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Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemia — A Brief Review

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

INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two of the most common and serious acute complications of diabetes mellitus. DKA is responsible for more than 500,000 hospital days annually in the United States, at an estimated annual cost of $2.4 billion. Both conditions are part of the spectrum of uncontrolled hyperglycemia, and there is sometimes overlap between them. This article will discuss and compare the two conditions, with a focus on key clinical features, diagnosis, and treatment.

DIAGNOSTIC FEATURES

In DKA, there is an accumulation of ketoacids along with a high anion gap metabolic acidosis (*see Table*).[1] The acidosis usually evolves quickly over a 24-hour period. The pH is often < 7.20 and initial bicarbonate levels are often < 20 mEq/L. DKA patients (especially children) often present with nausea, vomiting, hyperventilation, and abdominal pain. Blood sugar levels in DKA tend to be 300-800 mg/dL, but they are sometimes much higher when patients present in a comatose state.

In HHS, there is no (or little) ketonemia but the plasma osmolality may reach 380 mOsm/kg, and as a result, patients often have neurologic complications such as coma. Bicarbonate levels are usually > 18 mEq/L. Blood sugars are more elevated in HHS, often > 800-1000 mg/dL. Neurologic symptoms are common in HHS. In some series, up to 50% of HHS patients present with coma. Abdominal pain is unusual in HHS.

Neurologic symptoms (obtundation and coma) are more common in HHS because hyperosmolality is more severe in HHS than in DKA. The

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hyperosmolality is due to the glucose osmotic diuresis causing water loss. However, severe acidosis in DKA can also cause significant neurologic deterioration. Neurologic symptoms typically occur when the *effective* plasma osmolality approaches 320 mOsm/kg. The effective osmolality is calculated by the equation:
[2 × Na (meq/L)] +
[glucose (mg/dL)/18].

Note that the effective plasma osmolality does not account for urea because it is a freely permeable molecule and its accumulation does not induce major intracellular osmotic changes in the brain. If the patient's serum osmolality has already been measured, the effective plasma osmolality can be calculated by this equation:
measured serum osmolality – [BUN (mg/dL)/28].

Of note, stupor or coma in diabetic patients with an effective plasma osmolality < 320 mOsm/kg should prompt an investigation for another cause of the mental status change.

WHY ARE GLUCOSE LEVELS LOWER IN DKA?

DKA patients usually have lower blood sugar levels than HHS patients. One reason is that the acute acidosis in DKA causes distressing symptoms (e.g., nausea, dyspnea, abdominal pain) that encourage patients to seek attention at an earlier stage. In addition, DKA patients tend to be younger than HHS patients, and thereby have a higher glomerular filtration rate. Accordingly, DKA patients have a greater ability to excrete glucose in urine and can thereby limit the hyperglycemia. Of note, when end-stage renal patients develop severe hyperglycemia, they do not have the osmotic diuresis that leads to the extreme hyperosmolality. As a result, they rarely develop neurologic symptoms even though serum glucose levels may reach 1000-1500 mg/dL.

WHY DO PATIENTS HAVE ABDOMINAL PAIN?

DKA patients often have abdominal pain, but it is uncommon in HHS. The likely explanation for abdominal pain is ileus and delayed gastric emptying caused by the acidosis. In a prospective study of 200 hyperglycemic patients, abdominal pain occurred in 46% of DKA patients but in none of the HHS patients.[2] The incidence of abdominal pain correlated with the severity of the acidosis. However, there was no relationship between abdominal pain and the degree of dehydration or the level of hyperglycemia. Of note, if abdominal pain is still present after the ketoacidosis resolves, other causes for the pain need to be considered.

INITIAL EVALUATION

When a patient presents with DKA/HHS, one should strive to identify the precipitant. The most common culprits are infection or inadequate insulin therapy (i.e., poor compliance). Various acute illnesses can trigger DKA/HHS, including stroke, myocardial infarction, and pancreatitis. Cocaine use can also trigger DKA. Some medications affect carbohydrate metabolism, including corticosteroids, thiazide diuretics, second-generation antipsychotics, and sympathomimetrics (e.g., dobutamine). New onset type 1 diabetics commonly present in DKA.

During initial investigation, one should consider other causes of metabolic acidosis and coma. If an anion gap acidosis is present, consider medications (e.g., metformin, aspirin), ingestions (e.g., methanol and ethylene glycol), sepsis/infection, and advanced chronic kidney disease. Note that none of these entities cause ketoacidosis. If a ketoacidosis is present, consider alcoholic ketoacidosis (AKA) and starvation ketosis. In an alcoholic presenting with ketoacidosis and normal blood sugars, AKA is almost always the diagnosis.

Physical examination will often show signs of volume depletion. DKA

Table. Diagnostic Criteria for Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS)

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	> 250	> 250	> 250	> 600
Arterial pH	7.25-7.30	7.00-7.24	< 7.00	> 7.30
Serum bicarbonate (mEq/L)	15-18	10-15	< 10	> 18
Urine ketones	Positive	Positive	Positive	Small/absent
Serum ketones	Positive	Positive	Positive	Small/absent
Serum osmolality (mOsm/kg)	Varies	Varies	Varies	> 320
Anion gap	> 10	> 12	> 12	Variable
Mental status	Alert	Alert-drowsy	Stupor-coma	Stupor-coma

Adapted from Kitabchi AE, et al.[3]

patients may have a fruity odor due to exhaled acetone. The hypovolemia causes peripheral vasoconstriction, so fever is rare, even when there is an infection.

Initial tests should include serum electrolytes (including anion gap), complete blood count with differential, urinalysis with ketones dipstick, serum ketones (if urine ketones are present), arterial blood gas (if urine ketones or anion gap are present), plasma osmolality, electrocardiogram, and chest X-ray. If indicated, additional tests might include cultures of blood, urine, and sputum; liver function tests; and lipase/amylase. Hemoglobin A1c may be useful to determine whether the patient's blood sugars have been poorly controlled prior to this episode.

Laboratory abnormalities in DKA depend on the patient's fluid intake, underlying renal function, osmotic diuresis, and level of insulin deficiency. The *sine qua non* of DKA is an elevated anion gap and metabolic acidosis. Most patients also have acute elevations in blood urea nitrogen (BUN) and creatinine due to hypovolemia. The severity of the anion gap acidosis depends on the rate of ketoacid production, duration of the episode, and rate of excretion in the urine. Thus, patients with normal renal function can minimize the anion gap by losing large quantities of ketoacids into urine.

Serum sodium levels in DKA/HHS depend on the balance between two forces — the dilution of sodium caused by osmotic water movement out of cells and the concentration of sodium caused by glucosuria-induced water diuresis. Every patient is different, but in general, most patients with DKA/HHS present with mild hyponatremia. Rarely, some diabetics have such a brisk diuresis that they present with hypernatremia. When HHS patients have a normal or elevated serum sodium along with glucose levels > 1000 mg/dL, they are extremely hyperosmolar and at high risk for coma or seizure.

DKA/HHS patients have both potassium and phosphate deficits, even though most present with normal to high serum levels. The potassium deficit is a result of osmotic diuresis, insulin deficiency, and possibly gastrointestinal losses. Acidosis does not play a major role in the elevated serum potassium level seen in DKA. Hence, hyperkalemia also occurs in HHS. The phosphate deficit is a result of osmotic diuresis and decreased intake.

Most DKA/HHS patients present with a leukocytosis that is proportional to the ketonemia. Amylase and lipase are often elevated in DKA patients who do not have pancreatitis. Therefore, the diagnosis of pancreatitis in a DKA patient must be made using other clinical findings and radiology.

TREATMENT

Overall, the treatment principles for DKA and HHS are similar: intravenous fluids to restore volume, insulin to correct hyperglycemia, and electrolyte replacement. Protocols for DKA and

HHS are readily available online and in the literature.[1,3] The key points inherent to most of these protocols will be summarized.

Monitoring: Serum glucose should be measured hourly until stable. Serum electrolytes should be measured every 2-4 hours, depending on disease severity and response to therapy. In DKA, venous pH and serum beta-hydroxybutyrate measurements are an excellent way to monitor the response to therapy — if your hospital can return blood chemistry results in a prompt manner. However, monitoring the anion gap is a simpler approach. Normalization of the anion gap indicates the ketoacidosis has corrected. Serial arterial blood gases are unnecessary because a venous pH is ~0.03 units lower than arterial pH and can provide enough data for decision making without the pain of an arterial stick.

Fluid replacement: The initial goals of fluid administration are expansion of intravascular volume and restoration of renal perfusion. Because of the osmotic diuresis, the average patient's volume deficit is 3-6 liters in DKA and 8-10 liters in HHS. The goal is to replace volume deficits within the first 24 hours. Fluid repletion is initiated with isotonic saline (0.9% NaCl) at a rate of 10-15 mL/kg/hr ideal body weight. This replaces the volume deficit, lowers plasma osmolality (since it is hypo-osmotic to the patient), and reduces serum glucose (both by dilution and by increasing renal perfusion), which in turn increases urinary glucose losses. Subsequent fluid selection will depend on serial assessments of electrolytes, urine output, and volume status. If the corrected sodium level is normal/high, patients are switched to 0.45% NaCl at 250-500 mL/hr. If the corrected sodium serum sodium level is still low, continue with 0.9% NaCl. Recall that hyperglycemia resolves more quickly than ketoacidosis (mean 6 hours vs 12 hours, respectively). Therefore, fluids are switched to 5% dextrose when the serum glucose reaches 200 mg/dL in DKA or 250-300 mg/dL in HHS. This allows continued insulin administration and prevents hypoglycemia, while waiting for the ketoacidosis to resolve.

Insulin: The mainstay of DKA/HHS treatment involves regular insulin, given via either continuous infusion or by frequent subcutaneous/intramuscular injections. Randomized trials have shown that insulin is effective regardless of the chosen route.[4,5] Administering insulin through a continuous intravenous infusion allows more responsive control without the delayed onset and prolonged half-life issues of subcutaneous insulin. An initial bolus of insulin is not necessary provided the insulin is infused at a rate of 0.14 U/kg/hr (approximately 10 U/hour in a 70 kg patient).[6] Dosing is the same in DKA and HHS. Regular insulin usually causes a fall in serum glucose by 50-70 mg/dL every hour. However, fluid repletion can also initially reduce serum glucose by 30-70 mg/dL per hour. Thus, the rate of fall may be more pronounced in HHS patients who are typically more volume depleted. The hyperglycemic episode is considered "resolved" when the anion gap has normalized, patients with HHS are mentally alert, the effective plasma osmolality is < 315 mOsm/kg, and the patient is able to eat. Patients with known diabetes who were previously treated with insulin may now be given insulin at their home dose. Insulin-naïve patients should be started on a multidose regimen (total 0.5-0.8 U/kg/day). The infusion should overlap the scheduled regimen by 1-2 hours to avoid rebound hyperglycemia.

Potassium: Despite a total body potassium deficit, the serum potassium concentration is often initially normal (or elevated). To prevent hypokalemia, KCl 20-30 mEq/L is added to the fluids once the serum potassium level falls < 5.3 mEq/L. If the patient is hemodynamically stable, 0.45% NaCl is preferred because adding potassium to 0.9% NaCl would result in a hypertonic solution (which would delay correction of hyperosmolality). The goal is to keep the serum potassium between 4-5 mEq/L. Since insulin will worsen hypokalemia, insulin therapy should be delayed until the serum potassium is > 3.3 mEq/L. Patients who present with hypokalemia must be aggressively repleted. Otherwise, insulin may cause possible arrhythmias, cardiac arrest, or respiratory muscle weakness.

Phosphate: DKA/HHS patients have a phosphate deficit that is unmasked by insulin initiation. However, the fall in serum phosphate during treatment is acute, self-limited, and rarely serious. Prospective randomized trials have not found that routinely replacing phosphate has any beneficial effect on duration of ketoacidosis, amount of insulin required, glucose control, morbidity, or mortality.[7] In fact, it may have adverse effects such as hypocalcemia and hypomagnesemia. In general, phosphate replacement should only be given when serum levels are < 1.0 mg/dL or in patients with other indications such as cardiac dysfunction, respiratory depression, or hemolytic anemia.

Bicarbonate: Use of bicarbonate in DKA is controversial and there is no evidence of benefit.[8]

In a randomized trial of 21 DKA patients with an admission arterial pH of 6.90-7.14, bicarbonate therapy did not impact morbidity or mortality.[9] No randomized trial has looked at patients with a pH < 6.90. There is theoretical benefit for patients with a pH < 7.00 and decreased cardiac contractility, but most experts agree it is not necessary if the pH is > 7.00.

IS ICU ADMISSION NECESSARY?

DKA patients are often admitted to an ICU even though there is a low risk of mortality in this condition. In a recent observational study of 159 acute care hospitals in New York state, Gershengorn et al found significant variation in ICU admission practices for DKA patients.[10] Of the 15,994 patients studied, 53% were admitted to an ICU. Patients were more likely to be admitted to the ICU if they lived in a more affluent zip code, had more chronic illnesses, were admitted after an emergent presentation to the hospital, or were admitted on the weekend. ICU admission was less likely for older and nonwhite patients. ICU admission was more likely if the hospital had a higher utilization of ICU level care for non-DKA diagnoses. ICU admission was less likely if the hospital had a high volume of DKA patients. There was no association between ICU admission and hospital length of stay or mortality. In a multilevel regression model, more than half of the variation in ICU admission practice attributable to hospitals remained unexplained. Overall, this study suggests that many DKA patients can probably be safely managed outside the ICU. However, hospital staffing and policies will need to be aligned with the nursing demands and close monitoring inherent to DKA management. ■

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ABSTRACT & COMMENTARY

Crisis Checklists Improve Management of Rarely Occurring Events

By Leslie A. Hoffman, RN, PhD

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SYNOPSIS: In a simulation study, checklist use was associated with significant improvement in management of infrequent crisis events, suggesting the potential to improve care.

SOURCE: Arriaga AF, et al. Simulation-based trial of surgical-crisis checklists. *N Engl J Med* 2013;368:246-253.

This study, conducted using high-fidelity simulation, was designed to determine if a checklist could improve adherence to best practices during crisis events in the operating room (OR). The events selected were situations that required a rapid, coordinated, time-critical response, but were unlikely to be frequently encountered, e.g., failed airway, cardiac arrest, air embolism, anaphylaxis, massive hemorrhage, unstable bradycardia, unstable tachycardia, malignant hyperthermia, etc. Participants were 17 surgical teams recruited from one community and two academic institutions in the Boston area. The teams consisted of anesthesia staff (attending physicians, residents, certified registered nurse anesthetists, OR nurses, surgical technicians) and "mock" surgeons. Mock surgeons were used because few surgeons or surgical residents chose to volunteer. Each team was randomly assigned to manage half the scenarios with a set of crisis

checklists and the remaining from memory. The primary outcome was failure to adhere to critical processes of care. Key processes were identified for each scenario and scored by three physicians. Disagreements were resolved by expert review by senior faculty.

Checklist use resulted in a nearly 75% reduction in failure to adhere to critical steps in management ($P < 0.001$). Results were unchanged when the analysis was repeated after adjusting for simulation learning or fatigue effects (testing was done on 1 day). Also, there were no differences related to institution or setting (academic vs community hospital). Participants were asked to complete a brief four-question survey using ratings of 1 (disagree strongly) to 5 (agree strongly). Ratings for the four questions were: "checklist helped me feel better prepared" (4.4 ± 0.8), "easy to use" (4.3 ± 0.8), "would use again in an emergency" (4.5 ± 0.8), and "would want this checklist to be used if I were having an operation and experienced this emergency" (4.7 ± 0.6).

COMMENTARY

Although conducted in the OR, this study has parallel implications for critical care. The checklists (http://www.projectcheck.org/crisis) were formatted using 8 × 11 inch cards that listed appropriate actions, medications and dosages and a section titled, "Have we considered?" The intent was to select conditions in which prompt, targeted action could make the difference between survival and death. Termed "crisis-related cognitive aids," they were designed to ensure more rapid and appropriate actions in such emergencies. Checklists targeted to emergent events that occur in the ICU would likely be similarly beneficial. They could aid housestaff new to a particular service or setting, acute care nurse practitioners or physician assistants assigned to off tours, as well as experienced clinicians who might not have encountered such events in the recent past. Notably, 97% of participants gave a score of 4 or higher to the statement, "If I were having an operation and experienced this intraoperative emergency, I would want the checklist to be used." Examples of actions not taken or delayed in the absence of checklists were given for bradycardia (> 10-minute delay to transcutaneous pacing because the selected setting was insufficient to enable pacing of the heart) and for anaphylaxis (insufficient fluid resuscitation), as well as other conditions.

Although, as the authors note, a shift in culture may be necessary before we routinely consult a cognitive aid during an emergency, findings of this study suggest that reliance on such memory aids can improve patient safety. Checklists should be viewed as an additional resource that can be used as an adjunct in emergent real-life scenarios. ■

ABSTRACT & COMMENTARY

QI Project Reduces Severe Pain and Serious Adverse Events: A Systems Approach to Patient Safety

By Linda L. Chlan, RN, PhD

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Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

SYNOPSIS: A French multidisciplinary team conducted a quality improvement project that was successful in improving pain management and reducing serious adverse events associated with the routine ICU nursing care activities of bathing, massage, linen changes, and repositioning.

SOURCE: de Jong A, et al. Decreasing severe pain and serious adverse events while moving intensive care unit patients: A prospective interventional study (the NURSE-DO project). *Crit Care* 2013;17:R74. [Epub ahead of print.]

Despite the intensity and frequency of pain during common nursing care activities such as turning and repositioning, patients rarely receive premedication prior to these procedures. Pain can induce a stress response in these patients that can lead to serious adverse events (SAE). Documentation of SAEs impacting care quality is poorly understood. To address these care quality gaps, a systems approach by a multidisciplinary French ICU team was used to improve patient safety and quality of care through addressing pain management and

adverse events when routine nursing cares were performed. The Plan-Do-Check-Adjust method was used to guide this quality improvement (QI) project. Each phase of the project lasted 1 month, separated by a 4-6 month interstudy phase, for a total project period of 20 months. SAEs were defined as cardiac arrest, new arrhythmia event, and clinically relevant changes in heart rate, (tachycardia or bradycardia), blood pressure (hypotension or hypertension), oxygen desaturation, bradypnea, and ventilatory distress.

The QI project began with a questionnaire completed by nurses to assess their knowledge of sedation and analgesia guidelines and any associated challenges with these guidelines. Educational interventions were developed based on these responses, and included posters and face-to-face scheduled classes for all nursing and medical staff. The education consisted of pain assessment (numeric rating scale or behavioral pain scale) prior to any patient movement interventions, analgesic drug therapy, and instituting non-pharmacological interventions such as music in every patient room. Every day between 6 a.m. and 8 a.m., every patient turning was evaluated to measure the impact of the educational intervention on the pain level and physiological indicators of the stress response. Next, a 6-month period of adjusting the medical and nursing care strategies was undertaken. During this time, physicians wrote orders for one or more analgesic medications to be given before the morning nursing care procedures. Following this 6-month period, nursing care activities every day between 6 a.m. and 8 a.m. were evaluated to determine the impact of the care strategies adjustments made previously.

During the evaluation phase of this QI project, pain was assessed by the nurse prior to and during any care movement interventions. SAEs to assess for indicators of the acute stress response to these movement interventions were measured by physiological parameters. Provision of pharmacological and non-pharmacological therapies was recorded on a flow sheet. Evaluation of the educational interventions revealed that the incidence of severe pain and at least one SAE decreased over the project period, while analgesia administered prior to morning nursing care procedures increased. The incidence of SAEs was observed to decrease except with intubated patients and those with severe pain. This finding highlights the complicated nature of managing mechanically ventilated ICU patients. Unfortunately, the use of music over the project period was not consistently implemented, which may suggest a need for further education and practice implementing this integrative therapy.

■ COMMENTARY

Routine nursing care activities can induce or exacerbate pain, which can lead to a heightened stress response and include any number of adverse events in critically ill patients. Pain is a common experience in critically ill patients for which analgesic medications are frequently administered. However, as the authors point out, moving and other routine nursing care interventions are not perceived by clinicians to be painful. These data suggest otherwise. A number of patients experienced moderate-to-severe pain while receiving necessary routine nursing care such as bathing, turning, or linen changes. Over the course of 20 months, the QI project developed and evaluated demonstrated decreased severe pain and a change in practice to administer analgesic agents early in the day prior to movement-based care activities.

This well-described QI project is the third such project conducted by this multidisciplinary group. This group of clinicians is experienced in doing a quality project and they are well aware of the various pitfalls and challenges associated with implementing changes in practice. This paper by de Jong and colleagues can offer the QI novice a road map for how to conduct such important clinical practice change projects to improve care quality in the ICU. ■

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CME/CNE Questions

1. Which of the following is true about insulin during management of DKA and HHS?

a. Because of acidosis, DKA patients require much higher doses of insulin than HHS patients.
b. Randomized trials have shown that insulin is effective regardless of the chosen route.
c. Insulin should be abruptly stopped once the anion gap normalizes.
d. Insulin will not decrease serum blood glucose levels if the patient is not also receiving intravenous fluids.
e. Studies suggest that an initial bolus of insulin is essential.

2. When comparing DKA and HHS, which of the following is false?

a. Neurologic symptoms, such as obtundation and coma, are more common in HHS than in DKA.
b. DKA patients often have abdominal pain, but it is uncommon in HHS.
c. DKA patients usually have higher blood sugar levels than HHS patients.
d. Both DKA and HHS patients have significant potassium deficits.
e. Patients with HHS are usually younger than patients with DKA.

3. Participants in a simulation testing response to rare crisis events in the operating room:

a. performed better with the checklist approximately 50% of the time.
b. performed better with the checklist later in the day of testing, but not initially.
c. performed better if providing care in an academic vs community setting.
d. rated use of the checklist negatively due to its restrictive nature.
e. would want the checklist used if experiencing a similar emergency.

4. Which of the following statements best fits the potential value of checklists such as those studied for rare but serious events in the operating room?

a. They may be particularly valuable in the community hospital setting.
b. They could replace many aspects of staff inservice training.
c. The enthusiastic participation of staff and resident surgeons in the study suggests that they may be particularly well received by these groups.
d. They could be implemented routinely in most ICU settings with little modification of existing unit cultlure.
e. They should be viewed as a possible additional resource for use as an adjunct in emergent real-life scenarios.

5. The steps used to guide this quality improvement project included which of the following?

a. Assessment, Plan, Implement, Evaluate
b. Plan-Do-Check-Adjust
c. Think-Plan-Act-Measure
d. Background, Methods, Analysis, Findings
e. None of the above

6. One of the main findings from the quality improvement project described by de Jong et al was:

a. patients had less moderate pain at the beginning of the project.
b. patients had more severe pain at the end of the project.
c. patients received more analgesics prior to early-day care activities.
d. nursing staff did not regularly follow the QI guidelines.
e. physicians directed the nurses when to administer music.

CME/CNE Objectives

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

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

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Once-daily Tadalafil for ED: Efficacy and Safety

Source: Seftel AD, et al. *Int J Impot Res* 2013;25:91-98.

THE UTILIZATION OF PDE5 INHIBITION (PDE5-i) for restoration of sexual function in men suffering erectile dysfunction (ED) is well established, beginning with the introduction of sildenafil (Viagra) in 1998. In the earliest years of PDE5-i treatment, regimens were typically targeted to PRN use. Almost a decade later, consideration of lower-dose, daily use of tadalafil became popular.

In this retrospective analysis, Seftel et al report on the safety and efficacy of once-daily tadalafil (TAD-QD) in doses ranging from 2.5-10.0 mg/day. The rationale for their study was to specifically define whether age impacts the efficacy of TAD-QD, since older men (age > 50 years, by their definition) might be more refractory to PDE5-i than younger men (age < 50 years). Additionally, they wished to examine the tolerability profile of TAD-QD in men with mild-moderate ED, who comprise the largest segment of men taking PDE5-i. The dataset used in this analysis included 522 men, predominantly Caucasian (> 75%), most of whom had long-standing ED and about half of whom had comorbidities of hypertension and/or diabetes.

TAD-QD more than doubled the rates of successful intercourse (from 33.4% pretreatment to 76.8% on treatment), with no discernible difference in younger men vs older men. TAD-QD was also well tolerated, with the most common adverse events — headache, dyspepsia, and myalgias — consistent with what has been seen in prior literature.

The authors conclude that TAD-QD provides substantial improvements in ED, independent of age, in men with mild-moderate ED, and is well tolerated. ■

Psychological Disorders: How to Give Patients What They Want and What They Need

Source: McHugh RK, et al. *J Clin Psych* 2013;74:595-602.

COMMONPLACE PSYCHIATRIC DISORDERS such as anxiety, depression, post-traumatic stress disorder, and obsessive compulsive disorder respond to pharmacotherapy, psychotherapy, and their combination. The National Comorbidity Survey Replication data have indicated that persons with psychiatric disorders often do not use mental health services because of perceived barriers to access (e.g., cost, logistics). Identification of patient preferences for treatment is of value not only for patient satisfaction, but also because clinical outcomes are better among patients who receive their treatment of choice. Additionally, patients who are concordant with the therapeutic choice have been reported to be more adherent with therapy.

Data from 34 clinical trials (total patient n = 90,071) were assessed by meta-analysis. Overall, patients expressed a preference for psychological treatment over pharmacotherapy by 3:1. This preference was consistent irrespective of the underlying psychiatric disorder studied, including depression, anxiety, and hypochondriasis. The availability of additional alternatives (e.g., combination treatment, watchful waiting, no treatment) did not affect the balance of patient preferences.

At the current time, treatment of patients with mild-moderate psychiatric disorders with pharmacotherapy vs psychotherapy is at equipoise. Hence, identification of patient preference — in situations where outcomes are similar between choices — is a sensible direction to take. This large literature base suggests that as many as 75% of patients with commonplace psychiatric issues prefer psychological treatment to pharmacotherapy. Although pharmacotherapy is often a more expedient path for primary care clinicians, the importance of addressing patient preference is well highlighted by this study. ■

Reducing Stroke Risk After TIA or Minor Ischemic Stroke

Source: Wang Y, et al. *N Engl J Med* 2013;369:11-19.

THE VERY LARGE CLOPIDOGREL FOR HIGH Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) clinical trial concluded that dual antiplatelet therapy in stable ambulatory vasculopathic patients who are distant — at least 1 year post-MI, post-stroke — from their vascular event does not meaningfully reduce risk over monotherapy, and is associated with increased risk of bleeding. As convincing as this dataset is, it only addresses populations who are distant from their vascular event, rather

than subjects who are in the higher risk period immediately following an acute event.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled — within 24 hours of onset — Chinese subjects (n = 5170) who had sustained a minor ischemic stroke or transient ischemic attack (TIA). Subjects were randomized to treatment (double-blind) with low-dose aspirin (75 mg/d-300 mg/d) plus clopidogrel (300 mg on day 1, then 75 mg/d [CLO + ASA]) or low-dose aspirin plus placebo (ASA). The primary outcome was incidence of stroke (ischemic or hemorrhagic) over 90 days of follow-up.

CLO + ASA was associated with a 32% reduction in risk for stroke compared to aspirin alone. Risk for central nervous system hemorrhage was no different in the CLO + ASA group than ASA alone. In the immediate post-TIA/minor stroke period (up to 90 days), dual antiplatelet treatment meaningfully reduced risk without increasing bleeding. ■

Long-term Mortality Among Adults with Asthma

Source: Ali Z, et al. *Chest* 2013;143: 1649-1655.

In the United States, approximately 5000 persons die each year from asthma. Counterintuitively, deaths in asthma are equally distributed among patients identified as mild, moderate, and severe. Studies of patients with near-fatal asthma have found a decreased sensitivity to hypoxia, hypercapnea, and resistance loading, suggesting that persons destined to succumb to asthma may not fully appreciate the severity of their symptoms, placing them at risk for unrecognized deterioration.

The long-term picture of causes of death in asthmatic adults was the subject of this report by Ali et al. The authors drew on a population of asthmatics enrolled from 1974-1990 in Denmark at their first visit for asthma to the Copenhagen Frederiksbergy Hospital Allergy and Chest Clinic, having been referred there by their general practitioners in the community. More than 75% of the enrollees were younger than 50 years of age at the time of enrollment.

Compared with age- and sex-matched control subjects, all-cause mortality in asthmatic subjects was essentially doubled over 25 years of follow-up. The excess risk for death was primarily due to obstructive airways disease, but was unrelated to smoking status (hence deaths were predominantly *not* related to chronic obstructive pulmonary disease). Degree of peripheral blood eosinophilia correlated with mortality, intimating that unmitigated atopy in asthmatics may contribute to adverse outcomes. ■

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Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

Source: The Look AHEAD Research Group. *N Engl J Med* 2013;369:145-154.

Type 2 diabetes (DM2) is characterized by increased risk for cardiovascular (CV) events, which are not only more frequent but also more severe than similar events in non-diabetics. Most DM2 patients in America are overweight or obese. Weight loss and exercise have been shown to improve glucose control, lipids, blood pressure, and progression from pre-diabetes to diabetes, but no large clinical trials have confirmed risk reduction for CV events attributable to lifestyle intervention.

The Look AHEAD trial randomized overweight or obese DM2 patients (n = 5145) to intensive lifestyle or control (the control group still received education and support in reference to care of their DM2). The goal of intensive lifestyle was to reduce weight by at least 7% and participate in at least 175 minutes/week of moderate-intensity physical activity.

The trial was originally intended to go on for 13.5 years, but was stopped early (at 9.6 years) because futility analysis demonstrated no likely possible benefit of the intensive intervention for CV events compared to controls, despite greater weight loss and improved glycemic control attained in the intensive lifestyle group.

Intensive lifestyle intervention in DM2 improves glycemic indices and body mass index, but does not appear to improve CV risk. ■

New Hope for Hepatitis C Patients

Source: Jacobson IM, et al. *N Engl J Med* 2013;368:1867-1877.

The Centers for Disease Control and Prevention has recently advocated routine screening for hepatitis C (HEP-C) among all adults born from 1945-1965. These recommendations stem from the observation of the ever-growing burden of persons with HEP-C and its consequences who do not necessarily endorse traditionally recognized risk factors for HEP-C such as intravenous drug use, tattoos, etc. Early identification allows for potential cure of HEP-C, since as many as 80% of previously untreated individuals can achieve sustained virologic response with "standard" antiviral regimens (e.g., ribaviron plus interferon).

This does, however, leave a substantial minority of HEP-C patients (those who fail treatment, who are intolerant of treatment, or who have contraindications to it) at risk. Fortunately sofosbuvir, a new polymerase inhibitor, has demonstrated high efficacy in both untreated HEP-C and treatment failures.

Sofosbuvir was studied in two populations of HEP-C genotype 2 or 3: persons with contraindications to interferon and cases that had not responded to interferon therapy. Sustained virologic response was seen in 78% of subjects with interferon contraindications, and (at 16 weeks) 73% of interferon failures. Sofosbuvir was generally well tolerated, with a discontinuation rate of 1-2%. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Do Statins Prevent Parkinson's Disease?

In this issue: Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

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ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■