

A 71-Year-Old Man with Hyperglycemia and Mental Status Changes

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Hyperglycemic hyperosmolar syndrome is an extreme but relatively common presentation of uncontrolled or new-onset diabetes mellitus. The diagnosis of the disorder itself is fairly straightforward, but the search for an underlying cause can be challenging. Infections are the usual precipitating factor, but a variety of other stressors can be involved. We report herein a patient presenting with hyperglycemic hyperosmolar coma with three possible precipitating infections: pharyngitis, urinary tract infection, and infective endocarditis.

The diagnosis of the diabetic hyperosmolar state is not a difficult one. Patients present with an alteration of mental status and extreme hyperglycemia and dehydration. The syndrome most commonly occurs in elderly patients. As opposed to diabetic ketoacidosis, there is a mild metabolic acidosis, if any. Ketones are usually absent, but the presence of minimal ketonemia or ketonuria does not exclude the diagnosis.¹ The most important and often most challenging part of the work-up involves the search for a precipitating event. Usual precipitants include infections, ischemic events (e.g. myocardial infarction or stroke), acute pancreatitis, burns, and heat stroke. Other causes are insulin or insulin secretagogue

deficiency, nutritional indiscretion, and certain drugs (e.g. phenytoin, glucocorticoids, thiazide diuretics, cimetidine, or furosemide).²

Infections constitute the most common precipitating factor in patients presenting with a diabetic hyperosmolar state. Any infectious process can potentially trigger the cycle of hyperglycemia and dehydration. Common precipitating infections include pneumonia, urinary tract infections, and sepsis.³ Other infections that may be more easily overlooked include central nervous system (CNS) infections, abdominal infections, and infective endocarditis. Some disease states, such as acute pancreatitis, can be the cause or even a result of the hyperosmolar state.²

CME INFORMATION

TARGET AUDIENCE

The September/October Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, emergency medicine physicians, and pathologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to recognize and understand the clinical presentation, diagnosis, and treatment of hyperglycemic hyperosmolar syndrome.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Naquin has nothing to disclose.
Dr. Kumar has nothing to disclose.
Dr. Chen has nothing to disclose.
Dr. Zoorob has nothing to disclose.

Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.

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CASE REPORT

A 71-year-old Hispanic man from Honduras, with no known previous medical problems, was found unconscious by his friends. Although not responsive to verbal stimuli, he did respond to vigorous physical stimuli by eye opening and movement of extremities. There were no signs of physical trauma or evidence of possible toxic ingestion by the patient. He apparently had complained of a sore throat for one day. He was transported to the emergency room via emergency medical services. He had not seen a physician since his move to the United States two years earlier. The patient's friends denied any history of medication use, past operations, or allergies. They stated that he did not smoke, drink alcohol, or use any illicit drugs. The patient was married (his wife and son were living in Honduras) and was a retired construction worker. His closest family member in the United States was a nephew who frequently visited the patient. According to his friends, the patient had a glucose level of 550 mg/dL when it was checked with a friend's glucometer earlier in the day.

Upon initial examination in the emergency room, the patient had spontaneous eye opening but did not answer questions or follow commands. His axillary temperature was 102.8° F, pulse 128/minute, respirations 60/minute, blood pressure 190/124mmHg, and oxygen saturation 100% on 100% oxygen by non-rebreather face mask. His pupils were equal and responsive to light, and extraocular movements were intact. His tonsils were edematous and pharynx erythematous but without an appreciable posterior oropharyngeal exudate. His neck was supple, nontender, and without masses or significant jugular venous distension. At the lower left sternal border and cardiac apex, a grade 3/6 holosystolic murmur which radiated to the left axilla was heard. In addition, a 2/6 diastolic blowing murmur was appreciated at the aortic valve position. The patient was tachypneic but did not have any abnormal lung findings. He did have a reducible left inguinal hernia on abdominal exam. His skin showed poor turgor. There were no spider angiomas, splinter hemorrhages, Osler's nodes, or Janeway lesions. Neurologic examination revealed no focal deficits.

Initial laboratory results revealed a significantly elevated blood glucose of 1,602 mg/dL (normal range 70-110 mg/dL) with a blood urea nitrogen (BUN) of 116 mg/dL (normal range 7-21 mg/dL), and a creatinine (Cr) of 5.9 mg/dL (normal range 0.7-1.5 mg/dL). He had an increased anion gap of 28 (normal range 7-16) with a decreased bicarbonate level of 19 mEq/L (normal range 22-30 mEq/L). His serum phosphorus was elevated at 6.1 mg/dL (normal range 2.6-4.5 mg/dL) with a magnesium of 3.4 mg/dL (normal range 1.6-2.3 mg/dL). A complete blood count (CBC) yielded a white blood cell count of 19.9 X 10³/mcL (normal range 4.3-11 X 10³/mcL) with a normal hemoglobin and platelet count. The differential of the white cell count revealed a left shift of 82% neutrophils (normal range 34-72%) with no significant increase in the

percentage of band forms. Arterial blood gas revealed a pH of 7.45 (normal range 7.36-7.44), pCO₂ of 29 mmHg (normal range 35-45 mmHg), pO₂ of 354 mmHg (normal range 80-100 mmHg in air), bicarbonate of 20 mEq/L (normal range 22-26 mEq/L) with 100% oxygen saturation on a non-rebreather 100% oxygen mask. Urine was cloudy with 3+ glucose, 1+ ketones, 3+ blood, 2+ protein, >51 per high-power field white blood cell count, and many bacteria. Acetone was present in the serum. Blood alcohol and urine drug screens were negative. An electrocardiogram showed sinus tachycardia with nonspecific T-wave flattening in leads, II, III, AVF, and V₄ through V₆. A chest radiograph revealed a small amount of subsegmental atelectasis at the right lung base. Computerized tomography (CT) of the head showed diffuse central and cortical atrophy. Blood cultures, urine culture, and throat culture were obtained. A swab for rapid streptococcus testing of the oropharynx was negative, and the first set of cardiac enzymes was reported as normal.

Initial management included admission to the intensive care unit (ICU), aggressive hydration with intravenous (IV) fluids, IV insulin, and IV ceftriaxone for his presumed urosepsis. On day two in the ICU, the patient was more awake and conversant. His white blood cell count increased to 22.1 X 10³/mcL, but serum glucose decreased to 148 mg/dL along with an improvement in BUN and Cr to 89 mg/dL and 4.2 mg/dL, respectively. His sodium increased to 165 mmol/L (normal range 136-145 mmol/L), and the anion gap dropped to 13 with phosphorus and magnesium concentrations improving to 3.8 mg/dL and 2.7 mg/dL, respectively. There was no evidence of an acute myocardial infarction. Subcutaneous insulin was initiated, and IV insulin was discontinued. The patient ate his first meal at that time.

On day three, the patient tolerated oral feedings well and was able to answer questions but could not recall events prior to hospitalization. He denied having abdominal pain, nausea, bloody stools, or melena. Frequent, premature ventricular contractions were noted on the cardiac monitor. His blood chemistry values remained stable with glucose measurements in the 250 mg/dL range, a BUN that had decreased to 60 mg/dL, a serum creatinine of 2.9 mg/dL, and a sodium of 159 mg/dL. The white blood cell count remained high at 23.3 X 10³/mcL with 25% bands. The urine culture revealed the growth of an *E. coli* strain that was sensitive to ceftriaxone. It was assumed that urosepsis had precipitated the diabetic coma. An echocardiogram performed as part of the work-up for the patient's murmur revealed a vegetation on the mitral valve with moderate mitral regurgitation (Figure 1). The first positive blood cultures growing Gram-positive cocci in chains were reported on day three.

By day four, the patient was transferred to the telemetry unit. At that time the blood culture-associated bacteria was identified as *Streptococcus bovis*. Intravenous gentamicin and vancomycin (briefly) were added. A throat culture grew *Streptococcus agalactiae*, a beta-hemolytic

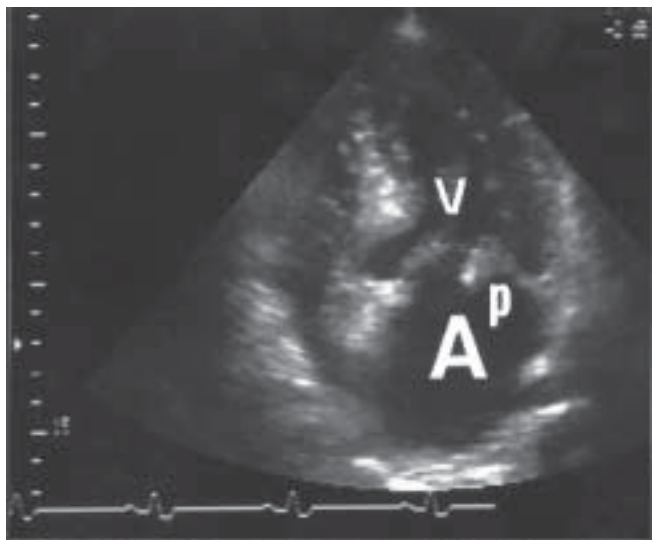


Figure 1. Apical two-chamber transthoracic echocardiographic view. The left atrial cavity (A) is slightly dilated. Between the atrium and the left ventricular cavity (V) is the mitral valve, shown here in early diastole. A vegetation can be seen on the anterior mitral leaflet (to the left), and an even larger vegetation is visualized on the atrial aspect of the posterior mitral leaflet (p). The scale at the left is in 1cm intervals. An electrocardiographic tracing at the bottom of the figure is for timing the cardiac cycle.

Group B streptococcus. On day five, ceftriaxone was stopped and ampicillin started based on susceptibility testing. A gastroenterology consult was obtained for colonoscopy to rule out neoplasm. The patient was subsequently started on oral hypoglycemics and continued on ampicillin and gentamicin. A transesophageal echocardiogram confirmed a large mucoid vegetation on the posterior mitral leaflet with severe mitral regurgitation. No clinical evidence of cardiac failure was appreciated. Colonoscopy revealed an obstruction secondary to an inguinal hernia, a hyperplastic polyp, diverticulosis, and internal hemorrhoids but no malignancy. Other lab results included a negative human immunodeficiency virus test, a normal thyroid-stimulating hormone level, negative rheumatoid factor and anti-nuclear antibody levels, an elevated hemoglobin A_{1c} level of 13.4%, and stool that was negative for occult blood. He received 6 weeks of IV antibiotics and began oral hypoglycemics and an angiotensin converting enzyme inhibitor. He was discharged with home health care and outpatient follow-up.

DISCUSSION

S. bovis has been linked to spondylodiskitis, vertebral osteomyelitis, and splenic abscess. To the best of our knowledge, however, no reports have been published of a case of diabetic nonketotic hyperosmolar coma associated with *S. bovis* infective endocarditis either alone or associated with urinary tract infection (UTI) and Group B streptococcal pharyngitis.

Diabetic nonketotic hyperosmolar coma is an acute

complication in type 2 diabetes. It is a syndrome of extreme hyperglycemia, typically greater than 600 mg/dL, hyperosmolality of greater than 310 mosm/kg, and dehydration. Hyperosmolar coma usually occurs in older patients when there is a concurrent illness that increases catecholamines leading to increased glucose production and relative insulin deficiency. The inability to ingest fluids because of illness leads to decreased urinary volume. With hyperglycemia, CNS dysfunction develops and contributes to decreased fluid ingestion and urine volume production. This ultimately results in extreme hyperglycemia, hyperosmolality, dehydration, and high mortality. Perhaps due to its increased incidence in elderly patients, diabetic nonketotic hyperosmolar coma carries a mortality rate up to 10 times greater than that of diabetic ketoacidosis. Stroke, myocardial infarction, burns, and heat stroke are typical predisposing events, but infectious causes are most common. Treatment typically includes fluid replacement, insulin, replacement of potassium and phosphate, and correction of the precipitating cause.

Most diabetic comas are precipitated by one cause, usually infectious in etiology.² What makes this case unusual is the detection of three infectious processes in the same patient all documented clinically and microbiologically. During our patient's admission work-up and initial urinalysis, findings suggested the precipitating factor was urosepsis, one of the most common causes for acute diabetic hyperosmolar complications. Our patient's blood and urine were sent for culture and appropriate empiric IV antibiotics for urosepsis were initiated. Urine cultures revealed the growth of *E. coli*. A throat culture, obtained due to the history of sore throat and the appearance of his tonsils, demonstrated *S. agalactiae*, an organism known to cause a variety of infections in uncontrolled diabetes in adults.⁴ Bacteremia secondary to *S. bovis* in the setting of a cardiac murmur led to the workup and eventual diagnosis of *S. bovis* infective endocarditis.

Although *S. bovis* can cause urinary tract infections, meningitis, and neonatal sepsis, the most important clinical infections are bacteremia and endocarditis. The usual portal of entry for *S. bovis* is the gastrointestinal tract, but it can occasionally enter through the hepatobiliary tree, urinary tract, and even during dental procedures. Endocarditis complicates about 25 to 50 percent of *S. bovis* bacteremia cases.⁵ Infective endocarditis caused by *S. bovis* usually presents as a subacute illness and is very similar to viridans streptococcal endocarditis with rare septic complications and an excellent response to antimicrobial therapy.⁵ However, in elderly patients, it is more commonly associated with heart failure and the need for extensive surgical interventions. In one study, *S. bovis* endocarditis was associated with a higher mortality.⁶

The Lancefield Group D streptococci are usually non-hemolytic and classified as either enterococci (*faecalis*, *faecium*, *durans*, and other species) or non-enterococcal (*bovis* and *equinus*). *S. bovis* is further differentiated into several biotypes: I (*S. bovis*), II/1, and II/2 (known as *S.*

bovis variants). *S. bovis* type I is commonly found in the feces of cattle, pigs, and sheep. In humans it has been isolated from the colon and from cardiac valves and in these situations has a strong correlation with gastrointestinal (GI) malignancy (74%) and with endocarditis (99%).⁷

S. bovis infections are important because of their significant association with colon cancer. Since the 1970s, several studies have reported an association between *S. bovis* endocarditis and GI lesions. In one study of patients with *S. bovis* endocarditis, pathologic GI lesions were detected in 45% of the patients.⁶ Several studies have shown a high prevalence of stool carriage of *S. bovis* in patients with malignant or pre-malignant lesions of the colon (56%) and infrequent isolation from stools of healthy individuals (5-16%).⁸ Zarkin, et al proposed hepatic dysfunction as a potential participant in this phenomenon, reporting liver disease in 27% of patients with *S. bovis* infective endocarditis and colonic pathology.⁹ It is still unclear, however, whether *S. bovis* is simply a marker for the disease or if it actually plays an etiologic role. A GI work-up, including colonoscopy, was pursued for our patient and no malignancy was discovered.

Unlike enterococci, *S. bovis* is highly sensitive to penicillin as monotherapy. Penicillin is the drug of choice for *S. bovis* infective endocarditis and has been shown to be quite effective when given for four weeks.¹⁰ Other effective antimicrobial agents include ampicillin, erythromycin, clindamycin, and vancomycin. Because of the high association of *S. bovis* infections with colonic neoplasms and possible hepatic dysfunction, patients should undergo colonic evaluation and liver imaging when appropriate.

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 287. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to October 31, 2004. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. Diabetic nonketotic hyperosmolar coma is characterized by all of the following except:
 - a) Hyperglycemia, typically greater than 600 mg/dL
 - b) Hyperosmolality of greater than 310 mosm/kg
 - c) Volume overload due to hyperglycemia
 - d) Dehydration
2. True or False. Diabetic ketoacidosis is more likely to result in death than diabetic nonketotic hyperosmolar coma.
3. All of the following statements about *Streptococcus bovis* infections are true except:
 - a) Infective endocarditis due to this organism has an association with colon cancer.
 - b) These infections may also be associated with liver dysfunction.
 - c) The usual portal of entry is a break in the skin.
 - d) Endocarditis complicates about 25 to 50 percent of *S. bovis* bacteremia cases.
4. True or False. Penicillin is no longer effective as part of the treatment regimen for *Streptococcus bovis* infective endocarditis.