Using a 10% reduction in lactate as a goal of adequate oxygen delivery in early goal-directed therapy in patients with severe sepsis results in similar outcomes as using continuous central venous oxygen saturation.

Background: The Surviving Sepsis Campaign international consensus guidelines recommend early resuscitation to optimize oxygen delivery. Although the best measure of oxygen delivery is debated, the published protocol utilized central venous oxygen saturation (ScvO2) of >70%. Serum lactate has been shown to prognosticate outcome, with higher levels being associated with worse morbidity and mortality.

Objective: To demonstrate that lactate falling by 10% results in similar outcomes as achieving 70% ScvO2 in early goal-directed therapy for patients with severe sepsis.

Design: Multicentered randomized open-label non-inferiority study.

Participants: 300 patients with severe sepsis and hypoperfusion or shock being treated in emergency departments of 3 urban U.S. hospitals.

Methods: All patients had baseline lactate drawn and central catheter capable of continuously measuring venous oxygen saturation placed. IV fluid resuscitation targeted central venous pressure of 8 to 12 and vasopressors were added to maintain mean arterial pressure of 65 mm Hg. Once these were achieved, a surrogate of adequate oxygen delivery was measured. If the lactate had not fallen by at least 10% from baseline (in the lactate clearance group) or ScvO2 was <70% (ScvO2 group), patients were transfused blood to hematocrit of 30 and then started on dobutamine. The early goal-directed therapy was discontinued at 6 hours and patients were admitted to the ICU where care was directed by non-study physicians.

Results: 80% had shock and 40% had lactate levels >4 at enrollment. Both groups received about 4.5 liters of crystalloid in the first 6 hours with three fourths requiring vasopressors. Only 5% of patients required blood transfusions and 4% dobutamine during the first 6 hours. Over the first 72 hours, there was no difference in need for mechanical ventilation (50% of patients) between groups. Hospital mortality was similar in both groups (23% targeting ScvO2 vs 17% with lactate). Both ICU (5.6 vs 5.9 days) and hospital (12.1 vs 11.4 days) lengths of stay were similar between groups.

Conclusions: Using lactate clearance resulted in similar clinical outcomes as ScvO2 in an algorithm of early goal-directed therapy in patients with severe sepsis.

Reviewer’s Comments: Since the publication of Rivers’ New England Journal of Medicine article describing the benefits of early goal-directed therapy, many have wondered if continuous venous oxygen saturation monitoring was required. The catheters designed to continuously monitor ScvO2 are expensive and require training to use. This article demonstrates that serial lactate measurements targeting a clearance of at least 10% produce similar clinical outcomes as targeting ScvO2 > 70%. I plan on incorporating lactate clearance in my practice in place of the expensive catheter as the goal for adequate resuscitation of patients with severe sepsis or septic shock. (Reviewer-Todd W. Rice, MD, MSc).

Keywords: Lactate, Severe Sepsis, Central Venous Oxygen Saturation

Print Tag: Refer to original journal article
Higher PEEP Reduces ARDS But Not ALI Mortality in Meta-Analysis

Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome: Systematic Review and Meta-Analysis.

Briel M, Meade M, et al:

JAMA 2010; 303 (March 3): 865-873

In this meta-analysis, lung protective ventilation strategies using higher levels of PEEP resulted in significantly lower mortality in a subgroup of patients with ARDS (ie, P/F<200).

**Background:** Lung protective ventilation strategies theorize that low tidal volumes prevent overdistention of alveoli while positive end-expiratory pressure (PEEP) prevents repetitive collapse and reopening of injured alveoli. The ARDS Network demonstrated that volume and pressure-limited ventilation decreased mortality and increased the number of days alive and off the ventilator. However, studies evaluating higher levels of PEEP have been less conclusive. Higher PEEP may both prevent collapse and exacerbate overdistention of more normal alveoli.

**Objective:** To determine the association of higher versus lower PEEP on outcomes in adults with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) being ventilated with low tidal volume strategies.

**Design:** Individual patient data meta-analysis; pre-specified subgroup analysis of patients with ALI versus ARDS.

**Participants:** 2299 patients with ALI or ARDS combined from 3 large randomized trials.

**Methods:** PEEP levels were set according to tables in 2 trials and titrated to plateau pressure in the third. The meta-analysis used individual patient, not aggregate data.

**Results:** Over 80% of patients had ARDS rather than ALI and most had medical etiologies for their lung injury (50% pneumonia, 50% sepsis, 20% aspiration). The mean PEEP was 15 in the higher PEEP group and 9 in the lower PEEP group. Overall, higher and lower PEEP had similar hospital mortality (32.9% vs 35.2%, respectively; \( P =0.25 \)). Complication rates such as pneumothorax and need for vasopressors were similar in the 2 groups. In the subgroup of patients who had P/F ratio <200 (ie, ARDS) at enrollment, higher PEEP resulted in marginally significantly lower mortality (34.1% vs. 39.1%; \( P =0.049 \)) and more days alive with unassisted breathing (12 vs 7; \( P =0.004 \)). However, in the smaller subgroup of patients with P/F ratios 200 to 300 at enrollment, higher PEEP resulted in a trend toward higher mortality (27.2% vs 19.4%; \( P =0.07 \)).

**Conclusions:** Higher PEEP did not result in improved mortality or clinical outcomes in all patients with ALI but did in the subgroup of patients with the more severe ARDS at enrollment.

**Reviewer's Comments:** This meta-analysis is methodologically interesting in that it used data from individual patients, rather than treating each study as a data point. While this improves the ability to detect relationships, it does not overcome the limitation of all meta-analyses that the studies only share some features in common. Higher PEEP did demonstrate a mortality benefit in the most severely hypoxic subgroup. Conversely, in patients with P/F ratios between 200 and 300, higher PEEP trended toward increasing mortality. Overall, these results are hard to incorporate into clinical practice due to the relatively arbitrary cut-off of P/F=200. If higher PEEP (lower oxygen) is going to be used, these data suggest it should be restricted to patients with P/F <200, while less ill patients should be managed with lower PEEP (higher oxygen). (Reviewer-Todd W. Rice, MD, MSc).

**Keywords:** Positive End-Expiratory Pressure, Acute Lung Injury, Acute Respiratory Distress Syndrome

Print Tag: Refer to original journal article
Unlike central venous catheters, the daily risk of colonization increases over time with arterial catheters, suggesting a potential benefit of scheduled replacement.

**Background:** Catheter-related blood stream infection prevention strategies have focused on central venous catheters (CVCs) rather than arterial catheters (ACs). Few studies have addressed the overall infection risk associated with ACs. While studies have shown that the daily infection risk remains constant for CVCs, this has not been evaluated for ACs.

**Objective:** To evaluate the incidence, daily risk, and risk factors for colonization and infection associated with CVCs and ACs.

**Design:** This was an analysis of data from a trial of 7 ICUs evaluating different dressing change intervals and methods for ACs and CVCs. In the original trial, participants were randomized to dressing changes every 3 or 7 days with or without chlorhexidine-impregnated sponges.

**Participants:** Adult medical and surgical ICU patients requiring CVC or AC for >48 hours.

**Methods:** Catheter colonization and catheter-related blood stream infection were defined according to guidelines. Only cultured catheters were included in this analysis. Hazard rates (HR) and risk factors were determined using a marginal Cox model.

**Results:** 3532 catheters comprising 27,541 catheter-days were cultured and analyzed. There were 1617 ACs and 1915 CVCs. The incidence of infection was 11.4 per 1000 AC days and 11 per 1000 CVC days ($P=0.80$).

For ACs, the daily HR of colonization increased from 1.3% on day 5 to 2.4% on day 10 and 3.0% on day 15. For CVCs, the daily HR of colonization remained constant from days 5 to 15, ranging from 1.2% to 1.6%. The distribution of microorganisms associated with colonization was similar between ACs and CVCs. Factors independently associated with increased AC colonization included femoral insertion (HR, 2.4; $P<0.01$), chronic heart failure (HR, 2.37; $P=0.01$), and chronic respiratory failure (HR, 1.62; $P=0.05$). For CVCs, factors independently associated with increased colonization included trauma (HR, 1.89; $P=0.02$) and non-subclavian insertion site (jugular HR, 3.1; femoral HR, 7.05; $P<0.01$).

**Conclusions:** Overall rates of colonization and infection were similar for ACs and CVCs. Daily hazard rates increased for ACs but remained stable for CVCs. Scheduled AC replacement, especially after the fifth day, may decrease catheter-related blood stream infection rates.

**Reviewer's Comments:** Catheter-related blood stream infections, an important cause of morbidity and mortality in the ICU, have now been proposed as a health care quality indicator. Data from several studies have demonstrated that the risk of infection from CVCs remains constant over time, and thus scheduled replacement is not indicated. These conclusions have been extrapolated to ACs without data to support them. Lucet and colleagues have made the important observation that the risk of colonization increases over time with ACs, suggesting that scheduled replacement may be of benefit. While this speculation needs to be examined prospectively, the observations reported here suggest that prolonged use of ACs without replacement increases the risk of infection. (Reviewer-M. Bradley Drummond, MD).
Of several proposed delirium assessment tools, the CAM-ICU demonstrates the best combined sensitivity and specificity for detecting delirium in surgical ICU patients.

**Background:** Due to the high prevalence of delirium in the ICU, guidelines recommend routine delirium assessments during ICU stay. While several different delirium assessment tools are available, few have been specifically designed to evaluate delirium in the ICU setting. Moreover, the performance of these scales has not been compared in the same patients.

**Objective:** To compare the validity and reliability of 3 different delirium assessment tools in ICU patients.

**Design:** Prospective cohort study.

**Participants:** 156 consecutive patients from a single surgical ICU age ≥60 years admitted for at least 24 hours.

**Methods:** Using trained staff, the Confusion Assessment Method for the ICU (CAM-ICU), Nursing Delirium Screening Scale (Nu-DESC), and the Delirium Detection Score (DDS) were performed daily and independently. As a gold standard, an independent expert used DSM-IV criteria to determine the presence of delirium daily in the participants.

**Results:** Of 156 subjects, 63 (40%) were diagnosed with delirium according to DSM-IV criteria during their ICU stay. Compared to those without delirium, patients in the delirium group were significantly older, had higher organ dysfunction scores, longer length of mechanical ventilation and ICU stay, and higher mortality. Using the DSM-IV diagnosis as the reference standard, during the first 21 days of ICU stay the CAM-ICU demonstrated 79% sensitivity and 97% specificity while the Nu-DESC demonstrated 82% sensitivity and 83% specificity. The DDS performed the worst, with a sensitivity of 25% and specificity of 89%. Interrater reliability was highest for the CAM-ICU, with a $\kappa$ of 0.89.

**Conclusions:** The CAM-ICU was the most valid and reliable assessment tool for the detection of ICU delirium when compared with Nu-DESC and DDS. The Nu-DESC was also valid and reliable to detect delirium, while the DDS showed a low sensitivity.

**Reviewer's Comments:** Delirium in ICU patients is associated with increased length of stay, hospital mortality, and hospital costs. The complex nature of ICU patients often precludes a formal assessment of delirium by physicians. Luetz and colleagues have provided insight into an appropriate standardized delirium assessment tool that has both validity and reliability in an ICU population. Although the older, post-surgical nature of the study population limits the generalizability of these findings to other ICU settings, these authors provide good evidence that the CAM-ICU is a useful tool for assessing delirium in the ICU. (Reviewer-M. Bradley Drummond, MD).

**Keywords:** Delirium, ICU, Critical Care, Detection

**Print Tag:** Refer to original journal article
Multidisciplinary care with daily rounds augments the efforts of physician staffing and improves mortality rates of medical ICU patients.

**Background:** Daily rounding by a multidisciplinary care team has been promoted as the best model for the delivery of ICU care, but the value of this approach has not yet been proven.

**Objective:** To determine if a relationship exists between 30-day mortality and daily multidisciplinary rounds.

**Design:** Retrospective cohort study of medical patients.

**Participants:** Adult patients admitted to ICUs in Pennsylvania over a 2-year period ending in June 2006.

**Methods:** This was a retrospective review of discharge data from non-federal acute care hospitals and a review of death records from the department of health. Hospital characteristics were obtained from the annual American Hospital Association survey. The model of ICU care delivery was obtained from hospital surveys completed by the chief nursing officer.

**Results:** 112 hospitals and 107,324 patients were included in the analysis. In total, 20% of hospitals had both high-intensity physician staffing and multidisciplinary care while 50% of hospitals provided neither. Overall 30-day mortality was 18%. After adjusting for illness severity risk factors and hospital characteristics, multidisciplinary care teams were associated with a reduction in mortality. Odds of death were lowest in ICUs with high-intensity physician staffing with multidisciplinary care (odds ratio, 0.78) followed by low-intensity staffing with multidisciplinary care (OR, 0.88) compared with low-intensity staffing combined with lack of multidisciplinary care (OR, 1.0).

**Conclusions:** In medical ICU patients, daily multidisciplinary rounds are associated with lower mortality. Hospitals without high-intensity physician staffing can improve mortality through the implementation of a multidisciplinary team model of care.

**Reviewer’s Comments:** Institutions that have adopted a multidisciplinary approach to ICU care have taken on faith that this improves patient outcomes. Given the complexity of ICU therapy, it seems intuitive that more hands on the oars would make for a smoother ride. This study provides evidence that hospitals adopting this approach are on the right track. Although odds of death were lowest in the ICUs with high-intensity physician staffing and multidisciplinary teams, multidisciplinary teams still seemed to have a benefit even with lower physician staffing. Limitations include the study being within a single geographic area, lack of data for patients outside of the MICU population, and lack of information as to what constitutes an optimal care team both in size and composition. As with all studies of this nature, it is impossible to account for unmeasured confounders. That is, multidisciplinary care may just be a co-traveler with some other characteristic that actually causes the benefit. If we wish to continue to reduce ICU mortality while being mindful of expense, we need more studies examining the effects of specific details of ICU care delivery. (Reviewer-Annette M. Rowden, PharmD).

Keywords: Multidisciplinary Care, Intensivist Care

Print Tag: Refer to original journal article
The data from this study support using standard dosing of oseltamivir in severely ill patients with H1N1. No dosing adjustment is needed in obesity, while reduced dosing is indicated in renal failure.

**Background:** The most appropriate dosing of oseltamivir for treatment of critically ill patients with the H1N1 pandemic flu is unknown. World Health Organization guidelines for managing severe infection suggest consideration of higher than normal dosing (>75 mg orally twice daily). A concern with patients who are severely ill is that gastrointestinal absorption of medications will be inadequate and could lead to therapeutic failure.

**Objective:** To determine the pharmacokinetic parameters of oseltamivir given orally or by nasogastric tube in patients admitted to the ICU with severe respiratory failure due to suspected or confirmed pandemic (H1N1) influenza.

**Design:** Prospective non-comparative observational study.

**Participants:** Patients aged >18 years admitted to 9 ICUs in Canada and Spain.

**Methods:** Multiple blood samples were obtained after receipt of the fourth or later oseltamivir dose. Results were normalized to 75 mg twice daily for patients receiving larger doses. Pharmacokinetic modeling was performed and kinetic parameters were determined. The impact of renal dysfunction on kinetic parameters was also evaluated.

**Results:** 43 pharmacokinetic analyses from 41 patients were performed. Mean patient age was 41 years and weight was 99 kg. Half of the patients had some degree of renal impairment and 17% required renal replacement therapy. At the time blood samples for oseltamivir were obtained, 73% of patients were receiving continuous enteral feeding and 32% were on vasopressors. Median steady state trough concentrations of the active carboxylate metabolite of oseltamivir were as high as or higher than levels seen in normal volunteers given the same dosage. There was a delay in peak serum concentrations in study patients, but the extent of drug absorption was comparable to that seen in ambulatory patients. There was no association between body weight and serum concentrations. Drug exposure was much higher in patients with renal impairment.

**Conclusions:** The data support using standard dosing of oseltamivir in severely ill patients with H1N1. No dosing adjustment is needed in obesity, while reduced dosing is indicated in renal failure.

**Reviewer's Comments:** During the outbreak of H1N1 pandemic flu over the last year, we faced severely ill patients without much information about how to care for them. During times of critical illness, there are frequently concerns about absorption of drugs administered through feeding tubes. This study is valuable because it demonstrates that this fear is unfounded for oseltamivir. In these large, critically ill individuals, standard dosing resulted in serum concentrations that were as high as or higher than that seen in normal volunteers. We still don't know if supra-normal dosing is more efficacious, but we now know that we need not increase dosing in obese patients or overcome impaired gastrointestinal absorption during critical illness. (Reviewer-Annette M. Rowden, PharmD).

**Keywords:** Oseltamivir, Dosing, H1N1, Obesity, Severe Respiratory Failure

**Print Tag:** Refer to original journal article
Mortality Rates Remain High for at Least 3 Years After ICU Discharge

Three-Year Outcomes for Medicare Beneficiaries Who Survive Intensive Care.

Wunsch H, Guerra C, et al:

JAMA 2010; 303 (March 3): 849-856

Long-term outcomes in Medicare patients who survive intensive care is impacted greatest by need for mechanical intubation and discharge to a skilled facility.

**Background:** Survival to hospital discharge of patients who receive intensive care is improving. Long-term survival rates of such patients are unclear.

**Objective:** To examine 3-year mortality for Medicare patients who receive intensive care and survive to hospital discharge.

**Design:** Matched retrospective cohort.

**Participants/Methods:** Data set consisted of a random sample of Medicare beneficiaries from 2002 to 2006. ICU survivors were defined as patients discharged alive treated with intensive care during hospitalization in 2003. Two control groups, a hospital control group (discharged alive without intensive care) and a general control group, were matched by age, sex, and race. Kaplan-Meier curves were used to assess 3-year mortality for the entire cohort and then by need for mechanical ventilation. Cox proportional hazards models were used to calculate risk ratios adjusted for age, comorbidities, admission to hospital or skilled nursing facility in the past year, and discharge destination.

**Results:** 35,308 patients received intensive care and survived to hospital discharge. Six-month mortality for ICU survivors was 14.1% compared with 10.9% and 2.7% for hospital and control groups, respectively. Comparing ICU survivors to the hospital controls, adjusted HRs (AHR) for 6-month mortality and 3-year mortality were 1.14 (95% CI, 1.10 to 1.19) and 1.07 (95% CI, 1.04 to 1.10), respectively. ICU survivors who underwent mechanical ventilation had a 6-month mortality of 30.1% versus 9.6% for hospital controls (AHR, 2.26; 95% CI, 1.90 to 2.69) and 3-year mortality of 57.6% versus 32.8% (AHR, 1.56; 95% CI, 1.50 to 1.73). Both ICU survivors and hospital controls who were discharged to a skilled nursing facility had a higher mortality than those discharged home. Six-month mortality was 24.1% versus 7.5% (AHR, 2.62; 95% CI, 2.50 to 2.74) and 3-year mortality was 54.6% versus 29.4% (AHR, 1.77; 95% CI, 1.72 to 1.82).

**Conclusions:** The number of Medicare beneficiaries who survive intensive care to hospital discharge is high. Six-month and 3-year mortality among ICU survivors is higher compared to matched controls. This risk is especially high in ICU survivors who underwent mechanical intubation.

**Reviewer’s Comments:** This study provides new insight into the long-term outcomes of not only those Medicare patients surviving intensive care, but also non-ICU hospitalization. Three-year mortality was much higher in both groups compared to the control population. The 2 characteristics that conferred the largest risk of dying after discharge included mechanical intubation for ICU survivors and discharge to a skilled facility for any hospitalized patient. These “at risk” groups will need to be examined more closely in future studies to see if there are any possible modifiers to decrease the high mortality rates. In addition, using reduced hospital mortality as a proxy for successful treatment of elderly patients is dubious, especially if patients are not discharged home. This information can be used to counsel patients and family about prognosis, even if they survive the ICU. (Reviewer-Timothy Scialla, MD).

**Keywords:** Health Outcomes, Medicare Beneficiaries, Intensive Care Unit

Print Tag: Refer to original journal article
Sustained Improvement in Sepsis Care Is Feasible

The Surviving Sepsis Campaign: Results of an International Guideline-Based Performance Improvement Program Targeting Severe Sepsis.
Levy MM, Dellinger RP, et al:
Crit Care Med 2010; 38 (February): 367-374

The Surviving Sepsis Campaign has shown increased compliance with guidelines and reduced hospital mortality over time in participating hospitals.

Background: The Surviving Sepsis Campaign (SSC) evidence-based guidelines were first published in 2002. Integration of similar practice guidelines into bedside practice has historically been slow. The SSC implemented a performance improvement program to improve clinical behavior.

Objective: To determine if a performance improvement program would improve compliance with bundled targets based on the SSC guidelines.

Design: Prospective observational study.

Participants: 15,022 patients from 165 hospitals in Europe, North America, and South America from January 2005 through March 2008.

Methods: The program included creation of 2 sepsis bundles: the "resuscitation bundle" to be completed within 6 hours and the "management bundle" to be completed within 24 hours. The program also developed educational materials, recruited hospitals and local doctors, and distributed data collection resources for practice audits and local feedback. Main outcome was change in compliance with bundles over time. Secondary outcome was hospital mortality. Logistical regression modeling was used to control for baseline characteristics.

Results: Compliance with the "resuscitation bundle" increased linearly from the first quarter to the end of 2 years from 10.9% to 31.3% (P <0.0001). For the "management bundle," the change was from 18.4% to 36.1% (P <0.008). The unadjusted hospital mortality dropped from the first quarter to the end of 2 years (37.0% to 30.8%; P =0.001). In adjusted models, the chance of death decreased the longer a site was in the program (0.8% per quarter and 5.4% over 2 years).

Conclusions: Participation in the SSC performance improvement program resulted in sustained compliance with evidence-based guidelines for sepsis care. This was associated with reduction in hospital mortality.

Reviewer's Comments: The most impressive finding of this study is the scale of the performance improvement efforts undertaken by the SSC. Hospitals in over 30 countries were involved in a voluntary fashion. I think that the authors demonstrate their primary outcome convincingly. It is clear that hospitals who participated over time showed increased compliance with the sepsis bundles. It is also clear that this enormous effort only led to compliance with guidelines about one third of the time. Less clear is why compliance remained low, and whether the increased compliance impacted overall quality of care and patient outcomes. The observational study design, the lack of a control group, and limited quality checks on data submission are major limitations, though unavoidable given the nature of the project and lack of funding. More rigorous trials that incorporate a control group are needed before the SSC evidence-based guidelines are definitively proven beneficial to patient outcomes. (Reviewer-Timothy Scialla, MD).

Keywords: Severe Sepsis, Performance Improvement, Surviving Sepsis Campaign

Print Tag: Refer to original journal article
Endocarditis Is a Different Disease in the Elderly

Age-Dependent Profile of Left-Sided Infective Endocarditis: A 3-Center Experience.

López J, Revilla A, et al:

Circulation 2010; 121 (February 23): 892-897

Older patients with left-sided endocarditis differ from younger patients in valvular involvement, bacterial causes, associated conditions, and outcome.

Background: The demographics of left-sided endocarditis have shifted to the elderly in the last 2 decades.

Objective: To evaluate the clinical characteristics, bacteriology, echocardiographic findings, and outcome in a cohort of patients with left-sided infective endocarditis across age groups.

Participants/Methods: 600 patients with documented left-sided endocarditis from 3 tertiary care hospitals were prospectively evaluated. All subjects were diagnosed using similar Duke criteria, and underwent similar testing including transthoracic and transesophageal echocardiography. Established criteria were used to diagnose complications of endocarditis and need for valve surgery. Patients were stratified into age quartiles.

Results: Demographics of left-sided endocarditis varied with increasing age, including a greater percentage of women, nosocomial endocarditis, and patients with pre-existing heart disease. Microbiology varied with increasing age including a higher incidence of Streptococcus bovis and enterococcus and decreasing incidence of Streptococcus viridians and Staphylococcus aureus. However, methicillin resistant S aureus increased with age. Echocardiographic findings also varied with age. Mitral valve involvement increased with advancing age while aortic valve endocarditis decreased. Younger patients more likely had valvular regurgitation and valve perforation. There were age-associated increases in heart failure and renal failure. Whereas two thirds of younger patients underwent surgery, only 40% of the oldest quartile had valve replacement. The percent of patients meeting indications for valve surgery but rejected due to comorbidity doubled from the youngest to the oldest quartile. Overall in-hospital mortality was 30%. In-hospital mortality increased from 20% in the youngest quartile to 36% in the older 2 quartiles.

Conclusions: In a large cohort of left-sided endocarditis, several age-related findings were determined. Endocarditis is more often nosocomial with a microbiology change to gut, genitourinary, or line-related sources. Young patients more likely have aortic valve endocarditis and more likely suffer regurgitation and valve perforation. Lastly, the percent of patients who underwent valve surgery was age related, with one half of older patients meeting surgical indications but rejected due to comorbidity.

Reviewer's Comments: The patient profile of endocarditis is changing. Contributing to this change is a fall in rheumatic heart disease, age-associated rise in calcific mitral and aortic disease, and an increasing number of devices and indwelling catheters that older patients now receive. The older endocarditis patient has comorbidity and frequently a nosocomial source of endocarditis (37% in the oldest quartile). The bacteriology has therefore changed away from Streptococcus viridians. The in-hospital mortality remains distressingly high for left-sided endocarditis. It is concerning that one half of older patients who met pre-established criteria for valve surgery did not receive this therapy. Nevertheless, surgical mortality was still greater in the older quartiles. Perhaps it is time for a randomized trial in older left-sided endocarditis patients to assess the benefit of valve surgery in this high-risk cohort. (Reviewer-Steven P. Schulman, MD).

Keywords: Age-Related Changes, Endocarditis, Valve Surgery

Print Tag: Refer to original journal article
Pharmacogenetics Predict Increased Responsiveness to Clopidogrel, Bleeding Risk

Cytochrome 2C19*17 Allelic Variant, Platelet Aggregation, Bleeding Events, and Stent Thrombosis in Clopidogrel-Treated Patients With Coronary Stent Placement.

Sibbing D, Kock W, et al:

Circulation 2010; 121 (February 2): 512-518

The CYP2C19*17 allele, which is involved in metabolism of clopidogrel to its active metabolite, results in an enhanced in vitro antiplatelet effect and an increased bleeding risk for patients following stent placement.

Background: Therapy with clopidogrel and aspirin reduces ischemic events and stent thrombosis, although bleeding risk increases as well. Clopidogrel is a prodrug, metabolized by the hepatic P450 system to its active metabolite. Prior studies show that a common single nucleotide polymorphism (SNP) of an important P450 enzyme, CYP2C19*2, results in a loss of function and less active clopidogrel metabolite, less antiplatelet effect in vitro, and a higher risk of recurrent ischemic events and stent thrombosis with aspirin plus clopidogrel therapy compared to wild-type patients. Another common SNP is CYP2C19*17, which results in increased function of this enzyme due to an increase in transcription.

Objective: To determine whether patients with the CYP2C19*17 SNP treated with clopidogrel prior to stent placement have a greater antiplatelet effect in vitro along with a greater bleeding risk and less ischemic risk over 30 days compared to wild-type patients.

Participants/Methods: 1524 patients receiving a stent were genotyped for the CYP2C19*17 SNP. Following a loading dose of clopidogrel, platelet aggregation studies were performed. Patients were followed 30 days for bleeding and ischemic events.

Results: 59% of patients were wild-type homozygous, 36% were heterozygous, and 5% were homozygous for the mutant *17 variant. There was a stepwise decrease in ADP-induced platelet aggregation from wild-type (wt/wt) to heterozygotes (wt/*17), to homozygotes (*17/*17). Carrying the CYP2C19*17 allele was independently associated with less ADP-induced platelet aggregation. There was a stepwise increased risk of both any and major bleeding from wild-type to heterozygotes to homozygotes for the *17 mutant allele. Carrying the CYP2C19*17 allele was an independent predictor of bleeding in this cohort. There were no differences by genotype in ischemic events or stent thrombosis.

Conclusions: The CYP2C19*17 allele, which is involved in metabolism of clopidogrel to its active metabolite, results in an enhanced in vitro antiplatelet effect and an increased bleeding risk for patients following stent placement. The dose-dependent effect from wild-type to heterozygotes and to homozygotes for both platelet aggregation and bleeding strengthens these conclusions.

Reviewer's Comments: This study would be strengthened by measuring the clopidogrel active metabolite by genotype. The lack of difference in ischemic events suggests that the wild-type patients had sufficient platelet inhibition with aspirin and a 600-mg load of clopidogrel. Further study will be needed to determine whether the *17/*17 patients could receive a lower clopidogrel dose without an increase in ischemic events and with less bleeding. Nevertheless, important SNPs of the CYP2C19 enzyme system have identified patients who have less platelet inhibition and an increased ischemic risk on clopidogrel (*2 allele) and a group with enhanced platelet inhibition to clopidogrel and an increased risk of bleeding (*17 allele). The era of pharmacogenetics and individualized patient care is here. (Reviewer-Steven P. Schulman, MD).

Keywords: Bleeding Risk, Pharmacogenetics

Print Tag: Refer to original journal article
The optimal timing for surgery is as soon as possible after signs of malignancy appear, but even bilateral dilated pupils should not be an absolute contraindication.

**Background:** Cerebral venous sinus thrombosis (CVT) can occasionally cause death due to transtentorial herniation. Decompressive surgery may be lifesaving.

**Objective:** To report 12 patients with malignant CVT, of whom 8 underwent operation.

**Design:** Retrospective study.

**Participants:** 12 of 255 patients with CVT who developed malignant CVT.

**Methods:** Malignant CVT was defined by the presence of supratentorial cortical lesions due to superficial venous system thrombosis with or without involvement of sinuses. The definition required clinical or radiological signs of transtentorial herniation, the former including decreased consciousness and dilated pupils.

**Interventions:** Decision to operate was at surgeon's discretion.

**Results:** Age range was 18 to 68 years. Most patients were female (9 of 12). The time between symptom onset and diagnosis ranged from 12 hours to 2 weeks. Signs of malignancy occurred rapidly over 2 to 30 hours, and included hemorrhagic parenchymal lesions in all but 1 patient with volume 57 to 262 mL. Three operated patients had a unilateral fixed dilated pupil and 2 had bilateral fixed dilated pupils at time of malignant worsening. All nonoperated patients had at least 1 fixed dilated pupil and died within 1 to 5 days after diagnosis. Operated patients had intravenous heparin restarted at a median of 12 hours after surgery. Only 1 operated patient died of a pulmonary embolism on day 9 despite anticoagulation. The other 7 survived with an ICU stay of 4 to 52 days. At median follow-up (23 months), median modified Rankin Score (mRS) was 1, with 6 patients having a complete recovery and 1 who was still dependent (mRS=3). Four of 7 patients returned to a job or study.

**Conclusions:** Decompressive surgery, either external, internal, or both for malignant CVT can be lifesaving and allow a good functional recovery even after developing clinical transtentorial herniation.

**Reviewer's Comments:** This small retrospective study is subject to the usual limitations of nonrandomization. Because the nonoperated cases had more severe clinical presentations at onset, it is not clear whether surgery, had it been performed early, would have been beneficial. It is remarkable that all nonoperated patients died, whereas no operated patient had a neurological death and that significant neurologic improvement occurred despite the presence of bilateral fixed dilated pupils in 2 cases. It is also worth noting that patients continued to improve for months after surgery. These represent far better outcomes than after hemicraniectomy for malignant middle cerebral artery infarction. Although heparin is the treatment of choice in CVT, the authors hypothesize that collapse of cerebral veins due to malignant vasogenic edema may hinder the effect of heparin. Decompressive surgery not only reduces the risk of herniation, but may also improve collateral cortical venous drainage preventing thrombus extension and possibly allowing better diffusion of heparin. (Reviewer-Wendy C. Ziai, MD).
Individual TBI patients have unique optimal CPP levels ranging from 60 to 100 mm Hg that achieve optimization of cerebral vasomotor reactivity.

**Background:** The method of optimizing the cerebral perfusion pressure (CPP) based on continuous monitoring of the cerebrovascular pressure reactivity (PRx) to spontaneous fluctuations in mean arterial pressure (MAP) in traumatic brain injury (TBI) patients may be associated with improved neurologic outcome.

**Objective:** To analyze the relationship between optimal CPP and partial pressure of brain tissue oxygen ($P_{br}O_2$).

**Design:** Prospective observational cohort study.

**Participants:** 38 patients with TBI with Glasgow Coma Scale score 3 to 13 and requiring neuromonitoring of intracranial pressure (ICP) and $P_{br}O_2$ using intraparenchymal probes inserted into frontal white matter of the more severely injured hemisphere.

**Methods:** PRx was calculated as a moving linear correlation coefficient between 30 consecutive samples of MAP and ICP. The optimal CPP ($CPP_{OPT}$) was the CPP group (range, 5 mm Hg) in which average PRx was lowest. The CPP level was identified at which $P_{br}O_2$ reached a plateau and was not pressure-dependent on CPP (called the $P_{br}O_2$ "change point").

**Results:** $CPP_{OPT}$ could be identified in 32 of 38 patients and ranged from 60 to 65 mmHg to 95 to 100 mm Hg (median, 70 to 75 mm Hg). CPP at the $P_{br}O_2$"change point" could be determined in 30 patients. This CPP ranged from 50 to 55 mm Hg to 95 to 100 mm Hg (median, 70 to 75 mm Hg). There was a significant correlation between $CPP_{OPT}$ and the CPP at the $P_{br}O_2$ "change point" (deviation <5 mm Hg in 67% of patients; <10 mm Hg in 93%). At $CPP_{OPT}$, PRx was -0.04 and $P_{br}O_2$ was 24.5 mm Hg. The $P_{br}O_2$ decreased in parallel with CPP at levels of CPP below $CPP_{OPT}$ and did not improve further at levels of CPP above $CPP_{OPT}$.

**Conclusions:** A relationship exists between CPP and $P_{br}O_2$. $P_{br}O_2$ reaches a plateau above $CPP_{OPT}$ and exhibits relative pressure passive behavior below $CPP_{OPT}$. Pushing CPP above $CPP_{OPT}$ does not improve brain oxygenation or perfusion and having a CPP below $CPP_{OPT}$ results in a decrease in autoregulatory vasomotor reactivity, pressure passive cerebral blood flow, and possible ischemia.

**Reviewer's Comments:** This is a conceptually appealing study that suggests that titrating CPP to individual physiology represents an improvement over using the same goal for all TBI patients. The methodology assumes that $P_{br}O_2$ is a surrogate for cerebral blood flow. This has been demonstrated, but does not take into account the impact of arteriovenous oxygen tension difference. Blood gas alterations, especially hypocapnia, may influence the PRx. $CPP_{OPT}$ cannot be identified in all patients (16%) and may occur because $CPP_{OPT}$ is outside the range studied or the patient has complete absence of autoregulatory function. In these patients, $P_{br}O_2$ may add important information about $CPP_{OPT}$. Whether this technology improves patient outcomes is not known. (Reviewer-Wendy C. Ziai, MD).

**Keywords:** Brain Injury, Brain Tissue Oxygen, Cerebrovascular Pressure Reactivity, Cerebral Perfusion Pressure, Neuromonitoring, Cerebral Autoregulation