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TOPICS

VIRUSES AND THE RESPIRATORY HEALTH OF INFANTS AND CHILDREN

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VIRUSES AND THE RESPIRATORY HEALTH OF INFANTS AND CHILDREN

Rubner FJ, Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Pappas TE, Gern JE, Lemanske RF Jr. **Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence**. *J Allergy Clin Immunol*. 2017; 139: 501-507.

Summary

Wheezing-associated respiratory tract infections have long been considered risk factors for asthma. In the Tucson Children's Respiratory Study, early childhood respiratory syncytial virus (RSV) lower respiratory tract illness was a risk factor for wheezing up to age 11 but not 13 years (Stein RT, et al. Lancet. 1999). Conversely, children hospitalized with RSV had a greater risk of asthma and allergy at age 7 (Sigurs N, et al. Am J Respir Crit Care Med 2000). More recently, the Childhood Origins of Asthma (COAST) study showed that wheezing with rhinovirus (RV) during the first 3 years of life was more strongly associated with asthma at age 6 than allergen sensitization or RSV (Jackson DJ et al. Am J Respir Crit Care Med 2008). In the present study, the COAST investigators examined the association of early life RV and RSV wheezing illnesses and aeroallergen sensitization with risk of asthma at adolescence. A total of 217 children were followed prospectively from birth to age 13 years. The investigators found that wheezing with RV but not RSV and early-life antigen sensitization was associated with asthma at age 13 years, with aeroallergen sensitization and RV wheezing having additive effects

Comments

1. These data seem to confirm that outpatient infections with RSV are not associated with asthma at age 13.
2. Based on the timing of allergic sensitization and viral infection (Jackson DJ et al. Am J Respir Crit Care Med 2012), it is unlikely that RV infection alone causes asthma.
3. Based on the additive effect of wheezing with RV and antigen sensitization, it is possible that early-life viral infection increases asthma risk by generating greater degrees of airway inflammation, airway remodeling and loss of lung function over time

RESPIRATORY VIRUSES AND THE DEVELOPMENT OF ASTHMA

Carroll KN, Gebretsadik T, Escobar GJ, Wu P, Li SX, Walsh EM, Mitchel E, Sloan CD, Dupont WD, Hartert TV. **Respiratory syncytial virus immunoprophylaxis in high-risk infants and development of childhood asthma.** *J Allergy Clin Immunol.* 2017; 139: 66-71.e3.

Summary

Another approach to determining whether early-life viral infections lead to asthma is to intervene against the infection and determine whether the intervention prevents asthma development. Hartert and colleagues undertook such a study, examining the effects of RSV immunoprophylaxis, which has been shown to reduce RSV-related hospitalizations and wheezing within the first year of life. The authors conducted a retrospective cohort investigation of children enrolled in Kaiser Permanente Northern California or Tennessee Medicaid and eligible to receive RSV immunoprophylaxis. They specifically investigated whether greater adherence to immunoprophylaxis in infants at high risk for severe RSV (estimated gestational age < 32 weeks) was associated with decreased childhood asthma. Asthma was defined at 4.5-6 years of age by health care visits and medication fills. The study was confounded by the fact that infants with greater adherence had a higher prevalence of chronic lung disease, lower birth weight, and longer nursery stays. Thus, using multivariable logistic regression and propensity score-adjusted analyses, higher adherence to RSV immunoprophylaxis was not associated with decreased asthma. However, in propensity score-matched analysis, children without chronic lung disease and greater than 70% adherence had decreased odds of asthma compared with those with less than 20% adherence

Comments

1. While the results are encouraging, they highlight the need for larger studies and prospective cohorts.
2. While propensity score matching allows for a comparison between treatment groups that is unbiased by measured confounders, it may overestimate the efficacy of an experimental treatment compared with a randomized controlled trial because it assumes that all potential confounding variables have been taken into account, when in fact there may be unobserved or inaccurately-measured confounders.
3. Even with propensity score matching, increased adherence to RSV immunoprophylaxis was not associated with decreased odds of asthma in infants with chronic lung disease, suggesting that underlying changes in physiology or pulmonary architecture are less amenable to treatment.

4. In a retrospective chart review of premature infants <29 weeks gestational age, palivizumab prophylaxis was associated with reduced wheezing episodes and hospitalizations during the first 2 years of life, but did not affect pulmonary outcome at age 7-10 years (Prais D, et al. Chest 2016).

INTERACTION OF VIRUSES AND BACTERIA IN THE DEVELOPMENT OF CHILDHOOD WHEEZING AND ASTHMA

Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, Schoos AM, Wolsk HM, Thorsteinsdóttir S, Hallas HW, Arianto L, Schjørring S, Krogfelt KA, Fischer TK, Pipper CB, Bønnelykke K, Bisgaard H. **Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo controlled trial**. *Lancet Respir Med*. 2016; 4: 1926.

Summary

Asthma-like symptoms in infants are largely viral-induced, and azithromycin may induce antiviral responses in cultured airway epithelial cells (Gielen V, et al. Eur Respir J 2010; Schögler A, et al. Eur Respir J 2015). In addition, colonization with Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis is associated with episodes of asthma-like symptoms in the first 3 years of life (Bisgaard H, et al. BMJ 2010). Thus, in this double-blind, placebo-controlled trial, children aged 1-3 years from the COPSAC birth cohort were randomly allocated to a 3-day course of azithromycin oral solution (10 mg/kg/day) or placebo for episodes of asthma-like symptoms lasting at least three days. Infants with clinical signs of pneumonia (respiratory rate ≥50 breaths/min; fever of ≥39°C; C-reactive protein ≥50 mg/L) were excluded. The primary outcome was diary-verified duration of cough, wheeze or dyspnea affecting the well-being of the child. A total of 158 asthma-like episodes in 72 children were allocated. The mean duration of the lung symptoms after treatment was 3.4 days for children receiving azithromycin compared with 7.7 days for placebo, a shortening of 63.3% ($p<0{\cdot}0001$). There were no differences in adverse events between azithromycin and placebo but bacterial resistance patterns after treatment were not assessed.

Comments

1. Results must be interpreted with caution because of the subjectivity of the primary outcome variable employed; a better outcome might have been the need for unscheduled medical attention, or the need for hospital admission.
2. In a recent study of 607 children aged 12-71 months with histories of recurrent, severe lower respiratory tract infections, treatment of infections with azithromycin (12 mg/kg/day for 5 days) significantly reduced the need for oral corticosteroids (Bacharier LB, et al. JAMA 2015).
3. Azithromycin may act as an acute anti-inflammatory agent; as an antibiotic against bacterial pathogens indirectly responsible for the respiratory episode through subsequent co-infection by a viral trigger; or as an antiviral agent.
4. Further data are needed to justify the use of azithromycin in young children with lower respiratory tract infections, and use should be limited to children at high risk for oral steroid use or hospitalization.

FACTORS DETERMINING THE SEVERITY OF VIRAL-INDUCED RESPIRATORY DISEASES: INTERACTION OF VIRUSES AND BACTERIA

de Steenhuijsen Piters WA, Heinonen S, Hasrat R, Bunsow E, Smith B, Suarez-Arrabal MC, Chaussabel D, Cohen DM, Sanders EA, Ramilo O, Bogaert D, Mejias A. **Nasopharyngeal microbiota, host transcriptome, and disease severity in children with respiratory syncytial virus infection**. *Am J Respir Crit Care Med*. 2016; 194:1104-1115.

Summary

RSV causes severe bronchiolitis in only a subset of infected infants. Thus, other factors may modify airway inflammation and the severity of illness during RSV infection. Mejias and colleagues postulated that the severity of RSV infection is influenced by the local bacterial ecosystem (microbiome), which in turn modulates the host immune response. Children less than 2 years of age with mild (outpatient) and severe RSV infection (inpatient) were studied. Nasopharyngeal microbiota profiles were obtained by 16S-rRNA sequencing and, in parallel, whole-blood transcriptome profiles were using Illumina HT12-V4 beadchips. The investigators identified five nasopharyngeal microbiota clusters characterized by enrichment of either Haemophilus influenzae, Streptococcus, Corynebacterium, Moraxella or Staphylococcus aureus. RSV infection and hospitalization were positively associated with H. influenzae and Streptococcus and negatively associated with S. aureus abundance, independent of age. Children with RSV showed overexpression of IFN-related genes, independent of the microbiota cluster. In addition, transcriptome profiles of children with RSV infection and H. influenzae- and Streptococcus-dominated microbiota were characterized by greater overexpression of genes linked to Toll-like receptor signaling and neutrophil and macrophage activation

Comments

1. The severity of RSV infection may depend on viral load, host factors – microbiome, immune response and genetic background – and environmental factors such as LPS or airborne pollutants.
2. Severe RSV infection has also been linked to TLR4 genotype, environmental exposure to LPS and immune cell Th2 polarization (Cabellero MT, et al. J Clin Invest. 2015).

3. Childhood asthma due to rhinovirus has also been linked to a specific genotype (variations at the 17q21 locus; Caliskan M, et al. N Engl J Med. 2013).
4. It is unclear from this study whether RSV promotes the expansion of pathologic bacteria, whether the microbiome was abnormal before RSV infection, or whether the bacteria contribute to illness severity, though H. influenza and Streptococcus have also been associated with infant wheezing (above).

FACTORS DETERMINING THE SEVERITY OF VIRAL-INDUCED RESPIRATORY DISEASES: HOST RESPONSE

Nicholson EG, Schlegel C, Garofalo RP, Mehta R, Scheffler M, Mei M, Piedra PA. **Robust cytokine and chemokine response in nasopharyngeal secretions: Association with decreased severity in children with physician diagnosed bronchiolitis**. *J Infect Dis.* 2016;214:649-55.

Summary

Inflammatory chemokines play both beneficial and harmful roles in infectious diseases caused by viruses. Historically, murine and human studies suggested that an exaggerated immune response is responsible for RSV-associated lung injury. Nicholson and colleagues studied children <24 months old who presented to the emergency department with signs and symptoms of bronchiolitis. Nasal wash specimens were analyzed for viral pathogens and cytokine/chemokine concentrations. Results were evaluated with regard to disposition (hospitalization or non-hospitalization). A total of 111 children were enrolled. A viral pathogen was identified in 91.9% of patients (RSV in 51.4%, rhinovirus in 11.7%). Higher levels of IFN-γ, IL-4, IL-15, IL-17, IFN-γ-inducible protein 10 (IP-10/CXCL10) and eotaxin (CCL11) were significantly associated with a decreased risk of hospitalization. IFN-γ, IL-4, IL-17 and CXCL10 remained statistically significant in the multivariate analyses. The involvement of chemokines from a wide range of functional groups (T-helper 1 and 2, regulatory, and chemoattractant) suggests that a broadly overlapping cytokine/chemokine response is required for control of virus-mediated respiratory disease in young children.

Comments

1. Increases in respiratory tract cytokines and chemokines after viral infection are well-documented, but their beneficial or harmful roles may depend on the type of virus, underlying medical condition and other factors.
2. This study is consistent with the notion that treatment with systemic corticosteroids could increase the severity of RSV-induced airways disease by suppressing the immune response.
3. While the treatment of viral-induced asthma exacerbations with systemic corticosteroids is widely accepted, viral detection is associated with failure of symptom management (Ducharme FM, et al. Lancet Respir Med. 2016; 4:990-998).
4. Few studies examining the host response to "natural colds" have been performed, as most cases do not come to medical attention or are treated on an outpatient basis.

OTHER ARTICLES OF INTEREST

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Skjerven HO, Megremis S, Papadopoulos NG, Mowinckel P, Carlsen KH, Lødrup Carlsen KC; ORAACLE Study Group. **Virus Type and Genomic Load in Acute Bronchiolitis: Severity and Treatment Response With Inhaled Adrenaline**. *J Infect Dis*. 2016 Mar 15;213(6):915-21.

O'Grady KF, Grimwood K, Sloots TP, Whiley DM, Acworth JP, Phillips N, Goyal V, Chang AB. **Prevalence, co-detection and seasonal distribution of upper airway viruses and bacteria in children with acute respiratory illnesses with cough as a symptom**. *Clin Microbiol Infect*. 2016;22:527-34.

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Environments) Study Group. T**he Early Development of Wheeze. Environmental Determinants and Genetic Susceptibility at 17q21.** *Am J Respir Crit Care Med.* 2016;193:889-97.

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DISPARITIES AND RESPIRATORY HEALTH

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UNDERSTANDING HEALTH DISPARITIES AND ACHIEVING RESPIRATORY HEALTH EQUALITY

Celedon, JC. **Achieving Respiratory Health Equality: A United States Perspective.** *Switzerland: Humana Press.*2017. 10.1007/978-3-319-43447-6.

Summary

The American Thoracic Society's subcommittee on health equality has defined respiratory health disparities as significant differences in respiratory health that are closely linked to racial ancestry, social, economic, and/or environmental differences. Additionally, respiratory health equality has been defined as the attainment of the highest level of respiratory health for all people. Achieving health equality requires valuing everyone equally, implementing and maintaining focused societal efforts to address avoidable inequalities and historical and contemporary injustices, and eliminating health care disparities. Respiratory health disparities exist across all age groups and all populations and nowhere are they more evident than in children. While many of the factors that lead to disparities that affect children are modifiable, children are not in a position to make the changes needed. Environmental, behavioral, social, cultural, geographic, organizational and genetic factors coalesce to both produce disparities as well as worsen them. This book explores the meanings of race and ethnicity, social and economic positions, as well as environmental influences on disparities. Four diseases affecting the pediatric population are discussed: bronchopulmonary dysplasia, cystic fibrosis, asthma, and sickle cell disease.

Comments

1. Childhood poverty is a driving force behind health disparities in respiratory diseases in children and is a major risk factor for increased morbidity and poorer outcomes across the disease spectrum.
2. While children with cystic fibrosis in the United States have health care costs covered by either government-funded or commercial insurance thereby reducing the barrier to access to care, poor children have worse lung function, increased morbidity and mortality, and are less likely to receive lung transplantations.
3. Children living in low-resource countries exposed to environmental toxins from the burning of solid fuels such as wood for indoor cooking and heating have higher rates of respiratory illnesses such as pneumonia compared to children in high-resource countries.
4. Exposure to secondhand smoke has been decreasing among some populations of children in high-income countries due to limits and/or bans placed on tobacco advertising, public smoking, as well as higher taxes on cigarettes and regulations on the tobacco industry however in low and middle income countries, smoking and hence, secondhand smoke exposure in children are increasing at alarming levels.

IDENTIFYING AND REDUCING HEALTH DISPARITIES IN RESPIRATORY MEDICINE

Gerald LB, Berry C. **Health Disparities in Respiratory Medicine.** *New Jersey: Humana Press.* 2016. 10.1007/978-3-319-23675-9.

Summary

Children living in economically disadvantaged families, communities, and countries along with children from certain racial and ethnic groups are at increased risk for poor outcomes from respiratory illnesses. This recently published book explores both the conditions that create health disparities and the effect of disparities on a variety of pulmonary diseases. Disparity in environmental exposures including tobacco smoke and indoor and outdoor air quality play a major role in the respiratory outcomes of children. Medication adherence in the context of disparities is another important factor that requires increased attention and innovation so that outcomes will improve. Uneven distribution of modifiable risk factors for pulmonary disease, unequal access to care, and un-level quality of health care merge to produce disparities in prevalence, morbidity, and mortality from diseases affecting children such as asthma, sleep-related breathing disorders, and tuberculosis. This book makes the case that closing the disparity gap would not only improve and save the lives of patients and their families, but would also result in significant health care cost savings.

Comments

1. Understanding that while certain groups of children are at increased risk for disparities related to race, ethnicity, gender, socioeconomic status, and geographic location, there are some conditions such as air quality and pollution that that are not contained by geographic borders thereby having a global impact.
2. Poverty affects children's access to health care and decreases the likelihood that preventive measures

such as obtaining influenza vaccinations or screening, detecting, and providing early treatment for respiratory infections such as tuberculosis are taken.
3. There are numerous studies that provide the data showing that disparities in respiratory diseases exist and well researched solutions that target drivers of disparities such as tobacco use, indoor and outdoor air quality, improved nutrition, however more advocacy, innovation, and action are needed immediately to address disparities.

DISPARITIES IN EXPOSURE TO SECONDHAND TOBACCO SMOKE

Welkom JS, Riekert KA, Rand CS, Eakin MN. **Associations between caregiver health literacy and preschool children's secondhand smoke exposure.** *J Pediatr Psychol* 2016; 41:462-472.

Summary

Young children ages 3-11 years are at the greatest risk for secondhand smoke exposure. The source of the indoor smoke is primarily from living with at least one smoker. This study examines the association of health literacy among smoking and nonsmoking caregivers on smoking-related outcome expectancies, home smoking bans, salivary cotinine levels, and home air cotinine levels. The data were from a longitudinal randomized controlled trial of an intervention aimed at reducing child secondhand smoke exposure. Two hundred sixty eight families who were predominantly African American and low income were enrolled in the study (185 caregivers were smokers, 83 were nonsmokers). Most (52%) households had more than 1 smoker, however less than 25% reported having a home smoking ban. Caregiver smokers were significantly less likely to have a car smoking ban ($p<.001$). Their children had significantly higher salivary cotinine ($p=.001$) and home air nicotine levels ($p=.02$). Rates of low health literacy did not differ between the groups. Overall, lower caregiver health literacy was associated with lower smoking-related outcome expectancies. Significantly more caregivers with low health literacy were not convinced that smoke exposure was bad for people's health ($p<.05$), were more likely to affirm that it was not worth the hassle to make people smoke outside ($p<.05$) or that it is inconvenient for smokers in the home to smoke outside ($p<.01$), pollution in the neighborhood is worse for the child that exposure to smoke ($p<.01$) and there is no good proof that children get sicker easier if they are exposed to smoke ($p<.05$). Among those is the low health literacy group, child salivary cotinine were significantly higher ($p=.002$) as were home air nicotine levels ($p=.004$). When stratified by smoking status, health literacy predicted smoking-related outcome expectancies among caregiver smokers, but not nonsmokers. Caregiver health literacy was not associated with having a home or car smoking ban.

Comments

1. Tobacco use and secondhand smoke exposure pose major national and international health risks to children and according to the World Health Organization as many as 40% of children worldwide are exposed to indoor secondhand smoke.
2. While advances have been made over the past 20 years to reduce secondhand smoke exposures, children continue to be disproportionately affected. Secondhand smoke exposure can aggravate rhinitis, asthma, cystic fibrosis, and other chronic lung diseases.
3. Low literacy has been significantly associated with higher rates of smoking and smoking relapse among those of low socioeconomic status and lower educational achievement. Moreover, smokers with low health literacy are more likely to have less knowledge about smoking health risks.
4. Secondhand smoke exposure is a modifiable risk factor that could significantly improve children's health outcomes. Interventions and education for high risk populations will require that health care providers communicate clearly with patients about the health consequences of smoking.
5. Motivational interviewing and education utilizing plain language has been shown to reduce air nicotine levels, increase home smoking bans, and reduce caregiver smoking. Additionally, routine reporting of the child's smoke exposure and cotinine levels has been shown to reduce secondhand smoke exposure.

DISPARITIES IN SLEEP DURATION

Combs D, Goodwin JL, Quan SF, Morgan WJ, Parthasarathy S. **Longitudinal differences in sleep duration in Hispanic and Caucasian children.** *Sleep Medicine* 2016;18:61-66.

Summary

Chronic sleep loss among children is a major public health problem that can lead to adverse health, behavioral, and cognitive consequences. This study focuses on ethnic-related differences in parent-reported sleep duration. Data from 338 elementary school-aged Hispanic and non-Hispanic white children enrolled in the Tucson Children's Assessment of Sleep Apnea cohort were analyzed. Follow-up analysis was performed 5 years later. Baseline data showed Hispanic children slept significantly shorter than non-Hispanic white children on weeknights (9.5 hours vs. 10 hours, $p<.0001$) and the shortened duration was mainly accounted for by later bedtimes (9 pm vs. 8:30 pm, $p<.0001$). Five years later ($n=313$), the difference in sleep duration was not significantly different between Hispanic and non-Hispanic white children however delayed bedtime remained significant ($p=.013$).In this study, Hispanic children slept 20 minutes shorter per night than non-Hispanic white children as elementary age children however the difference was in sleep duration was no longer significant 5 years later.

Comments

1. Despite the known health and quality of life consequences of shortened sleep duration, data consistently show that children from minority and socioeconomically disadvantaged communities experience more sleep curtailment, sleep problems, and poor sleep hygiene.
2. Several factors have been associated with shortened sleep duration in minority children including television viewing, having a television in the room where the child sleeps, use of electronic devices at bedtime, later bedtimes, lack of a set bedtime, and caffeine use.
3. A study by Buckhalt et al in 2007 showed that when African American children's sleep was disrupted or shortened, they have lower cognitive performance than non-Hispanic white children. A similar effect has been seen in children from families of lower socioeconomic status. However when sleep was more optimal, minority and poor children performed similarly to non-Hispanic white children on cognitive measures.
4. Even though sleep duration decline for both groups of children during adolescence, because the Hispanic group had shorter sleep duration, they may be at increased risk for the health effects that may not manifest until adulthood.

DISPARITIES IN CYSTIC FIBROSIS (CF) MORTALITY

Buu MC, Sanders LM, Mayo JA, Milla CE, Wise PH. **Assessing differences in mortality rate and risk factors between Hispanic and non-Hispanic patients with Cystic Fibrosis in California.** *Chest* 2016; 149:380-389.

Summary

Disparity in mortality among patients of Hispanic ethnicity with CF continues to persist despite significant advances made in early diagnosis and treatment. This retrospective analysis from the California CF Foundation Patient Registry characterizes patterns of mortality and risk factors for lower survival among 485 Hispanic patients over the last 20 years compared with 1234 non-Hispanic patients. Hispanic ethnicity was self/parent -reported. Hispanic patients had 2.81 times the rate of death compared to non-Hispanic patients (95% CI, 1.70-4.63) after adjusting for year and age of diagnosis, insurance status, neighborhood median household income, bacterial infection, CF-related diabetes (CFRD) diagnosis, and CFTR genotype, all factors that are known to be associated with mortality in CF. Survival analysis showed Hispanic patients had a lower survival rate 18 years after diagnosis (75.9% vs. 91.5%, p<.0001). Lower neighborhood median income was independently associated with a higher death rate and a higher proportion of patients living in economically disadvantaged communities were of Hispanic ethnicity. At age 6 years, mean FEV1 was lower in Hispanic children (p<.0001). The incidence of CF related complications (age at first acquisition of Pseudomonas aeruginosa, Burkholderia cepacia, CFRD) occurred earlier in Hispanic patients. While Hispanic patients were more likely to have ever had public health insurance and to have had it longer, there was no significant difference in health care use (mean number of clinic visits at CF centers in a 12-month period) between the 2 groups. The data showed greater heterogeneity in CFTR alleles in Hispanic patients. Specifically, they had significantly more mutations that had not been classified by functional class and carriers of 2 CFTR alleles of unclassified disease risk had a higher rate of death (hazards ratio 2.61; 95% CI, 1.25-5.43).

Comments

1. Over the past 3 decades, there have been significant advances in the diagnosis and treatment of children with CF. Across North America, western Europe, and Australia where most of the 90,000 patients with CF live, there has also been an increase in median survival.
2. Poverty as a risk factor for disease severity and increased mortality in CF has been documented in prior studies. Patients with CF living in poorly resourced countries, economically disadvantaged neighborhoods, and poor families have significantly higher risk of death.
3. Patients of Hispanic ethnicity have numerous risk factors known to be associated with increased mortality in CF. Future studies should examine causes for lower lung function and earlier acquisition of P. aeruginosa, B. cepacia, and CFRD in Hispanic children as these may be important factors in understanding the increased mortality.
4. The finding that Hispanic patients have different genotype patterns (more CFTR alleles that are unclassified) compared with non-Hispanic patients and that unknown CFTR genotype is associated with increased mortality risk is an area for future investigation. Unclassified CFTR alleles in Hispanic children may place them at further disadvantage and widen the survival gap as new gene-mutation-directed therapies are developed.
5. A limitation of the study is that Hispanic ethnicity is a social construct in part based on shared language and cultural identity. Data from asthma studies show that patients who identify themselves as Hispanic have wide variation in prevalence and severity of disease. Future studies may benefit from specifying regions of origin for patients who identify themselves as Hispanic. In the age of personalized medicine and targeted interventions, this will be essential in closing the mortality gap in CF

DISPARITIES IN ASTHMA PREVALENCE, MORBIDITY AND CARE

Mitchell SJ, Bilderback AL, Okelo SO. **Racial disparities in asthma morbidity among pediatric patients seeking asthma specialist care.** *Academic Pediatrics* 2016;16:64-67.

Summary

African American children have significantly higher prevalence and morbidity from asthma compared to white children. However they are less likely to receive

subspecialist asthma care and as a result, the asthma morbidity gap persists. This secondary analysis of data from a pulmonary clinic registry from a single institution included 117 African American and 156 white children. The study assess 5 morbidity indicators: 1) caregiver-reported lifetime hospitalizations; 2) caregiver-reported intensive care unit (ICU) admissions or intubations; 3) forced expiratory volume in 1 second (FEV1); 4) ratio of FEV1 to forced vital capacity (FVC); and 5) asthma control, using the Pediatric Asthma Control and Communication Instrument (PACCI). African American children had a higher morbidity threshold before they initially presented for asthma subspecialty care. African American children had been hospitalized twice as often ($p<.001$) and had significantly more intensive care stays ($p<.001$) than white children presenting to the subspecialist. Although percent predicted FEV1 was significantly lower at initial presentation, FEV1/FVC ratio was not significantly different between the 2 groups. Asthma control was significantly worse ($p=.02$) in African American children. There was no significant effect of parental education on any of the above outcomes.

Comments

1. The finding that African American children have more poorly controlled or more severe asthma when they present for their initial visit for subspecialty care suggests under-recognition or underestimation of asthma severity by both clinicians who are responsible for making referrals and by caregivers who may not realize the severity of illness.
2. Since referrals or insurance coverage were not required to schedule appointments in the subspecialty clinic, the threshold for accessing asthma care was low suggesting that caregivers may not have known how to access subspecialty care for their children.
3. Measurement of lung function and regular use of asthma control questionnaires by primary care clinicians may prompt subspecialty referrals earlier in the course to reduce morbidity.

OTHER ARTICLES OF INTEREST

Celedon JC, Roman J, Schraufnagel DE, Thomas A, Samet J. **Respiratory health equality in the United States: the American Thoracic Society perspective.** *Ann Amer Thorac Soc 2014;11:473-479.*

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ENVIRONMENTAL EXPOSURES AND RESPIRATORY HEALTH

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ASTHMA AND ALLERGIES AMONG AMISH AND HUTTERITE CHILDREN

Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, Ledford JG, Marques dos Santos M, Anderson RL, Metwali N, Neilson JW, Maier RM, Gilbert JA, Holbreich M, Thorne PS, Martinez FD, von Mutius E, Vercelli D, Ober C, Sperling AI. **Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children.** *N Engl J Med.* 2016 Aug 4;375(5):411-21.

Summary

The Amish and Hutterites are U.S. agricultural populations whose lifestyles are remarkably similar but whose farming practices differ; the Amish follow traditional farming practices whereas the Hutterites use industrialized farming practices.

Despite the similar genetic ancestries and lifestyles of Amish and Hutterite children, the prevalence of asthma and allergic sensitization was 4 and 6 times as low in the Amish, whereas median endotoxin levels in Amish house dust was 6.8 times as high. Differences in microbial composition were also observed in dust samples from Amish and Hutterite homes. Profound differences in the proportions, phenotypes, and functions of innate immune cells were found between groups. In a mouse model of experimental allergic asthma, the intranasal instillation of dust extracts from Amish but not Hutterite homes significantly inhibited airway hyperresponsiveness and eosinophilia. These protective effects were abrogated in mice that were deficient in MyD88 and Trif, molecules that are critical in innate immune signaling.

The results of these studies in humans and mice indicate that the Amish environment provides strong protection against asthma by engaging and shaping the innate immune response.

Comments

1. The rate of asthma and allergic sensitization in the Amish is among the lowest observed in epidemiological studies.
2. The strength of this study is the translation and replication of the epidemiological observations into experimental mouse studies.
3. The weakness of this study is the lack of more in-depth characterization of the environmental exposure.
4. Although numerous differences in immune responses were observed in Amish and Hutterite children, the likely primary mechanism may relate to engaging innate immunity.

SUSTAINED EFFECT OF EARLY LIFE FARM EXPOSURE INTO ADULTHOOD

House JS, Wyss AB, Hoppin JA, Richards M, Long S, Umbach DM, Henneberger PK, Beane Freeman LE, Sandler DP, Long O'Connell E, Barker-Cummings C, London SJ. **Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study.** *J Allergy Clin Immunol* 2016;

Summary

Previous studies suggest that early-life farming exposures protect against childhood asthma and allergy; few data exist on asthma and allergy in adults. Data from 1746 farmers and 1555 spouses (mean age, 63) from a case-control study nested within the Agricultural Health Study in Iowa or North Carolina was used. Current asthma and early-life farming exposures were assessed via questionnaires. We defined atopy based on specific IgE > 0.70 IU/mL to at least 1 of 10 allergens measured in blood. We used logistic regression, adjusted for age, sex, race, state, and smoking (pack years), to estimate associations between early-life exposures and asthma (1198 cases and 2031 non-cases) or atopy (578 cases and 2526 non-cases).

Exposure to the farming environment in utero and in early childhood had little or no association with asthma but was associated with reduced odds of atopy. The strongest association was seen for having a mother who performed farm activities while pregnant (odds ratio, 0.60; 95% CI, 0.48-0.74) and remained significant in models with correlated early-life exposures including early childhood farm animal contact and raw milk consumption.

Comments

1. This is a very large cross-sectional survey in rural areas of the U.S.
2. Many early life exposures may be cross-correlated so the exact important timing (pregnancy versus early postnatal period) may be hard to disentangle.
3. The data strongly suggest that the protective effect is sustained into adult life.

THE ROLE OF HOUSEHOLD CLEANING IN RHINITIS DEVELOPMENT

Liu X, Lao XQ, Won CC-Y, Tan L, Zilong Zhan Z, Wong TW, Tse L, Lau APS, Yu ITS. **Frequent use of household cleaning products is associated with rhinitis in Chinese children.** *J Allergy Clin Immunol* 2016;138:754-60.

Summary
Despite the popular use of household cleaning products worldwide, there is no published study investigating the health effects of these products on rhinitis in children.

A total of 2299 children were recruited from 21 primary schools with wide geographic coverage in Hong Kong. Self-administered questionnaires were completed by parents/guardians to collect detailed information on respiratory symptoms and household use of 14 types of chemical cleaning products, as well as clean water. Students were categorized into 4 mutually exclusive rhinitis patterns (never, occasional, frequent, and persistent). The total chemical burden (TCB) score was used as the exposure indicator by calculating the total time of exposure to the 14 cleaning products. Multinomial logistic regression was used to assess the relationship between rhinitis patterns and the use of household cleaning products.

Compared with the children within the lowest tertile of TCB scores, the adjusted ORs of occasional, frequent, and persistent rhinitis in children within the highest tertile were 1.29 (95% CI, 1.01-1.65), 1.97 (95% CI, 1.40-2.76), and 1.67 (95% CI, 1.10-2.54), respectively. No single product, but rather the sum of cleaning products used was responsible for the effect. After stratification into atopic and non-atopic rhinitis the effect was restricted to non-atopic rhinitis.

Comments
1. This study is a large well-conducted survey among Hong Kong adolescents.
2. The limitation of the study is its cross sectional nature thereby limiting causal inferences.
3. Reverse causation – cleaning because of frequent rhinitis – is therefore a potential explanation.

PREVENTION OF CHILDHOOD WHEEZE AND ASTHMA BY MATERNAL FISH OIL CONSUMPTION IN PREGNANCY

Bisgaard H, Stokholm J, Chawes BL, Vissing, Bjarnadóttir E, Schoos A-MM, Wolsk HM, Pedersen TM, Vinding RK, Thorsteinsdóttir S, M.D., Følsgaard NV, Fink NR, Thorsen J, Pedersen AG, Waage J, Rasmussen MA, Stark KD, Olsen SF, Bønnelykke K. **Fish Oil–Derived Fatty Acids in Pregnancy and Wheeze and Asthma in Offspring.** *N Engl J Med* 2016;375: 2530-9.

Summary
Reduced intake of n–3 long-chain polyunsaturated fatty acids (LCPUFAs) has been reported to play a role in the increasing prevalence of wheezing disorders.

Pregnant women were randomly assigned at 24 weeks of gestation to receive 2.4 g of n–3 LCPUFA (fish oil) or placebo (olive oil) per day. Their children were followed prospectively with extensive clinical phenotyping. Group assignments were blinded during follow-up for the first 3 years of the children's lives, after which there was a 2-year follow-up period during which only the investigators were unaware of group assignments.

The risk of persistent wheeze or asthma in the treatment group was 16.9%, versus 23.7% in the control group (P = 0.035), corresponding to a relative reduction of 30.7%. The effect was strongest in the children of women whose blood levels of eicosapentaenoic acid and docosahexaenoic acid were in the lowest third of the trial population at randomization: 17.5% versus 34.1% (P = 0.011). Supplementation with n–3 LCPUFA was also associated with a reduced risk of infections of the lower respiratory tract (31.7% vs. 39.1%; P = 0.033), but there was no statistically significant relation between supplementation and asthma exacerbations, eczema, or allergic sensitization.

Comments
1. Many epidemiological observations had suggested that LCPUFAs may play a role in asthma protection.
2. This well powered study adds evidence when administered prenatally.
3. The lack of effect on allergic sensitization may suggest that protection may be mediated by reduction of risk of lower respiratory tract infections.

SUSTAINED EFFECT OF FISH-OIL SUPPLEMENTATION IN PREGNANCY ON ASTHMA MEDICATION USE AND ATOPY

Hansen S, Strøm M, Maslova E, Dahl R, Hoffmann HJ, Rytter D, Bech BH, Henriksen TB, Granstr€omC, Halldorsson TI, Chavarro JE, Linneberg A, Olsen SF. **Fish oil supplementation during pregnancy and allergic respiratory disease in the adult offspring.** *J Allergy Clin Immunol* 2017;139:104-11

Summary
There is limited knowledge of the long-term programming effects of maternal supplementation with long-chain n-3 polyunsaturated fatty acids. In a randomized controlled trial from 1990 with 24 years of follow-up, the aim was to determine whether supplementation with 2.7 g of long-chain n-3 polyunsaturated fatty acids in pregnancy can reduce the risk of asthma in offspring.

A total of 533 women were randomly assigned to receive fish oil during the third trimester of pregnancy, olive oil, or no oil in the ratio 2:1:1. The offspring were followed in a mandatory national prescription register, with complete follow-up for prescriptions related to the treatment of asthma and allergic rhinitis. The offspring were also invited to complete a questionnaire (74% participated) and attend a clinical examination (47% participated) at age 18 to 19 years.

In intention-to-treat analyses the probability of having had asthma medication prescribed was significantly reduced in the fish oil group compared with the olive oil group (hazard

ratio, 0.54, 95% CI, 0.32-0.90; P=0.02). No associations were detected with respect to lung function outcomes or allergic sensitization at 18 to 19 years of age.

Comments

1. The loss to follow up over all the years is remarkably small.
2. The effect of fish oil seems sustained but no information was collected about post-study eating behavior.
3. The follow up was not unblended for participants.
4. Objective parameters such as lung function were not affected.

THE PROMISE AND CHALLENGE OF PRECISION MEDICINE IN CF AND BEYOND

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PREDICTING INDIVIDUAL RESPONSE TO CFTR RESTORATIVE THERAPIES USING INTESTINAL ORGANOIDS

Dekkers JF, Berkers G, Kruisselbrink E, Vonk A, de Jonge HR, Janssens HM, Bronsveld I, van de Graaf EA, Nieuwenhuis EE, Houwen RH, Vleggaar FP, Escher JC, de Rijke YB, Majoor CJ, Heijerman HG, de Winter-de Groot KM, Clevers H, van der Ent CK, Beekman JM. **Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis.** *Science Translational Medicine* 2016; 8 (344): 344ra84

Summary

The authors used intestinal organoid cultures derived from rectal biopsies from 71 patients with 28 different CFTR genotypes and healthy controls to study residual CFTR function and drug-modulated CFTR function in response to ivacaftor and lumacaftor. They found that the steady-state lumen area (SLA) differed between organoids derived from CF patients and healthy controls, and that forskolin-induced swelling (FIS) rates can be compared among CF rectal organoids but not between CF and healthy control organoids. They were able to demonstrate pharmacologic correction of CFTR function using the FIS assay in CF organoids and generate genotype-specific profiles. They found wide variability in CFTR function and response to modulators between organoids with the same CFTR mutations, suggesting that residual function and response to therapy are dependent on both the CF-causing mutation and additional subject-specific gene modifiers

Comments

1. Rectal organoid cultures are three-dimensional primary stem cell cultures that self-organize into tissue-recapitulating "mini-guts" in vitro, enabling long-term expansion and biobanking of primary patient tissue.
2. Rectal biopsies are a 10 to 15 minute procedure associated with minimal discomfort; freshly-isolated samples can be shipped for growth of organoids provided that the sample arrives in several days.
3. CFTR function can be precisely measured by stimulating intestinal organoids with forskolin, causing rapid fluid secretion into the lumen and organoid swelling in a CFTR-dependent fashion.

MONITORING INDIVIDUAL RESPONSE TO CFTR RESTORATIVE THERAPIES: THE EXAMPLE OF AMBULATORY SWEAT CHLORIDE SENSING

Choi DH, Kim JS, Cutting GR, Searson PC. **Wearable Potentiometric Chloride Sweat Sensor: The Critical Role of the Salt Bridge.** *Anal Chem.* 2016 Dec 20;88(24):12241-12247.

Summary

In the era of personalized medicine, home monitoring of pharmacodynamics (e.g., sweat chloride), efficacy (e.g., lung function, weight, quality of life) and adverse effects is of growing importance. Choi and colleagues report the development and initial feasibility testing of a wearable potentiometric sweat chloride sensor that provides accurate measurements over an extended period of time (>24 h). The device uses two silver chloride electrodes connected by a salt bridge. They demonstrate in three healthy volunteers that the device accurately measured sweat chloride concentrations during exercise over a one hour period.

Comments

1. The investigators report the results of a proof-of-concept study that sweat chloride can be measured accurately using a wearable device. As sweat chloride concentrations are the primary biomarker of pharmacodynamics of CFTR potentiators and correctors, such a device could play a critical role in monitoring response to therapy, particularly for N-of-1 trials.
2. The emerging field of wearable sensors and mobile health devices for home monitoring of key endpoints such as oxygen saturation, spirometry, respiratory rate, cough frequency and health related quality of life indicators will enable persons with CF to better monitor their own health and response to treatment, allowing increased personalization of care

THE PROMISE OF GENE EDITING AS A CFTR RESTORATIVE THERAPY

Slaymaker IM, Gao L, Zetsche B, Scott DA, Yan WX, Zhang F. **Rationally engineered Cas9 nucleases with improved specificity.** *Science.* 2016 Jan 1;351(6268):84-8.

Summary

The RNA-guided endonuclease Cas9 is a versatile genome-editing tool with a broad range of applications from therapeutics to functional annotation of genes. Cas9 creates double-strand breaks at targeted genomic loci

complementary to a short RNA guide. However, Cas9 can cleave off-target sites that are not fully complementary to the guide, which poses a major challenge for genome editing. In this report, the authors use structure-guided protein engineering to improve the specificity of Streptococcus pyogenes Cas9 (SpCas9). They demonstrate that "enhanced specificity" SpCas9 variants reduce off-target effects and maintain robust on-target cleavage.

Comments

1. Gene editing exploits the ability of cellular DNA repair pathways to use donor DNA molecules as a template to precisely alter the genomic DNA sequence.
2. The RNA-guided DNA-specific nuclease CRISPR/Cas 9 editing system could potentially be used for gene-edited cell-based therapy or potentially even for in vivo direct gene editing in the lung; however, many obstacles must be overcome.
3. CRISPR/Cas 9 relies on DNA repair pathways that are most active in dividing cells so will not work well in the terminally differentiated respiratory epithelial cells. Airway progenitor cells, which would be a more attractive target, lie beneath the respiratory epithelial cells and therefore are difficult to target with available vectors.

PERSONALIZING CHRONIC ANTIBIOTIC THERAPY: LOOKING OUT FOR POTENTIAL NEGATIVE INTERACTIONS

Nichols DP, Happoldt CL, Bratcher PE, Caceres SM, Chmiel JF, Malcolm KC, Saavedra MT, Saiman L, Taylor-Cousar JL, Nick JA. **Impact of azithromycin of the clinical and antimicrobial effectiveness of tobramycin in the treatment of cystic fibrosis.** *Journal of Cystic Fibrosis 2016*; pii: S1569-1993(16)30672-5.

Summary

In addition to developing personalized approaches to CFTR restorative therapies, ideally our chronic maintenance therapies such as antibiotics would also be individually tailored, based on pharmacogenomics or safety profiles. This manuscript raises concerns for a potential antagonistic interaction between oral azithromycin and inhaled tobramycin, which are used concomitantly in about half of U.S. CF patients. The authors performed post-hoc analysis of data from a clinical trial in which subjects received 4 weeks of inhaled tobramycin followed by 4 weeks of inhaled aztreonam. In patients reporting concomitant use of azithromycin, the response to inhaled tobramycin was much poorer than that to inhaled aztreonam; this differential effect was not observed in those not reporting concomitant azithromycin use. Informed by this observation, bacterial killing was assessed in vitro using 30 P. aeruginosa clinical isolates. Antimicrobial activity was selectively reduced when azithromycin was added to tobramycin but had either no effect or improved killing when added to other antibiotics. Azithromycin, particularly when combined with tobramycin, greatly increased gene expression of a Pseudomonas efflux pump, MexXY, which is a central mechanism of inducible aminoglycoside resistance.

Comments

1. These results suggest that azithromycin may antagonize the antimicrobial effect of tobramycin through increased gene expression of the Pseudomonas efflux pump MexXY.
2. However, there are clear limitations to retrospective review of clinical trial data, including limited characterization of subjects, small numbers in the defined subgroups and unequal prior exposure to inhaled tobramycin vs. inhaled aztreonam.
3. Thus, these investigators have initiated a prospective clinical trial to directly evaluate the possible antagonistic effect of oral azithromycin on inhaled tobramycin (NCT02677701).

THE IMPORTANCE OF MENTAL HEALTH IN PERSONALIZED APPROACHES TO CARE

Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck L, Smith B, Hempstead SE, Marshall B, Sabadosa KA, Elborn S; International Committee on Mental Health; EPOS Trial Study Group. I**nternational Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety.** *Thorax* 2016; 71(1):26-34

Summary

When personalizing CF therapies, evaluating and treating mental health must be an integral component. The prevalence of depression and anxiety are 2 to 3 times higher in CF patients and their parents than in community samples. For example, in the recent TIDES study in 6088 CF patients and 4102 parents from 9 countries, the prevalence of elevated symptoms of depression was 10% in adolescents, 19% in adults, 37% in mothers and 31% in fathers. Furthermore psychological symptoms in both patients and parents have been associated with decreased lung function, poorer nutritional status, worse adherence, worse health-related quality of life, more frequent hospitalizations and increased health care costs. This manuscript reports consensus recommendations for screening and treating depression and anxiety from the International Committee on Mental Health in CF, sponsored by the CF Foundation and the European CF Society. A multidisciplinary panel including health care providers and stakeholders from the CF community performed a systematic literature review and developed 15 guideline recommendations.

Comments

1. The committee recommended annual screening for depression and anxiety in patients 12 years and above using two validated screening tools.
2. When elevated levels of symptoms are detected, clinical diagnostic procedures should be implemented, followed

by evidence based psychological and/or pharmacological interventions, if needed.

3. These guidelines represent a major advance in highlighting the importance of screening for and treating psychological distress in CF patients and parents.
4. Offering individual treatment based on mental health screening has the opportunity to markedly

OTHER ARTICLES OF INTEREST

Alton EW, Boyd AC, Davies JC, Gill DR, Griesenbach U, Harrison PT, Henig N, Higgins T, Hyde SC, Innes JA, Korman MS. **Genetic medicines for CF: Hype versus reality.** *Pediatric Pulmonology* 2016; 51(S44):S5-S17

Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, Yamashita M, Rigo F, Hung G, Schneider E, Norris DA, Xia S, Bennett CF, Bishop KM. **Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study.** *Lancet* 2016; 388(10063):3017-3026

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Beekman JM. **Individualized medicine using intestinal responses to CFTR potentiators and correctors.** *Pediatric Pulmonology* 2016; 51(S44):S23-S34

NOTES

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