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INSIDE

Crystalloid Solutions Still Better than Colloid Solutions for Fluid Resuscitation

ABSTRACT & COMMENTARY

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

This article originally appeared in the September 2012 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

Synopsis: *This blinded, randomized, controlled trial reports a higher risk of mortality, need for renal replacement therapy, and blood product transfusion in patients treated with the colloid solution hydroxyethyl starch compared to those treated with the crystalloid solution Ringer's acetate.*

Source: Perner A, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;367:124-134. Erratum: *N Engl J Med* 2012;367:481.

This blinded, randomized, multicenter trial compared the colloid solution low-molecular-weight hydroxyethyl starch (HES 130/0.42) with the crystalloid solution Ringer's acetate for the treatment of severe sepsis. Patients 18 years of age or older diagnosed with severe sepsis (a defined focus of infection and at least two systemic inflammatory response syndrome criteria and at least

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one new organ failure) who needed fluid resuscitation were included. Patients were randomized in a 1:1 ratio, stratified by the presence or absence of shock, active hematologic cancer, and admission to a university or non-university hospital. Just over 1200 patients were screened, 407 were excluded, and 804 underwent randomization. Most patients were excluded for having received more than 1000 mL of synthetic colloid (37%) or having undergone renal replacement therapy (34%) prior to randomization. The median age was 66 years and 60% were male. At randomization, 84% of patients were in shock, 35% had acute kidney injury, and 61% were mechanically ventilated. Treatment groups were well balanced.

Patients judged to need fluid resuscitation by ICU clinicians were provided trial fluid up to a maximum of 33 mL/Kg of ideal body weight per day. This value was chosen to try to ensure that no patients received more HES than the manufacturer's recommended daily dose of 50 mL/Kg. If additional fluid was required, unblinded Ringer's acetate was used for all patients. Trial fluid was provided free of charge in identical bags prepared by the manufacturer. The manufacturer had no role in the protocol, trial conduct, data analysis, or reporting.

The composite primary outcome was either death or dependence on dialysis at 90 days and occurred more often in patients who received HES (51%) than in patients who received Ringer's acetate ([43%] relative risk, 1.17; 95% confidence interval [CI] 1.01 to 1.36; $P = 0.03$]. Since only one patient in each group was dependent on dialysis at 90 days, the primary difference in outcome was due to higher mortality among patients given HES. Many secondary outcome measures were also worse among patients given HES. More patients required renal replacement therapy (relative risk, 1.35; 95% CI, 1.01 to 1.80; $P = 0.04$) and blood transfusions (relative risk, 1.20; 95% CI, 1.07 to 1.36).

■ COMMENTARY

Strengths of this study include a large, heterogeneous patient population from both university and community hospitals in several countries with few exclusion criteria. Thus, the study is well generalizable. The trial was well blinded, minimizing bias. The authors had excellent follow-up with 798 of 804 patients contributing data at 90 days.

There seems to be an endless debate over the use of colloids and crystalloids for fluid resuscitation. Colloids are generally believed to raise oncotic pressure better than crystalloids, allowing for greater plasma volume expansion with less overall fluid requirements. For example, the natural colloid albumin may expand plasma volume 40% more than crystalloid. In the Saline vs Albumin Fluid Evaluation (SAFE) Study, a randomized controlled trial of albumin vs saline in an intensive care unit, patients given saline had a greater net fluid balance compared to those who received albumin.[1] However, the plasma volume expansion properties may differ among colloid solutions. There were no significant differences in fluid volume balance between patients who received HES and Ringer's Lactate in this study.

Those in favor of colloids argue that increased plasma volume expansion leads to a more rapidly improved blood pressure with less overall volume delivered. Despite these arguments, multiple trials have failed to show a benefit over crystalloids with respect to mortality. In the SAFE trial, 28-day mortality did not differ between the two groups. A recent Cochrane review of 66 randomized, controlled trials of various colloid solutions compared to crystalloids also found no difference in mortality.[2] We now have evidence of increased mortality with the use of HES compared to Ringer's acetate.

In summary, the use of HES compared to Ringer's acetate was associated with increased mortality, need for renal replacement therapy, and blood product transfusion. These data, coupled with numerous previous studies and the increased expense of colloids, argue that crystalloids should be used preferentially for most patients requiring fluid resuscitation. ■

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ICU Admission or General Ward for Diabetic Ketoacidosis? The Answer Varies Dramatically in Different Hospitals

ABSTRACT & COMMENTARY

By David J. Pierson, MD

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This article originally appeared in the September 2012 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD. Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

Synopsis: *In a large cohort of patients admitted to New York hospitals with diabetic ketoacidosis, about half were admitted to the ICU, with a range of 2% to 88% among individual hospitals. This large practice variation was unassociated with mortality or length of stay, and more than half of it remained unaccounted for after extensive adjustments for patient and institutional characteristics.*

Source: Gershengorn HB, et al. Variation in use of intensive care for adults with diabetic ketoacidosis. *Crit Care Med* 2012;40:2009-2015.

Using a statewide administrative database and other sources, Gershengorn and colleagues examined data on all adult patients with a primary diagnosis of diabetic ketoacidosis (DKA) who were admitted to hospitals in the state of New York from 2005-2007. The investigators sought to determine what proportion of these patients were admitted to the ICU, and what associations with patient or hospital characteristics or other identifiable aspects of care might explain any observed differences.

During the study period, there were 15,994 patient admissions for DKA to 159 hospitals. Most of the hospitals were in urban settings and about half of them were teaching hospitals. Median hospital size was 190 beds with 9.4% of these being ICU beds. The DKA admissions represented 0.4% of all hospital and 1.4% of all ICU admissions to the study hospitals during the 3-year study period. Median reliability- and risk-adjusted hospital mortality was 0.7% (range, 0.4% to 3.4%), and median hospital length of stay was 3 days (range, 1 to 6 days).

Of the admissions for DKA, 52.6% were admitted to an ICU. These patients tended to be younger, white, privately insured, from a higher-income zip code, and admitted on the weekend, with all these differences being statistically significant. They were also more likely to have chronic illnesses and be admitted emergently. The proportion of DKA admissions receiving intensive care varied dramatically across hospitals, with an adjusted range of 2.1% to 87.7%. However, this variation was not associated with mortality or hospital length of stay. ICU admission occurred less often in hospitals that admitted larger numbers of patients with DKA (highest quartile vs lowest, odds ratio 0.40, $P = 0.002$), but more often in hospitals with higher rates of ICU admission for non-DKA admissions (odds ratio 1.31, $P = 0.001$, for each additional 10% increase). Using multilevel modeling to account for individual patient and hospital factors, the authors were able to explain less than half of the observed variation in ICU utilization for patients with DKA: 58% of the variability attributable to hospitals could not be explained.

■ COMMENTARY

Like acute gastrointestinal bleeding without hypotension, DKA is a common reason for ICU admission that carries a low risk for mortality, and also has a thoroughly studied and highly protocolized management approach. The fact that this study found no differences in mortality or hospital length of stay in nearly 16,000 DKA admissions, only half of which included care in an ICU, reinforces the concept that a large proportion of such admissions can be handled safely and effectively on the acute-care wards. Despite the large number of patients included, this retrospective study based on administrative data cannot determine the reasons for the differences in ICU admission rates among the various hospitals. However, Gershengorn et al nicely demonstrate that the issue of where to manage DKA patients is currently being approached very differently in different institutions, with a rate of ICU admission varying from 1 in 50 to more than 4 out of every 5 such patients.

As the authors point out, their findings can be interpreted in various ways. It may be that patients admitted with DKA can be managed just fine without ICU admission. However, it is also possible that such patients are already being triaged appropriately at all the study hospitals, such that those who really need ICU care (and are thus having their outcomes improved accordingly) are getting it. The latter interpretation, while possible, seems less likely to me in view of the enormous practice variation documented across the 159 hospitals. I suspect that much of the observed variation relates to traditional practice patterns and other aspects of institutional culture in the different hospitals.

Practice variation has been identified as an important problem in health care,[1] and its reduction is currently a

major target for many quality and safety initiatives. However, as recently emphasized in a tri-society statement on the appropriate use of clinical research data and other types of knowledge in critical care, practice variation is inevitable in a high-stakes field with an incomplete and sometimes contradictory database.[2] How much this assertion applies to DKA is uncertain. As the authors of the current study caution, further research is needed to clarify the most effective and cost-efficient use of the ICU for patients admitted with DKA. ■

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Nasal site MRSA surveillance may miss colonization

ABSTRACT & COMMENTARY

By Joseph F. John Jr. MD, FACP, FIDSA, FSHEA

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Dr. John reports no financial relationships relevant to this field of study. This article originally appeared in the September 2012 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

Synopsis: *Nasal swabs identified only two-thirds of MRSA carriers.*

Source: Matheson A, Christie P, Stari T, et al. Nasal swab screening for methicillin-resistant Staphylococcus aureus—How well does it perform? A cross sectional study. *Infect Control Hosp Epidemiol* 2012;33:803-8.

David MZ, Medvedev S, Hohmann SF, et al. Increasing burden of methicillin-resistant Staphylococcus aureus hospitalizations at US Academic Medical Centers 2003-2008. *Infect Control Hosp Epidemiol* 2012;33:782-9.

The classic teaching is that if a human carries *Staphylococcus aureus*, it is most likely residing in the anterior nares. This concept held generally true for methicillin-susceptible *S. aureus* (MSSA) and for nosocomial methicillin-resistant *S. aureus* (MRSA) for many years. With the advent of community-based MRSA — so-called USA300 — there often was a conspicuous absence of nasal carriage in persons who had single or even multiple infections with community-MRSA/USA300. Thus, there has been an evolving question of what anatomic sites, if any, give the most reliable index of colonization and a risk of subsequent infection.

Now comes a study from Scotland in two of its acute care hospitals to determine which of four sites were the most likely to show colonization of MRSA at the time of admission. Four sites were swabbed for culture: nostrils, perineum, axilla and throat. Also a pooled swab was cultured in selective mannitol nutrient broth before being plated onto selective agar.

Of 12,889 admissions 6,533 patients were studied from Aberdeen Royal Infirmary and 3,781 from Crosshouse. When a positive wound or device culture was factored into the total positives, there were 298 positive colonizations. The nose was the most likely positive, (72.5%), followed by perineum (39.1%), throat (37.7%) and axilla (8.4%). The "gold standard" was the presence of at least one confirmed agar or broth/agar culture from any pooled swab. Nasal swabs identified 66% of the MRSA-positive admissions. Throat and perineal cultures add nearly 16%. Axillary cultures alone add only 2.4%.

■ COMMENTARY

Not all patients are Scots, but if they were, our current approach to pre-admission carriage of MRSA would have to change, or accept a recognition rate of just above two thirds. A rate of nearer to 50% may be true for a real world experience due to compliance, lack of standard training programs, etc. The Dutch routinely do nasal and throat swab looking for MRSA carriage and have reported throat carriage without nasal carriage previously. In the present study throat cultures plus nasal swabs would bring the screening accuracy to about 70%, not bad if a hospital wants to do something to recognize the MRSA carrier at admission and cohort these carriers. A positive culture of a preexisting infected site plus a nasal swab identified 100% of confirmed carriers.

The benefit of the study is to show that carriers may have colonization at one or more sites yet not have nasal colonization. The study also suggests that the nose is becoming less of a true focus of staphylococcal carriage, at least in terms of MRSA-colonized patients at the time of admission. The authors did a valiant job in organizing, implementing and analyzing the study and are to be congratulated for adding to this literature and to the Pathfinder study which is illuminating the role of MRSA in nosocomial infections. Of course

the overall rate of MRSA carriage in these two Scottish hospitals at admission was only 3%. So, hospital administrators would have to be convinced that isolation of that small a MRSA-colonized group would actually prevent significant spread and morbidity in their hospitals.

Additionally, in an article accompanying the Scottish report, David and co-investigators from the University of Chicago found that there was a doubling of MRSA-associated hospitalizations from 20.9 per 1000 discharges to 41.7 per 1000 discharges. This sharp increase was likely due in part to infection with community MRSA, the very issue that the Scottish paper highlights by showing nasal swabs alone will not uncover those patients who are transporting community MRSA into the hospital. ■

U.S. Rabies Update: Survival from Rabies, and Death in a Haitian Woman

ABSTRACT & COMMENTARY

By Michele Barry, MD FACP and Brian G. Blackburn, MD

Dr. Barry is the Senior Associate Dean for Global Health at Stanford University School of Medicine and Dr. Blackburn is a Clinical Assistant Professor in the Division of Infectious Diseases and Geographic Medicine at Stanford University School of Medicine.

Drs. Barry and Blackburn report no financial relationships to this field of study. This article originally appeared in the April 2012 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, MPH, and peer reviewed by Lin Chen, MD. Dr. Bia is* Professor (Emeritus) of Internal Medicine (Infectious Disease and Clinical Microbiology); Yale University School of Medicine, and Dr. Chen is *Assistant Clinical Professor, Harvard Medical School and Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA. Drs. Bia and Chen report no financial relationships to this field of study.*

Synopsis: *An 8-year-old girl from rural California who had been scratched by unvaccinated cats developed flaccid paralysis and rabies encephalitis. She was treated with a therapeutic coma protocol and survived after a 52-day hospitalization. This is the second report of recovery from rabies after induction of therapeutic coma and the third report of recovery from clinical rabies in an unvaccinated host. A 73-year-old woman who acquired rabies from a dog bite in Haiti died despite intensive supportive care without therapeutic coma induction. Since 1994, nearly all dog-associated rabies cases in the U.S. have been imported, and this was the third case of rabies imported from Haiti since that time.*

Sources: 1. CDC. Recovery of a Patient from Clinical Rabies – California 2011 *MMWR* 2012;61:61-65
2. CDC. Imported Human Rabies – New Jersey 2011 *MMWR* 2012 60;1734-1736

In May 2011, an 8-year-old girl developed sore throat, vomiting, and swallowing difficulties. During two emergency room visits with diffuse abdominal pain, she was given intravenous fluids and diagnosed with a viral illness. During a third emergency room visit for abdominal pain, weakness and sore throat, she was confused and choked while trying to drink radiographic contrast medium for a CT scan. She developed respiratory distress, was intubated and admitted to a pediatric intensive-care unit. She had bilateral lower extremity weakness, and a CSF analysis revealed 6 WBCs, protein 62 mg/dL and normal glucose concentration. Over the next few days she developed ascending flaccid paralysis, fever and decreased consciousness. MRI scanning revealed abnormalities in the periventricular white matter, cortical and subcortical regions. Electromyography revealed a severe demyelinating motor polyneuropathy.

IgG and IgM rabies virus specific antibodies were detected in both her serum and CSF by indirect fluorescent antibody (IFA) testing. With a presumptive diagnosis of rabies, the patient was sedated with ketamine and midazolam, then given amantadine, nimodipine, fludrocortisone, and hypertonic saline. To avoid blunting of an immune response, neither rabies immunoglobulin nor rabies vaccine were administered. Her course was complicated by severe autonomic instability, supraventricular tachycardia and significant hypertension. She was successfully extubated 15 days after hospitalization and discharged 37 days later with a residual foot drop that ultimately resolved. She has no lasting cognitive impairment.

The girl resided in rural Humboldt County, CA, and had not traveled internationally in the six months prior to illness onset. She had never been vaccinated against rabies. Although her family owned pigs, birds, dogs, and a horse, the most likely source of rabies in this case was felt to have been scratches by two different unvaccinated, free-roaming cats at her school 9 weeks and 4 weeks prior to her illness. Although only two cases of human rabies in the U.S. have been attributed to cats since 1960, the most recent rabid cat in California was reported from the same county as the patient's residence, in 2008.

In July 2011, a 73-year-old Haitian woman was admitted to a New Jersey hospital with right shoulder pain, chest pain, headaches and hypertension. When given oral pain medication she developed difficulty swallowing and refused further testing. She then visited two other emergency departments with shortness of breath, ataxia and hallucinations. A blood chemistry panel and head CT were normal, but when she developed incoherence, fever and upper extremity tremors, she was transferred to an ICU where a presumptive diagnosis of encephalitis was made. MRI scanning revealed only chronic periventricular white matter changes; EEG showed subclini-

cal seizures, and CSF revealed 7 lymphocytes/microliter. Rabies virus antigens were detected in a nuchal skin biopsy by direct fluorescent antibody testing, and rabies virus RNA was detected in the biopsy and saliva by PCR testing. Sequencing revealed a rabies virus associated with a Haitian canine variant. She was declared brain dead two weeks after admission and she expired despite supportive care in an intensive care unit. The patient had visited Haiti three months prior to her hospitalization, where she was bitten by a dog that she had adopted. A week before hospitalization, she had complained of right arm numbness and headaches.

■ COMMENTARY

Rabies is a neurotropic viral illness that is characterized by severe encephalopathy and generalized paresis. Although preventable by post-exposure prophylaxis, no proven therapy exists after the onset of clinical symptoms. Post-exposure prophylaxis for unvaccinated patients consists of wound washing, passive immunization with rabies immune globulin and a series of 4 doses of rabies vaccine for immunocompetent hosts[1,2] Survival has rarely been reported after onset of symptoms and death usually occurs within seven to fourteen days, as described in the imported case from Haiti.[2]

The young girl from California is the third unvaccinated person reported to have survived clinically apparent rabies in the United States. In two of these three cases, including the present case, coma induction by what is sometimes referred to as the "Milwaukee protocol" may have been life-saving.[3] Of note, both patients were young and healthy, and presented at an early stage of the disease. A third case of presumptive abortive human rabies that never required intensive care has been described in an adolescent girl from Texas with a history of encephalitis and positive serology after a history of bat exposure.[4] This case was extremely unusual, as case-fatality after onset of symptoms is essentially 100%, and it was suspected that abortive rabies may have occurred because of an exuberant host immune response.

The only suspicious animal contact for the 8 year old girl from California was with free-roaming cats at her school. Inspection of her home found no evidence of bats. The number of rabies cases among domestic animals has declined markedly in the United States, but varies regionally. Rabid cats represent the majority (62%) of reported rabid domestic animals presumably due to fewer cat vaccination laws and free-roaming of cats.[5] In 2010, 303 cats were reported rabid in the US compared with 69 dogs. However, only two cases of human rabies have been attributed to cats since 1960.[5] Risk between cats and dogs varies regionally and on the Texas-Mexico border dogs represent a greater risk. Most of the 303 rabid cats were reported from states where raccoon rabies is enzootic.[5]

For travelers, dogs remain the greatest risk for acquisition of rabies.[1] The history of the 73 year-old woman who had traveled to Haiti, had been bitten by a dog two months prior, and had not sought medical attention is typical for rabies. Since 2000, eight human rabies cases associated with dog bite exposures have been reported in the United States, all acquired abroad. In the developing world, dogs represent a major source of rabies, in contrast to the U.S. where the major reservoir is wild animals, and where 96% of all domestically acquired human rabies infections have been associated with bat rabies virus variants. This is the third U.S. case of rabies related to dog exposure imported from Haiti in recent years.

Rabies is frequently not considered early in the clinical course of affected patients, but clinicians caring for patients with acute progressive encephalitis should always consider rabies in the differential diagnosis. Although there is no standard treatment for rabies once symptoms begin, early diagnosis may allow consideration of experimental interventions in appropriate patients and can also limit secondary exposures, thus minimizing the need for post-exposure prophylaxis [PEP]. The incubation period can vary depending on bite site but is usually 1-3 months.[1] Ante-mortem diagnoses should include laboratory testing of serum, saliva, CSF and a nuchal skin biopsy to optimize yield as these tests have variable sensitivity. Interestingly, neither infectious virus, viral antigens nor rabies viral nucleic acid have been detected in any of the three surviving cases, raising the question of patient survival due to robust immune responses during intensive care support. For this reason, immunization with vaccine and human rabies immune globulin [HRIG] is not recommended once rabies encephalitis has been diagnosed in order to prevent blunting of the immune response.

A major clue to rabies in all of these cases was dysphagia and difficulty swallowing. This significant degree of dysphagia rarely is seen with encephalitis due to other causes. CDC recommends that all domestic cats, dogs and ferrets be vaccinated against rabies. Travelers to countries endemic for rabies should consider pre-exposure rabies vaccination, especially if immediate access to appropriate medical or biologics such as HRIG is limited or whenever the potential of exposure to rabies is high.[1] Even if an animal exposure does occur, rabies is preventable if post-exposure prophylaxis is administered soon after exposure. In countries where canine rabies is endemic, all dog bites should be managed as a rabies exposure unless the dog's disease-free status can be confirmed. ■

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Why Is the Rhythm VT?

ECG REVIEW

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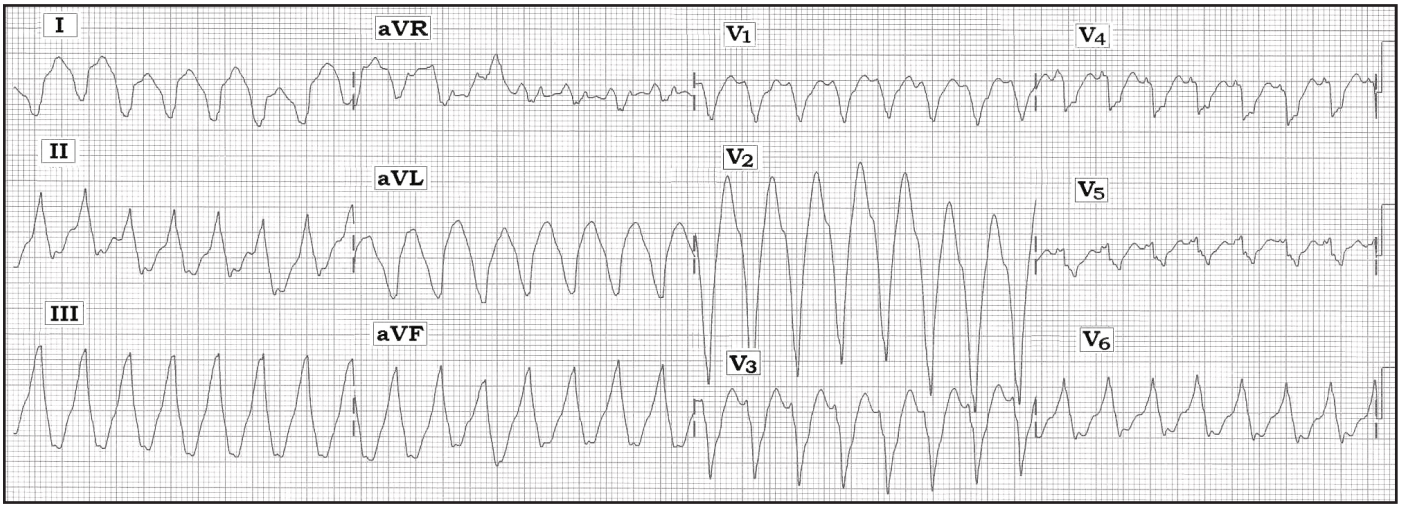
Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

This article originally appeared in the August 15, 2012, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Brunton serves on the advisory board for Lilly, Boehringer Ingelheim, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Lilly, Kowa, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*



Scenario: The ECG shown above was obtained from a patient whose blood pressure was dropping. How many reasons can you cite to support a diagnosis of ventricular tachycardia (VT)?

Interpretation: The 12-lead ECG in the Figure shows a regular wide complex tachycardia (WCT) rhythm at a rate of ~180/minute. Sinus P waves are absent. The rhythm is sustained VT and the patient is in need of immediate electrical therapy (synchronized cardioversion of defibrillation). Many reasons can be cited to support definitive diagnosis of sustained VT. These include:

1) Statistically, at least 80% of all *regular* WCT rhythms of uncertain etiology are VT. The likelihood of VT increases to *more than* 90% if the patient is middle-aged or older (especially if the patient has underlying heart disease).

2) Although on occasion regular WCT rhythms may be due to a supraventricular etiology with either preexisting bundle branch block or aberrant conduction — VT must *always* be assumed until proven otherwise, because it is a potentially life-threatening arrhythmia.

3) Extreme axis deviation is present. Mild-to-moderate left or right axis deviation may be seen with supraventricular rhythms. However, total negativity in either lead I or lead aVF suggests extreme axis deviation, and is virtually diagnostic of VT.

4) The QRS complex is both markedly widened (to over 0.16 second in many leads) — and the QRS is lacking in organized morphology (which we convey by describing the QRS as "ugly"). Both features are highly suggestive of VT. Aberrant conduction most often manifests a more organized QRS morphology that is consistent with some type of conduction defect (left or right bundle branch block with or without hemiblock).

5) There is ECG evidence of delayed initial ventricular activation. The presence of an r-to-S-nadir of more than 0.10 second in one or more precordial leads is highly suggestive of VT. This is best seen in lead V5.

6) Always assume VT until proven otherwise. Treat the patient accordingly.

For more information on this ECG Review, please visit: www.kg-ekgpress.com/acls_comments-_issue_11/. ■

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. ■

CME Questions

1. In the randomized controlled trial by Perner, et al., of patients with severe sepsis needing fluid resuscitation, patients receiving colloid (hydroxyethyl starch) instead of Ringer's lactate had which of the following outcomes?

a. Less renal replacement therapy.

b. Fewer blood transfusions.

c. Lower mortality.

d. Higher mortality.

2. In the retrospective cohort study by Gershengorn and colleagues of all patients admitted with the primary diagnosis of diabetic ketoacidosis (DKA) in New York between 2005 and 2007, which of the following observations were made?

a. Admission to an ICU was associated with decreased mortality.

b. Admission to a ward was associated with an increased length of stay.

c. Admission to an ICU was associated with a more rapid clearing of the acidemia.

d. No differences in outcomes based on admission to an ICU or ward could be identified.

3. Based on the study by Matheson et al., what percent of patients colonized with MRSA were detected by a positive nasal swab?

a. 2.4%

b. 16%

c. 66%

d. 97%

CME Instructions

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2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*

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Refining the Relationship Between Thyroid Hormones and Left Ventricular Mass

Source: Iida M, et al. *J Am Soc Hypertens* 2012;6:261-269.

Animal studies have shown that thyroid hormones (T3 and T4) induce hypertrophy of cardiac myocytes through stimulation of both structural and regulatory myocyte genes, which can be prevented by ACE inhibitors or beta-blockers. Such observations have led to the question of whether there might be a relationship between cardiac mass and thyroid hormones, even within the range currently defined as normal.

Hypothyroidism and hyperthyroidism are each considered a potential secondary cause of hypertension: the former through endothelial dysfunction that leads to vasoconstrictor hyperresponsiveness and subsequent increased peripheral resistance, and the latter through increased sympathetic tone. Iida et al investigated hypertensive subjects (n = 293) who had no known thyroid disease and whose thyroid function tests (T3, T4, and TSH) were within normal limits.

Among these euthyroid hypertensive study subjects, multiple linear regression found a positive relationship between T3 and T4 and ventricular mass (the higher the thyroid hormones, the greater the ventricular mass), and an inverse relationship between TSH and ventricular mass. When compared with normotensive controls, no such relationship could be identified. This would lead to consideration that in persons with hypertension, higher levels of thyroid hormone — even within the normal range — may be related to the development of left ventricular hypertrophy. ■

The ORIGIN Trial: Basal Insulin vs Standard Care for Early Type 2 Diabetes

Source: The ORIGIN Trial Investigators. *N Engl J Med* 2012;367:319-328.

Type 2 diabetes reflects insulin insufficiency. Early in the disease process, plasma insulin levels may actually be higher than normal, but insufficient to maintain euglycemia. By the time of formal diagnosis, approximately half of beta cell mass has been lost, and as the disease progresses, insulin levels continue to fall.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomized subjects with prediabetes or early diabetes (n = 12,537) to insulin glargine (GLAR) or standard treatment (STND) for 6.2 years (mean). The objective of the trial was to determine whether early institution of basal insulin, as compared to STND, improves cardiovascular outcomes. Standard treatment was simply treatment of diabetes as per the treating clinician's choice; by the end of the trial, only 11% of the STND group was receiving insulin. Eighty percent of the GLAR group was on insulin at the end of the trial.

There was no difference in cardiovascular outcomes between the two treatment groups. One notable difference between treatments was the likelihood of progression from prediabetes to diabetes. The GLAR group was 28% less likely to progress than the STND group; however, there was also more hypoglycemia and weight gain in the GLAR group.

Increased incidence of cancer — a concern generated by earlier insulin trial data — was *not* seen in this large trial, and hence should be very reassuring. ■

Bronchodilators in COPD and Arrhythmias

Source: Wilchesky M, et al. *Chest* 2012; 142:298-304.

For chronic obstructive pulmonary disease (COPD), except for the provision of oxygen in late-stage disease, no pharmacologic intervention has been confirmed to save lives. Nonetheless, since bronchodilators improve symptoms, quality of life, and exercise capacity, and reduce acute exacerbations of COPD, they play an important role in routine care. Concerns about the potential capacity for arrhythmogenicity of bronchodilators has arisen from clinical COPD trials such as the Lung Health Study (n = 5887), in which short-acting ipratropium bromide was associated with a three-fold greater incidence of arrhythmia than comparator groups. Other smaller trials have not confirmed these findings, hence clarification is needed.

Wilchesky et al analyzed data from the province of Saskatchewan, Canada, to identify COPD subjects (n = 6018) and compare the incidence of arrhythmia in new users of ipratropium, beta-agonists (short- and long-acting), and methyhlxanthines to non-users.

Short-acting anticholinergics were

associated with a 2.4 relative risk of arrhythmia, and long-acting beta-agonists with a 4.5 relative risk. No statistically significant increased risk was seen with short-acting beta-agonists or methylxanthines. Despite these concerns, the authors remind us that the absolute risk increase was very small, and "in most cases would be outweighed by the therapeutic benefit accrued through symptomatic relief and consequent improvements to quality of life." ■

Reversible Dementia from Corticosteroid Therapy

Source: Cipriani G, et al. *Clin Geriatrics* 2012;20:38-41.

Although there are many clinical situations in which corticosteroids (CTS) are disease modifying and life saving, one aspect of CTS that has not received much attention is the potential for central nervous system (CNS) adverse effects. CTS may be largely subgrouped into mineralocorticoids exemplified by aldosterone, and glucocorticoids (GLC) like prednisone, the latter of which is the object of this case report.

There are at least two types of CTS receptors in the brain: type I (mineralocorticoid receptors) and type II (glucocorticoid receptors). Type II receptors are found in the hippocampus as well as diffuse other sites throughout the brain. The hippocampus is required for voluntary recollection of learned information, such as recalling what you had for dinner last night. Even low doses of GLC have been shown to impair hippocampal function, despite being used for short time periods: doses of prednisone of 80 mg/day have been shown to alter cognitive function within 4-5 days.

The authors include discussion of a report detailing six cases of dementia-like cognitive decline (distinct from steroid psychosis) in patients whose cognitive function was restored upon GLC discontinuation.

Clinicians should be vigilant for decline in cognitive function in persons receiving GLC treatment, even over the short-term. ■

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Could Thinner be Worse for Newly Diagnosed Diabetics?

Source: Carnethon MR, et al. *JAMA* 2012;308:581-590.

Usually, we anticipate a direct relationship between overweight and cardiovascular adversity, attributed to increases in blood pressure, lipids, glucose, insulin resistance, and sympathetic tone that are associated with obesity. There appears to be some exception to this general rule in reference to diabetes. For instance, in the TRIAD study, diabetics who were normal weight at entry to the study had a *higher* mortality than overweight/obese study subjects; similarly, in the PROactive trial, normal weight subjects or those who lost weight had *higher* mortality than overweight subjects. Because these two studies included confounding issues such as diabetes of varying duration and pre-existing cardiovascular disease, a more clear-cut relationship between body mass index (BMI) and outcome in diabetes could be discerned by selecting newly diagnosed diabetics.

Carnethon et al performed a pooled analysis of five longitudinal cohort studies (n = 2625) to examine the relationship between mortality and BMI for persons with newly diagnosed diabetes. Overall, only 12% of study subjects had a BMI < 25 at the time of diagnosis, but the relative risk for total mortality during follow-up (up to 15 years) was essentially doubled in this population compared to overweight individuals.

The mechanism(s) by which lower BMI increases mortality risk are unknown. Clinicians must not be falsely reassured that this lower-BMI phenotype, which is commonly seen in Asian-Americans, portends a favorable future. ■

The Impact of Exercise on Depression in Heart Failure

Source: Blumenthal JA, et al. *JAMA* 2012;308:465-474.

It is estimated that 5 million Americans have chronic heart failure (CHF), and almost half of these patients fulfill diagnostic criteria for depression. Subsyndromal depression is present in as many as 75%. Notwithstanding the burden of depression on quality of life, a direct impact on mortality has been shown in post-myocardial infarction patients, and even in patients with hypertension in the Systolic Hypertension in the Elderly Program. Unfortunately, to date the information on the impact of treating depression is both limited and generally disappointing. For instance, a clinical trial of sertraline in depressed patients with CHF found no cardiovascular event outcomes benefit.

Exercise is a treatment for depression, and exercise has been shown to provide event reduction in CHF patients. Whether it might improve depression and cardiovascular events in CHF patients was the object of the HF-ACTION trial (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise Training).

More than 2000 patients with stable CHF were randomized to an aerobic exercise program. The exercise subjects enjoyed a statistically significant 11% reduction in mortality over the next 30 months. Although the mean score on the Beck Depression Inventory was statistically significantly lower in the exercise group, the improvement was sufficiently modest to be of uncertain clinical impact. Exercise in CHF reduces mortality and may have a modest effect on depression. ■

PHARMACOLOGY WATCH

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Statins and Cognition — More to the Story?

In this issue: Side effects of statins; effects of cannabis use; antihypertensives and lip cancer; and FDA actions.

Review challenges FDA warning

Do statins cause changes in cognition? In February, the FDA added warnings to statin labels regarding the risk of reversible memory loss and confusion. But a new review from the *Journal of the American College of Cardiology* reviews the evidence given to the FDA and concludes "that there is no increased risk of cognitive decline" with statin use. The State-of-the-Art Paper was a comprehensive review of case reports, observational research, and randomized, controlled trials of statins and cognitive change, as well as risk of cancer and diabetes. Most of the evidence for cognitive changes came from individual case reports, many of which were self-reported by consumers to the FDA. Observational studies gave mixed results on cognition with four of nine studies showing statins improved cognition, while three showed no change, and two studies found an increased risk of cognitive impairment. The authors suggest that these studies are inconclusive and prone to selection bias. Two large, randomized, controlled clinical trials specifically looked at the effect of statins on cognitive function as the major secondary endpoint. In both, no significant differences were seen between the study and control groups with regard to cognitive decline. Twelve smaller studies showed mixed results with the majority showing no change and only one in 12 showing a detrimental effect of statins on cognitive function, while two studies showed a benefit. Along with lack of evidence to suggest statins lead to cognitive decline, the authors also found no evidence that statins increase the risk of cancer. They did, however, find a small risk for development of diabetes, which they felt was "outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended" (*J Am Coll Cardiol* published online August 15, 2012). ■

Cannabis use and cognitive decline

Persistent cannabis use — particularly in adolescence — may lead to permanent cognitive decline, according to a new study. Researchers looked at a birth cohort of 1037 healthy individuals in New Zealand who underwent neuropsychological testing in the mid 1980s before the onset of cannabis use, and then again in 2010-2012 after some had developed a persistent pattern of cannabis use. Persistent cannabis use over 20 years (at least 4 days per week) was associated with neuropsychological decline, with greater decline evidence for more persistent users. This effect was only seen in adolescent-onset cannabis users and was associated with an average 8 point loss in IQ by age 38. The effect persisted after controlling for education, other drugs, or tobacco. The effects were not seen among adult-onset cannabis users. The authors conclude that increasing efforts should be directed toward delaying the onset of cannabis use by young people, "particularly given the recent trend of younger ages of cannabis use initiation in the United States and

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evidence that fewer adolescents believe that cannabis use is associated with serious health risk." (*Proc Natl Acad Sci U S A* published online August 27, 2012). This study and others are increasingly important as cannabis, the most widely used illicit drug in the world, is being considered for more medicinal uses as well as legalization. ■

Antihypertensives and lip cancer

Two photosensitizing antihypertensives, hydrochlorothiazide and nifedipine, may increase the risk for lip cancer in non-Hispanic white patients, according to a new study from Kaiser Permanente in California. From a large cohort of patients, 712 were identified with lip cancer along with nearly 23,000 matched controls. At least a 5-year supply of the drug resulted in the following odds ratios for lip cancer (95% confidence intervals) — hydrochlorothiazide 4.22 (2.82-6.31), hydrochlorothiazide-triamterene 2.82 (1.74-4.55), nifedipine 2.50 (1.29-4.84), and lisinopril 1.42 (0.95-2.13). When atenolol was given without other hypertensives, the odds ratio for lip cancer was 0.54 (0.07-4.08). The authors suggest that while antihypertensive therapy outweighs the risk of lip cancer, preventive measures should be taken for those at increased risk because of fair skin and long-term sun exposure (*Arch Intern Med* published online August 06, 2012). ■

FDA actions

The FDA has approved a delayed-release form of prednisone for the treatment of endocrine, inflammatory, and neoplastic conditions. Delayed-release prednisone should be taken once a day with timing to be determined by the disease being treated. For example, 10 p.m. dosing is recommended for rheumatoid arthritis, as it is more effective than immediate-release prednisone taken in the morning for treating morning stiffness associated with the disease. Dosing is based on the theory that both cytokines and endogenous cortisol follow a circadian rhythm, and that dosing the drug based on the condition being treated may afford more effective treatment than immediate-release prednisone. The new product delays the release of prednisone by approximately 4 hours. Side effects are the same as short-acting prednisone. Delayed-release prednisone will be marketed as RAYOS by Horizon Pharma.

The FDA has approved a new chlorofluorocarbon (CFC)-free, over-the-counter inhaled racepinephrine product for the treatment of asthma. The new product takes the place of the banned Primatene Mist, which was taken off the market at the end of 2011 because it contained CFCs. Inhaled epinephrine has been used for the treatment of asthma for more than 100 years. Marketed as Asthmanefrin, the new product will be sold as a starter kit and refill package. The starter kit will include 10 vials of racepinephrine along with the EZ Breathe Atomizer. The refill kit will include 30 vials of the drug. The drug is not without controversy, however, with many asthma experts feeling that the side effects of epinephrine are serious and well-documented, and over-the-counter use goes against published guidelines for treating asthma. Asthmanefrin will be marketed by Nephron Pharmaceuticals.

The FDA has approved linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. The drug is the first guanylate cyclase (GC-C) agonist that acts locally in the gut with minimal systemic exposure. The drug is taken once daily on an empty stomach at least 30 minutes before the first meal of the day. Safety and efficacy in the management of irritable bowel syndrome with constipation was established in two double-blind studies of nearly 1300 patients who were randomly assigned to linaclotide or placebo for 12 weeks. Patients taking the drug experienced more complete spontaneous bowel movements than those taking placebo. The drug should not be used in patients 17 years or younger. Linaclotide will be jointly marketed by Ironwood Pharmaceuticals and Forest Pharmaceuticals as Linzess.

Montelukast (Singulair), Merck's popular asthma and allergy medication, will soon be available as a generic. The leukotriene receptor antagonist will be manufactured by 10 generic companies in tablet form, oral granules, and chewable tablets. The FDA warns that montelukast should not be used for relief of sudden asthma attacks and further warns that patients should contact a clinic immediately if they are experiencing behavior and mood-related changes such as aggression, depression, or hallucinations.

The FDA has approved the first generic version of pioglitazone (Actos). The drug is approved along with diet and exercise to improve blood sugar control in adults with type 2 diabetes. This happens as thiazolidinediones have generally fallen out of favor for use in type 2 diabetes due to side effects including worsening heart failure and edema. The FDA also recently issued a warning for pioglitazone regarding increased risk of bladder cancer if the drug is taken for more than 1 year. The first generic pioglitazone will be manufactured by Mylan Pharmaceuticals. ■