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Abstracts' Service

Evaluating the Risks of Clinical Research

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The ethical appropriateness of clinical research depends on protecting participants from excessive risks. Yet no systematic framewor has been developed to assess research risks, and as a result, investigators, funders, and review boards rely only on their intuitive judgments. Because intuitive judgments of risk are subject to well-documented cognitive biases, this approach raises concern that research participants are not being adequately protected. To address this situation, we delineate a method called the systematic evaluation of research risks (SERR), which evaluates the risks of research interventions by comparing these interventions with the risks of comparator activities that have been deemed acceptable. This method involves a 4-step process: (1) identify the potential harms posed by the proposed research intervention; (2) categorize the magnitude of the potential harms into 1 to 7 harm levels on a harm scale; (3) quantify or estimate the likelihood of each potential harm; and (4) compare the likelihood of each potential harm from the research intervention with the likelihood of harms of the same magnitude occurring as a result of an appropriate comparator activity. By explicitly delineating, quantifying and comparing the risks of research interventions with the risks posed by appropriate comparator activities, SERR offers a way to minimize the influence of cognitive biases on the evaluation of research risks and thereby better protect research participants from excessive risks.

Diagnosing and Managing Common Food Allergies: A Systematic Review

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Context. There is heightened interest in food allergies but no clear consensus exists regarding the prevalence or most effective diagnostic and management approaches to food allergies.

Objective. To perform a systematic review of the available evidence on the prevalence, diagnosis, management, and prevention of food allergies.

Data Sources. Electronic searches of PubMed, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials. Searches were limited to English-language articles indexed between January 1988 and September 2009.

Study Selection. Diagnostic tests were included if they had a prospective, defined study population, used food challenge as a criterion standard, and reported sufficient data to calculate sensitivity and specificity. Systematic reviews and randomized controlled trials (RCTs) for management and prevention outcomes were also used. For foods where anaphylaxis is common, cohort studies with a sample size of more than 100 participants were included.

Data Extraction. Two investigators independently reviewed all titles and abstracts to identify potentially relevant articles and resolved discrepancies by repeated review and discussion. Quality of systematic reviews and meta-analyses was assessed using the AMSTAR criteria, the quality of diagnostic studies using the QUADAS criteria most relevant to food allergy, and the quality of RCTs using the Jadad criteria.

Data Synthesis. A total of 12 378 citations were identified and 72 citations were included. Food allergy affects more than 1% to 2% but less than 10% of the population. It is unclear if the prevalence of food allergies is increasing. Summary receiver operating characteristic curves comparing skin prick tests (area under the curve [AUC], 0.87; 95% confidence interval [CI], 0.81-0.93) and serum food-specific IgE (AUC, 0.84; 95% CI, 0.78-0.91) to food challenge showed no statistical superiority for either test. Elimination diets are the mainstay of therapy but have been rarely studied. Immunotherapy is promising but data are insufficient to recommend use. In high-risk infants,

hydrolyzed formulas may prevent cow's milk allergy but standardized definitions of high risk and hydrolyzed formula do not exist.

Conclusion. The evidence for the prevalence and management of food allergy is greatly limited by a lack of uniformity for criteria for making a diagnosis.

Genetic Ancestry in Lung-Function Predictions

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Background. Self-identified race or ethnic group is used to determine normal reference standards in the prediction of pulmonary function. We conducted a study to determine whether the genetically determined percentage of African ancestry is associated with lung function and whether its use could improve predictions of lung function among persons who identified themselves as African American.

Methods. We assessed the ancestry of 777 participants self-identified as African American in the Coronary Artery Risk Development in Young Adults (CARDIA) study and evaluated the relation between pulmonary function and ancestry by means of linear regression. We performed similar analyses of data for two independent cohorts of subjects identifying themselves as African American: 813 participants in the Health, Aging and Body Composition (HABC) study and 579 participants in the Cardiovascular Health Study (CHS). We compared the fit of two types of models to lung-function measurements: models based on the covariates used in standard prediction equations and models incorporating ancestry. We also evaluated the effect of the ancestry-based models on the classification of disease severity in two asthma-study populations.

Results. African ancestry was inversely related to forced expiratory volume in 1 second (FEV_1) and forced vital capacity in the CARDIA cohort. These relations were also seen in the HABC and CHS cohorts. In predicting lung function, the ancestry-based model fit the data better than standard models. Ancestry-based models resulted in the reclassification of asthma severity (based on the percentage of the predicted FEV_1) in 4 to 5% of participants.

Conclusions. Current predictive equations, which rely on self-identified race alone, may misestimate lung function among subjects who identify themselves as African American. Incorporating ancestry into normative equations may improve lung-function estimates and more accurately categorize disease severity. (Funded by the National Institutes of Health and others.)

Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma

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Background. Whether it is possible to reduce the intensity of treatment in early (stage I or II) Hodgkin's lymphoma with a favorable prognosis remains unclear. We therefore conducted a multicenter, randomized trial comparing four treatment groups consisting of a combination chemotherapy regimen of two different intensities followed by involved-field radiation therapy at two different dose levels.

Methods. We randomly assigned 1370 patients with newly diagnosed early-stage Hodgkin's lymphoma with a favorable prognosis to one of four treatment groups: four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 30 Gy of radiation therapy (group 1), four cycles of ABVD followed by 20 Gy of radiation therapy (group 2), two cycles of ABVD followed by 30 Gy of radiation therapy (group 3), or two cycles of ABVD followed by 20 Gy of radiation therapy (group 4). The primary end point was freedom from treatment failure; secondary end points included efficacy and toxicity of treatment.

Results. The two chemotherapy regimens did not differ significantly with respect to freedom from treatment failure (P=0.39) or overall survival (P=0.61). At 5 years, the rates of freedom from treatment failure were 93.0% (95% confidence interval [CI], 90.5 to 94.8) with the four-cycle ABVD regimen and 91.1% (95% CI, 88.3 to 93.2) with the two-cycle regimen. When the effects of 20-Gy and 30-Gy doses of radiation therapy were compared, there were also no significant differences in freedom from treatment failure (P=1.00) or overall survival (P=0.61). Adverse events and acute toxic effects of treatment were most common in the patients who received four cycles of ABVD and 30 Gy of radiation therapy (group 1).

Conclusions. In patients with early-stage Hodgkin's lymphoma and a favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. Long-term effects of these treatments have not yet been fully assessed. (Funded by the Deutsche Krebshilfe and the Swiss Federal Government; ClinicalTrials.gov number, NCT00265018.)

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

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Background. Although we know that exacerbations are key events in chronic obstructive pulmonary disease (COPD), our understanding of their frequency, determinants, and effects is incomplete. In a large observational cohort, we tested the hypothesis that there is a frequent-exacerbation phenotype of COPD that is independent of disease severity.

Methods. We analysed the frequency and associations of exacerbation in 2138 patients enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study. Exacerbations were defined as events that led a care provider to prescribe antibiotics or corticosteroids (or both) or that led to hospitalization (severe exacerbations). Exacerbation frequency was observed over a period of 3 years.

Results. Exacerbations became more frequent (and more severe) as the severity of COPD increased; exacerbation rates in the first year of follow-up were 0.85 per person for patients with stage 2 COPD (with stages defined in accordance with Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages), 1.34 for patients with stage 3, and 2.00 for patients with stage 4. Overall, 22% of patients with stage 2 disease, 33% with stage 3, and 47% with stage 4 had frequent exacerbations (two or more in the first year of follow-up). The single best predictor of exacerbations, across all GOLD stages, was a history of exacerbations. The frequent-exacerbation phenotype appeared to be relatively stable over a period of 3 years and could be predicted on the basis of the patient's recall of previous treated events. In addition to its association with more severe disease and prior exacerbations, the phenotype was independently associated with a history of gastroesophageal reflux or heartburn, poorer quality of life, and elevated white-cell count.

Conclusions. Although exacerbations become more frequent and more severe as COPD progresses, the rate at which they occur appears to reflect an independent susceptibility phenotype. This has implications for the targeting of exacerbation-prevention strategies across the spectrum of disease severity. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT00292552.)

Four-arm Robotic Lobectomy for the Treatment of Early-Stage Lung Cancer

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Objectives. We investigated the feasibility and safety of four-arm robotic lung lobectomy in patients with lung cancer and described the robotic lobectomy technique with mediastinal lymph node dissection.

Methods. Over 21 months, 54 patients underwent robotic lobectomy for early-stage lung cancer at our institute. We used a da Vinci Robotic System (Intuitive Surgical, Inc, Mountain View, Calif) with three ports plus one utility incision to isolate hilum elements and perform vascular and bronchial resection using standard endoscopic staplers. Standard mediastinal lymph node dissection was performed subsequently. Surgical outcomes were compared with those in 54 patients who underwent open surgery over the same period and were matched to the robotic group using propensity scores for a series of preoperative variables.

Results. Conversion to open surgery was necessary in 7 (13%) cases. Postoperative complications (11/54, 20%, in each group) and median number of lymph nodes removed (17.5 robotic vs 17 open) were similar in the 2 groups. Median robotic operating time decreased by 43 minutes (P = .02) from first tertile (18 patients) to the second-plus-third tertile (36 patients). Median postoperative hospitalization was significantly shorter after robotic (excluding first tertile) than after open operations (4.5 days *vs* 6 days; P = .002).

Conclusions. Robotic lobectomy with lymph node dissection is practicable, safe, and associated with shorter postoperative hospitalization than open surgery. From the number of lymph nodes removed it also appears oncologically acceptable for early lung cancer. Benefits in terms of postoperative pain, respiratory function, and quality of life still require evaluation. We expect that technologic developments will further simplify the robotic procedure.

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

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Background. In patients undergoing mechanical ventilation for the acute respiratory distress syndrome (ARDS), neuromuscular blocking agents may improve oxygenation and decrease ventilator-induced lung injury but may also cause muscle weakness. We evaluated clinical outcomes after 2 days of therapy with neuromuscular blocking agents in patients with early, severe ARDS.

Methods. In this multicenter, double-blind trial, 340 patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (178 patients) or placebo (162 patients). Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of less than 150, with a positive end-expiratory pressure of 5 cm or more of water and a tidal volume of 6 to 8 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died either before hospital discharge or within 90 days after study enrollment (i.e., the 90-day in-hospital mortality rate), adjusted for predefined covariates and baseline differences between groups with the use of a Cox model.

Results. The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68% (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for both the baseline PaO_2:FIO_2 and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium

group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups.

Conclusions. In patients with severe ARDS, early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness. (Funded by Assistance Publique-Hopitaux de Marseille and the Programme Hospitalier de Recherche Clinique Regional 2004-26 of the French Ministry of Health; ClinicalTrails.gov number, NCT00299650.)

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network

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Background. Sildenafil, a phosphodiesterase-5 inhibitor, may preferentially improve blood flow to well-ventilated regions of the lung in patients with advanced idiopathic pulmonary fibrosis, which could result in improvements in gas exchange. We tested the hypothesis that treatment with sildenafil would improve walk distance, dyspnea, and quality of life in patients with advanced idiopathic pulmonary fibrosis, defined as a carbon monoxide diffusion capacity of less than 35% of the predicted value.

Methods. We conducted a double-blind, randomized, placebo-controlled trial of sildenafil in two periods. The first period consisted of 12 weeks of a double-blind comparison between sildenafil and a placebo control. The primary outcome was the proportion of patients with an increase in the 6-minute walk distance of 20% or more. Key secondary outcomes included changes in oxygenation, degree of dyspnea, and quality of life. The second period was a 12-week open-label evaluation involving all patients receiving sildenafil.

Results. A total of 180 patients were enrolled in the study. The difference in the primary outcome was not significant, with 9 of 89 patients (10%) in the sildenafil group and 6 of 91 (7%) in the placebo group having an improvement of 20% or more in the 6-minute walk distance (P=0.39). There were small but significant differences in arterial oxygenation, carbon monoxide diffusion capacity, degree of dyspnea, and quality of life favoring the sildenafil group. Serious adverse events were similar in the two study groups.

Conclusions. This study did not show a benefit for sildenafil for the primary outcome. The presence of some positive secondary outcomes creates clinical equipoise for further research. (Funded by the National Heart, Lung, and Blood Institute and others; ClinicalTrials.gov number, NCT00517933.)

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