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Abstracts' Service

Hospital Mortality, Length of Stay, and Preventable Complications Among Critically Ill Patients Before and After Tele-ICU Reengineering of Critical Care Processes

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Context. The association of an adult tele-intensive care unit (ICU) intervention with hospital mortality, length of stay, best practice adherence, and preventable complications for an academic medical center has not been reported.

Objective. To quantify the association of a tele-ICU intervention with hospital mortality, length of stay, and complications that are preventable by adherence to best practices.

Design, Setting, and Patients. Prospective stepped-wedge clinical practice study of 6290 adults admitted to any of 7 ICUs (3 medical, 3 surgical, and 1 mixed cardiovascular) on 2 campuses of an 834-bed academic medical center that was performed from April 26, 2005, through September 30, 2007. Electronically supported and monitored processes for best practice adherence, care plan creation, and clinician response times to alarms were evaluated.

Main Outcome Measures. Case-mix and severity-adjusted hospital mortality. Other outcomes included hospital and ICU length of stay, best practice adherence, and complication rates.

Results. The hospital mortality rate was 13.6% (95% confidence interval [CI], 11.9%-15.4%) during the preintervention period compared with 11.8% (95% CI, 10.9%-12.8 %) during the tele-ICU intervention period (adjusted odds ratio [OR], 0.40 [95 % CI, 0.31-0.52]). The tele-ICU intervention period compared with the preintervention period was associated with higher rates of best clinical practice adherence for the prevention of deep vein thrombosis (99% vs 85%, respectively; OR, 15.4 [95% CI, 11.3-21.1]) and prevention of stress ulcers (96% vs 83%, respectively; OR, 4.57 [95% CI, 3.91-5.77], best practice adherence for cardiovascular protection (99% vs 80%, respectively; OR, 30.7 [95% CI, 19.3-49.2]), prevention of ventilator-associated pneumonia (52% vs 33%, respectively; OR, 2.20 [95% CI, 1.79-2.70]), lower rates of preventable complications (1.6% vs 13%, respectively, for ventilator-associated pneumonia [OR, 0.15; 95% CI, 0.09-0.23] and 0.6% vs 1.0%, respectively, for catheter-related bloodstream infection [OR, 0.50; 95% CI, 0.27-0.93]), and shorter hospital length of stay (9.8 vs 13.3 days, respectively; hazard ratio for discharge, 1.44 [95 % CI, 1.33-1.56]). The results for medical, surgical, and cardiovascular ICUs were similar.

Conclusion. In a single academic medical center study, implementation of a tele-ICU intervention was associated with reduced adjusted odds of mortality and reduced hospital length of stay, as well as with changes in best practice adherence and lower rates of preventable complications.

Comparison of Effect Sizes Associated With Biomarkers Reported in Highly Cited Individual Articles and in Subsequent Meta-analyses

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Context. Many biomarkers are proposed in highly cited studies as determinants of disease risk, prognosis, or response to treatment, but few eventually transform clinical practice.

Objective. To examine whether the magnitude of the effect sizes of biomarkers proposed in highly cited studies is accurate or overestimated.

Data Sources. We searched ISI Web of Science and MEDLINE until December 2010.

Study Selection. We included biomarker studies that had a relative risk presented in their abstract. Eligible articles were those that had received more than 400 citations in the ISI Web of Science and that had been published in any of 24 highly cited biomedical journals. We also searched MEDLINE for subsequent meta-analyses on the same associations (same biomarker and same outcome).

Data Extraction. In the highly cited studies, data extraction was focused on the disease/outcome, biomarker under study, and first reported relative risk in the abstract. From each meta-analysis, we extracted the overall relative risk and the relative risk in the largest study. Data extraction was performed independently by 2 investigators.

Results. We evaluated 35 highly cited associations. For 30 of the 35 (86%), the highly cited studies had a stronger effect estimate than the largest study; for 3 the largest study was also the highly cited study; and only twice was the effect size estimate stronger in the largest than in the highly cited study. For 29 of the 35 (83%) highly cited studies, the corresponding meta-analysis found a smaller effect estimate. Only 15 of the associations were nominally statistically significant based on the largest studies, and of those only 7 had a relative risk point estimate greater than 1.37.

Conclusion. Highly cited biomarker studies often report larger effect estimates for postulated associations than are reported in subsequent meta-analyses evaluating the same associations.

Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer

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Context. The Orphan Drug Act incentivizes medication development for rare diseases, offering substantial financial benefits to the manufacturer. Orphan products constitute most new drug approvals in oncology, but safety and efficacy questions have emerged about some of these agents.

Objectives. To define characteristics of orphan cancer drugs and their pivotal clinical trials and to compare these with nonorphan drugs.

Design and Setting. We identified all new orphan and nonorphan drugs approved between 2004 and 2010 to treat cancer. We then collected data on key development variables from publicly available information on the US Food and Drug Administration's Web site and in the Code of Federal Regulations.

Main Outcome Measures. We assessed clinical testing dates, approved indications, and regulatory characteristics (regular vs accelerated review, advisory committee review, postmarketing commitments). We then compared design features (randomization, blinding, primary end point) of pivotal trials supporting approval of orphan and nonorphan drugs and rates of adverse safety outcomes (deaths not attributed to disease progression, serious adverse events, dropouts) in pivotal trials.

Results. Fifteen orphan and 12 nonorphan drugs were approved between January 1, 2004, and December 31, 2010. Pivotal trials of orphan drugs had smaller participant numbers (median, 96 [interquartile range {IQR}, 66-152] vs 290 [IQR, 185-394] patients exposed to the drug; $P< .001$) and were less likely to be randomized (30% vs 80%; $P=.007$). Orphan and nonorphan pivotal trials varied in their blinding ($P=.04$), with orphan trials less likely to be double-blind (4% vs 33%). Primary study outcomes also varied ($P=.04$), with orphan trials more likely to assess disease response (68% vs 27%) rather than overall survival (8% vs 27%). More treated patients had serious adverse events in trials of orphan drugs vs trials of nonorphan drugs (48% vs 36%; odds ratio, 1.72; 95% confidence interval, 1.02-2.92; $P=.04$).

Conclusion. Compared with pivotal trials used to approve nonorphan cancer drugs, pivotal trials for recently approved orphan drugs for cancer were more likely to be smaller and to use nonrandomized, unblinded trial designs and surrogate end points to assess efficacy.

Television Viewing and Risk of Type 2 Diabetes, Cardiovascular Disease, and All-Cause Mortality

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Context. Prolonged television (TV) viewing is the most prevalent and pervasive sedentary behavior in industrialized countries and has been associated with morbidity and mortality. However, a systematic and quantitative assessment of published studies is not available.

Objective. To perform a meta-analysis of all prospective cohort studies to determine the

association between TV viewing and risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality.

Data Sources and Study Selection. Relevant studies were identified by searches of the MEDLINE database from 1970 to March 2011 and the EMBASE database from 1974 to March 2011 without restrictions and by reviewing reference lists from retrieved articles. Cohort studies that reported relative risk estimates with 95% confidence intervals (CIs) for the associations of interest were included.

Data Extraction. Data were extracted independently by each author and summary estimates of association were obtained using a random-effects model.

Data Synthesis. Of the 8 studies included, 4 reported results on type 2 diabetes (175 938 individuals; 6428 incident cases during 1.1 million person-years of follow-up), 4 reported on fatal or nonfatal cardiovascular disease (34 253 individuals; 1052 incident cases), and 3 reported on all-cause mortality (26 509 individuals; 1879 deaths during 202 353 person-years of follow-up). The pooled relative risks per 2 hours of TV viewing per day were 1.20 (95% CI, 1.14-1.27) for type 2 diabetes, 1.15 (95% CI, 1.06-1.23) for fatal or nonfatal cardiovascular disease, and 1.13 (95% CI, 1.07-1.18) for all-cause mortality. While the associations between time spent viewing TV and risk of type 2 diabetes and cardiovascular disease were linear, the risk of all-cause mortality appeared to increase with TV viewing duration of greater than 3 hours per day. The estimated absolute risk differences per every 2 hours of TV viewing per day were 176 cases of type 2 diabetes per 100 000 individuals per year, 38 cases of fatal cardiovascular disease per 100 000 individuals per year, and 104 deaths for all-cause mortality per 100 000 individuals per year.

Conclusion. Prolonged TV viewing was associated with increased risk of type 2 diabetes, cardiovascular disease, and all-cause mortality.

Effect of Bronchoalveolar Lavage-Directed Therapy on *Pseudomonas aeruginosa* Infection and Structural Lung Injury in Children With Cystic Fibrosis: A Randomized Trial

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Context. Early pulmonary infection in children with cystic fibrosis leads to increased morbidity and mortality. Despite wide use of oropharyngeal cultures to identify pulmonary infection, concerns remain over their diagnostic accuracy. While bronchoalveolar lavage (BAL) is an alternative diagnostic tool, evidence for its clinical benefit is lacking.

Objective. To determine if BAL-directed therapy for pulmonary exacerbations during the first 5 years of life provides better outcomes than current standard practice relying on clinical features and oropharyngeal cultures.

Design, Setting, and Participants. The Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) randomized controlled trial, recruiting infants diagnosed with cystic fibrosis through newborn screening programs in 8 Australasian cystic fibrosis centers. Recruitment occurred between June 1, 1999, and April 30, 2005, with the study ending on December 31, 2009.

Interventions. BAL-directed (n=84) or standard (n=86) therapy until age 5 years. The BAL-directed therapy group underwent BAL before age 6 months when well, when hospitalized for pulmonary exacerbations, if *Pseudomonas aeruginosa* was detected in oropharyngeal specimens, and after *P aeruginosa* eradication therapy. Treatment was prescribed according to BAL or oropharyngeal culture results.

Main Outcome Measures. Primary outcomes at age 5 years were prevalence of *P aeruginosa* on BAL cultures and total cystic fibrosis computed tomography (CF-CT) score (as a percentage of the maximum score) on high-resolution chest CT scan.

Results. Of 267 infants diagnosed with cystic fibrosis following newborn screening, 170 were enrolled and randomized, and 157 completed the study. At age 5 years, 8 of 79 children (10%) in the BAL-directed therapy group and 9 of 76 (12%) in the standard therapy group had *P aeruginosa* in final BAL cultures (risk difference, -1.7% [95% confidence interval, -11.6% to 8.1 %]; *P*=.73). Mean total (CF-CT scores for the BAL-directed therapy and standard therapy groups were 3.0% and 2.8%, respectively (mean difference, 0.19% [95% confidence interval, -0.94% to 1.33%]; *P*=.74).

Conclusion. Among infants diagnosed with cystic fibrosis, BAL-directed therapy did not result in a lower prevalence of *P aeruginosa* infection or lower total CF-CT score when compared with standard therapy at age 5 years.