

In Brief

Acute care for patients with diabetes varies greatly depending on the nature of the patients' primary illness and physical condition during hospitalization. The following two case studies review common considerations when treating 1) diabetic patients who develop infections; and 2) hyperglycemic inpatients who have had an acute myocardial infarction or cerebrovascular accident.

Case Study: Infections in Diabetes Mellitus

Dennis S. Schaberg, MD, FACP, and John M. Norwood, MD

Presentation

P.F., a 67-year-old man, presented to the emergency room at the Memphis Veterans Administration Hospital with a 5-day history of progressively worsening left-sided facial pain. The pain initially began in his ear. He also noted purulent drainage from the ear. The patient also complained of subjective fevers and chills. His hearing remained normal. He had no cough, sinus drainage, dysuria, nausea, vomiting, rashes, back pain, or cutaneous ulcers.

His medical history was significant for poorly controlled diabetes of 25 years' duration. He did not follow a meal plan. His hemoglobin A_{1c} concentration measured 2 months previously was 11.8%. He also had a history of nonproliferative diabetic retinopathy and peripheral sensory neuropathy and a 10-year history of hypertension.

Medications at admission included glyburide, 5 mg twice a day, and benazepril, 10 mg daily. He had no allergies. He neither smoked cigarettes nor drank alcohol, and he had no history of substance abuse. His family

history was significant for diabetes and hypertension in his father and grandfather.

Physical examination revealed an elderly Caucasian man in obvious discomfort. His temperature was 100.0° F. His pulse was 100, respiratory rate was 19, and blood pressure was 130/70 mmHg.

His left external auditory canal was erythematous and edematous. It was exquisitely tender on examination. Granulation tissue was visible. The tympanic membrane was obscured by debris. The external ear was warm to touch, erythematous, and tender. A 2-cm ring of erythema surrounded the ear. The right external ear, external auditory canal, and tympanic membrane were normal.

The oropharynx had no masses or erythema. Nasal mucosa was normal. Sclerae were nonicteric, conjunctivae were noninjected, and ocular movements and reflexes were normal. Fundoscopic examination revealed some arterio-venous crossing changes of hypertension.

The patient's neck was supple

without lymphadenopathy or thyromegaly. His chest was clear. Cardiovascular and abdominal examinations were normal. Rectal examination revealed a diffusely enlarged prostate without nodules. Stool was brown and heme-negative.

P.F. was awake, alert, and communicative. Cranial nerve examination was normal. Decreased sensation to light touch and pinprick was noted in a stocking distribution in the lower extremities. Reflexes were absent in the ankles.

Laboratory studies revealed a leukocyte count of 9,000 with 30% band forms. Hematocrit was 42. Platelet count was 421. Serum chemistries revealed a sodium of 132 mEq/L, a potassium of 3.8 mEq/L, chloride of 106 mEq/L, bicarbonate of 26 mEq/L, BUN of 38 mg/dl, and a creatinine of 2.3 mg/dl. Serum glucose was 426 mg/dl. Hepatic functions were normal. Urinalysis revealed 1+ protein. Chest X-ray was normal. Electrocardiogram revealed a sinus tachycardia and was otherwise normal.

Commentary

Individuals with diabetes can have any infection that affects the general population. However, people with diabetes are at increased risk of a variety of specific infectious complications. Infections associated with either increased frequency or severity among

individuals with diabetes include mucormycosis; cystitis; complicated urinary tract infections, including pyelonephritis; intrarenal abscesses; perinephric abscesses; pneumonia; lower-extremity soft tissue infection, including polymicrobial gangrene;

emphysematous cholecystitis; and malignant otitis externa (Table 1).¹ Individuals with diabetes also have increased carriage rates of *Staphylococcus aureus*, which likely translates into increased risk for infection with this organism.² The pathophysi-

Table 1. Infectious Complications of Diabetes Mellitus

Disease	Organism	Risk Factor
Mucormycosis	Rhizopus Spp, Rhizomucor	Hyperglycemia
Staphylococcal carriage	<i>Staphylococcus aureus</i>	Hyperglycemia
Urinary tract infection	<i>E. coli</i> , other gram-negatives	Hyperglycemia, female sex
Pneumonia	<i>S. pneumonia</i> , influenza, fungi	Hyperglycemia, age
Emphysematous cholecystitis	<i>Clostridium perfringens</i>	Hyperglycemia, age, male sex
Polymicrobial soft tissue infection	Streptococci, anaerobes, gram-negatives	Hyperglycemia, angiopathy
Malignant otitis externa	<i>Pseudomonas aeruginosa</i>	Hyperglycemia

ology of infection associated with diabetes is incompletely understood. Defects in leukocyte function, especially chemotaxis, have been described in people with diabetes.³ Complement dysfunction has also been encountered in some patients with diabetes.⁴ These abnormalities have been found inconsistently by investigators. When found, they appear to be most strongly associated with poor glycemic control, which also contributes directly to microvascular angiopathy. Angiopathy is predictive of the soft tissue and organ infections of diabetic patients.

The most dramatic example of the interaction of angiopathy, acidosis, and poor glycemic control in infection is mucormycosis. Mucormycosis is a severe infection caused by fungi of the order Mucorales. These fungi are ubiquitous and are often found on decaying matter, such as moldy bread. Patients with diabetes are at particular risk of a form of the disease known as rhinocerebral mucormycosis.

This infection is thought to be caused by inhalation of the spore forms of the organisms, which are presumed to then lodge in the nasal tissue. The spores subsequently germinate and invade adjacent tissue, with a particular tropism for blood vessels. The orbit and central nervous system can subsequently become affected. The infection usually presents with facial or ocular pain. Fever and symptoms of sinusitis may be present. About 50% of patients are in diabetic ketoacidosis (DKA) at the time of presentation.⁵

Severe infection is associated with cranial nerve abnormalities, altered mental status that persists after DKA resolution, and evidence of orbital cellulitis. The presence of necrotic lesions involving the palate or nasal tissue is a specific, but not sensitive, finding.⁶

Complications of the infection include cavernous sinus thrombosis, retinal artery invasion, carotid artery thrombosis, and intracerebral abscess and infarction.

Diagnosis is made by a biopsy specimen demonstrating organisms invading tissue. Therapy involves a combination of correction of any DKA, surgical debridement, and treatment with amphotericin B. Some case reports have suggested benefit from adding hyperbaric oxygen to standard therapy.⁷ In one series, overall mortality from orbital involvement was 33%, with significant improvement being seen in the past two decades.⁸ Survival has been shown to be dependent on early diagnosis and initiation of treatment.⁹

P.F. was examined by his admitting physician and otolaryngologist shortly after admission. No suspicious lesions were noted on nasopharyngeal examination. The patient had no cranial nerve, ocular, or sinus symptomatology.

Several studies have linked patients with diabetes, particularly those who inject insulin, to a higher incidence of carriage of *Staphylococcus aureus* than the general population.¹⁰ Other studies have failed to link Staphylococcal carriage to insulin injection but have shown a high carriage rate for both insulin- and noninsulin-using diabetic patients.¹¹ Some investigators have suggested that individuals with diabetes have a higher incidence of both Staphylococcal bacteremia and excess mortality.¹² However, those studies remain inconclusive.

There does appear to be evidence that individuals with a clear focus of a staphylococcal infection have a higher incidence of infective endocarditis.¹³ Clearly, patients with renal failure have a high incidence of clinically relevant staphylococcal infection because

of infected temporary and permanent access grafts.¹⁴ P.F., however, had negative blood cultures, and careful examination failed to reveal a focus of staphylococcal infection.

Urinary tract infections are also more common among patients with diabetes. Women with diabetes are at a particularly increased risk of urinary tract infection.¹⁵ Upper tract infection has been shown to be significantly more common in patients with diabetes. *E. coli* is the most common causative organism, followed by other gram-negative bacteria. Because of the high incidence of often unsuspected upper tract infection, a 7- to 14-day course of therapy has been recommended for treatment of cystitis among patients with diabetes.¹⁶

Pyelonephritis is clearly more common in patients with diabetes. It is treated similarly to pyelonephritis in nondiabetic patients. Other renal infections that are more common in individuals with diabetes include renal carbuncles (intrarenal abscesses caused by the hematogenous spread of *S. aureus*), renal corticomedullary abscesses (intrarenal foci of infection associated with reflux and obstruction caused by the same organisms that typically cause pyelonephritis), and the rare but devastating emphysematous pyelonephritis, associated with gas formation within the kidney.

The latter infection is usually caused by *E. coli* or other gram-negatives and is typically detected by a routine X-ray of the abdomen. A combination of surgery and medical therapy is usually required. Perinephric abscesses are caused either by the rupture of intrarenal abscesses into tissue surrounding the kidney or by the hematogenous or lymphatic deposition of organisms into that tissue. Gram-negative organisms such as *E. coli* are the most common reported causative bacteria. However, a wide variety of organisms, such as *S. aureus*, fungi, anaerobes, and mycobacteria, have been reported as causes.

Diabetes is very clearly associated with these infections. Underlying renal pathology, such as vesicovesicular reflux and obstructive uropathies, are also strongly associated with these abscesses.

Presenting symptoms are quite variable and most commonly include flank pain. Diagnosis is usually made by radiographic studies, such as ultrasound or CT scans, to evaluate flank pain or persistent fever. Appropriate

therapy consists of a combination of abscess drainage through either surgery or percutaneous drainage and appropriate antibiotic therapy. This patient had no urinary symptoms, no flank discomfort, and his urinalysis revealed no evidence of a urinary tract infection.

Pneumonia has traditionally been described as a major cause of morbidity and mortality among patients with diabetes. An increased incidence of pneumonia from *S. aureus* secondary to nasal carriage, particularly among recently hospitalized diabetic patients, has been described.¹⁷ Pneumonia due to both gram-negative organisms and fungi has also been described as being more frequent among diabetic patients.¹⁸ An increased risk of developing active tuberculosis among diabetic patients with a positive reaction to tuberculin (a positive PPD) has long been described. *Streptococcus pneumoniae* and influenza have been described as causing more severe infection in people with diabetes than that found in the general population.^{19,20} It is not clear whether the latter organisms cause pneumonia with an increased frequency when diabetes is present or instead cause a more severe pneumonia presentation.

Pneumonia and influenza vaccination have long been advocated for widespread use among people with diabetes. Management of bacterial pneumonia is the same for diabetic patients as for those without diabetes. Antiviral agents are generally recommended for treatment of influenza pneumonia in this population. In P.F.'s case, there was no evidence of pneumonia: he had no respiratory symptoms and a normal chest X-ray.

Emphysematous cholecystitis is a rare but severe infection associated with gas-forming organisms such as *Clostridial* species and other anaerobes. A significant portion of patients with this illness are men, and 20–30% have diabetes.²¹ Presentation is similar to other forms of cholecystitis, with fever and right-upper-quadrant pain. However, patients with this illness are usually more ill. Diagnosis is often made by the detection of gas in the gallbladder on radiographic imaging of the abdomen. Treatment is with a combination of surgical intervention and antibiotic therapy. In our case above, P.F. had no abdominal symptomatology and a normal abdominal examination.

Soft tissue infections of the lower extremities and gangrene are among the most dreaded complications associated with diabetes. Patients with diabetes clearly have an elevated risk of infected lower-extremity ulceration and subsequent amputation.²²

Foot ulcers usually occur in patients with sensory polyneuropathy who develop skin breakdown after unrecognized trauma. Infection, usually polymicrobial, then easily occurs in tissue with an inadequate microvascular or macrovascular blood supply. Uncontrolled soft tissue infection can then lead to necrotizing processes and systemic sepsis. Chronic infection, such as osteomyelitis, can also occur in conjunction with cutaneous ulcers. Treatment of these infections involves a combination of early surgical intervention for debridement or amputation and any necessary vascular repair, antibiotic therapy, and local wound care.

Osteomyelitis is usually diagnosed by nuclear studies, such as gallium and bone scanning. The best treatment of these infections is clearly prevention by a combination of proper glycemic control and foot care. In this case, P.F. had evidence of a peripheral neuropathy, but he had no ulcers, erythema, evidence of tissue necrosis, or other signs of lower-extremity infection.

Malignant otitis externa is a potentially severe infection caused almost exclusively by *Pseudomonas aeruginosa*, which invades the ear and adjacent structures. In the past, most cases were described among elderly patients with long-standing diabetes. Recently, however, cases have been described in patients without diabetes.²³

Pseudomonas aeruginosa is not a part of the normal flora of the ear. The presence of that organism is thought to be increased in the presence of hot, humid conditions or following irrigation of the ear with non-sterile water.

The organism is thought to penetrate the cartilage in the external auditory canal through the naturally occurring fissures of Santorini. A necrotizing cellulitis exacerbated by microvascular disease then occurs. Infection then involves mastoid air cells and the temporal bone. Subsequently, the base of the skull becomes involved. Complications of this infection include cranial nerve palsies, thromboses of lateral and sigmoid sinuses, extension to the con-

tralateral base of the skull, and cavernous sinus thrombosis.

Symptoms include otalgia, which occurs in more than 75% of patients, and otorrhea, which occurs in more than 50% of patients.²⁴ Hearing loss is another common symptom. Trismus and transmandibular joint (TMJ) pain may also occur. Swelling and erythema with a purulent drainage is usually noted on examination. Granulation tissue is often noted, and the tympanic membrane may be perforated. Erythema of the external ear and adjacent tissue may also be found. Ipsilateral cervical and auricular lymphadenopathy may be present. Parotid swelling may occasionally be noted. Cranial nerve palsies may occur with the facial nerve most commonly involved.²⁵ The erythrocyte sedimentation rate is uniformly elevated. Laboratory findings are otherwise highly variable and usually not helpful.

CT or MRI imaging studies are helpful to define the extent of disease. The diagnosis is confirmed by the isolation of *Pseudomonas aeruginosa* from cultures of drainage from the ear in cases in which patients have severe ear pain, with granulation tissue present in the external auditory canal with or without radiographic evidence of disease. Other organisms rarely cause this disease.

Treatment involves a combination of surgical debridement and antibiotic therapy. There is some controversy regarding the appropriate antibiotic choices. Traditionally, standard therapy has been a combination of an extended spectrum penicillin and an aminoglycoside given for 4–8 weeks, depending on the severity of illness. Use of a single drug, such as ciprofloxacin given orally or ceftazidime given intravenously for 6 weeks, has shown success in less severely ill patients.^{26,27} Early initiation of antibiotic therapy and surgical intervention are important for optimal outcomes.

P.F. had cultures from the external auditory canal that were positive for *Pseudomonas aeruginosa*. His other findings, including the otalgia, otorrhea, and erythema of the canal, were also typical of malignant otitis externa. CT scan revealed temporal bone erosion. He was treated with debridement and a 6-week course of an anti-pseudomonal penicillin and an aminoglycoside to which the organism was sensitive. He recovered without further complication.

In patients with diabetes mellitus, a variety of common infections, in particular *Staphylococcus aureus*, may be seen with increased frequency because of alterations in the mechanical barrier of the skin and vascular abnormalities common in people with diabetes. There are also a number of infections as described above that are virtually unique in patients with diabetes. A heightened sense of awareness will lead to the early diagnosis and subsequent treatment of these potentially life-threatening complications of this common metabolic disorder.

References

- ¹Joshi N, Caputo G, Weitekamp M, Karchmer AW: Infections in patients with diabetes mellitus. *N Engl J Med* 341:1906-1912, 1999
- ²Leibovici L, Yehezkeili Y, Porter A, Regev A, Krauze I, Harrell D: Influence of diabetes mellitus and glycemic control on the characteristics and outcome of common infections. *Diabet Med* 13:457-463, 1996
- ³Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allanic H, Genetet B: Impaired leukocyte functions in diabetic patients. *Diabet Med* 14:29-34, 1997
- ⁴Hostetter MK: Handicaps to host defense: effects of hyperglycemia on C3 and candida albicans. *Diabetes* 39:271-275, 1990
- ⁵Parfrey NA: Improved diagnosis and prognosis of Mucormycosis: a clinicopathologic study of 33 cases. *Medicine* 65:113-123, 1986
- ⁶Sugar AM: Mucormycosis. *Clin Infect Dis* 14 (Suppl. 1):S126-S129, 1992
- ⁷Giitter MF, Henderson LT, Afsari KK: Adjunctive hyperbaric oxygen therapy in the treatment of rhinocerebral mucormycosis. *Infect Med* 13:130-136, 1996
- ⁸Peterson KL, Wang M, Canalis RF, Abemayer E: Rhinocerebral mucormycosis: evolution of the disease and treatment options. *Laryngoscope* 107:855-862, 1997
- ⁹Yohai RA, Bullock JD, Aziz AA, Market RJ: Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmology* 39:3-22, 1994
- ¹⁰Tuazon Cu, Perez A, Kishaba T, Sheagren JN: Staphylococcus aureus among insulin injecting diabetic patients. *JAMA* 231:1272, 1975
- ¹¹Lipsky BA, Pecoraro RE, Chen MS, Koepsell TD: Factors affecting staphylococcal colonization among NIDDM outpatients. *Diabetes Care* 10:483-486, 1987
- ¹²Cluff LE, Reynolds RC, Page DL, Breckenridge JL: Staphylococcal bacteremia and altered host resistance. *Ann Int Med* 69:859-873, 1968
- ¹³Cooper G, Platt R. Staphylococcus aureus bacteremia in diabetic patients: endocarditis and mortality. *Am J Med* 73:658-652, 1982
- ¹⁴Quarles LD, Rutsky EA, Rostand SG: Staphylococcus aureus bacteremia in patients on chronic hemodialysis. *Am J Kidney Dis* 6:412-419, 1985
- ¹⁵Geerlings SE, Stolk RP, Camps MJ, Netten PM, Collet TJ, Hoepelnon AI: Risk factors for symptomatic urinary tract infection in women with diabetes. *Diabetes Care* 23:1737-1741, 2000
- ¹⁶Stamm WE, Hooten TM: Management of urinary tract infections in adults. *N Engl J Med* 329:1328-1334, 1993
- ¹⁷Germaud P, Caillet S, Allenet MC: Community-acquired pneumonia caused by Staphylococcus aureus in non-HIV infected adult patients. *Rev Pneumol Clin* 52:83-87, 1999
- ¹⁸Kozziel H, Kozziel MJ: Pulmonary complications of diabetes mellitus: pneumonia. *Infect Dis Clin North Am* 9:65-96, 1995
- ¹⁹Bouter KP, Diepersloot RJ, Van-Romunde LK, Uitslager R, Masurel N, Hoekstra JB, Erkelens DW: Effect of epidemic influenza on ketoacidosis, pneumonia, and death in diabetes mellitus: a hospital register survey of 1976-1979 in The Netherlands. *Diabetes Res Clin Pract* 12:61-68, 1991
- ²⁰Watanakunakorn C, Greifenstein A, Stroh K, Jarjoura DG, Blend D, Cugino A, Ognibene AJ: Pneumococcal bacteremia in three community teaching hospitals from 1980-1989. *Chest* 103:1152-1156, 1993
- ²¹Mentzer RM Jr, Golden GT, Chandler JG, Horsley JS III: A comparative appraisal of emphysematous cholecystitis. *Am J Surg* 129:10-15, 1975
- ²²Most RS, Sinnock P: The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care* 6:8-9, 1983
- ²³Hern JD, Almeyda J, Thomas DM, Main J, Patel KS: Malignant otitis externa in HIV and AIDS. *J Laryngol Otol* 111:770-775, 1996
- ²⁴Doroghazi RM, Nadol HB Jr, Hyslop NE, Baker AS, Axelrod L: Invasive external otitis: report of 21 cases and review of the literature. *Am J Med* 71:603-614, 1981
- ²⁵Rubin J, Yu VL: Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis, and therapy. *Am J Med* 85:391-398, 1988
- ²⁶Johnson MP, Ramphal R: Malignant external otitis: report on therapy with ceftazidime and review of therapy and prognosis. *Rev Infect Dis* 12:173-180, 1990
- ²⁷Levenson MJ, Parisier SC, Dolitsky J, Bindra G: Ciprofloxacin: drug of choice in the treatment of malignant external otitis (MEO). *Laryngoscope* 101:821-824, 1991

Dennis S. Schaberg, MD, FACP, is a professor of internal medicine and chair of the Department of Medicine, and John M. Norwood, MD, is an associate professor of medicine in the Division of Infectious Diseases at the University of Tennessee College of Medicine in Memphis.

Case Study: The Recipe for Diabetes Success in the Hospital

Claresa Levetan, MD, and Meeta Sharma, MD

Presentation

N.D., a 48-year-old, obese, African-American man, was admitted to intensive care unit with crushing, substernal chest pain. This was associated with dizziness, nausea, vomiting, and diaphoresis. The electrocardiogram on admission revealed T wave inversions

in the anterior and lateral leads. He ruled in for a myocardial infarction (MI) by serial cardiac enzymes. His glucose level on admission was 203 mg/dl with a bicarbonate of 24 mg/dl. A hemoglobin A_{1c} (HbA_{1c}) performed in the hospital revealed a value of 8.1%.

The patient's father had a history of heart disease and had suffered a heart attack at the age of 52 years. His grandmother had a history of type 2 diabetes controlled with insulin. N.D. stated that for a few months before admission, he had been feeling

fatigued and had been experiencing increased urination, especially at night.

N.D. is a computer programmer and had led a sedentary lifestyle, with-

out a regular exercise regimen. He had steadily gained weight over the years, to his present weight of 220 lb. He does not smoke and occasionally

drinks beer on the weekend. He consistently drinks more heavily during an annual Super Bowl party in January of each year.

Commentary

Ingredients for diabetes success

- Regardless of whether this patient has “stress hyperglycemia” or unrecognized diabetes, treat aggressively with intravenous rather than subcutaneous insulin coverage.
- Understand that definitive diabetes is not necessary to demonstrate improved outcomes by controlling glucose as close to normal as possible.
- Realize that morbidity and mortality from stroke, MI, and bypass surgery are affected most by glucose levels in the hospital.

Does controlling hyperglycemia in the hospital really matter?

The data on the importance of controlling glucose in the hospital span diverse disciplines of medicine. Studies in the areas of stroke, MI, bypass surgery, and wound and nosocomial infections all point to the tremendous potential to reduce morbidity and mortality among hospitalized patients with hyperglycemia. It is essential that hyperglycemia is identified from the time of hospital admission and that therapy is implemented to achieve and maintain glucose levels as close to normal as possible regardless of a patient's primary reason for admission or previous diabetes status.

In the United States, there are more than 4.2 million hospitalizations annually among people with diabetes.¹ Additionally, there are as many as 1.5 million hospitalized individuals who have significant hyperglycemia but no history of diabetes.² Identification of and therapeutic interventions to treat hyperglycemia must be initiated in tandem with the presenting medical problem rather than days after admission, when many of the acute issues have already been addressed. Existing data strongly suggest that an early and aggressive approach to the management of hyperglycemia may reduce mortality, morbidity, excessive hospital stays, and added costs.

Diabetes is the secondary, not primary, problem.

Hyperglycemia is often overlooked

when a hospitalized patient is acutely ill and facing a life-threatening illness. A common scenario is that of a patient admitted with an acute MI or cerebrovascular accident who is coincidentally found to have an elevated admission glucose value. Often, such patients have no history of glucose intolerance.

For patients who do have pre-existing diabetes, physicians routinely discontinue their patients' previous outpatient diabetes regimen and initiate sliding-scale insulin coverage in the hospital.³ Many physicians consider this practice the standard of care. Concerns about precipitating hypoglycemia may limit more aggressive strategies for managing hyperglycemia, particularly when many of these patients are not tolerating regular meals or their intake is being limited for a variety of reasons, including pending surgical procedures or diagnostic tests.

Despite the ease and high frequency of use, sliding-scale insulin coverage often results in a deterioration of, rather than an improvement in, glycemic control.³ While concerns about hypoglycemia are warranted, hyperglycemia, regardless of whether a previous diabetes diagnosis has been made, may pose even greater risks by reducing hospital survival rates among patients admitted with stroke or MI.⁴⁻⁶

Is hyperglycemia caused by stress or diabetes? It doesn't matter—treat it.

There are no unique diagnostic criteria to account for stress in acutely ill patients, nor are there recommendations for making a definitive diagnosis of diabetes in the hospital. Despite the well-defined pathophysiology of intercurrent illness and surgery on carbohydrate metabolism that may lead to hyperglycemia, many studies have also demonstrated that stress may result in diminished glucose values.⁷⁻¹⁹ This reduction in glucose seen in times of stress is frequently attributed to insufficient administration of exogenous glucose.

Among hospitalized patients with acute MI, an admission glucose value

of ≥ 180 mg/dl predicted undiagnosed diabetes rather than stress hyperglycemia in a study in which newly recognized hyperglycemic individuals had subsequent glucose tolerance testing performed 2 months after hospital discharge.^{4,5}

The Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) trial demonstrated significant reductions in mortality when an intensive insulin regimen was administered to hyperglycemic patients hospitalized with acute MI.^{4,5} Subjects in the DIGAMI study included all patients with glucose values >198 mg/dl without regard to previous diabetes status. Nearly 15% of the study population did not have a history of glucose intolerance.

Is the hospital really the time to consider diabetes? Yes.

Mortality rates among patients with diabetes are known to be significantly higher than those of nondiabetic individuals.²⁰ The Whitehall Study reported a mortality rate of 12/1,000 person-years for nondiabetic individuals, a rate of 40 for people with undiagnosed diabetes, and a rate of 27 for people with diagnosed diabetes.²¹ The Paris Prospective Study demonstrated comparable differences between the mortality rates among patients with undiagnosed diabetes (23%) versus those with a definitive diagnosis of diabetes (20%) and patients without diabetes (9%).²² In both studies, 60–70% of the deaths were attributed to cardiovascular disease.²³

Where is the best place to find unrecognized diabetes? In the hospital.

It is estimated that 5.3 million Americans have undiagnosed diabetes. As many as one-third of the patients who have significant hyperglycemia during their hospital admission do not have a history of diabetes.² Given the 7- to 10-year delay between the actual onset of diabetes and the time of diagnosis, there is a high likelihood that patients exhibiting hyperglycemia without a history of glucose intolerance may indeed have unrecognized diabetes.²⁰ The beneficial impact of

interventions that improve hyperglycemia and lead to better outcomes is based on the presence of diabetes regardless of whether a physician has made the diabetes diagnosis.

Health care providers should assume that a hyperglycemic patient has diabetes and initiate treatment to control glucose levels as close to normal as possible. Further evaluation of the patient's diabetes status can occur after hospitalization. Failure to treat and address hyperglycemia in the hospital is a missed opportunity to not only reduce hospital morbidity and mortality, but also initiate interventions that may delay the long-term complications of diabetes.

What if the hyperglycemia is caused by medication? Treat it like diabetes.

Often medications such as steroids and thiazide diuretics, which have been associated with worsening glycemic control, are required in the care of patients with diabetes. Dozens of medications have been described as inducing diabetes, yet there has been poor documentation of the glycemic status of patients using the offending drugs before these drugs were initiated.

Decades ago, corticosteroids were studied as a means of unmasking impaired glucose tolerance.²⁴ When evaluating the impact of corticosteroids on normal control subjects, only 3% had positive glucose tolerance tests when pretreated with corticosteroids.

Other studies among corticosteroid-treated individuals have found that fewer than 20% of steroid-treated individuals develop diabetes. This indicates that hyperglycemia in the setting of the hospital should be assumed to be diabetes,^{25,26} even when medications that potentially produce hyperglycemia are required to treat another medical problem. In such cases, treatment of hyperglycemia should be initiated.

Is there a diagnostic role for HbA_{1c}? Maybe.

Many clinicians have advocated the use of HbA_{1c} measurement in the diagnosis of diabetes.²⁷⁻³⁰ But although an elevated HbA_{1c} measured when hyperglycemia is first noted can help determine that the hyperglycemia existed before hospitalization, a normal HbA_{1c} concentration does not preclude the diagnosis of diabetes. In one study, normal HbA_{1c} concentra-

tions measured during hospital admission did not exclude the diagnosis of diabetes when glucose tolerance testing was performed after discharge.³¹

As more laboratories adopt the standardized methodologies for performing HbA_{1c} as established by the National Glycohemoglobin Standardization Program (NGSP), it will be easier to establish guidelines for the diagnosis of diabetes based on elevated HbA_{1c} concentrations. Laboratories certified by the NGSP all have equivalent HbA_{1c} assays and can be compared nationally regardless of location or laboratory performing the test. When the NGSP's norms and ranges for HbA_{1c} are adopted universally, the HbA_{1c} assay may become a more useful tool for establishing the pre-existence of hyperglycemia before a hospital admission. Normal HbA_{1c} concentrations in the hospital setting still will not preclude the diagnosis of diabetes, however, and such patients will still need follow-up to evaluate diabetes status.

Diabetes isn't the reason for admission, so why treat it? Hyperglycemia DOES impact the primary medical problem.

Ninety percent of hospitalizations among patients with a known diagnosis of diabetes are for reasons other than diabetes. Approximately 75% of hospital admissions for people with diabetes are attributable to cardiovascular disease.³² When hyperglycemia is not addressed until after the presenting medical problems have been treated, the length of hospital stay can be significantly longer than that of nondiabetic patients with similar primary diagnoses. Addressing diabetes along with other acute problems results in not only improved outcomes, but also potentially shorter hospital stays.³³

Shouldn't the MI be managed first? Treat the hyperglycemia aggressively and sequentially with the MI.

Diabetes has been demonstrated to be an independent risk marker for morbidity and mortality among patients who have suffered an MI.^{4,5,34-37} Soler and Frank observed that patients with the highest glucose values following an acute MI also had the highest mortality rates.³⁴

The DIGAMI study underscores the importance of early and aggressive interventions designed to bring glucose levels into the normal range

regardless of a patient's prior diabetes status.^{4,5} This large, randomized, prospective trial enrolled 620 patients with admission glucose values of >198 mg/dl. Hyperglycemic individuals were randomized to receive either conventional diabetes care or intravenous insulin followed by four insulin injections daily.

One year after admission, there was a 30% reduction in mortality among the intervention patients. The greatest benefits from intensive insulin therapy were seen in the subgroup that included patients without a history of diabetes, who had a 58% risk reduction in hospital mortality and a 52% risk reduction in mortality when followed for 1 year when compared to conventionally treated patients.

When outcomes were tracked for a mean of 3.4 years, intervention patients had a 25% lower death rate. The DIGAMI study demonstrated that for every nine patients receiving intensive glucose control, one life was saved.

Summary and clinical keys

Inpatient studies have been designed to evaluate the impact of potentially correcting the pathophysiological changes that accompany hyperglycemia. Studies among patients with MI suggest that treatment of hyperglycemia can potentially affect morbidity and mortality, and similar benefits may apply to controlling hyperglycemia regardless of whether patients have a prior diagnosis of diabetes.

- When patients present with an acute illness and hyperglycemia, it is often difficult to differentiate stress hyperglycemia from previously undiagnosed diabetes.
- The lack of a definitive diagnosis of diabetes should not preclude aggressive glycemic management, especially in patients with suspected MI.
- Hyperglycemia accompanied by an elevated HbA_{1c} concentration suggests previously undiagnosed diabetes.
- The DIGAMI study demonstrated that for every nine patients receiving intensive glucose control regardless of their baseline diabetes status, one life was saved.

References

¹U.S. Center for Health Statistics: 1997 National Hospital Discharge Survey (Public Use Data)

- Tape). Washington, D.C., U.S. Department of Health and Human Services, 1999
- ²Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE: Unrecognized diabetes among hospitalized patients. *Diabetes Care* 21:246-249, 1998
- ³Queale WS, Alexander JS, Brancati FL: Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. *Arch Intern Med* 157:545-552, 1997
- ⁴Malmberg K, Ryden L, Efendic S, Herlitz J, Nocol P, Waldenstrom A, Wedel H, Welin L: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 26:57-65, 1995
- ⁵Malmberg K, Ryden L: Myocardial infarction in patients with diabetes mellitus. *Eur Heart J* 9:256-264, 1988
- ⁶Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS: Stroke in patients with diabetes: the Copenhagen Stroke Study. *Stroke* 25:1977-1084, 1994
- ⁷Gavin LA: Management of diabetes mellitus during surgery. *West J Med* 151:525-529, 1989
- ⁸Gavin LA: Perioperative management of the diabetic patient. *Endocrinol Metab Clin North Am* 2:457-475, 1992
- ⁹Chase HP, Jackson GG: Stress and sugar control in children with insulin-dependent diabetes mellitus. *J Pediatr* 98:1011-1013, 1981
- ¹⁰Gonder-Frederick LA, Carter WR, Cox DJ, Clarke WI: Environmental stress and blood glucose change in insulin-dependent diabetes mellitus. *Health Psychol* 9:503-515, 1990
- ¹¹Hanson CL, Pichert JW: Perceived stress and diabetes control in adolescents. *Health Psychol* 5:439-442, 1988
- ¹²Vandenbergh RL, Sussman KE, Titus CC: Effects of hypnotically induced acute emotional stress on carbohydrate-lipid metabolism in patients with diabetes mellitus. *Psychosom Med* 28:382-390, 1966
- ¹³Vandenbergh RL, Sussman KE, Vaughan GD: Effects of combined physical-anticipatory stress on carbohydrate-lipid metabolism in patients with diabetes mellitus. *Psychosomatics* 8:16-19, 1967
- ¹⁴Kemmer FW, Sisping R, Steingruber HJ, Baar H, Hardtmann F, Schlaghecke R, Berger M: Psychological stress and metabolic control in patients with type 1 diabetes mellitus. *N Engl J Med* 314:1078-1084, 1986
- ¹⁵Gilbert BO, Johnson SB, Silverstein J, Malone J: Psychological and physiological responses to acute laboratory stressors in insulin-dependent diabetes mellitus adolescents and non-diabetic controls. *J Pediatr Psychol* 14:577-591, 1989
- ¹⁶Delamater AM, Bubb J, Kurtz SM, Kuntze J, Smith JA, White NH, Santiago JV: Physiologic responses to acute psychological stress in adolescents with type 1 diabetes mellitus. *J Pediatr Psychol* 13:69-86, 1988
- ¹⁷Goetsch VL, Wiebe DJ, Vetum LG, Van Dorsten B: Stress and blood glucose in type 2 diabetes mellitus. *Behav Res Ther* 28:531-537, 1990
- ¹⁸Fletcher J, Langman MJS, Kellock RK: Effect of surgery on blood-sugar levels in diabetes mellitus. *Lancet* ii:5255, 1965
- ¹⁹Hirsch IB, Paauw DS, Brunzell J: Inpatient management of adults with diabetes. *Diabetes Care* 18:870-878, 1995
- ²⁰Husband DJ, Alberti KG, Julian DG: Stress hyperglycemia during acute myocardial infarction: an indicator of pre-existing diabetes? *Lancet* ii:52-55, 1965
- ²¹Harris MI: Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 16:642-652, 1993
- ²²Jarrett RJ, Shipley MJ: Type 2 (non-insulin dependent) diabetes mellitus and cardiovascular disease—putative association via common antecedents: further evidence from the Whitehall Study. *Diabetologia* 31:737-740, 1988
- ²³Eschwege E, Richard JL, Thibault N, Duchimetièrre P, Warnet JM, Claude JR, Rosselin GE: Coronary heart disease mortality in relation with diabetes, blood glucose, and plasma insulin levels, the Paris Prospective Study ten years later. *Hormone Metab Res* 15 (Suppl):41-46, 1985
- ²⁴Fajans SS, Conn JW: An approach to the prediction of diabetes mellitus by modification on the glucose tolerance test with cortisone. *Diabetes* 3:296-304, 1954
- ²⁵Landy HJ, Isada NB, McGinnis J, Ratner R, Grossman JH: The effect of chronic steroid therapy on glucose tolerance in pregnancy. *Am J Obstet Gynecol* 159:612-615, 1988
- ²⁶Weisz A, Ratner R: Factors in renal transplant-induced diabetes mellitus (Abstract). *Diabetes* 35 (Suppl. 1):72A, 1986
- ²⁷Santiago JV, Davis JE, Fisher F: Hemoglobin A1c levels in a diabetes detection program. *J Clin Endocrinol Metab* 47:578-580, 1978
- ²⁸Svendsen PA, Jorgensen J, Nerup J: HbA_{1c} and the diagnosis of diabetes mellitus. *Acta Med Scand* 210:313-316, 1981
- ²⁹Little RR, England JD, Wiedmeyer HM, McKenzie EM, Pettitt DJ, Knowler WC, Goldstein DE: Relationship of glycosylated hemoglobin to oral glucose tolerance: implications for diabetes screening. *Diabetes* 37:60-64, 1988
- ³⁰Peters AL, Davidson MB, Schriger DL, Hasselblad V: A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels: Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. *JAMA* 276:1246-1252, 1996
- ³¹Levetan C, Dawn K, Ayala A, Ratner R: Characteristics of hospitalized patients with unrecognized diabetes (Abstract). *Diabetes* 36 (Suppl. 1):183A, 1997
- ³²Lewis GF: Diabetic dyslipidemia: a case for aggressive intervention in the absence of clinical trial and cost effectiveness data. *Can J Cardio* 11 (Suppl. C):24C-28C, 1995
- ³³Levetan CS, Salas JR, Wilets IF, Zumoff B: Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes. *Am J Med* 99:22-28, 1995
- ³⁴Soler G, Frank S: Value of glycosylated hemoglobin measurements after acute myocardial infarction. *JAMA* 246:1690-1693, 1981
- ³⁵Kannel WB, McGee DL: Diabetes and cardiovascular disease: The Framingham Study. *JAMA* 241:2035-2038, 1979
- ³⁶Johnson WD, Pedraza PM, Kayser KL: Coronary artery surgery in diabetics: 261 consecutive patients followed four to seven years. *Am Heart J* 104 (4 Pt 1):823-827, 1982
- ³⁷Abbud Z, Shindler D, Wilson A, Kostis J: Effect of diabetes mellitus on short and long-term mortality cases of patients with acute myocardial infarction: a state-wide study. *Am Heart J* 130:51-58, 1995

Claresa Levetan, MD, is director of diabetes education at MedStar Research Institute in Washington, D.C. Meeta Sharma, MD, is medical director of the diabetes team at the MedStar Diabetes Institute at Washington Hospital Center in Washington, D.C.