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To Cut or Not To Cut: Early Cholecystectomy May Improve Outcomes.

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Dr. DeWaay reports no financial relationships in this field of study

SYNOPSIS: Early cholecystectomy for acute cholecystitis is associated with less major bile duct injury and a shorter length of stay.

SOURCE: Mestral C, Rotstein O, Laupacis A, Hoch J, Zagorski B, Alali A, Nathens A. Comparative Operative Outcomes of Early and Delayed Cholecystectomy for Acute Cholecystitis. *Annals of Surgery* 2014; 259:10-15

While acute cholecystitis is a very common cause of admission to the hospital, the evidence is not clear as to the best time to operate. Some surgeons operate early while others prefer to have the gallbladder "cool off," allowing a delay up to 6-12 weeks. Early studies have suggested the benefit of doing an early cholecystectomy is shorter length of stay without an increase in the conversion rate to an open procedure. However, there is also evidence that the risk of death and major bile duct injury is greater when operating on an inflamed gallbladder. Although the risk of major gallbladder injury during cholecystectomy is minimal, when it occurs there is significantly increased morbidity, mortality, and subsequent litigation. Researchers conducted this retrospective, cohort study to better understand how the timing of laproscopic cholecystectomy impacted the rate of surgical complications such as major bile duct injury, death and conversion to an open procedure.

Patients emergently admitted for acute cholecystitis and treated with cholecystectomy over a 7-year period were included in this study. Researchers extracted data from administrative records for the province of Ontario, Canada that includes more than 13 million residents. 31,667 patients were admitted for acute cholecystitis, as determined by ICD-10 coding, without prior history of gallstone disease. 22,202 were included in the study. Patients were excluded for the following: severe cholecystitis (admitted to intensive care unit or cholecystostomy tube was placed), no

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cholecystectomy was performed, missing data on income quintile, missing data for 6 month post-operative follow-up, or the presence of biliary malignancy or cyst. The patients were divided into an early cholecystectomy group, those that received surgery within 7 days of admission, and a delayed cholecystectomy group, those that had surgery delayed more than 7 days after presentation. Primary and secondary endpoints respectively were: major biliary duct injury requiring operative repair, major biliary duct injury combined with death, completion of a cholecystectomy via an open approach, 30-day postcholecystectomy mortality, total hospital length of stay and conversion from a laparoscopic procedure to an open approach. The authors analyzed the data for the following potential patient confounders including but not limited to: sex, age, and comorbidity burden. They also analyzed for the potential physician confounders including years since medical graduation and the number of cholecystectomies performed the year prior to the surgery.

There were significant differences between the two groups initially. For example, the early cholecystectomy group was more likely to be younger, female, less likely to have a biliary obstruction or pancreatitis on admission. To account for these differences in the groups, the authors calculated propensity scores for each patient. Potential confounders were regressed using logistical regression modeling in order to give the appropriate score. Patients from the early cholecystectomy group were matched with patients from the late group based up similar propensity scores. The pairs had to be within 5 years for age and be of the same sex. After matching, there were no significant differences in confounders between the two groups or their surgeons.

The patients with early cholecystectomy were less likely to have a major bile duct injury (RR 0.53 (CI 0.31-0.90; $P = 0.025$) and less likely to have combined major bile duct injury or death RR 0.72 (CI 0.56-0.94; $P = 0.016$). There was no significant difference between the two groups regarding 30-day post-cholecystectomy mortality, open cholecystectomy or conversion from a laparoscopic to an open case. Finally, the early cholecystectomy group had a lower length of stay compared to the delayed group (mean difference = 1.9 days, 95% CI 1.7-2.1).

This study demonstrated a benefit to early cholecystectomy. The authors hypothesize that the reason for the increased complications from major biliary duct injury in the delayed group may be secondary to the subsequent development of fibrosis around Calot's triangle after the initial inflammation improves. The risk of this fibrosis may increase if there is another bout of acute cholecystitis before the surgery is performed.

The limitations of the study are the following. First, there can be residual confounding variables not addressed by propensity scoring. Second, inclusion into the study was based on administrative data and ICD-10 coding which may not be accurate. Third, whether or not the surgeon had subspecialty training in hepatobiliary or minimally invasive surgery was not obtained. There also was no mention of the presence of a trainee during the surgery. Fourth, the cause of death was not available. Finally, this study only identified biliary leaks that were managed surgically. Those that were managed with percutaneous or endoscopic intervention were not included.

■ COMMENTARY

This study is important to review not only because of the question asked, but also because of how the researchers chose to obtain the answer. Clearly, randomized control trials (RCTs) and meta-analyses are the "best." However, when resource limitations preclude large scale RCTs, retrospective, cohort studies using propensity scoring offer an elegant solution. Researchers in this study were able to include over 20,000 patients, which would be impossible with an RCT. Clearly, there are multiple limitations as described above, however, the sheer volume of patients included and the use of propensity scoring mean that the results have validity and should be considered when caring for patients with cholecystitis.

Patients with severe abdominal

pain are often admitted to a hospitalist service for diagnosis of the abdominal pain and subsequently diagnosed with cholecystitis. Although when a cholecystectomy should be performed for a particular patient will be up to the surgeon, this study indicates that hospitalists should consult surgery early once a diagnosis of acute cholecystitis is made so that an early surgery can be performed if possible. ■

ABSTRACT & COMMENTARY

Efficacy and Safety of Very Early Mobilization After Onset of Acute Stroke

By Harold L. Karpman, MD., FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: The higher dose, very early (within 24 hours) mobilization protocol was associated with a reduction in the odds of a favorable outcome at 3 months after stroke occurrence.

SOURCE: Bernhardt J and the AVERT trial collaboration group. Efficacy and safety of very early mobilization within 24 hours of stroke onset (AVERT): A randomized controlled trial. *Lancet* 2015;386:46-55.

Very early (i.e., within 24 hours) mobilization after stroke onset comprised of out-of-bed sitting, standing, and walking is thought to contribute to the positive effects of stroke-unit care and is therefore recommended in many guidelines.[1,2] However, positive evidence for recommending early mobilization has been quite limited.[3] The biological rationale for early mobilization has centered around the clinical conclusions that bedrest negatively affects the musculoskeletal, cardiovascular, respiratory, and immune systems[4] and might slow recovery, since immobility-related complications are common after stroke in patients who remain inactive.[5] Finally, it has been argued that there is a narrow window for opportunity for brain plasticity to repair itself, and the optimum time for positive change is thought by many clinicians to occur soon after the stroke occurs.[7,8]

The AVERT Trial Collaboration group was formed to perform a study investigating the relative efficacy of a protocol intended to compare earlier-than-usual mobilization after a stroke with the usual care, which traditionally has begun 24 or more hours after the stroke.[10] The researchers performed a parallel-group, single-blind, multicenter, international, randomized, controlled trial at 56 stroke units in five countries (Australia, New Zealand, Malaysia, Singapore, and the United Kingdom)[9] to determine if early mobilization would improve functional outcomes, reduce immobility-related complications, and accelerate walking recovery at 3 months post-stroke occurrence with no increase in neurological complications. A total of 2104 patients were enrolled and randomized to an early mobilization group and to a usual care group. The results demonstrated that very early mobilization after a stroke was associated with a significant reduction in the odds of a favorable outcome at 3 months after the stroke; however, the number of patients who died or had serious adverse events at 3 months after the stroke did not differ significantly between groups.

■ COMMENTARY

The results of this very large and complex clinical trial comparing a high-dose, frequent mobilization protocol starting within 24 hours after a stroke appeared to be no better than "usual" care. However, careful analysis of the usual care protocols in the stroke care units will be required before drawing final conclusions, since components of early care intervention were already part of routine clinical care in many locations. The AVERT researchers indicated that they were going to further analyze the data and do a dose-response analysis to establish the effect of dose of rehabilitation on efficacy and safety outcomes. It should be noted that 26% of all patients were > 80 years of age and 24% of patients had received recombinant tissue plasminogen activator. Early mobilization did not reduce the incidence of immobility-related complications or significantly accelerate walking recovery. In fact, it reduced the odds of a favorable outcome at 3 months after the stroke occurred.

The results of the AVERT trial are incomplete since the authors indicated that they are now undertaking a dose-response analysis to establish the effect of dose of rehabilitation on efficacy and safety outcomes and to establish a better understanding of exactly which patients best respond to rehabilitative treatments, be they early or later, and which do not. It would appear that, for the time being, early mobilization would be

appropriate and useful in carefully selected but not in all stroke patients. Until a deeper understanding evolves regarding which patients best respond to rehabilitative treatment and which patients do not is firmly established, clinicians would be advised to be cautious about early mobilization post-stroke. ■

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ABSTRACT & COMMENTARY

Clostridium difficile Infection — Back to the Future

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Professor of Medicine, Stanford University, CA.

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: This study provides strong evidence that the diagnosis of *Clostridium difficile* infection (as opposed to colonization) should be made on the basis of evidence of toxin production, not the mere presence of the organism as detected by glutamate dehydrogenase testing or the presence of toxin genes.

SOURCE: Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of Clostridium difficile infection in the molecular test era. *JAMA Intern Med* 2015 Sep 8:1-10.[Epub ahead of print.]

Hospitals that introduced polymerase chain reaction (PCR) testing for *Clostridium difficile* toxin genes in stool were suddenly confronted with an apparent 40% to 50% increase in detection of the organism — not a good thing in a world of public reporting and value-based purchasing. This did not represent an increased infection rate, but, rather, the detection of colonization by the organism, something that is found in as many as 8% of patients without diarrhea admitted to the hospital. This is not just a bad thing for the reputation and finances of the hospital, it is a bad thing for the patients who receive unnecessary treatment.

In 2013, Planche and colleagues reported the results of a large study evaluating the ability of various diagnostic methods to predict outcomes in those with positive results.[1] They found that the detection of *C. diff* by PCR for toxin gene or by a glutamate dehydrogenase assay was not predictive of increased mortality in the absence of a positive test by either enzyme immunoassay (EIA) or cytotoxigenic culture positivity, with the latter being the most highly correlated with fatality. In contrast, Rao et al, using a two-step system that detects *C. diff* glutaraldehyde dehydrogenase and toxin, recently concluded that toxin detection was not predictive of severe disease or mortality,[2] although their results have been questioned by Planche and colleagues.[3]

Thus, we have a problem and a controversy, one that now has been addressed by another group. Polage

and colleagues set out "to determine the natural history and need for treatment of patients who are toxin immunoassay negative and polymerase chain reaction (PCR) positive (Toxin–/PCR+) for CDI." They performed a series of tests on unformed PCR of stool samples submitted to their laboratory for *C. diff* testing that began with PCR for toxin gene (the result of which was not reported to the clinician) and toxin immunoassay.

Of the 1416 hospitalized adults whose stools were tested, 131 (9.3%) were Toxin+/PCR+, 162 (11.4%) Toxin–/PCR+, and 1123 (79.3%) were Toxin–/PCR–. Patients who were Toxin+/PCR+ had had greater prior antibiotic exposure, more frequently had leukocytosis, had more diarrhea on day 1, and were more likely to have elevated fecal lactoferrin than those in the other groups — who largely did not differ from each other clinically. They also had a longer duration of diarrhea than Toxin–/PCR+ patients and Toxin–/PCR– patients ($P < 0.001$), and had a greater risk of diarrhea during the follow-up. In multivariate analysis, Toxin+/PCR+ status had the strongest effect on the duration of diarrhea. Toxin–/PCR+ status and pretest exposure to metronidazole or oral vancomycin were not significant predictors in the multivariable model. One hundred percent of Toxin+/PCR+ patients were treated for a median duration of 14 days with vancomycin or metronidazole. Among the Toxin–/PCR+ patients, 40.7% were treated, but only for a median duration of 6 days; 32.1% of those Toxin–/PCR– received one of these antibiotics for a median of 5 days.

Complications, such as megacolon, need for colectomy or intensive care unit care, and death, occurred in 10 (7.6%) of 131 Toxin+/PCR+ patients, compared to 0 of 162 who were Toxin–/PCR+ and 3 (0.3%) of 1123 ($P < 0.001$) Toxin–/PCR– patients. There was no significant difference between the latter two groups. In addition, 11 (8.4%) Toxin+/PCR+ patients died compared to 1 (0.6%) and none ($P < 0.001$) who were Toxin–/PCR+ and Toxin–/PCR–, respectively. The single death in the Toxin–/PCR+ group occurred in a patient with severe comorbidities who had uncomplicated recurrent diarrhea that had resolved prior to withdrawal of care.

These data provide a strong argument that the diagnosis of disease caused by *C. diff* should be made on the basis of the detection of toxin, not toxin gene (or glutamate dehydrogenase). This would appear to reduce unnecessary treatment, as well as heartburn, for Infection Prevention Programs and hospital administrators.

The data also provide an argument for antimicrobial stewardship — and not just regarding apparent unnecessary anti-*C. diff* treatment in Toxin–/PCR+ patients. Why was a median duration of 6 days of such treatment administered to approximately one-third of patients who were Toxin–/PCR–? ■

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ABSTRACT & COMMENTARY

Acetaminophen for Fever in the ICU

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Clinical Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine.

Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Seven hundred ICU patients with fever and known or suspected infection were randomly assigned to receive acetaminophen 1 g IV or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death. Early administration of acetaminophen did not affect number of ICU-free days.

SOURCE: Young P, et al. Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med 2015 Oct. 5; [Epub ahead of print].

Seven hundred adult intensive care unit (ICU) patients with fever (temperature ≥ 38°C) and known or suspected infection were randomized to receive either acetaminophen 1 g

IV or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death. The primary outcome was ICU-free days (days alive and free from need for ICU care) from randomization to day 28.

Baseline characteristics of the patients were similar between the groups. Common coexisting conditions included cancer (20-21%), chronic pulmonary disease (12-14%), diabetes (25-26%), and ischemic heart disease (15%). Virtually all patients met criteria for "sepsis," 50-53% required vasopressors, and 57-60% required mechanical ventilation.

There was no difference between the acetaminophen and placebo groups in the primary outcome (23 ICU-free days in acetaminophen group vs. 22 days in the placebo group), nor in the secondary endpoints (hospital-free days, days free from mechanical ventilation, days free from inotropes/vasopressors, renal replacement therapy, or days free from ICU support). Similarly, there was no difference between the groups in death by day 28 (13.9 vs. 13.7%), and death by day 90 (15.9 vs. 16.6%) in the acetaminophen and placebo groups, respectively. Hospital length of stay among non-survivors was significantly longer (13.9 days vs. 7.7 days), as was ICU length of stay in non-survivors (10.4 days vs. 4.0 days) in acetaminophen-treated patients compared to placebo-treated patients. There was no difference between the groups in either hospital length of stay or ICU length of stay in survivors.

There were no discernible differences in adverse events between acetaminophen- and placebo-treated patients. Slightly more than 8% of acetaminophen-treated patients and 9.9% of placebo-treated patients experienced liver dysfunction leading to study drug discontinuation.

■ COMMENTARY

This is an interesting study, conducted in New Zealand, which demonstrates no discernible benefit from routine administration of acetaminophen in critically ill febrile patients with known or suspected sepsis. The use of acetaminophen in this setting also did not appear to result in any obvious harm. The observation that ICU and hospital lengths of stay were longer in acetaminophen-treated patients who eventually died is intriguing. This result is consistent with an earlier study, which showed that physical cooling to normothermia delayed death in mechanically ventilated patients with septic shock.[1] Similarly, an older retrospective cohort study in ICU patients showed that acetaminophen-treated patients had a significantly longer time to death than did those who did not receive acetaminophen.[2] This effect of acetaminophen delaying death without affecting mortality at day 28 or day 90 is intriguing and potentially generates many different hypotheses as to why this phenomenon is observed. ■

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ABSTRACT & COMMENTARY

Beta-blocker Dose More Important Than Heart Rate in Systolic Heart Failure

By Van Selby, MD

Assistant Professor of Medicine, UCSF Cardiology Division, Advanced Heart Failure Section, San Francisco

Dr. Selby reports no financial relationships relevant to this field of study.

SOURCE: Fiuzat M, et al. Heart rate or beta-blocker dose? Association with outcomes in ambulatory heart failure patients with systolic dysfunction: Results from the HF-ACTION trial. *JACC: Heart Failure* 2015. doi:10.1016/j.jchf.2015.09.002.

Beta-blockers reduce both morbidity and mortality in chronic heart failure with reduced ejection fraction (HFrEF). More recently, heart rate (HR) reduction has been

associated with better outcomes in HFrEF.

Fiuzat et al aimed to determine whether higher beta-blocker doses or reduced HR has a greater impact on outcomes in chronic HFrEF.

To compare the relative effects of HR reduction and higher beta-blocker dose, they performed a secondary analysis of the HF-ACTION trial. HF-ACTION randomized 2331 patients with ambulatory NYHA functional class II-IV heart failure and left ventricular ejection fraction < 35% to exercise training vs usual care.

Patients were on stable doses of heart failure therapies for at least 6 weeks prior to study enrollment, with 94.5% receiving beta-blockers.

Secondary analysis patients were categorized as either high (≥ 25 mg/day of carvedilol equivalent) or low beta-blocker dose and high (≥ 70 bpm) or low HR. The primary endpoint was the composite of death or all-cause hospitalization, and median follow-up was 2.5 years.

In unadjusted analyses, both higher beta-blocker dose and lower HR were associated with reduced risk of death or hospitalization.

However, after adjusting for other predictors, only higher beta-blocker dose was significantly associated with the primary outcome (hazard ratio 0.77; $P = 0.03$).

Higher beta-blocker dose was associated with improved outcomes regardless of the achieved HR. There was no increased risk of bradycardia among patients on higher doses of beta-blockers. The authors concluded that in HFrEF, titrating beta-blocker doses may confer a greater benefit than reducing HR.

■ COMMENTARY

Multiple large randomized trials have shown that treatment with beta-blockers leads to symptomatic improvement, reduced hospitalization, and increased survival in HFrEF. These trials generally targeted high doses, and as a result current guidelines recommend treatment with moderate to high doses of beta-blockers in HFrEF.

However, evidence of a strong dose-response relationship for beta-blockers is somewhat limited, and one meta-analysis found no association between beta-blocker dose and outcome.

The findings from the current analysis show that patients with higher beta-blocker doses have a lower risk of hospitalization or death, even after adjusting for other clinical predictors, and support the current recommendations.

Despite clear guideline recommendations, multiple studies have found that most patients with HFrEF are not titrated to target doses.

There are many reasons for this, including concern for side effects, health system barriers that prevent easy medication titration, and possibly a lack of clear evidence that outcomes improve at higher doses.

With the recent FDA approval of ivabradine, clinicians may be tempted to keep beta-blockers at lower doses and instead initiate ivabradine to achieve HR goals in patients with HFrEF.

Ivabradine effectively lowers HR without many of the side effects associated with beta-blockers, and does not affect blood pressure.

FINDINGS

The findings of Fiuzat and others remind us that such practices are unacceptable for patients with HFrEF. Beta-blockers have beneficial effects in HFrEF beyond lowering HR, and titrating to target doses must be considered the first-line treatment.

This was a post-hoc analysis with several limitations. It is possible that patients on lower doses of beta-blockers were sicker, and therefore unable to tolerate target doses.

The authors adjusted for many clinical characteristics, but residual confounders are a possibility. Furthermore, this study did not evaluate the strategy of using a non-beta-blocking medication such as ivabradine to lower HR; rather, it studied the association between baseline HR and outcomes.

Certain strategies can help reach target beta-blocker doses, and there are published guidelines to help increase the chance of successful up-titration.

Always start with low doses (i.e., carvedilol 3.125 mg twice per day), and there should be minimal or no evidence of fluid retention when beta-blockers are initiated or up-titrated.

Patients should be instructed to check their weight every morning after every dose increase to identify worsening fluid retention, and they should be advised that any initiation or dose increase may be associated with mild worsening of heart failure symptoms that often resolves after several weeks.

A growing body of literature shows the importance of reaching target doses of beta-blockers in HFrEF. It can be difficult at times, and may require close monitoring.

Nevertheless, given the clear benefit this must be the goal for all HFrEF patients.

The approval of ivabradine will be a useful addition for a small portion of HFrEF patients, but absolutely cannot substitute for higher beta-blocker doses in those patients who can tolerate it. ■

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CME QUESTIONS

1. All of the following are complications to a cholecystectomy except:

a. Conversion from a laparoscopic to an open procedure

b. Death

c. Graft infection

d. Major biliary ductal injury

e. Wound infection

2. According to the AVERT trial, very early mobilization after onset of acute stroke led to which of the following outcomes:

a. A decreased risk of death after 3 months

b. A decreased risk of serious adverse events after 3 months

c. A significant improvement in the odds of a favorable outcome after 3 months

d. An increased risk of recurrent stroke after 3 months

e. None of the above

3. The study by Young, et al., demonstrated that the use of acetaminophen for fever in the ICU leads to:

a. More rapid resolution of septic shock

b. Decreased mortality

c. Increased risk of acute hepatic failure

d. No difference in ICU-free days or hospital-free days

e. All of the above

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

[IN FUTURE ISSUES]

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