MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

April 17, 1975

INFECTION IN THE COMPROMISED HOST

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INTRODUCTION

Patients with significant impairments in host immune mechanisms are being encountered in medical practice increasingly more frequently. The reasons underlying this phenomenon are numerous and include an increased life span in many hematologic malignancies, the use of cytotoxic drugs to combat solid tissue tumors, the utilization of renal transplantation to deal with endstage chronic renal failure, and the development of the science of immunotherapy to control disorders such as systemic lupus erythematosus and rheumatoid arthritis. Although it is hoped that in the future advances in understanding etiology and pathogenesis will enable more specific and less toxic therapy, at the present time infection would appear to be the limiting factor in current attempts to control the disease processes mentioned.

In this review, we will describe three cases, each exemplifying a common infectious disease problem encountered in dealing with patients who have compromised immune function. The first case represents the problem of acute leukemia, granulocytopenia and sepsis; the second case relates the problem of an undiagnosed pulmonary infiltrate in a patient with chronic lymphocytic leukemia; the third case describes a renal transplant recipient with a persisting tolerated infection who develops a fever of undetermined origin. Although the cases describe patients who have a predominant specific abnormality in host immunity (Case #1, granulocyte bactericidal function; Case #2, humoral antibody synthesis; Case #3, cell mediated immunity), it will be apparent that in present day practice, it is not unusual to have all three categories of immune function affected.

CASE #1: Acute Leukemia, Granulocytopenia and Sepsis.
A 47 year old woman with Philadelphia chromosome positive chronic granulocytic leukemia entered the hospital in a blastic crisis. The admission white blood cell count was 210,000 with 95% myeloblasts. In an attempt to induce remission, combination chemotherapy with vincristine, cyclophosphamide, prednisone and cytosine arabinoside was begun. Eight days after admission, when the white blood cell count reached 1,300 with 26% polymorphonuclear cells, she developed cramping abdominal pain and fever. Physical examination at that time revealed an acutely ill woman with a temperature of 104.2°. In addition to the findings present on admission, the abdomen was distended; there was diffuse mild tenderness without rebound and bowel sounds were decreased. Abdominal x-ray revealed distended loops of small bowel with several air-fluid levels consistent with small bowel obstruction. An intravenous line was in place but there was no associated phlebitis. Examination of the perianal area revealed no abnormalities. The chest x-ray was unchanged and the urinalysis was within normal limits.

The management of this critically ill patient included obtaining sputum, urine and blood cultures. The site of the intravenous infusion was changed with a new bottle of fluid and fresh intravenous tubing. Empiric antibiotic therapy was begun: gentamicin, 1.5 mg/kg q8h, and sodium carbenicillin, 30 gm IV per day. Surgical consultation recommended the use of the Miller-Abbott tube for decompression and noted that thrombocytopenia precluded operative intervention. The hematologist consulting on the case thought the picture of small bowel obstruction was compatible with vincristine neurotoxicity. The patient improved with this therapy and antibiotics were discontinued after a 14-day course. Blood cultures later returned positive for *Pseudomonas aeruginosa*.

This patient represents the problem of sepsis in the patient with a diminished level of circulating granulocytes and a consequent defect in granulocyte bactericidal function.

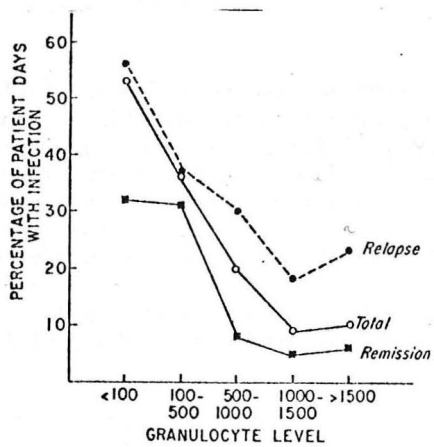

FIGURE 1. The effect of granulocyte level on the presence of identified infection. The percentage of days spent with infection is plotted at each level of circulating granulocytes. This percentage decreased with increasing granulocyte level and was always higher during relapse than during remission.

As can be seen in Figure 1, the percentage of time with infection in acute leukemia increases with decreasing levels of circulating granulocytes. The breaking point appears to be a mature granulocyte count of 500/mm^3. At the same granulocyte level, patients in relapse from their primary disease process have an increased period of time spent with infection, suggesting an additional qualitative defect in bactericidal function (16). As collected in a recent representative series, the types of infection encountered in acute nonlymphocytic leukemia are shown in Table 1 (108).

TABLE 1

INFECTIONS IN 48 PATIENTS WITH ACUTE NONLYMPHOCYTIC LEUKEMIA

Site	*Documented Infection*		*Probable Infection*	*Total*
	With Bacteremia	*Without Bacteremia*		
Pneumonia	11	9	8	28
Anorectal lesions	12	2	2	16
Skin lesions	1	10	4	15
Pharyngitis	5	4	5	14
Urinary tract infection	1	9	0	10
Nasal infection	2	1	0	3
Vaginal lesion	1	1	0	2
Platelet transfusion	1	-	-	1
Unknown	6	-	-	6
Miscellaneous	0	8*	8†	16
Total	40	44	27	111

* Bronchitis 1, liver abscess 1, sinusitis 2, retinitis 1, esophagitis 2, and phlebitis 1.

† Dental lesion 4, sinusitis 1, colitis 1, cholangitis 1, lung abscess 1

Five sources accounted for 89/111 (80%) of the episodes of documented and probable infection encountered in this series. These five sources were pneumonia, anorectal lesions, skin lesions, pharyngitis and urinary tract infection. Although pneumonia and urinary tract infection can be expected as usual occurrences, the frequency of infections related to anorectal lesions, skin lesions and pharyngitis represents a unique set of circumstances in the leukemic patient.

The organisms causing documented infections in this same representative series are shown in Table 2 (108).

TABLE 2

BACTERIA AND FUNGI CAUSING DOCUMENTED INFECTION

	With Bacteremia	*Without Bacteremia*	*Total Documented Infections*
Pseudomonas aeruginosa	16*	7	23
Klebsiella species	6	3	9
Escherichia coli	5	6	11
Serratia species	3	0	3
Diplococcus pneumoniae	2	1	3
Staphylococcus aureus	2	9	11
Group D streptococcus	2	2	4
Candida albicans	2	10	12
Mima polymorpha	1	0	1
Enterobacter aerogenes	1	1	2
Enterobacter cloacae	1	1	2
Bacteroides fragilis	1	0	1
Candida tropicalis	1	0	1
Alpha streptococcus	0	1	1
Staphylococcus epidermidis	0	1	1
Proteus mirabilis	0	1	1
Phycomycete species (Mucor)	0	1	1
Total	43†	44	87

* Three patients each had two bacteremias from immunotypically different *Pseudomonas aeruginosa*, for a total of 19 bacteremias

† Three infections each led to two bacteremias (different organisms)

Although many different organisms were encountered in this series, several generalizations can be made: (1) The predominant group of organisms causing infection in these patients are gram negative bacilli (GNB), usually acquired during hospitalization. These organisms, e.g., *Pseudomonas aeruginosa*, the klebsiella-enterobacter-serratia group, can be thought of as those associated with the hospital environment and relate to the fact that patients become colonized during hospitalization. (2) In recent times, *Staphylococcus aureus* has become a less frequent cause of bacteremic fatal infection. In the late 1950s and early 1960s prior to the advent of penicillinase resistant semisynthetic penicillins, staphylococcal infections were a much more important cause of mortality. At the present time, patients are being treated effectively at an early phase of illness before the infections can become established and bacteremic. This is not to diminish the potential significance of staphylococci as pathogens in the leukemic patient; it is to focus attention to the predominant role of GNB in present circumstances. (3) In every series, fungi constitute an emerging and increasing problem as suprainfecting agents. The fungi that are the most frequent pathogens are ubiquitous agents that are usually dismissed as

contaminants when isolated from secretions of immunologically normal patients. In patients with granulocyte functional defects, *Candida spp.*, *Aspergillus spp.* and *Phycomycetes spp.* can cause invasive and fatal disease. In dealing with these patients, the physician must expect to encounter these fungi as an increasing threat and begin to learn their clinical presentations.

The emergence of GNB as the major pathogens in leukemic patients is not unexpected. The epidemiological aspects of the problem are similar to the present epidemiology of hospital-acquired infections in general. Beginning in the 1960s, a body of information has been developed that states that hospitalized patients, particularly when significantly ill, become colonized with GNB whose origin lies in the hospital environment (Tables 3 and 4) (119,64).

TABLE 3

CARRIAGE OF STAPHYLOCOCCUS AUREUS AND GRAM-NEGATIVE BACILLI BY HOSPITALIZED PATIENTS

Patients	*No.*	*Site*	*Staphylococcus aureus (%)*	*Gram-negative (%)*
Severely ill medical (initial series)	266	NT	15	20
		A/G	6-7	19
Ambulant psychiatric	100	NT	61	3
Surgical (elective)	100	NT	27	3
		A	8	2
		G	25	3
Surgical (sick)	50	NT	32	60
		A	12	10
		G	26	16
General medical	50	NT	34	44
		A	18	6
		G	28	20

NT = nose and throat, A = axillae, G = groin

TABLE 4

*RESULTS OF SINGLE-CULTURE SURVEYS**

Study Group	*No. of Subjects*	*Cultures Containing Gram-Negative Bacilli* %
Normal Subjects:		
Nonhospital associated	82	2
Hospital associated	47	2
Patients:		
Psychiatry service	20	0
Moderately ill	81	16
Moribund	23	57

* Nasopharyngeal cultures

Areas of the body colonized by these GNB include the nasopharynx, the gastrointestinal tract, and skin regions such as the axillae and groin. The particular GNB involved in colonization is to a certain extent determined by the epidemiological setting at any given institution. In most institutions *Pseudomonas aeruginosa* with multiple pyocin types and different antibiotic sensitivity patterns has been the major problem. Although the administration of antibiotics to an individual patient can pave the way for colonization with resistant GNB, the problem is a much broader one and involves the pattern of antibiotic administration in the hospital, the continued repeated exposure to GNB while in the hospital environment and a variety of factors, related primarily to the degree of illness and essentially preventing the clearance and removal of these organisms.

Perhaps the most fundamental study of the factors promoting colonization of hospitalized persons with GNB is the report by Drs. Johanson, Pierce and Sanford detailing nasopharyngeal acquisition of these organisms in the Medical Intensive Care Unit at Parkland Memorial Hospital (Table 5) (65). These authors showed that nasopharyngeal colonization with GNB was related to a variety of factors such as prior antibiotic administration but more important to circumstances that were best correlated with the degree of illness of the patients, viz., coma, hypotension, presence of sputum, tracheal intubation, acidosis, azotemia and the white blood cell count. The leukemic patient reflects this phenomenon and colonization with GNB shapes the manifestations of ensuing infectious disease problems which may occur.

TABLE 5

*VARIABLES ASSOCIATED WITH COLONIZATION OF THE RESPIRATORY TRACT WITH GRAM NEGATIVE BACILLI (GNB) IN 213 PATIENTS**

Variable	*GNB Colonization*		
	Yes	*No*	
Sex			
Men	57	66	
Women	38	52	NS
Smoker			
Yes	56	67	
No	39	51	NS
Coma			
Yes	35	26	
No	60	92	$P < 0.05$
Hypotension			
Yes	19	6	
No	76	112	$P < 0.01$
Sputum present			
Yes	71	46	
No	24	72	$P < 0.001$
Tracheal intubation			
Yes	36	20	
No	59	98	$P < 0.001$
Inhalation therapy			
Yes	88	98	
No	7	20	NS
Antimicrobial drugs			
Yes	38	12	
No	57	106	$P < 0.001$
Arterial pH $\leq$ 7.31			
Yes	33	16	
No	62	102	$P < 0.001$
BUN $\geq$ 50 mg/100 ml			
Yes	10	2	
No	85	116	$P < 0.05$
WBC > 15,000 or < 4000			
Yes	37	18	
No	58	100	$P < 0.001$
Hgb $\leq$ 8 gm/100 ml			
Yes	2	1	
No	93	117	NS

* Patients admitted to a medical intensive care unit.

NS = not significant

The leukemic patient is also given potent cytotoxic drugs which impair gastrointestinal tract and mucosal integrity. In the setting of diminished granulocytes, organisms resident on mucosal surfaces invade and it is this circumstance that accounts for the high incidence of infections related to anorectal lesions, skin lesions, and pharyngitis. Bacteremia eventuates and the infection can be fulminant. With pseudomonas infections, in particular, the cycle can be self-perpetuating. A necrotizing vasculitis may result. This accounts for the classical skin lesion, ecthyma gangrenosum, but the vasculitis may also affect vessels in the bowel wall, giving rise to further extensive invasion by resident microorganisms.

It is in this setting that antimicrobial administration for sepsis in the setting of leukemia and granulocytopenia as illustrated in Case #1 must be considered. If success is to be achieved, it must be recognized that the majority of febrile episodes (temperature > 101°) in such patients are accounted for by infection and antibiotic therapy must be prompt and appropriate. Table 6 depicts an analysis of 11 recent series outlining survival statistics in patients with bacteremia and acute leukemia, chronic leukemia in a blastic crisis and advanced malignancy as treated by different antibiotic regimens.

In recent times, before the advent of gentamicin there was no effective therapy for this problem, particularly with pseudomonas infections. Gentamicin was a major advance but still proved ineffective when used alone in severely granulocytopenic patients. In one series, continued bacteremia with *Pseudomonas aeruginosa* occurred in such patients despite the administration of gentamicin (107). The next advance was the introduction of sodium carbenicillin; reasonable results were obtained with pseudomonas infections but this antibiotic was ineffective, particularly with klebsiella and serratia infections. In an attempt to achieve a broader antimicrobial spectrum, gentamicin and carbenicillin were used together. This antibiotic combination shows synergy in vitro against the majority of pseudomonas isolates, the exception being against those strains of pseudomonas that have a high level of gentamicin resistance. In at least one series, however, including all patients with *E. coli* infections (bacteremic and non-bacteremic), the combination of gentamicin and carbenicillin was ineffective in 10/15 (67%). More recently, this lack of efficacy of gentamicin and carbenicillin against GNB other than pseudomonas has been questioned and further data are needed. The use of carbenicillin and cephalothin has also been suggested and in one series was equivalent to gentamicin and carbenicillin as empiric antibiotic therapy.

Combinations of more than two antibiotics have also been suggested (gentamicin, carbenicillin and cephalothin; methicillin, carbenicillin, cephalothin, gentamicin and clindamycin). As sensitivities return, the antibiotic regimen is simplified but these combinations are associated with a high incidence of suprainfection.

At the present time, there is a multi-institutional study proceeding to test the efficacy of gentamicin-carbenicillin vs gentamicin-cephalothin vs carbenicillin-cephalothin in the treatment of such patients. Pending the results of such studies, the following recommendations appear rational: (1) In leukemic patients with an adequate

TABLE 6

*THERAPY AND SURVIVAL OF BACTEREMIA IN PATIENTS WITH ACUTE LEUKEMIA, CHRONIC LEUKEMIA IN BLASTIC CRISIS AND ADVANCED MALIGNANCY**

Antibiotics	*Organism*								*Ref.*
	Pseudomonas aeruginosa			*Klebsiella-Enterobacter*	*E. coli*	*Serratia*	*Gram Neg. Rods (unsp.)*	*Staph. aureus*	
	↓ WBC	*Adeq. WBC*	*Unsp. WBC*						
Penicillin, kanamycin, colistin			1/9 (11)	0/6 (0)	1/4 (25)				103
Cephalothin, kanamycin			0/6 (0)	0/4 (0)	1/5 (20)				34
Gentamicin	1/10 (10)		6/23 (26)						120
	1/8 (13)								107
						8/15 (53)			18
Carbenicillin			27/38 (71)						20
			9/14 (64)	0/4 (0)	2/5 (40)	0/3 (0)			17
Carbenicillin, gentamicin	6/18 (33)		7/20 (35)						120
			8/13 (62)				5/13 (38)		107, 109
			3/3 (100)	6/12 (50)	1/4 (25)				103
							9/11 (82)		68
Carbenicillin, cephalothin							16/20 (80)		68
Methicillin, carbenicillin, cephalothin, gentamicin, clindamycin			6/7 (86)	1/1 (100)				2/2 (100)	121

* No. recovered/no. treated (%)

granulocyte level in whom sepsis is suspected and where the bacterial etiology cannot be ascerained with certainty, gentamicin plus a penicillinase resistant semisynthetic penicillin or a cephalosporin should be used. As the responsible bacterial species is determined and sensitivities return, one of these antibiotics can be discontinued. (2) In the same clinical setting but with the addition of granulocytopenia, either gentamicin and carbenicillin or cephalothin and carbenicillin can be used. Combination antimicrobial therapy should be continued until the infection is under control or until the granulocyte level rises.

To attempt to avoid suprainfection, antimicrobial therapy should not be prolonged, e.g., 14 days or 5-7 days past resolution of the fever. With the use of these potent antimicrobials, toxicity is a significant problem (azotemia and ototoxicity with gentamicin; hypokalemia, platelet functional defects and sodium loads with carbenicillin). When suprainfection does occur, fungi are usually the responsible pathogens, viz., *Candida spp.*, *Aspergillus spp.*, and *Phycomycetes spp.*

Fungal suprainfection should be suspected in the setting of recurrent or continued fever or the appearance of new pulmonary infiltrates despite the administration of potent antibacterial drugs. The essential problem with significant and invasive fungal suprainfection is its early recognition. Table 7 lists the organ systems involved in invasive disease caused by these three fungal species (59).

TABLE 7

SITES OF FUNGAL INFECTION IN COMPROMISED PATIENTS AT AUTOPSY

Site	*Candida*	*Phycomycetes*	*Aspergillus*
Lung	19	4	8
Kidney	15	1	0
GI	11	0	2
Heart	5	1	0
CNS	5	1	1
Liver	2	1	1
Spleen	4	0	4
Thyroid	4	0	0
Rhinocerebral	0	2	0
Pancreas	0	0	1
Prostate	1	0	0
Mandible	0	0	0

Table 8 lists sites where positive cultures were obtained in these same patients (59).

TABLE 8

FREQUENCY OF ISOLATION OF FUNGI FROM DIFFERENT SITES

Source	*Fungus isolated (no. positive/No. cultured)*		
	Candida	*Phycomycetes*	*Aspergillus*
Blood	21*/35	0/6	0/8
Urine	20/37	0/5	0/8
Sputum	10/32	0/6	0/6
Stool	3/18	0/1	0/1
CSF	0/17	0/3	0/4
Trachea	5/13	0/1	0/2
Peritoneal fluid	4/12		0/1
Pleural fluid	3/10	0/1	1/2

* Two had only a single positive blood culture

The difficulty in recognizing invasive disease due to *Candida spp.* lies in the fact that it can be cultured so easily and frequently from hospitalized patients and is most commonly not a significant pathogen. The difficulty in recognizing invasive disease due to *Aspergillus spp.* and *Phycomycetes spp.* is twofold: (1) when either fungal species is isolated from clinical specimens from immunologically normal patients, it is regarded as a contaminant, and (2) paradoxically, with invasive disease, blood, urine, sputum and other cultures are negative. To diagnose aspergillosis or phycomycosis in the leukemic patient may require a tissue diagnosis. Particularly suggestive of aspergillosis or phycomycosis is the appearance of solitary or multiple pulmonary nodules which rapidly cavitate. Although rhinocerebral phycomycosis is a known complication of diabetic ketoacidosis, this presentation is not common in leukemia.

Table 9 depicts an analysis attempting to identify prognostic factors suggesting invasive candidiasis vs benign transient candidemia (134).

TABLE 9

PROGNOSTIC FACTORS SUGGESTING INVASIVE CANDIDIASIS

Factors	*Autopsy-Proved Disseminated Candidiasis (29 patients)*	*Clinically Diagnosed Disseminated Candidiasis (8 patients)*	*Transient Catheter-Induced Candidemia (8 patients)*	*Unexplained Isolations (3 patients)*
Neutropenia*	24	5	1	1
Immunosuppressive therapy*	25	7	2	1
Positive catheter culture*	4	3	8	0
Hematologic-lymphoreticular malignancy	24	7	4	1
Number of positive blood cultures:				
1	8	0	2	3
2-4	19	5	6	0
5-9	2	3	0	0
Positive cultures from other sites	26	7	7	3
Positive cultures at more than 3 other sites*	11	7	2	0

* Comparison between groups with disseminated candidiasis and the two groups having only candidemia is significant at $P < 0.05$, by chi square with Yates correction

Factors that suggested invasive candidiasis in this series were the presence of neutropenia, immunosuppressive therapy and multiple cultures positive from distant sites. Benign transient candidemia was best signalled when the intravenous catheter could be implicated as the source of the candidemia. Several centers have reported success in diagnosing invasive candidiasis by the serial determination of serum candidal agglutinating antibody. Since these patients may have problems in antibody synthesis, a positive result (increase in antibody) is obviously more significant than a negative one.

If and when fungal infection is recognized, therapy with amphotericin B is indicated. The choice of this agent rests upon the gravity of the underlying illness and the necessity of controlling the infection as rapidly as possible. 5-fluorocytosine may be considered as adjunctive therapy, particularly in invasive candidiasis and since the two drugs may be synergistic. Primary reliance must be placed in this clinical situation, however, upon amphotericin B.

Certain experimental approaches have been attempted in order to control infection in acute leukemia. A polyvalent pseudomonas vaccine has been found to result in a significantly reduced incidence of fatal pseudomonas infection (13 deaths/176 vaccinees vs 31 deaths/185 controls) (133). The vaccine, however, was associated with a high incidence of side effects and the authors concluded by calling attention to these opposing effects and stating that "the results should be a spur to the development and evaluation of less toxic but immunogenic lipopolysaccharide preparations or the assessment of rapidly administering immunoglobulins to high-risk patients."

Experience is now being gathered concerning granulocyte transfusions. New developments such as the continuous flow filtration technique of collecting granulocytes may make this procedure widely available. It is highly suggestive that in certain patients such transfusions are a helpful adjunct to therapy. This is particularly true if a sufficient number of granulocytes ($> 2 \times 10^{10}$) are given in a repetitive fashion throughout the acute illness. At issue presently is the type of donor (chronic granulocytic leukemia vs normals), the extent to which HL-A matching should be performed (it appears probable that an ABO compatible relative with a close HL-A match would be the best donor), whether granulocyte packs should be routinely irradiated (to prevent graft versus host disease by contaminating lymphoblasts or potential acceptance of leukemic myeloblasts) and how best to prevent complications (pyrogen reactions, bronchospasm, transmission of viruses, etc.). In the long range, if granulocytes from patients with chronic granulocytic leukemia are to be used, the potential transmission of oncogenic RNA viruses must also be weighed.

A third experimental approach is to reduce the patient's own endogenous flora [gut sterilization (GS) with oral non-absorbable antibiotics, e.g., gentamicin, vancomycin and nystatin] and to place the patient in a protected, "sterile" environment, generally a room with laminar air flow (isolator). The four controlled series attempting to analyze whether or not prevention of infection can be achieved under these circumstances and whether complete or partial remission (CR or PR) can be attempted are shown in Table 10 (19,73,110,132).

TABLE 10

OBSERVATIONS FROM MAJOR ISOLATOR STUDIES WHERE RESULTS FROM WARD PATIENTS VS ISOLATOR PATIENTS RECEIVING ANTIMICROBIAL PROPHYLAXIS WERE COMPARED

	Acute myelocytic leukemia / Acute leukemia	*Median Age (range)*	*Mean study days*	*Previously untreated*	*Days PMN < 100 / Total study days*	*Days PMN < 100 & severe infection / Days PMN < 100*	*CR + PR / Total patients*
Bodey et al Conventional care	76% (25/33)	30 (12-62)	37	30%	15%	21%	64%
Isolator with GS	82% (27/33)	36 (15-64)	53	45%	33%	18%	61%
Levine et al Conventional care	68% (19/28)	36 (16-64)	54	82%	9%	40%	43%
Isolator with GS	68% (15/22)	34 (15-62)	42	82%	28%	12%	45%
Yates & Holland Conventional care	100% (39/39)	49 (19-78)	34	59%	55%	12%	31%
Isolator with GS	100% (27/27)	49 (17-73)	32	56%	56%	9%	33%
Schimpff et al Conventional care	100% (21/21)	52 (21-73)	57	67%	48%		24%
Isolator with GS	100% (24/24)	43 (20-70)	47	67%	47%	↓	54%
GS	100% (19/19)	45 (20-72)	50	68%	42%	↓	63%

Although all four studies show a decreased incidence of severe infection, only one study shows an increased remission rate. Since there are major problems associated with these programs (expense, emotional disturbance with isolation, non-acceptance of oral antibiotics because of taste, emergence of resistant isolates when antibiotics are given in a conventional care setting, rebound infection when patients discontinue the program during relapse), they now should probably be carried out only in a few centers and mainly on a research basis. If better drugs capable of inducing leukemic remission are developed, then depending on further study, such isolator and gut sterilization programs can be made more widely available.

CASE #2: *Undiagnosed Pulmonary Infiltrate.* A 65 year old woman with chronic lymphocytic leukemia maintained on 20 mg of prednisone per day entered the hospital with a three-day history of cough and fever. Physical examination revealed a temperature of 102° and a respiratory rate of 36/min. Generalized lymphadenopathy was present. Chest exam revealed bilateral end inspiratory sticky rales without evidence of consolidation. The admission white blood cell count revealed 134,000 cells, 99% of which were mature lymphocytes. Arterial blood gas values on room air showed a pO_2 of 36, a pCO_2 of 25, and a pH of 7.52. Chest x-ray revealed a pulmonary infiltrate bilaterally that was of combined interstitial and alveolar nature. It was more pronounced on the right. Gram stain of the sputum showed a nonspecific flora and culture results returned later without any bacterial pathogen being isolated. The patient was noted to have decreased gamma globulin levels on serum protein electrophoresis.

With oxygen therapy, the pO_2 improved but the pulmonary infiltrates increased despite penicillin and gentamicin treatment. Bronchoscopy and brush biopsy was performed, but no pathogen could be demonstrated. Finally, a closed needle biopsy of the involved lung was performed after a chest tube had been inserted prophylactically. Gomori-methenamine-silver stain of the lung imprint showed organisms typical of *Pneumocystis carinii*. The penicillin and gentamicin were discontinued and pentamidine isethionate, 4 mg/kg IM per day, was begun for 14 days. The pentamidine was obtained from the Parasitic Diseases Drug Service of the Center for Disease Control in Atlanta, Georgia. Resolution of the infiltrates occurred slowly and the course of therapy was marked by the development of mild azotemia and sterile abscesses at the site of drug injection which later became infected with pseudomonas.

The problem represented by this case is that of a progressive pulmonary infiltrate in a compromised host that could not be diagnosed by conventional means. The approach to such a patient requires recognition of the fact that he or she is immunosuppressed plus a categorization of the predominant abnormality in immune competence. The patient presented has chronic lymphocytic leukemia and a demonstrated low level of gamma globulin on serum protein electrophoresis. Such patients can have recurrent pneumonia and the pneumococcus is characteristically involved. Patients with a deficit in humoral antibody synthesis also

may show an increased incidence of infection with *Pneumocystis carinii*. This patient also was on long term steroid therapy, a factor which depresses cell mediated immunity or T lymphocyte function. Patients with Hodgkin's disease particularly when advanced are representative of patients with a T cell functional deficit. It is well established that such patients are particularly prone to develop significant infection with organisms such as *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Listeria monocytogenes*, *Nocardia asteroides* and varicella-zoster virus. When treated with potent chemotherapy, patients with Hodgkin's disease may develop abnormalities in humoral antibody synthesis and granulocyte bactericidal defects. Then the types of organisms causing infection increase in number and the problem is not unlike that presented by Case #1.

The next step in approaching an immunosuppressed patient with an undiagnosed pulmonary infiltrate is to attempt categorization of the process by its roentgenographic appearance. Here it must be realized that any such classification has multiple limitations. A scheme has been proposed for classifying the roentgenographic patterns encountered in renal transplant recipients (Table 11) (13).

TABLE 11

ROENTGENOGRAPHIC MANIFESTATIONS OF PNEUMONIA IN THE TRANSPLANT PATIENT: INDICATIONS AS TO ETIOLOGY

Roentgenographic pattern	*Suggested etiology*
1. Homogeneous non-segmental or segmental consolidation	
a. With expansion of lobe (bulging fissures)	Klebsiella-Aerobacter species or other gram negative organisms
b. With rapid cavitation	Anaerobic organisms
2. Multiple masses, with or without cavitation	a. Fungus b. Staphylococci c. *Ps. aeruginosa* d. Septic emboli e. Anaerobic organisms
3. Diffuse parenchymal disease	
a. With predominant acinar pattern	*Pneumocystis carinii* or mixed pathogens
b. With predominant reticular pattern	Cytomegalovirus or mixed pathogens

Obvious problems exist with this scheme and it is presented primarily as a basis for discussion. The transplant recipient can have pneumonia due to the pneumococcus or *Mycoplasma pneumoniae*, yet these common pathogens are not included. Table 11 does indicate that different pathogens may have the same roentgenographic appearance. It is also clear that one pathogen may present in a variety of ways (Table 12) (84).

TABLE 12

PREDOMINANT TYPES OF PULMONARY INVOLVEMENT WITH ASPERGILLOSIS

Type of Involvement	*No. of Cases*
Bronchopneumonia	34
Hemorrhagic infarction	32
Focal necrosis	5
Aspergilloma (cavitating)	5
Bronchitis	5
Microabscesses	4
Interstitial	2
Lobular pneumonia	2
Lobar pneumonia	1

It should also be remembered that more than one organism may be operative in causing the infiltrate.

Appropriate cultures (sputum, blood, transtracheal, urine) should be obtained. Sputum and/or transtracheal aspirates should be stained in multiple ways in order to search for the exact etiology. A synthesis of the problem is then attempted. Although unusual organisms can be expected, a process such as pneumococcal pneumonia can be present. A problem in dealing with such patients is to expect the worst or the unusual and to delay therapy. Case #2 had bilateral interstitial and alveolar infiltrates. The spectrum of agents causing this roentgenographic pattern is outlined in Table 13 (52).

TABLE 13

AUTOPSY RESULTS IN PATIENTS WITH TERMINAL DIFFUSE INTERSTITIAL PNEUMONIA - RETROSPECTIVE SERIES

Autopsy Results	*Number of Patients*
Proved *Pneumocystis carinii* pneumonia	8
Aspergillosis	1
Aspergillosis/cytomegalic inclusion disease	2
Cytomegalic inclusion disease	2
Bilateral necrotizing bronchopneumonia	1
Cryptococcosis	1
Toxoplasmosis (probable)	1
Granulomatous interstitial pneumonia (measles)	1
Idiopathic pulmonary hemorrhage	1
Interstitial metastatic melanoma of lung	1
Diffuse interstitial pneumonia, cause unknown (methenamine-silver stains negative)	3
Total	22

Not included in this list are drugs such as busulphan (Myleran®) and bleomycin.

As in Case #2, if a definite etiologic diagnosis is not forthcoming from conventional studies or if improvement does not result from presumptive empiric antibiotic therapy, an attempt must be made to make a tissue diagnosis. Different procedures have been tried with various rates of success and complications. Perhaps the most important factor to be considered in the evaluation of these methods is operator skill and familiarity with a given technique. Table 14 compares various diagostic procedures for the antemortem diagnosis of pneumonia due to *Pneumocystis carinii* (127). The standard for comparison should be the open-lung biopsy since not all the patients included in the table actually had pneumocystis pneumonia.

At Parkland, a present plan of approach is to identify immunosuppressed patients with undiagnosed pulmonary infiltrates as rapidly as possible. If a diagnosis is not readily apparent, fiberoptic bronchoscopy, bronchial brush washings and transbronchial biopsies will be attempted. Specimens will be submitted for routine, mycobacterial, fungal and viral cultures. Stains (gram, PAS, GMS, AFB) on washings and the tissue will be done. If a diagnosis is not made, then a closed-lung biopsy will be performed. For localized infiltrates, fluoroscopic guidance will be essential to guide biopsy. At other institutions, operator familiarity with a given technique will result in higher success rates for that method, e.g., Stanford University where needle aspiration of the lung has been a successful first attempt.

TABLE 14

COMPARISON OF ANTEMORTEM DIAGNOSTIC PROCEDURES FOR PNEUMOCYSTIS CARINII PNEUMONIA

	Procedures Done	*Procedures Positive for P. carinii*	*Yield*
	number		*%*
Open-lung biopsy	87	56	64
Closed-lung biopsy	57	29	51
Lung biopsy, type unspecified	24	14	58
Lung aspirate (needle)	62	34	55
Bronchial biopsy	8	5	62
Bronchial aspirate	11	4	36
Sputum, tracheal aspirate	?	19*	?
Gastric aspirate	?	2*	?
Total†	249	142	57

* Not included in total

† Possibly more than one antemortem diagnostic procedure was performed in an individual patient

In Table 13, certain etiologies are apparent by their absence. Although it is recognized that, e.g., tuberculosis, coccidioidomycosis and histoplasmosis can cause these clinical pictures, the quantitative contribution of these agents in the causation of diffuse interstitial pneumonia in the compromised host would appear to be relatively limited. Since multiple agents can cause this entity, an aggressive diagnostic approach appears warranted, particularly since the antimicrobials that would be used are so potentially toxic. The therapy of pneumocystis pneumonia is with pentamidine isethionate, 4 mg/kg/day x 14 days. Troublesome common complications with this drug include azotemia, hypoglycemia, hypotension and sterile abscesses. Encouraging case reports detailing the use of sulfadiazine and pyrimethamine or sulfa-trimethoprim are now emerging, but the majority of clinical experience is with pentamidine.

We still have fundamentally very little information on the nature of *Pneumocystis carinii*. It is not known definitely whether it is a fungus or a protozoan. Its epidemiology has not been elucidated. Some progress has been made by workers at the Center for Disease Control, where they have been able to estimate an attack rate per year for pneumocystis pneumonia for various disease states (Table 15) (127).

TABLE 15

*FREQUENCY OF PNEUMOCYSTIS CARINII PNEUMONIA IN PATIENTS WITH SELECTED DISEASES**

	Disease Prevalence (United States, 1968-1970)	*Number with P. carinii Per Year (1968-1970)*	*P. carinii Attack Rate Per Year*
			%
Leukemia			
Acute lymphatic	1,680	18.3	1.1
Chronic lymphatic	10,500	5.7	0.05
Acute myelocytic	1,008	2.5	0.2
Chronic myelocytic	1,680	0.9	0.05
Hodgkin's disease	14,840	6.6	0.04
Other lymphomas	38,750	4.1	0.01
Renal transplantation	2,795	6.6	0.2

* Because the incidence and median survival data from which this information was derived are only estimates, the attack rates are approximate and should be considered only in relation to one another

Serological studies with the indirect fluorescent antibody test have only recently been applied to the study of *P. carinii* (127). The results are depicted in Table 16 and show that less than half of patients with confirmed and suspected pneumocystis pneumonia have positive antibody tests. Interestingly, immunosuppressed patients without pulmonary disease also are antibody positive. Healthy contacts of patients have a lesser prevalence of antibodies and it is infrequent to find healthy controls with antibodies. Extrahuman sources of this organism have not been delineated and the mode of spread is unknown.

TABLE 16

RESULTS OF THE INDIRECT FLUORESCENT ANTIBODY TEST FOR SERUM ANTIBODIES TO PNEUMOCYSTIS CARINII

Group	*Number Tested*	*Per Cent Positive*	
		$\geq$ 1:8	$\geq$ 1:40
Patients			
Confirmed *P. carinii* pneumonia	45	38	20
Suspected *P. carinii* pneumonia	49	43	33
Immunosuppressed, but without pulmonary disease	20	25	10
Healthy contacts of *P. carinii* patients	93	8	4
Healthy controls (no contacts with *P. carinii* patients)	74	1	0

CASE #3: Persisting Tolerated Infection and Fever of Undetermined Origin.

A 28 year old man had a renal transplant from a living related donor because of chronic urinary tract obstruction, stones, and infection. He was placed on azathioprine and prednisone following transplant. Three months after transplant, he developed malaise, fatigue, fever, myalgias, and hepatic functional disturbances. Hepatitis B antigen studies were negative, but he had serological evidence of cytomegalovirus infection. Liver biopsy revealed a portal mononuclear cell infiltrate and occasional foci of single parenchymal cell necrosis. Biopsy tissue grew out cytomegalovirus. The liver functional abnormalities persisted. One and a half years following transplant, he again developed fever and arthritis in the right knee. Physical examination revealed a man with Cushingoid features with a temperature of 102° and an effusion in the right knee. The white blood cell count was 3,700. Chest x-ray was normal and tuberculin skin test was negative. Barium enema, upper gastrointestinal x-rays and a gallbladder series were within normal limits. Serological studies for histoplasmosis and coccidioidomycosis were negative. A bone marrow biopsy revealed a single noncaseating granuloma. Synovial biopsy revealed multiple noncaseating granulomas and later the biopsy grew out *Mycobacterium tuberculosis*. Repeat liver biopsy showed nonspecific active hepatitis. His fever abated with isoniazid and ethambutol therapy, and during this patient's post-transplant course repeated urine specimens have grown cytomegalovirus.

Renal transplant recipients probably have as their predominant immunological abnormality a T cell defect. However, they also can have problems related to humoral antibody synthesis and diminished numbers of circulating granulocytes. Case #3 had a persisting tolerated infection with cytomegalovirus (CMV) for over a two-year period of time. This type of persisting infection stands in sharp contract to the fulminant infectious disease problems as seen in Case #1. CMV is a ubiquitous infection in the period following renal transplantation. For the most part, infection is asymptomatic. However, in the renal transplant recipient it can cause interstitial pneumonia, fever of undetermined origin and hepatic functional disturbances (Figure 2) (78).

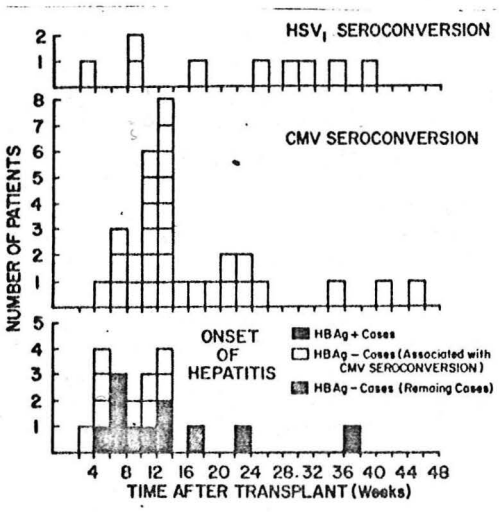

FIGURE 2. Development of antibodies to herpes simplex virus type 1 (HSV_1) and to cytomegalovirus and onset of hepatitis after renal transplantation. (There were nine episodes of HSV seroconversion in eight patients.)

In patients with neoplastic disease, CMV excretion is common, particularly in those receiving steroid therapy. In these patients, CMV infection was generally asymptomatic, although it also appeared to have been associated with pneumonitis and febrile transient exanthems (Table 17) (40).

TABLE 17

CMV EXCRETION (URINE AND/OR SPUTUM) IN PATIENTS WITH NEOPLASTIC DISEASE BY STATUS

Patient Status	*Virus-Positive Patients (11)*		*Virus-Negative Patients (21)*	
	No.	*%*	*No.*	*%*
Receiving chemotherapy*	7	64	12	57
Receiving steroid therapy*†	7	64	5	24
Hypogammaglobulinemia	4	36	3	14
Terminal disease§	3	27	7	33

* Therapy within 1 month of initial culture

† Statistical significance: p = 0.05 (Fisher Exact Test)

§ Dying within 1 month of initial culture

CMV infections in patients receiving bone marrow transplants in the course of leukemia therapy have been noted to have a high incidence of interstitial pneumonitis, most of which has been associated with this virus. Other causes of persisting tolerated infections can include herpes simplex virus, varicella-zoster virus and hepatitis B virus. The immunosuppressed patient with hepatitis B viral infection may have little in the way of hepatic functional abnormalities but may have high titered HB Ag in serum.

The first episode of fever in Case #3 was probably related to CMV infection. The second episode represents disseminated infection with an agent, *Mycobacterium tuberculosis*, that is a known threat to patients with T lymphocyte functional defects. In immunosuppressed patients, serological and skin tests may be falsely negative. In delineating the cause of fever in these patients when it is protracted and fits the classical descriptions of fever of unknown origin, by far the most important tests are tissue biopsy and bacteriology or the direct demonstration of the organism.

This review has focused on common clinical presentations of infection in compromised hosts. Although each of the patients presented with a predominant abnormality in host immune function, it is also apparent as each case is considered in detail that other elements were involved. This is now increasingly the problem as it is seen in clinical medicine.

We should expect to see more of these patients in the future. With reasonably aggressive diagnostic approaches and the prompt institution of appropriate therapy, many can be cured of their infection and helped substantially to live longer and meaningful lives.

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