimate Fatal Anaphylaxis Risk in Children

Fatal anaphylaxis is a fortunately rare event among children with food allergies. Healthcare professionals' knowledge of this risk may affect their behavior and their message to parents. This study assessed British healthcare providers' estimates of the risk of fatal anaphylaxis in food-allergic children.

The survey study included 30 primary care nurses, 30 school "first aiders," and 30 community pharmacists. Participants used a risk ladder tool to estimate the risks of fatal and nonfatal anaphylaxis, as well as all-cause mortality, in children. Knowledge and skills in managing anaphylaxis were also assessed.

All three groups overestimated the risk of fatal anaphylaxis in a food-allergic child—the average estimate was 13.5 times higher than the actual risk. In contrast, they did not systematically overestimate the risks of nonfatal anaphylaxis or all-cause mortality. Risk estimates were unrelated to the participants' ability to administer epinephrine to a child experiencing anaphylaxis.

Nurses, pharmacists, and school personnel greatly overestimate the risk of fatal anaphylaxis in children with food allergies. These inaccurate perceptions may contribute to excessive anxiety in both parents and professionals. Community practitioners need education about the risks and management of anaphylactic reactions to foods.

COMMENT: Awareness of food allergy is likely higher than it ever has been, yet fatal food anaphylaxis remains quite rare. This study evaluated perceptions of the frequency of food allergic reactions, fatal food anaphylaxis, and pediatric all-cause mortality among UK pharmacists, school "first aiders," and primary care practitioners. All groups were fairly accurate in estimating risk of death and nonfatal food reactions—yet they overestimated the risk of fatal food anaphylaxis by more than 10-fold. Despite this, all groups demonstrated relatively poor knowledge of how to treat anaphylaxis and when to administer epinephrine. With no obvious benefit, this overestimation of risk may have untoward effects, including increased anxiety for the child and family.

D.A.K.

Hanna HJ, Emmanuel J, Naim S, et al: Community healthcare professionals overestimate the risk of fatal anaphylaxis for food allergic children.
Clin Exp Allergy. 2016;46:1588-1595.

Keywords: anaphylaxis, epinephrine, food allergy

Adolescent Food Anaphylaxis: More Common than We Realize

Little is known about the occurrence of anaphylaxis and other severe reactions to foods among adolescents. This issue was addressed in a study of adolescents from a population-based birth cohort.

The analysis included 3,153 children born in Stockholm in 1994-96. Of these, 8.5% had food-related symptoms before their 16-year assessment. Parental questionnaires suggested that 24 adolescents (0.8%) met criteria for anaphylaxis. Just 8 of these patients accessed healthcare during anaphylaxis. Twelve percent of cohort members had a physician diagnosis of food allergy, while an epinephrine autoinjector was dispensed to just 2.6%.

Three-fourths of adolescents with anaphylaxis had experienced food-related reactions in infancy. The implicated foods were peanut in 7 cases, tree nuts in 5, and egg and soya in 3 each. Of 17 adolescents tested, 16 had positive serum IgE to the culprit foods. Among teens with non-anaphylactic food reactions (mainly oral itching), fruits and vegetables were the main culprits. Those with anaphylaxis were more likely to have polysensitization, especially to peanut and multiple tree nuts.

The results show a high rate of food-related anaphylaxis among adolescents. Many of these patients don't seek medical care, and thus may be missed in estimates of incidence.

COMMENT: Few studies have evaluated adolescent food anaphylaxis in a population-based setting. This study examined food reactions and food anaphylaxis among children from a Swedish birth cohort. The results showed a high incidence of food anaphylaxis among adolescents, 0.8%; yet less than one-third of affected patients sought medical care. Not surprisingly, peanut and tree nut were the most common allergens. The biggest limitation is that anaphylaxis was defined by parental report of symptoms. However, the study does suggest that epidemiologic studies of anaphylaxis from the emergency department may miss a number of reactions, since adolescents may not seek treatment.

D.A.K.

Vetander M, Protudjer JLP, Lilja G, et al: Anaphylaxis to foods in a population of adolescents: incidence, characteristics and associated risks.
Clin Exp Allergy. 2016;46:1575-1587.

Keywords: adolescents, anaphylaxis, food allergies

Blood Neutrophils: A Potentially Useful Asthma Biomarker?

Asthma is characterized by blood neutrophilia and eosinophilia. In contrast to eosinophils, relatively little is known about blood neutrophil patterns as an asthma biomarker. This study evaluated blood eosinophils and neutrophils for association with asthma control outcomes.

The study included 474 patients with asthma, drawn from the first follow-up of the Epidemiological Study on the Genetics and Environment of Asthma (EGEA2). Of these, 242 patients were already aged 16 years or older a decade earlier (EGEA1). Asthma control at EGEA2 was assessed

using the Global Initiative for Asthma 2015 definition asthma exacerbations were defined by the need for urgent care or oral corticosteroids in the past year. Cutoffs for high versus low blood granulocyte counts were 250/mm^{-3} for eosinophils and 5,000/mm^{-3} for neutrophils.

After adjustment for age, sex and smoking, high blood neutrophils at EGEA2 were associated with asthma exacerbations and poor asthma control, odds ratio. In contrast, high eosinophils were associated with increased bronchial hyperresponsiveness (BHR), decreased lung function, and higher total IgE. From EGEA1 to EGEA2, nearly half of patients had a persistent blood granulocyte pattern. Patients with persistently high neutrophils were about three times more likely to have poor asthma control at EGEA2. Both initial and persistent high eosinophils were associated with increased BHR, decreased lung function, and higher IgE.

At baseline and follow-up, blood granulocyte patterns show significant and distinct associations with asthma outcomes. The findings suggest specific roles for blood neutrophils and eosinophils, which could be tested as "predictive signatures" for subsequent asthma burden.

COMMENT: The use of biomarkers to determine treatment strategies for asthma continues to expand. Most attention has been given to eosinophils and exhaled nitric oxide as a surrogate marker of eosinophilic inflammation. This study brings forward a newer thesis regarding the use of peripheral neutrophil counts. These data are significant and should be validated by subsequent studies. There appears significant value in following neutrophil counts to guide therapy.

B.E.C.

Nadif R, Siroux V, Boudier A, et al: Blood granulocyte patterns as predictors of asthma phenotypes in adults from the EGEA study.
Eur Respir J. 2016;48: 976-978.

Keywords: asthma (adult), biomarkers, phenotypes

FOCUS ON COPD

Once-Daily Fluticasone-Vilanterol: Real Life Clinical Trial

The characteristics of patients enrolled in clinical trials of treatments for chronic obstructive pulmonary disease (COPD) may differ from those seen in everyday clinical practice. This study evaluated the safety and efficacy of once-daily inhaled fluticasone furoate-vilanterol in a "real life" clinical setting.

The Salford Lung Study included 2,799 COPD patients from 75 UK general practices, in an area with an established electronic health record system linking primary and secondary care. Patients were randomly assigned to once-daily combination of inhaled fluticasone-vilanterol, 100/25 μg, or usual care. The main study outcome was the rate of moderate or severe exacerbations among patients (81% of the sample) with exacerbations in the preceding year.

The fluticasone/vilanterol group had a significant 8.4% reduction in the rate of moderate to severe exacerbations, compared to usual care. All secondary outcomes were similar between groups, including COPD-related primary or secondary care contacts and time to first moderate or severe exacerbation. Pneumonia and other serious adverse events were not significantly different between groups.

The results support the use of once-daily combination therapy with fluticasone-vilanterol for COPD patients in routine clinical practice. Among those with previous exacerbations, this treatment reduces the risk of exacerbations compared to usual care, with no increase in serious adverse events. The results illustrate the importance of controlled effectiveness trials in translating the results of efficacy studies to clinical practice or everyday clinical care.

COMMENT: In this large, randomized, real-life study, once-daily treatment with an inhaled combination of fluticasone furoate and vilanterol was superior to usual care with regard to the frequency of moderate or severe exacerbations. There was no increased risk of serious adverse events, although a higher incidence of mild pneumonia with fluticasone-vilanterol could not be ruled out. Future effectiveness studies are likely to influence clinical guidelines—not only for COPD but also for many other chronic diseases.

C.D.

Vestbo J, Leather D, Bakerly ND, et al: Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice.
N Engl J Med. 2016;375:1253-1260.

Keywords: COPD, exacerbations

Stable COPD–Is It Time to Put Down the Oxygen Cannula?

Despite a lack of evidence for efficacy, long-term supplemental oxygen is commonly recommended for patients with stable chronic obstructive pulmonary disease (COPD) and moderate desaturation. The results of a randomized controlled trial of long-term oxygen therapy for patients with COPD and moderate resting or exercise desaturation are reported.

The Long-Term Oxygen Treatment Trial (LOTT) was originally designed to assess the effects of supplemental oxygen on time to death among patients with stable COPD and moderate resting desaturation of 89% to 93%. After several months, the study was modified to include stable COPD patients with moderate exercise-induced desaturation. The study intervention consisted of 24-hour supplemental oxygen for patients with resting desaturation and oxygen during exercise and sleep for those with exercise desaturation.

The analysis included data on 738 patients at 42 centers, followed up for 1 to 6 years. The modified primary composite outcome of time to death or first hospitalization was not significantly different for patients assigned to long-

term oxygen versus controls. Secondary outcomes were similar as well, including overall hospitalizations, COPD exacerbations, and COPD-related hospitalizations. Quality of life, pulmonary function, and 6-minute walking distance were also comparable between groups.

The LOTT results question the use of long-term supplemental oxygen therapy for patients with stable COPD and moderate desaturation, whether at rest or only during exercise. Mortality, hospitalization, exacerbations, and other long-term outcomes appear similar, with or without supplemental oxygen.

COMMENT: In the largest randomized trial on this question, long-term supplemental oxygen therapy for patients with stable COPD and resting or exercise-induced moderate desaturation did not improve clinically relevant, daily-life outcomes. In the accompanying editorial *(N Engl J Med.* 2016;375:1683-1684), Ekström suggests that perhaps this therapy may be better suited for patients with COPD and chronic, severe resting hypoxemia.

C.D.

The Long-Term Oxygen Treatment Trial Research Group: A randomized trial of long-term oxygen for COPD with moderate desaturation.
N Engl J Med. 2016;375:1617-1627.

Keywords: COPD, desaturation, oxygen therapy

To Predict Uncontrolled Asthma, Two Biomarkers Are Better Than One

Identifying clinically useful asthma biomarkers is an active area of research. In a previous study, the authors found that exhaled nitric oxide and blood eosinophil count provide additive information on asthma exacerbations. They evaluated the relationship of these markers to asthma control and other outcomes of interest.

The study included data on exhaled NO and blood eosinophils in 406 patients with asthma, aged 10 to 35 years. Cutoff points for elevated levels were 20 to 25 ppb or higher for exhaled NO and 0.3 × 10^9/L or higher for blood eosinophil count. Associations with lung function, bronchial hyperresponsiveness, and asthma control were assessed.

Uncontrolled asthma (Asthma Control Test score less than 20) was present in 40.5% of patients with elevated levels of both markers, compared to 21.1% of those with increased blood eosinophils only. The difference remained significant on adjusted analysis. There was also a significant difference between patients with elevated levels of both exhaled NO and blood eosinophils and those in whom both levels were normal. Simultaneous increases in both biomarkers were also associated with a higher prevalence of moderate-to-severe bronchial hyperresponsiveness, compared to increased levels of neither or just one marker.

In a large group of young patients with asthma, simultaneously elevated markers of local and systemic type 2 inflammation—exhaled NO and blood eosinophils—are associated with increased rates of uncontrolled asthma and BHR. This combination of biomarkers could provide a more complete picture of the risk of impaired lung function, and add useful information for treatment decision making.

COMMENT: Identifying patients with Th2 asthma could help target therapies. These Swedish researchers found that the combination of elevated blood eosinophils and exhaled NO together helped identify asthmatic patients who were likely to have reduced lung function, greater BHR, and difficulty with asthma control. An interesting finding was that biomarkers used separately were not as helpful as when blood eosinophils and exhaled NO were used together. The authors suggest that simultaneous measurement of these markers might help predict asthma morbidity and the need to intensify controller therapy.

S.M.F.

Malinovschi A, Jansen C, Borres M, Alving K: Simultaneously increased fraction of exhaled nitric oxide levels and blood eosinophil counts relative to increased asthma morbidity.
J Allergy Clin Immunol. 2016;138:1301-1308.

Keywords: asthma (adult), biomarkers

Fixing Indoor Air Quality Can Improve Asthma

The indoor environment can have a major impact on asthma morbidity in children. Indoor exposures include not only allergens such as dust mite but also pollutants such as secondhand smoke. This report highlights the role of indoor environmental control practices in the management of childhood asthma.

Environmental control measures should be tailored to the individual child, based on knowledge of allergic sensitivities and relevant indoor exposures. An environmental history can be performed, addressing key exposures known to trigger the child's asthma symptoms and exacerbations. The presence of furred pets and indoor pests should be evaluated; dust mite exposure is a factor in all but arid environments. In addition to the presence of smokers in the household, evaluation of indoor pollutants should address the use of gas stoves and other appliances.

Specific IgE testing, or referral to an allergist for skin testing, can guide efforts to identify the clinically relevant indoor allergens. The report provides information on specific allergens, including dust mite, pets, rodents, cockroach, and dampness and mold; as well as indoor pollutants, including particulate matter, secondhand smoke, and nitrogen dioxide. Environmental control measures include removal or control of the exposure source, as well as mitigation measures such as high-efficiency particulate air purifiers and allergen-proof mattress and pillow covers. Education may be provided • • •

by primary care clinicians or specialists or by trained community health workers.

The report outlines the importance of indoor exposures in childhood asthma, including evaluation and control measures for indoor allergens and pollutants. The authors point out that public and private insurance generally do not cover the cost of environmental assessment and control measures, despite evidence of their cost-effectiveness.

COMMENT: This excellent clinical report emphasizes that indoor allergens and pollutants are major contributors to asthma morbidity. Some tailored environmental control practices can reduce asthma symptoms and exacerbations, with comparable efficacy and cost to controller medications. Strategies that can be delivered by primary care physicians, specialists, and other health care workers are discussed.

C.D.

Matsui EC, Abramson SL, Sandel MT: Indoor environmental control practices and asthma management. Pediatrics. 2016;138(5):e20162589.

Biomarkers and Biologics–an Evolving Story

Anti-IgE therapy with omalizumab reduces exacerbation risk in severe allergic asthma, although the benefits vary between patients. Free serum IgE might be a useful marker of treatment response. This study evaluated biomarkers as predictors of response to omalizumab in patients with severe allergic asthma.

The prospective observational study included 30 patients with severe allergic asthma treated with omalizumab for at least 1 year, and most for 2 years. Markers of type 2 inflammation were evaluated as predictors of response to omalizumab, defined as freedom from asthma exacerbations during the first year of treatment. Free serum IgE levels were monitored for 2 years, and associations with baseline biomarker levels and exacerbations were analyzed.

Patients with no exacerbations during the first year on omalizumab had higher baseline serum periostin levels and blood eosinophil counts, compared to those with exacerbations. At 16 and 32 weeks, baseline periostin was negatively associated with free serum IgE; there was no such association for eosinophil count. At a cutoff of 60 ng/mL or higher, serum periostin was associated with a lower exacerbation rate, 38% versus 89%; and a higher rate of clinically important change on the Asthma Quality of Life Questionnaire, 86% versus 33%.

Patients whose free serum IgE level decreased with omalizumab treatment had fewer exacerbations over 2 years. In 14 patients with continued exacerbations, the number of events decreased over 2 years as free serum IgE levels declined.

Among patients with severe allergic asthma, a higher baseline serum periostin level is associated with a better response to omalizumab. Reduction of free serum IgE during treatment may also be useful in evaluating treatment response.

COMMENT: When considering the use of a biologic agent such as omalizumab, we must consider the financial burden to the healthcare system. Certainly, optimizing the choice for patients most likely to have maximal efficacy with omalizumab is one way to improve the therapeutic index. This study by Tajiri and colleagues reinforces the work of Hanania et al *(Am J Respir Crit Care Med.* 2013;187:804-811): relying on additional surrogates for Th2-high asthma improves the likelihood of reducing exacerbation rates when omalizumab is added to treatment.

J.J.O.

Tajiri T, Matsumoto H, Gon Y, et al: Utility of serum periostin and free IgE levels in evaluating responsiveness to omalizumab in patients with severe asthma.
Allergy. 2016;71:1472-1479.

Keywords: asthma (adult), biologics, biomarkers, omalizumab

Coconut Really Is a Tree Nut...or Is It?

Even though it is actually a drupe, coconut is classified as a tree nut by the US Food and Drug Administration. There is little evidence to guide patients with tree nut allergies on the safety of consuming coconut. This study assessed sensitization to coconut among children with tree nut allergy.

The single-center study included 298 children (median 5.7 years) who underwent coconut-specific IgE measurement between 2000 and 2012. Most of the children were tested for specific IgE to tree nuts. The rate of co-sensitization to coconut and tree nuts was assessed.

Thirty percent of children had positive results for coconut-specific IgE: mean level 1.70 kU/L. The strongest correlation was noted for coconut; for most other tree nuts, the correlation was significant but low. Adjusted analysis showed significant correlations between coconut and macadamia, odds ratio (OR) 7.39; as well as coconut and almond, OR 5.32. Macadamia sensitization was 93% sensitive and 86% specific in predicting coconut sensitization.

An apparent correlation between coconut and tree nut sensitization is mainly explained by sensitization to macadamia. The authors plan a further study to compare their specific IgE results with clinical symptoms.

COMMENT: Patients with nut allergy frequently seek the advice of allergists regarding coconut consumption. While increasing numbers of patients have peanut and tree nut allergy, limited information regarding allergy to coconut exists. This study found high rates of co-sensitization between coconut and macadamia. There was a correlation between coconut and tree nuts, explained by sensitization to macadamia. Interestingly, no allergenic proteins have

been described for macadamia. Studies are needed to further define the clinical significance.

V.H.-T.

Polk BI, Dinakarpandian D, Nanda M, et al: Association of tree nut and coconut sensitizations.

Ann Allergy Asthma Immunol. 2016;117:412-416.

Keywords: cross-sensitization, food allergy, tree nut allergy

Does Allergic Rhinitis Reduce Cardiovascular Risk?

Both atherosclerotic cardiovascular disease (ACVD) and allergic disease involve inflammation. While asthma has been linked to increased ACVD and all-cause mortality, there is conflicting evidence on association of allergic rhinitis (AR). This study assessed the incidence of ACVD and mortality in a large cohort of patients with AR.

Data from a large managed care system were used to match 110,207 AR patients for age, sex, and ethnicity to the same number of controls without AR. Analysis showed a significantly lower risk of myocardial infarction among the AR patients: hazard ratio (HR) 0.63. Allergic rhinitis was also associated with a lower overall risk of coronary heart disease, HR 0.81; and cerebrovascular disease, HR, 0.67; as well as lower all-cause mortality, HR 0.42. The associations were even stronger on analysis excluding patients with asthma.

The decreased risk of coronary heart disease was also seen in patients with positive environmental allergen-specific IgE test results: relative risk 0.87. There were no significant associations with cerebrovascular disease and mortality in this group.

Patients with AR may be at lower risk of coronary and cerebrovascular disease and all-cause mortality, compared to matched controls. The associations are maintained after exclusion of patients with asthma; risk of cardiovascular events is also lower in AR patients with positive results on specific IgE testing. Atopy may not contribute to the increased cardiovascular risk associated with asthma.

COMMENT: Prior studies have demonstrated an association between asthma and ACVD. Surprisingly, this large cohort study found that adults with physician-diagnosed AR had decreased risk of coronary heart disease, cerebrovascular disease, and all-cause mortality. Further studies in patients of different ages are needed to validate this observation.

V.H.-T.

Crans Yoon AM, Chiu V, Rana JS, Sheikh J: Association of allergic rhinitis, coronary heart disease, cerebrovascular disease, and all-cause mortality.

Ann Allergy Asthma Immunol. 2016;117:359-364.

Keywords: allergic rhinitis, cardiovascular disease

Does Omalizumab Decrease Angioedema?

Angioedema is a troublesome symptom that may occur in 40% of patients with chronic idiopathic/spontaneous urticaria (CIU/CSU). Anti-IgE therapy with omalizumab has been approved for treatment of CIU/CSU that does not respond to H_1-antihistamines. Data from pivotal clinical trials were analyzed to assess omalizumab's effects on angioedema in these patients.

The researchers analyzed pooled data on 975 patients from three phase 3 randomized trials of omalizumab for CIU/CSU. The percentage of patients reporting angioedema symptoms at baseline ranged from 40.7% to 53.1%. Compared to placebo, a 300 mg sc dose of omalizumab significantly reduced angioedema symptoms. Mean percentages of angioedema-free days in the three trials were 96.1% versus 88.2%, 95.5% versus 89.2%, and 91.0% versus 88.7%, respectively. Patients generally reported using no treatment or medications only for angioedema.

At a 300 mg dose, omalizumab appears to reduce the angioedema that is common among patients with CIU/CSU. Most patients don't seek medical care for their angioedema symptoms.

COMMENT: The authors analyzed the data from pivotal trials of omalizumab for chronic idiopathic urticaria. Nearly half of the subjects enrolled in these trials also experienced angioedema, and this pooled analysis concluded that omalizumab also reduces angioedema symptoms. An accompanying editorial *(Ann Allergy Asthma Immnunol.* 2016;117:339-340) questions the clinical relevance of this finding. However, it seems reasonable to counsel patients that omalizumab may help both their urticaria and angioedema symptoms.

C.C.R.

Zazzali JL, Kaplan A, Maurer M, et al: Angioedema in the omalizumab chronic idiopathic/spontaneous urticaria pivotal studies.

Ann Allergy Asthma Immunol. 2016;117:370-777.

Keywords: angioedema, chronic idiopathic urticaria, omalizumab

Determinants of Exhaled NO Are More Complex than You Might Think!

Exhaled nitric oxide is a potentially useful marker in asthma management, but a wide range of other individual factors may also affect these measurements. This study analyzed determinants of exhaled NO in asthma patients.

Exhaled NO measurements were obtained from 557 patients enrolled in the Swedish Global Asthma and Allergy Excellence Network study. Constitutive and individual factors affecting exhaled NO were analyzed, along with the

effects of age at menarche and parental smoking.

Exhaled NO levels were higher for males, taller patients, and those sensitized (by skin prick test) to perennial allergens and pollen. Current smokers had lower values, as did those whose parents both smoked during the patient's childhood. Among females, exhaled NO was lower for those with menarche between age 12 and 14, compared to older ages.

The study identifies several determinants of exhaled NO values, besides inflammation, in patients with asthma. These complex factors should be taken into account in clinical interpretation of exhaled NO. Age at menarche and parental smoking are newly identified factors that warrant further study.

COMMENT: Although exhaled NO has been used in the diagnosis and management of asthma for some time, the impact of many constitutional determinants have not been well studied. This study confirmed that allergic sensitization, male gender and greater height are associated with higher exhaled NO, while current smoking and current use of inhaled corticosteroids are associated with lower levels. It includes the novel findings that parental smoking during childhood and younger age at menarche are both associated with lower exhaled NO levels in adulthood. We need to consider the impact of these determinants when determining a target exhaled NO in our asthmatic patients. The study also questions the use of a simple normogram for exhaled NO measurement.

J.J.O.

Al-shamkhi N, Alving K, Dahlen SE, et al: Important non-disease-related determinants of exhaled nitric oxide levels in mild asthma: results from the Swedish GA²LEN study. Clin Exp Allergy. 2016;46:1185-1193.

Keywords: asthma, biomarkers, exhaled nitric oxide

Patients Do Listen to Their Doctors (Sometimes!)

Recommendations for infant age at introduction of allergenic foods have been revised twice in the past decade. This survey evaluated the rate at which parents followed these recommendations.

Parents completed surveys regarding their infant's diet at well-child checkups between age 4 and 36 months. The study included surveys from 86 parents at urban clinics with a high rate of Medicaid coverage and from 99 parents at a suburban practice where most patients had private insurance. Differences in infant age at introduction of different foods were analyzed.

Age at introduction of solid foods was about 5 months in both demographic groups. Urban parents reported earlier introduction of allergenic foods, with significant differences for whole milk, peanut, fish, and egg. The main factor affecting timing was the healthcare provider's recommendation.

Parents are influenced by healthcare providers' recommendations on the timing of introduction of foods in the infant diet. This finding highlights the importance of educating pediatricians and other providers as to current data and recommendations.

COMMENT: As allergists, we may question whether patients truly follow our recommendations. This study demonstrated that healthcare providers' recommendations influenced the timing of introduction of allergenic foods to infants, in both urban and suburban populations. The authors remind allergists to educate all providers on current guidelines, as this was an important factor in food introduction.

V.H.-T.

Hartman H, Dodd C, Rao M, et al: Parental timing of allergenic food introduction in urban and suburban populations.
Ann Allergy Asthma Immunol. 2016;117:56-60.

Keywords: diet, food allergy, socioeconomic factors

REVIEWS OF NOTE

COMMENT: This is an insightful review regarding the safety of using selective beta-blockers in patients with chronic obstructive pulmonary disease.

B.E.C.

Lipworth B, Wedzicha J, Devereux G, et al: Beta-blockers in COPD: time for reappraisal. Eur Respir J. 2016;48:600-603.

COMMENT: This is an insightful review of asthma-COPD overlap syndrome, including definition and treatments.

B.E.C.

Sin DD, Miravitlles M, Mannino DM, et al: What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion.
Eur Respir J. 2016;48:664-673.

COMMENT: This is a case-based, detailed review of the evaluation and management of chronic cough. In the instance of chronic cough with no identifiable underlying cause, the authors suggest that options to consider include slow-release low-dose morphine sulfate, gabapentin or pregabalin, or speech and language therapy.

C.D.

Smith JA. Woodcock A: Chronic cough. N Engl J Med. 2016;375:1544-1551.

COMMENT: This is a nice review article on primary ciliary dyskinesia, including clinical manifestations and expected outcomes.

B.E.C.

Goutaki M, Meier AB, Halbeisen FS, et al: Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis.
Eur Respir J. 2016;48:1081-1095.