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Advancing Evidence-Based Practice

A Quarterly Compilation of Research Updates Most Likely to Change Clinical Practice

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INFECTIOUS DISEASE

Addition of Co-trimoxazole to Cephalexin Does Not Increase Cure Rate of Uncomplicated Cellulitis

Antibiotics that target methicillin-resistant *S. aureus* (MRSA) are often prescribed for patients with uncomplicated cellulitis. A new randomized trial assessed the benefits of targeting MRSA in 153 patients. Patients aged 3-74 years (median age 29 years) with uncomplicated cellulitis for <1 week were randomized to co-trimoxazole plus cephalexin vs cephalexin alone (with placebo) for at least 7 days and followed for 30 days. Patients were instructed to continue antibiotic treatment for up to a total of 14 days. MRSA was endemic in the areas in which the patients lived, and 13% of patients in the trial had associated purulence.

At the end of follow-up, the cure rate was 85% with combination treatment and 82% with cephalexin alone (not significant) [*Clin Infect Dis* 2013 Jun;56(12):1754]. The infection progressed to abscess in 6.8% in each group (not significant). There were also no significant differences in the rates of diarrhea, nausea and vomiting, or other adverse events (level 1 [likely reliable] evidence). Neither presence of purulence nor nasal colonization with MRSA appeared to influence outcomes.

NEUROLOGY

Intensive Blood Pressure Control Might Not Reduce Death or Major Disability, but May Improve Quality of Life After Acute Intracerebral Hemorrhage

The INTERACT2 randomized trial compared intensive blood pressure (BP) control to American Heart Association guideline-recommended treatment in 2,839 patients within 6 hours of onset of intracerebral hemorrhage who had systolic BP 150-220 mmHg. Patients were randomized to 1 of 2 treatment strategies and followed for 90 days. The intensive control strategy targeted a systolic BP of <140 mmHg with the goal of reaching the target within 1 hour and then maintaining it for 7 days. Under the guideline-recommended strategy, the target systolic BP was <180 mmHg. Agents used for BP control were at the treating physicians' discretion. All patients received oral antihypertensive drugs or topical nitrates within 7 days. History of hypertension was common (72%), and 45% were already taking antihypertensive drugs. The mean systolic BP attained at 1 hour was 150 mmHg with intensive control and 164 mmHg with guideline-recommended treatment (33.4% in the intensive control group achieved target systolic pressure at 1 hour).

The primary outcome was a composite of death or major disability (defined as modified Rankin score 3-5). Intensive control was associated with a nonsignificant decrease in the primary outcome (52% vs 55.6%, P=0.06), but there was no significant difference in mortality (11.9% vs 12%) [*N Engl J Med* 2013 Jun 20;368(25):2355]. There were also no significant differences in the rates of nonfatal serious adverse events (23.3% vs 23.6%) or neurologic deterioration in first 24 hours (14.5% vs 15.1%). However, intensive BP control was associated with improved quality-of-life outcomes. At 90 days, patients in the intensive control group had significantly lower rates of problems with self-care (46.8% vs 51.6%, P=0.02, number needed to treat [NNT] 21), usual activities (60.8% vs 66.1%, P=0.006, NNT 19), and pain and discomfort (39.8% vs 45%, P=0.01, NNT 20) (level 2 [mid-level] evidence).

Addition of Vasopressin Plus Steroids to Epinephrine Increases Survival to Discharge With Favorable Neurologic Outcomes After In-Hospital Cardiac Arrest

The addition of vasopressin and steroids to epinephrine during resuscitation has previously been shown to improve survival following in-hospital cardiac arrest compared to epinephrine alone. A new randomized trial assessed the efficacy of treatment

Level 1 [likely reliable] Evidence: research results addressing clinical outcomes and meeting an extensive set of quality criteria that minimize bias.

Level 2 [mid-level] Evidence: research results addressing clinical outcomes and using some method of scientific investigation, but not meeting the quality criteria to achieve level 1 evidence labeling.

Level 3 [lacking direct] Evidence: reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion, and conclusions extrapolated indirectly from scientific studies.

with vasopressin plus steroids plus epinephrine (VSE) in 300 adult patients with in-hospital cardiac arrest.

Patients were randomized to the VSE group (vasopressin 20 units/cycle + epinephrine 1 mg/cycle for the first 5 resuscitation cycles + methylprednisolone 40 mg on first cycle) or to the epinephrine alone group (epinephrine 1 mg/cycle plus normal saline placebo for the first 5 cycles) during resuscitation and followed until death or hospital discharge. All patients could receive additional epinephrine as needed. Patients in the VSE group who had postresuscitation shock also received intravenous hydrocortisone 300 mg/d for up to 7 days with gradual taper (patients in the epinephrine group with postresuscitation shock received placebo saline.) Favorable neurologic outcome was defined as a Cerebral Performance Category score of 1 (conscious, alert, and able to work, with possible mild neurologic or psychologic deficit) or 2 (moderate disability, but sufficient cerebral function for independent activities of daily life).

The rate of survival to discharge with favorable neurologic outcome was 13.9% with VSE vs 5.1% with epinephrine alone (P=0.02, NNT 12) [*JAMA* 2013 Jul 17;310(3):270]. VSE was also associated with a higher rate of return of spontaneous circulation for at least 20 minutes (83.9% vs 65.9%, P=0.005, NNT 6). In a subgroup analysis of 149 patients who had postresuscitation shock, 21.1% of the VSE group and 8.2% of the epinephrine group survived to discharge with good neurologic outcome (P=0.02, NNT 8). There were no significant differences in the rates of complications, postarrest morbidity, or causes of death in analysis of 162 patients who survived ≥4 hours (level 1 [likely reliable] evidence).

ONCOLOGY

In Patients With High-Risk Smoldering Myeloma, Early Treatment May Delay Disease Progression and Increase Survival

A recent unblinded randomized trial evaluated the efficacy of early treatment in 125 patients with high-risk smoldering myeloma. Patients aged 38-91 years were randomized to early treatment vs observation. Early treatment consisted of induction with lenalidomide 25 mg/d on days 1-21 plus dexamethasone 20 mg/d on days 1-4 and 12-15 every 4 weeks for 9 cycles, followed by maintenance therapy with lenalidomide 10 mg/d on days 1-21 every 4 weeks for 2 years. High-risk disease was defined as either plasma-cell bone marrow infiltration ≥10% plus a monoclonal component (IgG level ≥3 g/dL, IgA level ≥2 g/dL, or urinary Bence Jones protein level >1 g/d) or 1 of these criteria plus ≥95% phenotypically aberrant plasma cells in the bone marrow plasma cell compartment with ≥25% decrease in 1-2 uninvolved immunoglobulins.

After median follow-up of 40 months, early treatment was associated with longer time to progression than observation (hazard ratio for progression 0.18, P<0.001). The median time to progression was not reached in the early treatment group (ie, fewer than half the group had progression during follow-up) vs 21 months in the observation group. Early treatment was also associated with significantly higher 3-year survival (94% vs 80%, P=0.03, NNT 8) [*N Engl J Med* 2013 Aug 1;369(5):438]. In the early treatment group, at least partial response was observed in 79% during the induction phase and 90% during maintenance (level 2 [mid-level] evidence).

PULMONARY MEDICINE

In Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease, 5-Day Course of Prednisone Is as Effective as 14-Day Course for Reducing Reexacerbation

The REDUCE trial compared the efficacy of a 5-day corticosteroid course to the recommended treatment duration for patients presenting to the emergency department with acute chronic obstructive pulmonary disease (COPD) exacerbations. A total of 314 patients >40 years old (mean age 70 years) were randomized to oral prednisone treatment (40 mg/d) for 5 days vs 14 days and were followed for 6 months. All patients received intravenous methylprednisolone 40 mg on the first day, and oral prednisone treatment began on the second day. Patients also received broad-spectrum antibiotics for 7 days plus inhaled and nebulized short-acting bronchodilator 4-6 times daily while hospitalized. During follow-up they had

inhaled glucocorticoids, beta-2 agonists, and tiotropium. All patients had a history of ≥20 pack-years of cigarette smoking.

There were no significant differences in the rates of reexacerbation in either intention-to-treat (35.9% with 5-day course vs 36.8% with 14-day course) or per-protocol analyses (36.7% vs 38.3%) in analysis of 296 patients [*JAMA* 2013 Jun 5;309(21):2223]. The median time to reexacerbation was 43.5 days with the 5-day course vs 29 days with the 14-day course, and 5-day treatment was associated with significantly reduced cumulative steroid doses (mean 379 mg vs 793 mg, $P<0.001$) (level 1 [likely reliable] evidence). In analysis of 289 patients (92%) who were admitted to the hospital, 5-day treatment was associated with shorter hospital stay (median 8 days vs 9 days, $P=0.04$). There were no significant differences in mortality, need for mechanical ventilation, or adverse events.

VASCULAR MEDICINE

Intermittent Pneumatic Compression Appears to Reduce Risk of Deep Vein Thrombosis After Acute Stroke

The CLOTS 3 trial evaluated the use of intermittent pneumatic compression (IPC) for prevention of deep vein thrombosis (DVT) in 2,876 patients (median age 76 years) with acute stroke within 3 days who were unable to walk to the toilet without help. Patients were randomized to IPC for ≥30 days vs no IPC and were followed for 6 months. IPC was applied continuously except during washing, physical therapy, and compression duplex ultrasound. Patients in each group could receive heparin for prophylaxis or treatment at the discretion of treating clinicians; 24% in each group were receiving warfarin or heparin at recruitment or had received thrombolysis (alteplase) for treatment of acute stroke. The primary outcome was any proximal DVT (symptomatic or asymptomatic detected on ultrasound) within 30 days.

Median duration of IPC use was 9 days (only 31% used the device every day). The primary outcome occurred in 8.5% with IPC vs 12.1% without IPC ($P<0.05$, NNT 28) [*Lancet* 2013 Aug 10;382(9891): 516]. Symptomatic proximal or calf DVTs occurred in 4.6% vs 6.3% ($P=0.045$, NNT 59). The beneficial effects of IPC on DVT rates were similar in subgroup analyses of patients who did or did not receive heparin, warfarin, or alteplase. Rates of prophylactic and therapeutic heparin use after randomization were similar between the IPC and no IPC groups. IPC was also associated with a reduced rate of any DVT at 6 months (16.7% vs 25.1%, $P=0.001$, NNT 12) and with nonsignificant reductions in mortality at 30 days (10.8% vs 13.1%, $P=0.057$) and at 6 months (22.3% vs 25.1%, $P=0.059$) (level 2 [mid-level] evidence). Skin breakdown was more common in the IPC group. There was no significant difference in the rate of falls.

Apixaban Is as Effective for Treatment of Acute Venous Thromboembolism as Conventional Therapy and Reduces Bleeding Risk

The AMPLIFY trial compared the efficacy of the factor Xa inhibitor apixaban to conventional therapy for treatment of acute venous thromboembolism (VTE) in 5,395 adult patients (mean age 57 years) with acute symptomatic proximal deep vein thrombosis or pulmonary embolism. Patients were randomized to 1 of 2 interventions and followed for 7 months. The conventional therapy group received enoxaparin 1 mg/kg subcutaneously every 12 hours for ≥5 days plus warfarin with target international normalized ratio (INR) 2-3 for 6 months. The apixaban group received apixaban 10 mg orally twice daily for the first 7 days, then 5 mg twice daily for 6 months. Blinding was maintained through placebo subcutaneous injections and placebo warfarin with sham INR monitoring. The primary outcome was a composite of recurrent symptomatic VTE and VTE-related death.

Primary outcome events occurred in 2.3% with apixaban vs 2.7% in the conventional therapy group (not significant) [*N Engl J Med* 2013 Jul 1 early online]. The apixaban group had lower rates of major bleeding (0.6% vs 1.8%, $P<0.001$, NNT 84) and clinically relevant nonmajor bleeding (3.8% vs 8%, $P< 0.05$, NNT 24). There were no significant differences in all-cause mortality (1.5% vs 1.9%) or in serious adverse events (level 1 [likely reliable] evidence). Apixaban is currently FDA approved only for use in patients with nonvalvular atrial fibrillation.

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