ATS 2020 | Virtual

Pediatric Year in Review

Bibliography

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BPD DIAGNOSIS AND PHENOTYPING


Summary
This study used a cohort of preterm infant with severe BPD to assess the frequency of three disease components: moderate-severe parenchymal disease, pulmonary hypertension (PH), or large airway disease. Inclusion criteria included infants with severe BPD who underwent both chest computed tomography with angiography (CTA) and echocardiography between 40 and 50 weeks PMA. The association was assessed between each component and a primary composite outcome that included death before hospital discharge, tracheostomy, or home pulmonary vasodilator therapy. Moderate-severe parenchymal lung disease was defined as an Ochiai score ≥8 on CTA. PH was diagnosed by echocardiogram using standard criteria. Large airway disease was defined as tracheomalacia or bronchomalacia on bronchoscopy and/or tracheoscopy or CTA. Of 76 evaluated infants, 73 (96%) were classifiable into phenotypic subgroups: 57 with moderate-severe parenchymal disease, 48 with PH, and 44 with large airway disease. The presence of all three disease components was most common (n = 23). Individually, PH and large airway disease, but not moderate-severe parenchymal disease, were associated with increased risk for the primary study outcome. Having more disease components was associated with an incremental increase in the risk for the primary outcome (2 vs. 1: odds ratio, 4.9; 95% confidence interval, 1.4-17.2 and 3 vs. 1: odds ratio, 12.8; 95% confidence interval, 2.4-70.0).

Comments
1. BPD is a heterogenous condition with poorly characterized disease subgroups.
2. Although characterization of BPD severity according to the level of respiratory support administered to very preterm infants at 36 weeks PMA provides important prognostic information, these standard diagnostic criteria do not distinguish between the possible causes of an infant’s respiratory support requirements.
3. Infants with severe BPD are variable in their predominant pathophysiology and can be classified into phenotypic subgroups based on the relative contribution of parenchymal, vascular, and large airway disease.
4. Disease phenotyping may enable better risk stratification and targeted therapeutic intervention.
5. The pediatric pulmonologist has a role in the NICU with imaging, PH management, and airway evaluation.

BPD IMAGING


Summary
This study utilizes respiratory-gated, ultrashort echo time MRI to test the hypothesis that cystic regions of the lung will exhibit a quantifiable tidal volume (TV) that will correlate with ventilator settings and clinical outcomes. MRI of 17 non-sedated, quiet-breathing, severe BPD infants were reconstructed into end-inspiration and end-expiration images. Cysts were identified and measured using density threshold combined with manual identification and segmentation. Regional TVs were calculated by subtracting end-expiration from end-inspiration volumes in total lung, non-cystic lung, total-cystic lung, and individual large-cysts. Cystic lung areas averaged larger TVs than non-cystic lung when normalized by volume (0.8 ml TV/ml lung vs 0.1 ml TV/ml lung, p<0.002). Cyst TV correlates with cyst size (p=0.012 for total lung cyst and p<0.002 for large cysts), although there was variability between individual cysts TV with 22% of cysts demonstrating negative TV. Peak Inspiratory Pressure positively correlated with total lung TV (p =0.027) and non-cystic TV (p=0.015), but not total lung cysts TV (p=0.8). Inspiratory time and respiratory rate did not improve TV of any analyzed lung region.

Comments
1. BPD is a heterogeneous lung disease characterized by regions of simplified alveoli (cysts), fibrosis, and emphysema.
2. Our understanding of the heterogeneous nature of severe BPD lung disease has been limited by the lack of objective analysis of the regional lung structure, as methods for evaluating lung function capture whole lung rather than specific regions of interest.
3. Cystic regions of the lung are not merely trapped air and have greater normalized tidal volume when compared to non-cystic lung.
4. Ventilator pressure increases non-cystic lung tidal volume, but inspiratory time and respiratory rate do not correlate with tidal volume of normal or cystic lung.
5. The ability to obtain imaging that corresponds to differences in regional ventilation in intubated neonates has the potential to provide precision medicine to infants with BPD.

BPD MANAGEMENT: HOME OXYGEN THERAPY


Summary
The Recorded Home Oximetry (RHO) Trial sought to determine if a home oxygen therapy (HOT) management strategy that includes analysis of RHO data, compared with standard monthly clinic visit assessments, reduces duration of HOT without harm in premature infants. This unmasked randomized clinical trial was conducted in 9 US medical centers from November 2013 to December 2017, with follow-up to February 2019. The intervention was an analysis of transmitted RHO between clinic visits (n = 97); the standard-care group received monthly clinic visits with in-clinic weaning attempts (n = 99). The primary outcomes were the duration of HOT and parent-reported quality of life. There were 2 prespecified secondary safety outcomes: change in weight and adverse events within 6 months of HOT discontinuation. In the RHO group, the mean time to discontinue HOT was 78.1 days (SE: 6.4), compared with 100.1 days (SE: 8.0) in the standard-care group (P = .03). The quality-of-life scores improved from baseline to 3 months after discontinuation of HOT in both groups (P = .002), but the degree of improvement did not differ significantly between groups (P = .75).

Comments
1. BPD Guidelines recommend home oxygen therapy for chronic hypoxemia to facilitate NICU discharge, but its use is highly variable.
2. The RHO Trial is the first randomized clinical trial to compare oxygen weaning strategies in infants on home oxygen.
3. Use of home oxygen data can decrease duration of home oxygen compared with routine assessments alone.
4. An important safety concern addressed in this study is that RHO infants were able to maintain weight while being weaned and were able to grow appropriately and significantly better than standard-care infants.
5. A critical knowledge gap not addressed in the RHO Trial is the risks and benefits of supplemental home oxygen for infants with BPD.

BPD MANAGEMENT: RSV IMMUNOPROPHYLAXIS


Summary
This study assessed the severity of RSV-acute lower respiratory tract infection (ALRI) in children less than 5 years old with BPD. A systematic review of standard databases identified 29 studies of RSV-ALRI in children that compared morbidity and mortality in children with BPD compared with those without (non-BPD). Risks were higher among children with BPD compared with non-BPD: RSV hospitalization (odds ratio [OR], 2.6; 95% confidence interval [CI], 1.7-4.2; P < .001), ICU admission (OR, 2.9; 95% CI, 2.3-3.5; P < .001), need for oxygen supplementation (OR, 4.2; 95% CI, .5-33.7; P = .175) and mechanical ventilation (OR, 8.2; 95% CI, 7.6-8.9; P < .001), and hospital case fatality rate (OR, 12.8; 95% CI, 9.4-17.3; P < .001). Median LOS (range) was 7.2 days (4-23) (BPD) compared with 2.5 days (1-30) (non-BPD). Median duration of oxygen supplementation (range) was 5.5 days (0-21) (BPD) compared with 2.0 days (0-26) (non-BPD). The duration of mechanical ventilation was more often longer (>6 days) in those with BPD compared with non-BPD (OR, 11.9; 95% CI, 1.4-100; P = .02).

Comments
1. RSV is among the most important causes of acute lower respiratory tract infection (ALRI) in young children.
2. The risk of severe RSV disease is considerably higher among children with BPD.
3. There is an urgent need to establish standardized BPD case definitions, review the RSV prophylaxis guidelines, and encourage more specific studies on RSV infection in BPD patients, including vaccine development and RSV-specific treatment.
4. The cost limitation of RSV immunoprophylaxis may more seriously affect low-income countries, where RSV disease incidence is reported to be higher compared with higher income countries.
BPD MANAGEMENT: ENVIRONMENTAL CONCERNS


Summary
Little is known regarding environmental factors that can impact outcomes in BPD. A total of 784 subjects were included from the Johns Hopkins BPD clinic. In order to assess the role of traffic-related air pollution (TRAP) on respiratory outcomes in BPD, caregivers completed questionnaires on environmental exposures and respiratory outcomes. Distance to the nearest major roadway was derived from subjects’ geocoded residential addresses. Approximately half of the subjects (53.8%) lived within 500 m of a major roadway. Subjects who lived within 500 m of a major roadway were more likely to be non-white (P = .006), have a lower estimated household income (P < .001) and live in more densely populated zip codes (P < .001) than those who lived further than 500 m away. For every 1 km increase in distance between residence and roadway, the likelihood of activity limitations decreased by 35% (P = .005). No differences in acute care use were seen with proximity to major roadways. Proximity to a major roadway was associated with chronic respiratory symptoms, such as activity limitations (eg, dyspnea), and tended to be associated with nighttime symptoms as well. Self-reported minorities and families with lower estimated household incomes may be more likely to be exposed to TRAP.

Comments
1. Given the burden that BPD and other respiratory complications of preterm birth impose on patients, their families, and society, it is important to identify modifiable factors that impact outcomes.
2. Traffic-related air pollution (TRAP), which includes both particulate matter and gaseous air pollutants is associated with wheezing and respiratory tract infections during infancy and early childhood, decreased lung function, and the development of asthma.
3. Proposed mechanisms by which particulate matter adversely affects the pulmonary system include oxidative stress, impaired respiratory tract defense mechanisms, and altered lung function leading to injury, inflammation, and infection.
4. The results of this study may not be restricted to U.S.-based populations since the World Health Organization reports that traffic-related air pollution accounts for 12% to 70% of air pollution, with low- and middle-income countries experiencing this disproportionately due to old or inefficient vehicles and lack of public transportation services.
5. Further research is necessary to define the effects of TRAP versus other sources of indoor and outdoor air pollution as well as to determine the best ways of combatting pollution-related respiratory morbidities.

OTHER ARTICLES OF INTEREST

BPD DIAGNOSIS AND PHENOTYPING


BPD GUIDELINES


BPD MANAGEMENT: HOME OXYGEN THERAPY


BPD MANAGEMENT: RSV IMMUNOPROPHYLAXIS


BPD MANAGEMENT: ENVIRONMENTAL CONCERNS


BPD HEALTH-CARE DISPARITIES

CHILDHOOD HEALTH CONSEQUENCES OF ELECTRONIC CIGARETTES

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AGE OF TOBACCO PRODUCT INITIATION AS SUSCEPTIBILITY FACTOR FOR NICOTINE DEPENDENCE


Summary
With tobacco product use, distinct transition points describe the evolution from experimentation to over nicotine addiction. In pediatric populations, there is an accelerated transition from initiation of use to nicotine dependence. This study uses the New York Tobacco Survey cohort of 19,580 youth to examine whether initiation of tobacco product use (specifically cigarettes, electronic cigarettes, cigars, smokeless tobacco, hookahs) at age < 13 years is associated with greater daily use and nicotine dependence than initiation at >13 years. Analysis showed that young age of initiation, for all tobacco products studied, significantly associated with both daily use and ever use over past 30 days. Data also showed that young age of initiation associated with nicotine cravings and, except for e-cigarettes, short time to product use in the morning.

Comments
1. Tobacco product initiation at age 13 years or younger is associated with greater current use and increased nicotine dependence.
2. Up to three-quarters of youth ever users of e-cigarettes, cigars, smokeless tobacco and hookahs initiated at <16 years of age.
3. Clear physiologic differences in risk of nicotine dependence exist between early and late adolescence. Approaches to prevention and treatment may need to be customized.

EVALI IN PEDIATRIC POPULATIONS


Summary
Between the summer and fall of 2019 in the United States, more than 2000 cases of acute lung injury associated with e-cigarette use were described and termed EVALI (e-cigarette or vaping associated lung injury). Ultimately, the vast majority of the cases were ascribed to the use of the additive vitamin E acetate in illicitly or informally obtained vaping solutions. Since affected patients were disproportionately teenagers or young adults, the authors used database of CDC-reported cases to examine whether adolescent EVALI (13-17 years of age) differed from either young adult EVALI (18-24 years of age) or adult EVALI (25-49 years of age). They examined adjusted prevalence ratios for demographics, substance use and clinical characteristics. Combustible cigarette use and daily THC use were underrepresented in adolescent EVALI compared with both adult cohorts. However, any nicotine use and use of e-cigarette solutions containing THC and nicotine were overrepresented in adolescent EVALI compared to adult, but not young adult, EVALI. Adolescent EVALI patients were significantly more likely to obtain their nicotine and THC solutions from informal sources. ADHD was overrepresented in adolescent EVALI patients. History of asthma and gastrointestinal symptoms at EVALI presentation were both overrepresented in adolescent EVALI compared to adult EVALI patients.

Comments
1. Compared with adults and age proportions in general population, adolescents and young adults disproportionately develop EVALI. Diagnosis is underrepresented among NHW adolescents.
2. Adolescents with EVALI more frequently report obtaining vaping products and solutions from “informal sources”.
3. Compared with adults, adolescents with EVALI more frequently have a history of asthma and mental, emotional or behavioral health disorders. They also more frequently develop gastrointestinal symptoms possibly reflecting vaping topography.

YOUTH TRANSITIONS FROM E-CIGARETTE TO COMBUSTIBLE TOBACCO USE

Summary
The MMWR Report in 2018 showed a dramatic escalation in youth e-cigarette use from 1.5% in 2011 to 20.8% in 2018. Coupled to this increase was the emerging evidence in observational studies and meta-analyses that e-cigarette users had increased odds of subsequent combustible cigarette initiation. The 2018 National Academy of Sciences Report asserted substantial evidence that e-cigarette use increased the risk of ever-using combustible cigarettes in both youth and adults. The authors used the Population Assessment of Tobacco and Health (PATH) Study cohort to examine this association. The study was restricted to 6123 youths 12-15 years of age who were tobacco naïve at the Wave 1 of the study. The primary outcome was ever-use and current-use at wave 3 and whether the risk propensity score mediated this association. Both prior e-cigarette use and prior tobacco product use significantly associated with subsequent ever use and current use of combustible cigarettes. Youth with a high risk propensity score showed a positive association between prior e-cigarette use and prior other tobacco product use and use of combustible cigarettes. Surprisingly, youth with a low risk propensity score showed an even stronger association between e-cigarette use and ever or current use of combustible cigarettes.

Comments
1. Using e-cigarettes as one’s first tobacco product increases the odds of future cigarette use over 2 yr followup. The odds are greater than first use of all other tobacco products combined.
2. The odds of e-cigarette associated subsequent cigarette use are surprisingly higher in youth with low risk propensity scores than youth with high risk propensity scores. Propensity for risk-taking behaviors may not be a strong contributor to the association of e-cigarette use with combustible cigarette uptake in youth.
3. Future studies should focus on the unique aspects of e-cigarette initiation that contribute to polytobacco use.

E-CIGARETTES AND SUBSEQUENT POLYSUBSTANCE USE

Summary
Co-occurrence of e-cigarette use and alcohol, tobacco and opioid use is well-established, especially in youth and young adults. Adolescents who smoke are 8 times more likely to use illicit drugs and 11 times more likely to drink alcohol. These associations are stronger in children than in adults. Additionally, a high persistence of cigarette smoking is observed even after successful treatment of other substance use. In this study, the authors explored the use of e-cigarette trajectories as a predictor of subsequent alcohol and marijuana use patterns among youth. The authors conducted an on-line observational study of 801 adolescents (13-15 yo) over a 2-year period. Their primary outcome was a latent growth analysis of developmental courses of e-cigarette use, alcohol abuse (drinking to intoxication) and marijuana use. Three patterns of early e-cigarette use were explored: high and increasing, low and increasing and never. Results showed that both high and increasing and low and increasing e-cigarette use associated with an increasing trajectory of subsequent alcohol abuse and marijuana use. Household income was negatively associated with increasing marijuana use trajectory in this cohort.

Comments
1. Increasing e-cigarette use trajectory, even with low initial use, associates with later alcohol abuse and marijuana use.
2. Low e-cigarette use in early adolescence may be a risk marker for subsequent polysubstance abuse.
3. Future studies should explore differences between concurrent and prospective polysubstance use among adolescents who use e-cigarettes and the factors that contribute to increasing e-cigarette use during adolescence.

TREATMENT FOR PEDIATRIC NICOTINE DEPENDENCE

Summary
Despite escalating use of e-cigarettes among youth and the tethered increased prevalence of high nicotine dependence, no studies of nicotine dependence interventions have been conducted in pediatric or adult populations of e-cigarette users. Limited and methodologically flawed studies exploring tobacco dependence interventions in youth smokers have not shown convincing efficacy evidence with either nicotine replacement therapies or with bupropion. This study was a two-group, single center randomized placebo-controlled double-blind trial of varenicline in treatment-seeking adolescent or young adult smokers aged 14-21 years of age. The study involved a 12-week treatment course with brief initial counseling. The primary efficacy outcome was biochemically-confirmed 7 day abstinence using two methods and a safety assessment. The cohort was overrepresented young adults with a mean age of 19.1 in the treatment and control groups. Despite this, the results showed no efficacy of varenicline for smoking cessation at 12 weeks. Significant attrition resulted in a loss of 43% of enrollees at end of study. Increased biochemical efficacy in the varenicline group was observed during active treatment. Confounders such as concurrent e-cigarette...
and other tobacco product use as well as polysubstance use during the study both potentially compromising biochemical efficacy data and overall abstinence behaviors respectively.

Comments
1. Varenicline, in combination with brief counseling, did not promote long-term smoking cessation in a cohort of teenagers and young adults but concerning confounders. However, it was well tolerated.
2. Varenicline with counseling may hasten abstinence during active treatment, possibly reflecting a reinforcement effect. Distinct transition mechanisms should be further examined in cohort.
3. Study highlights need for customized therapies for nicotine-dependent youths, e.g., multiple substance abusers, high levels of dependence. Alternative trial designs that are less burdensome might reduce attrition in adolescents and teens.

OTHER ARTICLES OF INTEREST


ASSESSMENT OF RESPIRATORY FUNCTION IN DUCHENNE MUSCULAR DYSTROPHY


Summary
The Collaborative International Neuromuscular Research Group (CINRG) Duchenne Muscular Dystrophy (DMD) conducted the Duchenne Natural History Study (DNHS) at 20 sites internationally since 2006. Data were collected at 3, 6, 9, 12, 18, and 24 months and then annually thereafter. 397 patients completed at least one study visit and there were 2822 total discrete data encounters. The sum data demonstrated a significant positive correlation between loss of upper extremity function, as defined by the Brooke score, and a decline in FVC as a percent of predicted (FVC%). The data were divided into 2 cohorts of patients based on glucocorticoid (GC) use or not. In patients on GC the FVC% remained stable until 10 years of age after which it began to decline, while in patients not on GS the FVC% started declining at 7 years of age; however, the rate of decline was not significantly different. In addition, patients on GC had a peak FVC had a peak FVC (L) occurring 5 years later and at a mean volume almost 200 mL higher than patients not on GC. Finally, the age at which FVC (L) declined below 1 L was 3 years later in patients on GC. The FVC (L) declined below 1 L there was a 4-fold increased risk of death. There was a very close correlation between FVC% and peak expiratory flow percent predicted (PEF%) with nearly identical rates of decline. MIP% and MEP% also showed a similar relationship with a delay in the rate of decline of about 3 years in patients on GC compared to GC non-users; however, the maximal values for MIP% and MEP% were already low at entry to the study and declined at a lower rate through the study.

Comments
1. The use of glucocorticoids delays the onset of loss of lung function by 3 years.
2. Use of glucocorticoids does not delay the rate of decline of lung function
3. There is a similar trend in the rate of decline of PEF% as for FVC%.


Summary
Duchenne muscular dystrophy (DMD) causes a progressive loss of skeletal and cardiac muscle function and both muscle atrophy and fatty infiltration has well characterized using magnetic resonance imaging (MRI) of the muscles of the thigh and the structural changes correlated well to measures of function. While the diaphragm is too thin to allow similar measures of atrophy and fatty infiltration, dynamic MRI imaging can be used to measure diaphragm motion and chest wall excursion during tidal breathing. However, the muscles of exhalation and thoracic support, rectus abdominus, external oblique, internal oblique, psoas, and paraspinals, are large enough to be evaluated. 36 subjects with DMD and 12 age-matched unaffected subjects were studied. Forced vital capacity (FVC), peak cough flow (PCF), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were collected along with dynamic MRI imaging for chest and diaphragm motion and static MRI imaging for assessment of fat fraction (FF). On dynamic imaging DMD patients had a lower sagittal plane and craniocaudal expansion on both tidal and maximal inspiration and this correlated positively with FVC%. MIP correlated positively with the extent of diaphragm descent, and MEP correlated with the extent of inward chest wall motion and elevation of the diaphragm during exhalation. FF of the expiratory muscles increased with age in subjects with DMD. However, FF was not correlated with PCF and explained only 10% of the variance in MEP% beyond age alone.

Comments
1. MRI imaging can be used to measure respiratory motion and the longitudinal change.
2. The dynamic MRI measurements correlate to pulmonary function measures of volume and force
3. Fat fraction of the expiratory muscles increases with age in DMD
4. Increase in fat fraction in the expiratory muscles does not closely correlate to PCF or MEP.

**Summary**

As the primary inspiratory muscle and one that is dramatically impacted in DMD the diaphragm is the respiratory muscle of interest. Pennati, et.al. were able to produce MRI imaging with the precision to measure not only fat fraction of the crural diaphragm, but also to evaluate dynamic diaphragm motion and the change in contour during contraction. In 26 subjects with DMD and 12 age-matched controls static MRI measurements were made at full expiration and inspiration, spirometry was performed, and thoracoabdominal MRI measurements were assessed using optoelectronic plethysmography. Fat fraction increased in both the diaphragm and paraspinal muscles, used as a control, with age in subjects with DMD, but remained stable in the control subjects. Similarly diaphragm excursion, both total, in the dome and along the rib cage, decreased with age in DMD and remained unchanged in controls. Both fat fraction was higher and diaphragm excursion lower in subjects over 15 years of age compared to younger subjects. There was a strong positive correlation between FVC%, FEV1% and PEF% and diaphragm excursion and a negative correlation with fat fraction. Similarly, there was a strong positive correlation between inspiratory capacity and diaphragm excursion and a negative correlation with fat fraction. As expected there is a strong negative correlation between fat fraction and diaphragm excursion.

**Comments**

1. Fat fraction of the diaphragm can be accurately assessed by MRI and it increases with disease progression.
2. Diaphragm fat fraction is negatively correlated with diaphragm excursion and a positive correlation with fat fraction. 
3. FVC%, FEV1% and PEF% decreased with increasing fat fraction.

**SPINAL MUSCULAR ATROPHY THERAPY**


**Summary**

Spinal muscular atrophy (SMA) is caused by the homozygous deletion of the survival motor neuron 1 (SMN1) gene and rely on the residual less efficient transcription of the paralogous SMN2 gene to produce usable SMN protein. Al-Zaidy, et.al. report the respiratory outcomes of 12 subjects with SMA-1 with 2 copies of SMN2 who received AVXS-101 (SMN1 gene delivered in an AAV-9 vector) at a mean of 6.3 months. While at vector dosing three subjects required non-invasive ventilation (NIV) and two started it during acute illnesses, no patients died or required permanent ventilation (> 16 hours/day for > 14 days) and their need remained stable. There was a total of 10 patients who had at least one acute respiratory illness and of these three patients were started on NIV, but were weaned from it before hospital discharge. There were fewer hospital days compared to untreated external controls. Through the study bulbar function improved substantially with an increase in the number of patients able to swallow thin liquids and swallow well enough to allow oral feedings, and of the 7 patients exclusively orally fed at dosing 6 remained so at 2 years.

**Comments**

1. Patients receiving AVXS-101 did not progress to respiratory failure as would be expected by natural history.
2. The patients who received NIV during an acute illness could be weaned from it at the end of the illness.
3. Patients had fewer hospital days.
4. Bulbar function allowing swallowing and oral feeding improved or was preserved well above natural history.


**Summary**

Nusinersen (Zolgensma®) is an antisense oligonucleotide that increases the efficiency of transcription of the SMN2 gene to produce functional SMN protein. The efficacy was established based on the ENDEAR study of infants the SMA-1 and the CHERISH study of SMA-2. De Vivo, et.al. report data from the NURTURE study of 25 infants with genetically confirmed SMA-1 who were dosed pre-symptomatically. All subjects were dosed with nusinersen before 6 weeks of age. The primary endpoint was time to death or > 6 hours of mechanical ventilation for > days or invasive ventilation via tracheostomy tube and the secondary endpoints were motor function and nerve function studies. By 12 months no patients had died or required mechanical ventilation. Through the study 4 subjects reached the endpoint of > 6 hours of mechanical ventilation; however, two were weaned successfully from ventilation and by the end of study monitoring one of the two remaining subjects required ventilation for 10 hours daily and the other for two. None of the subjects with 3 copies of SMN2 reached the endpoint. Similar trends were seen with motor function with 90% of subjects with 3 copies of SMN2 attaining normal infant motor function and over 60% of subjects with 2 copies of SMN2 reaching normal motor milestones.
Comments
1. Early presymptomatic treatment with nusinersen in SMA-1 allows for near normal motor function development
2. Almost no patients with SMA-1 started on nusinersen early developed respiratory failure
3. The vast majority of patients with SMA-1 treated with nusinersen had normal motor function development
4. Patients with SMA-1 and 3 copies of SMN2 had better functional outcomes than patients with 2 copies of SMN2.

OTHER ARTICLES OF INTEREST


MANAGEMENT OF MILD ASTHMA


Summary
Since 2019 the Global Initiative for Asthma (GINA) has no longer recommended treating adults and adolescents with short acting beta agonists (SABA) alone, due to concerns about the safety of SABA only treatment. For adults and adolescents with mild asthma, symptom driven management is recommended to reduce the risk of exacerbations. However, there is a lack of evidence in younger children to support such a fundamental change in this age group. This study compared symptom based, as needed inhaled corticosteroids (ICS), used whenever SABA were needed, with regular ICS in 206 African American children with mild asthma. There were no significant differences in changes in Asthma Control Test score (or childhood ACT), exacerbations or lung function between the groups. However, those in the intermittent ICS group used significantly less ICS (526mcg/month (95% CI, 412 – 639mcg/month) versus 1961mcg/month (95% CI, 1681 – 2241mcg/month); p<0.001).

Comments
1. The treatment regimens were equally effective; however, those in the intermittent arm were exposed to significantly less ICS
2. In contrast to recent as needed ICS-formoterol studies in adults and adolescents, the participants in this study had separate ICS and SABA inhalers and there was no SABA only arm
3. This was a pragmatic, open label real world study, thus it is likely to have good external validity
4. Both groups reported high satisfaction with the management strategy; however more children and their caregivers in the intermittent group felt that they were managing their asthma, rather than their Primary Care Physician
5. Although this study provides further evidence for the utility of symptom driven intermittent ICS for children with mild asthma, further evidence is still needed before this strategy can be recommended for all children with mild asthma.

ADD ON TREATMENT FOR CHILDREN WITH PERSISTENT ASTHMA


Summary
In children with poor asthma control despite low dose inhaled corticosteroid (ICS), step up options include addition of a long acting beta agonist (LABA) or increasing the ICS dose. However, in most previous studies comparing step up treatments only a minority of participants were black. In this study participants of black heritage were enrolled in one of two double blind randomized placebo controlled cross over trials (one in 280 children and the other in 294 adolescents and adults) comparing four different step up regimes: doubling or quintupling the dose of ICS with or without LABA. Most children had a differential response to one of the treatments whereas 20-25% of adults and adolescents did not have a differential outcome.

Comments
1. The primary outcome was a hierarchical composite measure that sequentially evaluated asthma exacerbations, asthma control days and FEV1 to determine differential response to each of the regimes.
2. In adults and adolescents addition of LABA was more likely to produce a superior response than increasing the dose of ICS; whereas almost half the children had improved outcomes with an increase in the dose of ICS
3. In children the highest dose of ICS (fluticasone 500mcg/day) was associated with a decrease in urinary free cortisol, suggesting a degree of adrenal suppression
4. Differential responses were not related to patterns of genetic markers associated with African ancestry, phenotypic or biomarker characteristics.

5. Whilst this complex study may not help to guide choice of step up treatment in the individual child; it highlights that results cannot be extrapolated between cohorts of different age groups and ethnicities.

**MANAGEMENT OF SEVERE ASTHMA: MEPOLIZUMAB**


**Summary**

Mepolizumab, the monoclonal antibody to IL-5 was approved for use in children aged 6 -11 years by the FDA in September 2019. The approval was largely based on this open label study that investigated the pharmacokinetics pharmacodynamics and safety of mepolizumab. Thirty-six children were enrolled in the initial 12-week study, of whom 29 entered the extension phase and received treatment for 52 weeks. Adverse events were similar in nature and frequency to those reported in adult and adolescent Phase III studies.

**Comments**

1. Data from the 36 children enrolled in this study were compared to over 1800 adults (of whom 34 were adolescents) enrolled in the four Phase 3 studies for mepolizumab and were reported as “comparable”

2. Although efficacy data are reported, there was no comparator placebo group and almost 50% of children had an asthma attack on mepolizumab

3. Blood eosinophilic counts remained suppressed up to 4 weeks post final mepolizumab dose

4. Real world studies of mepolizumab are needed in children and adolescents to assess the efficacy, effectiveness and markers of response.

**MACROLIDES FOR ACUTE EPISODES OF ASTHMA AND PRE SCHOOL WHEEZE**


**Summary**

The role of antibiotics in the management of acute wheeze and asthma attacks remains contentious. This systematic review included randomized controlled trials of macrolides compared to placebo or standard treatment given for acute attacks in children up to 18 years of age. Only three studies met the eligibility criteria; 2 in pre school wheeze and one for asthma attacks in school aged children. Children treated with macrolides had a shorter time to resolution than the comparator group; there was no difference in hospitalizations or time to next episode.

**Comments**

1. Meta-analysis was possible for only one outcome variable (time to next episode) in view of the heterogeneity and distribution of the data

2. It is likely that potential benefit from macrolides is due to their immunomodulatory and anti-inflammatory properties rather than antimicrobial; however, the precise mechanism of action is not known

3. In view of the limited evidence and concerns around macrolide resistance, antibiotics should continue to be used judiciously for acute attacks of asthma and wheeze

4. In one study 69% of potentially eligible children were excluded because they had received antibiotics within the previous 30 days.

**LONG TERM OUTCOMES OF PAEDIATRIC ASTHMA**


**Summary**

New treatments and novel management strategies are needed to improve asthma control and improve long term outcomes for young people with asthma. This study linked health and education data in over 680 000 Scottish children, of whom 45 900 had asthma. Those with asthma had lower educational attainment, performed worse in school exams, had higher absenteeism and were more likely to have special educational needs for mental health reasons than their peers.

**Comments**

1. This is one of the largest non-selective population-based studies of long-term health, educational and social outcomes of children with asthma

2. The poorer educational outcomes in children with asthma are largely related to absenteeism

3. Developing strategies to improve school attendance is key

4. The changes in delivering asthma care and treatments brought about by the COVID pandemic could help to address these needs.
OTHER ARTICLES OF INTEREST


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