MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

January 19, 1967

PREVALENCE OF INFECTIONS IN THE DIABETIC

- Bacteriuria
- Gram-Negative Bacteremia
- Staphylococcal Sepsis and Bacteremia
- Tuberculosis
- Opportunistic Fungi

HOST DEFENSE MECHANISMS

- Humoral
- Cellular

UNUSUAL MANIFESTATIONS OF INFECTION IN THE DIABETIC

Diabetes With Emphysematous Cholecystitis

[redacted]

The patient is a 67-year-old [redacted] male with adult onset diabetes mellitus who presented in [redacted] 1965 with a 4-day history of cramping epigastric and right upper quadrant pain and vomiting following attempts at oral intake. There had been no fever or chills and his stools had not changed in frequency or character. Prior to the onset of the present illness, there had been no abdominal pain or food intolerance. Carbohydrate metabolism had been well controlled on 2.5 gm. of Orinase daily with fasting blood sugars in clinic of 180 to 200 mg.%. He had had a CVA 5 years prior to this admission and had mild right hemiparesis as residual. He had been on digitalis for congestive heart failure for 5 years and was well compensated.

Physical examination on admission revealed a blood pressure of 150/90, pulse 90 and irregular, temperature 98° rectally, and respirations 14/minute. The right carotid pulsation was diminished but no bruit was heard. The chest was clear. The heart was slightly enlarged to the left; auricular fibrillation was present. There was slight tenderness to firm pressure in the right upper quadrant, but spasm and rebound were absent. The liver was palpable some 6 cm. below the right costal margin and was non-tender. There was a sensation of a cystic mass below the liver but borders could not be delineated. Bowel sounds were of normal frequency and amplitude.

Admission laboratory work revealed hemoglobin of 12 gm.%, white count of 6,000 per mm^3 with a normal differential. Blood sugar was 200 mg.%, and urinalysis revealed 2+ glycosuria without acetone. BUN, sodium, and potassium were normal. Chest x-ray and KUB were negative. Liver function tests revealed a bilirubin of 1.2 mg. total with 0.8 mg. direct, thymol turbidity of 2, SGOT of 40, and alkaline phosphatase of 3.

A presumptive diagnosis of cholecystitis was considered and the patient was treated conservatively with nasogastric suction and parenteral fluids. On the 4th hospital day the right upper quadrant tenderness was slightly increased, the patient had low-grade fever for the first time, and the white count had increased to 14,000 with a left shift. No abdominal masses other than the liver could be delineated. A repeat KUB revealed gas in the wall of a greatly enlarged gallbladder and the diagnosis of emphysematous cholecystitis was established. The patient was started on penicillin, kanamycin, and chloramphenicol, and a cholecystostomy was performed. The patient rapidly defervesced and abdominal tenderness subsided. The patient was discharged with external biliary drainage some 10 days after surgery. He was readmitted in [redacted] of 1966 for elective cholecystectomy and at surgery an obstructing common duct stone was found and removed. The patient's postoperative course was uneventful, and he is at present doing well.

Diabetes With Emphysematous Cystitis and Pneumaturia

[redacted]

The patient is a 30-year-old [redacted] male with known diabetes mellitus since age 2. He was admitted on [redacted]/67, with the history of flank pain and intermittent chills of 2 weeks' duration. He stated that for the past 24 hours his urine "had been bubbly and looked like beer with a head on it." On past admissions the patient had been shown to have severe complications of diabetes with near-blindness from retinopathy, peripheral and autonomic neuropathy, and a nephrotic state. Urinary tract infections had not been a problem until some 3 months ago, when he was hospitalized in New Orleans with fever and chills and was told that he had a serious urinary tract infection. He was treated at that time with unknown medication and had been free from symptoms of urinary tract infection until the onset of the present illness. His carbohydrate metabolism had recently been fairly well controlled on 40 units NPH insulin daily.

Physical examination on admission revealed temperature of 99°, pulse of 80, blood pressure 135/85, and respirations 12. There was periorbital edema and 2+ peripheral edema. Marked diabetic retinopathy was present. The chest was clear. The heart was normal size and there were no murmurs. Abdominal exam was negative and there was no CVA tenderness. Neurological exam revealed decreased pinprick on all extremities; light touch evoked feeling of "pins and needles". Vibratory sense was depressed bilaterally and position sense was poor.

Admission laboratory work revealed a hemoglobin of 11.6 gm.%, white count of 8,000 with normal differential. Blood glucose was 300 mg.% and there was 4+ glycosuria without acetonuria. Na, K and CO_2 were normal. Examination of the urinary sediment revealed over 50 cells per high power field, 3-5 red cells and many bacteria. Because of the history suggestive of pneumaturia, an upright KUB was obtained which showed an air-fluid shadow in the bladder and gaseous dissection along the upper portion of the bladder wall. A diagnosis of emphysematous cystitis was made and the patient was started on kanamycin and chloramphenicol. Pneumaturia was not demonstrated after admission to the hospital and a repeat KUB 72 hours after institution of antimicrobial therapy revealed no gas in the bladder or bladder wall. Urine culture ultimately grew out Aerobacter aerogenes.

Diabetes With Emphysematous Cellulitis and Myositis

[redacted]

The patient is a 53-year-old [redacted] male who had had diabetes mellitus known some 12 years and had apparently been well controlled on 2.0 gm. Orinase per day. Some 24 hours before coming to the hospital, he noted redness and swelling over the dorsum of his right foot. There was little pain and no appreciable tenderness at the outset. However, over the next several hours the area of swelling and redness extended up the leg and he began to appreciate subjective fever. After experiencing a hard shaking chill, he presented himself for evaluation. He stated that several days before the onset of the present illness he had sustained a blister on the right foot when wearing some tight shoes and that subsequent to that injury he had noted "low-grade infection" and intermittent red streaking.

Physical examination on admission revealed pulse 110, blood pressure 130/70, temperature 103°. The remainder of the physical exam was unremarkable except for the appearance of the right lower extremity. The leg was tightly swollen to the knee and there was slight tenderness to pressure. By firm pressure, deep crepitation could be detected. There was an indolent-appearing ulcer over the medial aspect of the right foot.

Laboratory work revealed a white count of 18,000 with a left shift. Hemoglobin was 14 gm.% and the plasma revealed no evidence of hemolysis. BUN was 23, CO_2 25, sodium and potassium normal. Blood sugar was 260. Urinalysis revealed gaseous dissection along the muscle planes. A presumptive diagnosis of clostridial cellulitis and myositis was made and therapy was instituted of large parenteral doses of penicillin. He was given 200 units of polyvalent gas antitoxin intravenously. At the time of A-K amputation, some 6 hours later, the extremity revealed gas and white exudate in all muscle planes and necrosis of the muscle bellies. A gram-stained smear of the exudate revealed a large number of polys and sheets of gram-negative rods without gram-positive rods or cocci. At that point, his therapy was changed from penicillin to streptomycin and tetracycline. On this program, the patient defervesced over a 5-day period. Admission blood cultures and the smear of the exudate taken at the time of amputation ultimately revealed Escherichia coli. Postoperative course was uneventful.

Diabetes With Coliform "Erysipelas"

[redacted]

The patient is a 71-year-old [redacted] female who was admitted to [redacted] on [redacted]/66 with a history that 2 days prior to admission she noted a red, painful area on the medial aspect of the right thigh. Some 24 hours after initial onset of symptoms, she developed severe pain, swelling, redness, and heat in the right leg. Because of the progressive swelling of the extremity amd the onset of fever and chills, the patient presented herself to the hospital. The patient admitted to giving insulin subcutaneously in the right thigh, but stated that she carefully boiled needles and syringes for several minutes prior to use. She had not previously been bothered by infection and had no vascular ulcers on the extremities.

For approximately one year prior to this admission, the patient had carried the diagnosis of siderochrestic anemia, which had been treated with pyridoxine and Halotestin. One month prior to admission it was found that she had developed a positive Coombs' and prednisolone 40 mg. per day was started. Because of the subsequently increased glucose intolerance, the patient's insulin was increased from 15 to 30 units NPH insulin per day.

Physical examination on admission revealed a blood pressure of 130/50, pulse of 130, respirations of 20, and temperature of 103°. Neck veins were distended to 3 cm. above the suprasternal notch. Fine rales were heard at both bases. The heart was slightly enlarged to the left; the rhythm was basically regular with frequent PVCs. A grade 2/4 harsh systolic murmur was heard at the apex with radiation into the axilla. The spleen was palpable 2 fingerbreadths below the left

costal margin. Liver was not palpable. The right leg was tautly swollen with 4+ edema extending up to mid-thigh. The skin was quite hot and tender to touch. No ulcerations or breaks in the skin were found at any point. Left dorsalis pedis pulse was strongly palpable; the right could not be felt through the edema.

Admission laboratory work revealed a hemoglobin of 5.3, white count of 8,500 with a normal differential. The blood glucose was 205 mg.% and the urine contained neither sugar nor acetone. The BUN was 23; CO_2 and electrolytes were normal. Saline injected into and withdrawn from the area of cellulitis revealed a few PMNs but no organisms.

It was felt the patient had cellulitis of the right extremity and that she was probably in early congestive heart failure. After culture of blood and the aspirate from the area of cellulitis, therapy was started with methicillin and kanamycin. Digitalization was instituted, and because of the possibility of underlying thrombophlebitis, anticoagulants were started. She was slowly transfused to a hemoglobin of 7.0 gm.%.

The patient's response was favorable with temperature progressively returning to normal over a 4-day period, and with tenderness and edema of the leg subsiding by 7 days. On the 3rd hospital day, the admission blood cultures and the aspirate from the area of cellulitis revealed *E. coli*.

This case serves to emphasize the fact that diabetic "erysipelas" is frequently caused by organisms other than the Group A streptococci or staphylococci classically associated with that disease in non-diabetics. Efforts to characterize the etiologic agent should be made; if smear is not diagnostic, the use of broad antimicrobial coverage should be considered while cultures are pending.

PREVALENCE OF BACTERIURIA IN PATIENTS WITH DIABETES MELLITUS

Author	Category	Diabetics No. Patients (% Bacteriuric)	Controls No. Patients (% Bacteriuric)
Boshell (5)	Hosp.	100 ♂ (8%)	100 ♂ (3%)
Huvos (6)	Hosp.	9 ♂ (11%)	9 ♂ (22%)
		41 ♀ (29%)	41 ♀ (23%)
Kass (7)	Out-Patient	37 ♂ (5%)	102 ♂ (4%)
		54 ♀ (18%)	337 ♀ (6%)
Parrish (8)	Out-Patient	342 ♂ (2%)	—
		177 ♀ (14%)	—
Hansen (9)	Out-Patient	67 ♂ (7%)	67 ♂ (3.0%)
		81 ♀ (18%)	81 ♀ (3.7%)
Vejlsgaard (10)	Out-Patient	141 ♂ (0.7%)	146 ♂ (2.1%)
		128 ♀ (18.8%)	114 ♀ (7.9%)
Etzwiler (12)	Out-Patient Children	76 ♂ (0)	—
		94 ♀ (1%)	—
Kunin (13)	School-children	—	1647 ♂ (0)
		—	1410 ♀ (1%)

FACTORS RELATED TO BACTERIURIA (11)

Correlated With ↑ Bacteriuria	Not Correlated With ↑ Bacteriuria
Previous catheterization*	Degree of glycosuria
Duration of diabetes > 20 years	Insulin requirement
Onset of diabetes > 60	Peripheral neuropathy
Peripheral vascular disease	Nephropathy
Advanced age	

* The incidence of induced bacteriuria after single catheterization in a non-diabetic female has been shown to be 2%-4% and after 72 hours of open drainage by indwelling Foley catheter, the incidence of induced bacteriuria is > 90% (7).

The increased prevalence of bacteriuria shown by most series to exist in the adult diabetic women may be largely due to repeated catheterizations rather than a basic defect in host defense mechanisms.

PREVALENCE OF GRAM-NEGATIVE BACTEREMIA IN DIABETES

Author	No. Patients	% Diabetics
Martin (14)	137	10%
McHenry (15)	113	11%
Maistequi (16)	100	16%
Owen (17)	55	18%
Munroe (18)	44	11%
Hodgin (19)	100	8%

The diabetic appears in collected series of gram-negative bacteremia with a frequency approximately equal to that of the patient with cirrhosis or neoplastic disease. This observation has supported the concept that the diabetic is intrinsically a defective host. An alternate view comes from consideration of the following ecologic factors relating to gram-negative sepsis:

1. Many gram-negative bacteremias are hospital-acquired (45% [19] to 80% [20])
2. Urinary tract is the single most common portal of entry (39% [19] to 65% [14,15,16]) in the total patient population and 80% in diabetics (14,15,16)
3. Up to 50% of urinary tract-associated bacteremias follow catheterization (20)

Consideration of these factors would suggest that while the diabetic may have intrinsic defects in the host defense mechanism, the frequency of gram-negative bacteremia in this disease could well reflect the fact that the diabetic is subjected to frequent hospitalization and instrumentation.

PREVALENCE OF STAPHYLOCOCCAL INFECTION IN DIABETES

In collected series of staphylococcal infection in septicemia, the diabetic comprises 10-16% of the infected group (22-25), an incidence of association similar to that shown by neoplastic and renal disease. It is of note that 45% of potentially serious staphylococcal infections occur after the patient is admitted to the hospital (24,26).

The experience with staphylococcal septicemia at Parkland Memorial Hospital is summarized in the following table:

Staphylococcal Septicemia in 79 Adult Patients at Parkland Memorial Hospital (27)

Underlying Condition	No.
Diabetes mellitus	10
Cirrhosis	5
Renal failure	5
Head injury with coma	3
Paraplegia	3
Neoplastic disease	3
Heart disease	3
None	47

Portal of Entry

Non-Hospital Acquired 57 cases (72%)		Hospital-Acquired 22 cases (28%)	
Skin	20	Surgery	9
Paranutritis	4	Venous cutdown	7
Pneumonia	5	Pneumonia	2
Unknown	28	Peritoneal dialysis	2
		Skin (burn)	2

One diabetic developed septicemia following surgery and another in association with venous cutdown. The remaining 8 entered with septicemia associated with skin infections.

Although the total series is small, the incidence of acquired infection in diabetics was 20%. As with gram-negative bacteremia, the hospital environment may contribute to the prevalence of staphylococcal infection in the diabetic.

The relative susceptibility of the diabetic to hospital-acquired staphylococcal disease is shown in the following table, adapted from Keene (24):

Associated Disease	Hospital-Acquired Infections* %	Hospital Population† %	Susceptibility Index‡
Dermatologic	14.0	3.6	3.89
Hepatic	19.3	6.1	3.16
Diabetic	15.8	10.0	1.58
Neoplastic	21.0	13.4	1.57
Renal	10.5	8.1	1.30
Connective tissue	8.8	7.3	1.21
Cardiovascular	46.0	40.0	1.15
Bronchopulmonary	14.0	20.0	0.70

* 57 patients
† 247 patients
‡ Incidence among infections ÷ incidence among general hospital population

PREVALENCE OF TUBERCULOSIS IN DIABETICS

Study	Category	No. Patients	% Tuberculosis
*Boucot (28)	Clinic diabetics	3,106	8.4 %
	Industrial workers	71,767	4.3 %
**Warwick (30)	Clinic diabetics	1,851	1.8 %
	Non-diabetics	58,000	0.5 %
**Silwer (29)	Population Survey		
	Non-diabetics	259,165	0.88%
	Diabetics	1,326	3.6 %

* Contains active and inactive cases
** Active cases

Since the pathogenesis of tuberculosis is relatively independent of mechanical and nosocomial factors, the increased prevalence of tuberculosis in diabetics supports the view that the diabetic patient has defective host defense mechanisms.

PREVALENCE OF SYSTEMIC INFECTION BY OPPORTUNISTIC FUNGI IN THE DIABETIC

Mucormycosis: Mucorales are simple molds usually known as bread or sugar molds. They are ubiquitous saprophytes requiring only sugar and simple carbon compounds as nutrients. The genera infecting man are mucor, absidia or rhizopus.

Uncontrolled diabetes mellitus is the underlying condition most often associated with this relatively rare infection. The prevalence of disease states associated with mucormycosis was reviewed by McBride (32):

Associated Condition	No. Cases
Diabetes mellitus	23
Neoplasm	13
Other debilitating diseases	16
None recognized	3
Not stated	2

Patterns of Involvement	In Series	No. Diabetics
Sinus, orbital and cerebral	20	14
Pulmonary	15	3
GI tract	7	1
Disseminated	14	4
Skin	1	1

The mechanism by which the diabetic acquires susceptibility to mucor has not been delineated. The acutely alloxanized animal exhibits a slight, transient increase in susceptibility to challenge infection (38) but the chronic alloxan animal does not (39).

HOST DEFENSE MECHANISMS IN THE DIABETIC

Humoral	Status in Diabetic
Opsonin	Intact (40)
Complement	Intact (41)
Antibody	Intact (42)
Cellular	
Phagocytosis	
Migration	Subject to environmental factors
Engulfment	
Intracellular killing	

Phagocytosis is an energy-requiring activity dependent upon active glycolysis. Although slight reduction in glycogen content has been found in PMNs from poorly controlled, non-ketotic diabetics (43, 44), that abnormality has not been associated with defective phagocytosis.

Influence of environmental factors upon migration and phagocytosis by human polymorphonuclear leucocytes:

1. Ketoacidosis

   a. Reduces <u>in vitro</u> phagocytosis and killing of cocci (45)

	Phagocytosis	
	Ketotic Serum	Non-Ketotic Serum
Ketotic Cell	↓	↓
Non-Ketotic	Nl	Nl

   Defect subsides with correction of ketosis.

   b. Reduces rate of PMN migration to local area of injury (Rebuck window). Normals and non-ketotic diabetics had brisk response in 1-1/2 hours; ketotic (46) diabetics had little cellular response in 3-5 hours.

   The delayed PMN response renders the host vulnerable since it has been shown that infection is established within 3 hours after challenge in case of inadequate phagocytosis (47).

c. The *in vitro* rate of migration of leucocytes was shown to remain the same over a pH range of 7.0-7.8 (48).

2. Osmolarity

a. *In vitro* migration rate is unchanged over a glucose range of 50-1200 mg.% (48)

b. *In vitro* phagocytosis and killing are normal until concentrations of > 400 mOsm/L sodium or glucose are reached (49)

c. Osmolarity of urine has been shown to reach levels which arrest phagocytosis and thereby may predispose to infection (50,51).

UNUSUAL MANIFESTATIONS OF INFECTIONS IN DIABETIC PATIENTS

Emphysematous cholecystitis presents with clinical features of cholecystitis and reveals on radiographic examination gas within the wall and/or cavity of the gallbladder. Occasionally gas may be seen dissecting into the biliary radicals. In the diabetic, the principal organisms involved are *E. coli*, aerobacter and anaerobic streptococci; clostridia are on occasion the etiologic agent.

Emphysematous cystitis: Patients present with symptoms of cystitis with or without pneumaturia. Occurs almost exclusively in diabetics but may rarely be seen in obstructed non-diabetics infected with *E. coli* or *Aerobacter aerogenes*. Diagnosis is established by the demonstration of gas within the bladder wall and/or cavity. Treatment is that of cystitis without gas.

Emphysematous cellulitis and myositis: Clinical features are those usually associated with clostridial infections with subcutaneous crepitation and x-ray evidence of gaseous dissection along fascial planes. Etiologic agents in the diabetic are usually *E. coli* or *Aerobacter aerogenes*, but clostridia must be considered. Diagnosis can usually be established by stained smear of aspirated exudate.

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