MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

May 24, 1973

"Sepsis"

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The term "sepsis" in clinical medicine at the present time is one of those words whose meaning is apparently supposed to be self-evident. For the most part medical authors simply use the term without definition. Others such as Cluff, deplore the use of the term "septicemia" as imprecise. (17) Still others may use the term inconsistently. For example, one recent article reports detailed clinical observations on 692 patients with "sepsis", including a computerized analysis of the data, defining sepsis in terms of bacteremia despite the fact that only 35% of the patients had bacteremia. (75) Indeed, some of the patients had disorders such as acute pancreatitis which were in all likelihood not microbially induced. Despite the obvious deficiencies of this term, I believe the concept we propose to discuss is a clinically useful one and I would like to define it at the outset.

In terms of this discussion, by "sepsis" is meant a constellation of symptoms, signs and laboratory abnormalities. Primary considerations relate to the presence of signs of infection: fever, tachycardia and subjective symptoms of severe illness. Fever tends to reach high levels and to exhibit wide swings each day. Careful history and physical examination will, in a high proportion of cases, indicate a source of infection. Appropriate cultures will very frequently yield invaluable diagnostic information, but it is important to emphasize that blood cultures alone in this setting will probably not be positive in more than 30-40% of the patients designated as "septic".

Vital to the evaluation of the patients with "sepsis" is an assessment of the many "risk-factors" such as age, presence of diabetes, cardiac or renal disease, immunosuppression, etc, which may not only predispose to sepsis but may significantly alter the clinical findings as well as the outcome of treatment. The syndrome must be recognized to be accompanied frequently by several major complications, especially hypotension, shock, renal failure and disseminated intravascular coagulation which may significantly alter the clinical outcome.

The syndrome is produced by a wide variety of clinical disorders and the following tables list the most common ones. In considering the various syndromes it is useful to think of them as to whether there are identifying local symptoms or signs, and especially whether surgically amenable lesions are present. The latter distinction is highly significant, in that appropriate surgery may frequently be the single most definitive therapeutic measure.

1) Systemic infection without significant recognizable local disease

Meningococcemia
Salmonellosis
Rickettsial disease
Leptospirosis

2) With significant local sites of infection

a) Seldom or never with the local lesion amenable to surgery.

Meningitis
Pneumonia
Endocarditis (non-prosthetic)
Exfoliative dermatitis

b) Frequently associated with surgically amenable lesions.

Urinary tract infections
Empyema
Liver abscess
Appendicitis
Diverticulitis
Peritonitis
Various intraabdominal abscesses
Furuncles - carbuncles
Streptococcal cellulitis
Wound infections
Septic arthritis

Incidence

The frequency of sepsis is difficult to estimate. Although most discussions today concentrate on gram negative rod bacteremia, it is worth pointing out that many infections can produce the syndrome. The general variety and local variability of the causes of bacteremia may be appreciated by first looking at some data from other countries.

A 10-year study of bacteremia in Finland 1960-1970 (54)

Total patients 6113
Patients with positive cultures 335

Microorganism	% of total positives
Viridans streptococci	4
Beta Hemolytic streptococci	4
Streptococcus fecalis	5
Pneumococcus	32
N. meningitidis	2
H. influenza	3
Staph. aureus	14
"Coliforms"	23
Salmonella	9
Others	4

This table would not be generally representative of most U.S. hospitals today in that the frequency of gram negative rod infections probably would be much greater,

and the relative frequency of pneumococci less.

Another recent report from two British hospitals gives additional figures. (10) The frequency of positive cultures among the total blood cultures varied from 5.4% to 10.8%. The incidence of bacteremia was 2.1 per 1000 admissions. Various other studies of a few years ago range from 1.7 per 1000 admissions (Hammersmith Hospital, 1967) to 5.7 per 1000 (Boston City Hospital, 1959).

The various organisms isolated in the British report (11) were as follows:

Microorganism	% of total positives
Group A streptococcus	2.3
Pneumococcus	6
Viridans streptococcus	6
Enterococcus	6
Non-hemolytic streptococcus	0.5
Staph. aureus	13
Staph. albus	9
Clostridium welchii	0.5
E. coli	20
Proteus	16
Klebsiella species	4.5
Pseudomonas	11
Salmonella	2.3
Bacteroides	1.7
N. meningitidis	0.5

As with most discussions nowadays, we will deal mainly with infections due to gram negative rods. The next two tables give a detailed summary of experiences at the University of Minnesota (35).

Yearly Incidence of Positive Blood Cultures and Fatality Rate

Years	Total Hospital admissions	Total hospital mortality	Number cultures taken	Number patients bacteremia	Number per 1000 admissions	Mortality bacteremia
1958	15,879	649	5,944	78	4.9	29 (37%)
1959	16,322	810	7,103	86	5.3	43 (50%)
1960	16,096	839	8,791	71	4.4	40 (56%)
1961	15,561	871	10,123	98	6.3	44 (45%)
1962	15,542	813	7,098	84	5.4	44 (52%)
1963	16,929	759	8,214	83	4.9	44 (53%)
1964	16,685	756	9,654	103	6.2	51 (50%)
1965	15,982	725	11,254	134	8.4	72 (54%)
1966	15,288	701	13,728	123	8.1	70 (57%)

This suggests an increasing incidence, and a much higher incidence of gram negative bacteremia than the prior figures quoted.

Bacteriology According to Hospital Service

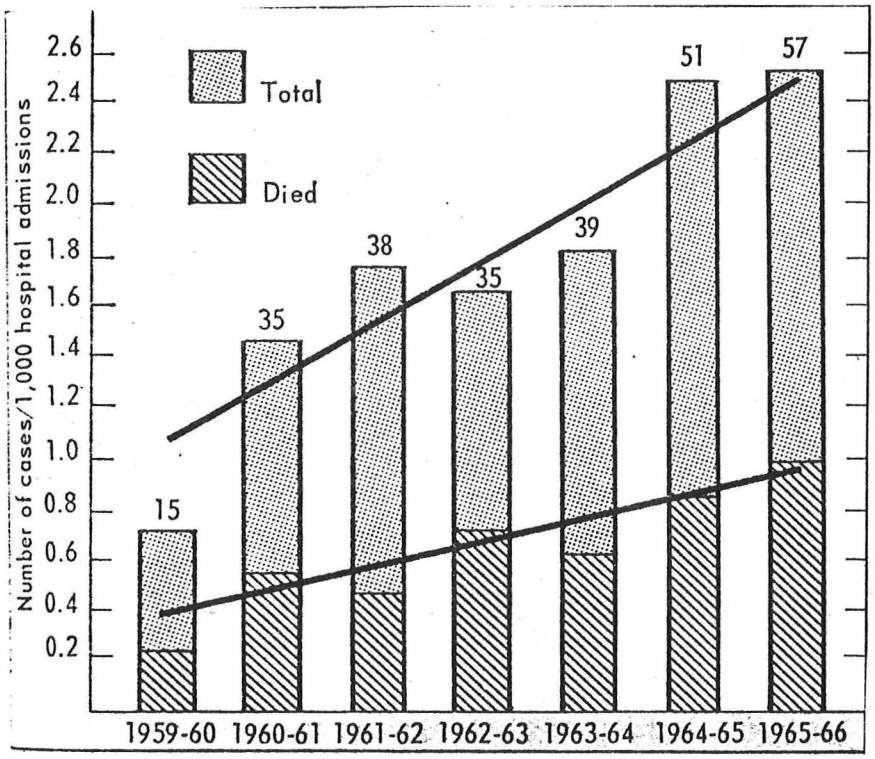
Species	Medicine	Surgery	Urology	Gyn-OB	Pediatrics
E. coli	86	51	37	16	56
K.E.S.*	32	80	24	2	28
Pseudomonas	28	32	5	2	35
Proteus	25	14	23	1	9
Bacteroides	8	17	2	8	10
Miscellaneous	11	13	5	3	19
Multiple	42	69	16	3	48
Total	232	276	112	35	205

*Klebsiella-Enterobacter-Serratia Group

This shows the distribution by services in the University of Minnesota study. (35)

McCabe (66) has recently estimated that gram negative rod bacteremia occurs at a rate of 1 per 100 hospital admissions and that approximately 70,000 deaths occur each year in the United States from this.

Graphic evidence of this is shown below (42) indicating a steady increase in frequency and mortality.



Yearly incidence and fatality of gram-negative bacteremia during a seven-year period.

McCabe and Jackson (67,68) have published an excellent review of gram negative bacteremia and were among the first to emphasize the significance of the various underlying diseases. Hodgin and Sanford (50) from Parkland Hospital in 1965 provided an excellent review of this problem. The microorganisms involved in this institution are shown below.

Mortality Correlated with Organism

Organism	No.	Mortality (%)
Mixed	14	71
Esch. coli	32	34
A. aerogenes	23	48
Proteus	9	45
Pseudomonas	7	57
Herellea	2	50
Paracolon*	12	40
Alkaligenes faecalis	1	0

* A heterogeneous group of enterobacteriaceae characterized by slow lactose fermentation. (50)

Other representative series are as follows.

Microorganism	% of total cases	% Mortality
E. coli	36	18
Serratia	16	54
Klebsiella	14	13
Pseudomonas	13	57
Proteus	8	16
Enterobacter	5.5	0
Salmonella	3	0
Bacteroides	2	0

Peter Bent Brigham Hospital, 1971 (74)

Polymicrobial bacteremia, although receiving little attention generally has been noted to be associated frequently with serious underlying disease. A recent study from the Mayo Clinic gives some details. (47) Forty-six such patients were seen in 18 months. This represented 6% of bacteremic patients. The mortality was 37%.

Microbial combinations	Total cases
E. coli & enterococcus	5
E. coli & Klebsiella	2
Klebsiella & Enterobacter	3
Klebsiella & Pseudomonas	2
Klebsiella & enterococcus	2
Bacteroides & enterococcus	3
Viridans streptococcus & Staph	5
Proteus & enterococcus	2
Pseudomonas & Serratia	2

Although it is apparent that sepsis may be produced by a variety of Gram negative and Gram positive organisms, the increasing frequency of Gram negative rod infections together with certain problems in recognition and management warrant emphasis on them at this time. (63) Two groups are of special importance also, namely Bacteroides and Pseudomonas. Increasing interest in anaerobic infections and the availability of better techniques for isolation of anaerobes have resulted in much more frequent recognition of these infections. (39,93). In a nationwide study of cultures submitted to the Center for Disease Control, 1963-1969, a total of 433 cultures from 250 patients yielded nine Bacteroides species and four species of Fusobacterium. (39) This study emphasized the association of gastrointestinal disease, and especially neoplasms of the gastrointestinal tract, with Bacteroides sepsis.

Neoplasms Associated with "Bacteroides" Bacteremia

Neoplasm	Cases
Adenocarcinoma of colon	28
Cervical or uterine tumor	8
Leukemia or lymphoma	6
Bronchogenic carcinoma	3
Prostatic carcinoma	3
Esophageal carcinoma	2
Hepatoma	2
Pharyngeal carcinoma	2
Renal carcinoma	1
Cerebral carcinoma	1
Multiple myeloma	1

This represents therefore 57 patients with neoplasms, or 23% of the total cases of Bacteroides bacteremia. Note the frequency of carcinoma of the colon. (39)

Another study (37) reported 37 cases of Bacteroides sepsis. In the 18 patients over 45 years of age in whom details were given, 50% had cancers. The experience at Memorial Hospital in New York (55) although obviously weighted heavily with cancer patients, again emphasizes the occurrence of Bacteroides sepsis with tumors of the gastrointestinal tract.

The frequent association of Bacteroides infections with phlebitis has been noted by many authors. Of interest in this regard is the capability of some Bacteroides

strains to degrade heparin and other mucopolysaccharides possibly contributing to development of phlebitis. (43).

A second group of microorganisms, Pseudomonas, also deserves special mention. A number of excellent articles give descriptions of these infections. (3,38,40,42, 64, 73, 102, 111) A very good survey is that in reference 28, describing 88 patients with Pseudomonas bacteremia. It emphasizes the frequency of Pseudomonas sepsis in infants, in patients with blood dyscrasias, and following urologic instrumentation. Whitecar, Luna and Bodey (107) reported 67 cancer patients with Pseudomonas bacteremia, prior to the introduction of carbenicillin and gentamicin. The overall mortality was 79%, and the mortality in the 44 patients with leukemia, 82%. This study calls attention to the correlation between the level of the leukocyte count in these patients and the chances for recovery. Sixty-four percent of the patients whose absolute neutrophile count increased during the week after onset recovered, compared to 8% of those whose neutrophile count decreased during that period.

Sepsis with unusual organisms only serves to stress the unpredictability of the causes for sepsis and a few of these are listed in the references. (30,44,61)

Pathophysiologic Data

Among the events of major importance in patients with sepsis is the occurrence of certain cardiovascular changes, the most severe of which result in shock. Some of the physiologic data collected in patients with septic shock will be reviewed. (59,60,104)

MacLean and his co-workers (59,60) have done a detailed study of 56 patients with septic shock in an attempt to define the hemodynamic alterations. The authors recognize a complex set of clinical syndromes which in a sense represent a sequential series of pathophysiologic changes. The first of these is a syndrome of what they term early septic shock.

Syndrome of Early Septic Shock in Normovolemic Man (59,60)

Hyperventilation
Respiratory alkalosis
High central venous pressure
High cardiac index
Low peripheral resistance
Hypotension
Oliguria
Lacticacidemia
Warm, dry extremities

These patients were among those with a relatively good prognosis, with only 4 deaths from shock among the 28 patients. The authors felt that all of these 28 patients were normovolemic.

In another group, all were hypovolemic at the outset, the picture differing in that there was low central venous pressure, low cardiac output, high peripheral resistance, and cold, cyanotic extremities. Early in the course some of these patients were alkalotic, but as a general rule they were acidotic at this time.

SEPTIC SHOCK

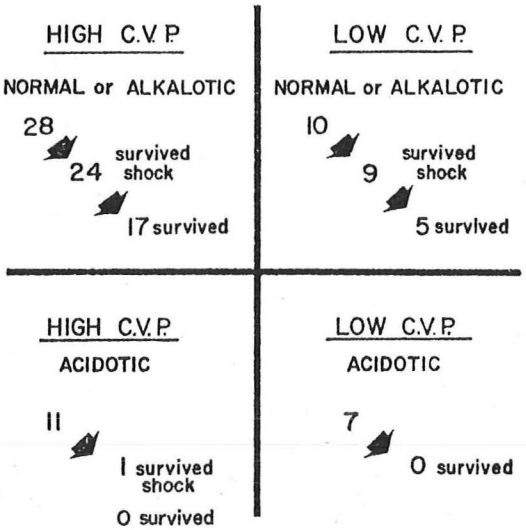


FIG. 14. Mortality in 56 patients with septic shock. Only 6 of 38 patients died of shock if treatment was started before the onset of metabolic acidosis. Only 1 of 18 patients survived when treatment was started after the onset of metabolic acidosis.

These authors feel that a useful classification of septic shock is based on central venous pressure and arterial pH measurements, and they felt these values were especially important as a guide to treatment and prognosis.

A major question exists as to whether the patients in the "warm stage" in which hypotension exists should really be referred to as patients in shock. Additionally, numerous observers have felt that the majority of these patients are also hypovolemic, but further data on this need to be obtained. The recognition of this constellation of symptoms however is of importance in management of patients.

Additional data of interest are given in reference 92. This is a study of the pathophysiologic changes in shock and the findings suggest that cardiovascular function and oxygen utilization in patients hypotensive due to sepsis exhibited abnormalities different from those in shock due to other causes. These patterns indicated that, as noted in many other studies, these patients may initially have hyperdynamic circulatory function, but pass rapidly into a stage of normal and then hypodynamic circulation. These authors give some rationale for the use of inotropic agents. These and additional experimental studies in endotoxin shock (91) have concluded that only an inotropic vasodilator, isoproterenol hydrochloride, was able to achieve two significant actions, namely to increase myocardial contractility and to decrease renovascular resistance.

Pulmonary problems are a common accompaniment of sepsis, and a good deal of attention has been directed to what is termed "shock lung". Collins (19) has written an excellent review of problems related to the lung in patients with sepsis.

The points emphasized by Collins may be outlined as follows:

Sepsis and the lung

Major respiratory impairment is a very common accompaniment of sepsis.

Mortality and hypoxemia are closely correlated.

The spectrum of pulmonary disease is broad, varying from transient hypoxemia to fatal obliteration of functioning lung.

Clinical manifestations

Hypoxemia
Right to left shunts
Increased alveolar dead space
Pulmonary edema, congestion and pneumonia
Loss of surfactant

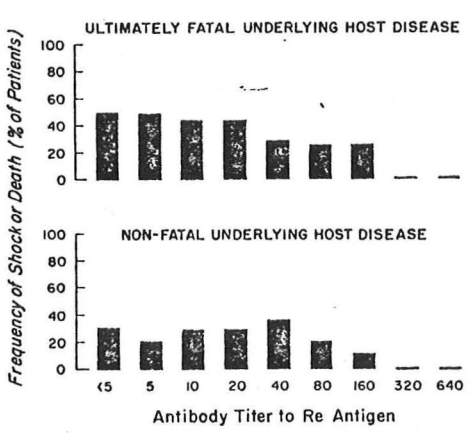
Onset frequently at the time of shock
Resistance to conventional methods of respiratory therapy

Pulmonary problems which may be involved in sepsis include:

1. Pre-existing lung disease.
2. Trauma or other restrictive process.
3. Left heart failure.
4. Fluid overload.
5. Pulmonary infection.
6. Shock
7. Thromboembolism
8. Abdominal distention.
9. Oxygen therapy with high O_2 concentrations.
10. Recumbency
11. Fat embolism
12. Narcotic administration
13. Aspiration

The problem of gram negative rod bacteremia and the frequent predictability of situations in which it may occur have led to interest in antibody studies. McCabe and his co-workers (69) have studied several antibodies in patients with gram negative rod bacteremia. They have studied both O-specific and cross-reactive antigens (common enterobacterial antigen or CA) along with Re antigen of rough bacilli in a group of 175 patients. The most significant aspect of this study was that there was no correlation between the height of CA antibodies and the frequency of shock or fatal outcome. In contrast, both shock and death were only one-third as frequent

among patients with high titers of Re antibody. This suggests some possibility that immunization may reduce the seriousness of gram negative rod bacteremia.



Bleeding

In recent years, considerable interest has developed in certain changes in the blood coagulation system associated with septicemia. (22,31,65) Corrigan and his co-workers (22) have done detailed coagulation analyses in 36 pediatric cases of septicemia, including 22 with gram negative infections and 8 with gram positive infections. These authors felt that among the various clinical parameters, the occurrence of coagulation abnormalities correlated best with the presence of hypotension.

Summary of the Relations between Blood Pressure and Coagulation Data in Children with Septicemia

Blood Pressure	Platelets	"Consumption Factors"*	"Vitamin K Factors"**	Fibrinolysis	
				Euglobulin Lysis Time	Fibrinolytic Split Products
Normal	Normal or reduced	Normal or increased	Normal or reduced	Normal	Absent
Reduced	Reduced	Reduced	Normal or reduced	Normal	Present

*Factors II,V & VIII & fibrinogen ** Factors II,VII,IX & X.

Various changes in the clotting mechanism were encountered regardless of the infectious agent. The most frequent abnormality was thrombocytopenia, occurring in 61% of the cases. The multiple coagulation changes regularly noted in patients with hypotension or shock were interpreted as being secondary to diffuse intravascular coagulation. The most reliable laboratory guide seem to be a reduced platelet count, low factor V levels in plasma and fibrin split products in the serum.

Another recent study (72) has elucidated something of the mechanism of the hemorrhagic shock syndrome (Dengue) occurring in children. In those patients who develop shock there appears to be activation of the complement system, with consumption of complement. Lowering of C_3 is noted to occur at the same time as activation of the coagulation system, and the appearance of disseminated intravascular coagulation.

One may conclude that a spectrum of coagulation abnormalities may occur in the presence of any septicemia, varying from inconsequential lowering of the platelet count to the most severe disseminated intravascular coagulation. It is of interest to note that this is not restricted to bacterial infections, but has been described in rickettsial disease, in systemic candidiasis (22,84) and in at least one viral infection as mentioned previously. (72)

Two additional laboratory tests have attracted some attention and need to be mentioned here. The first is a test for demonstration of circulating endotoxin (58,66). The profound physiologic changes produced by endotoxin of gram negative rods has naturally led to considerable interest in the role of endotoxin in the production of shock in patients with septicemia. In this connection, a number of recent studies have attempted to relate endotoxinemia to the clinical picture. (48,49,58,66) The article of Levin and his associates (58) has attracted considerable attention in this respect. These authors tested patients' blood with the Limulus test, which depends upon the capacity of endotoxin to cause gelation of protein-containing fluid derived from the blood cells of the horseshoe crab (Limulus). They studied 98 patients with so-called septicemia and found that 17% of them had endotoxin in their blood. It should be noted that not all of these patients had positive blood cultures, nor did all of the patients with positive blood cultures have endotoxin. The number of false positives and false negatives with this test certainly make it seem of limited value.

The same may be said of the Nitroblue-Tetrazolium test which has been advocated as a test to determine the presence of bacterial infection. (33,34,77,79,109) This test depends on the spontaneous reduction of nitroblue-tetrazolium (NBT) by neutrophiles and has been advocated as a useful test in the detection of bacterial infections, especially in those patients who are uremic and patients who are immunosuppressed at the time of renal transplants. Despite early interest in this, a variety of technical difficulties with the test as well as the occurrence of many false negatives and false positives also limit the usefulness of this test.

"Risk factors"

A number of analyses of large series of cases have emphasized the very great importance of certain risk factors in relationship to the outcome of gram negative rod bacteremia. In judging the severity of the clinical situation and the prognosis, these are unquestionably of great importance. The first detailed analysis of this was done by McCabe and Jackson (67). More recent series have been published by Freid and Vosti (42) and by Bryant and his associates (13).

Freid and Vosti studied 270 patients with gram negative bacteremia and in each case categorized the underlying disease the patient had as "Rapidly Fatal",

"Ultimately Fatal" or "Non-Fatal". As examples of the type of underlying disease, they list the following.

"Rapidly fatal illnesses"

Acute leukemia	30
Cardiac arrest	1
Arsenic poisoning	1
Postnecrotic cirrhosis	1
Bacterial endocarditis (staph)	1
Blastic crisis (myeloid leukemia)	1

Freid & Vosti (42)

"Ultimately fatal illnesses"

Lymphoma	23
GI neoplasm	13
Gyn cancer	8
Renal cancer	6
Chronic leukemia	5

(65 of 92 patients had malignant disease)

Freid & Vosti (42)

In this particular study no significant difference in mortality was noted with different age groups. In many series, however, aging itself was apparently significant, with considerably greater mortality in the older age groups.

The significance of these underlying diseases in relation to their fatality rates is evident from their statistics listed below.

Fatality ratios in patients with gram negative bacteremia related to severity of underlying disease.

Underlying disease	Dead/Total	%
Rapidly fatal	31/36	86
Ultimately fatal	42/92	46
Non-fatal	23/142	16
Total	96/270	36

Freid & Vosti (42)

Bryant and his co-workers (13) have done a similar retrospective analysis of 218 patients with very much the same results. Additional factors they noted to be associated with increased mortality were shock, azotemia, the presence of Pseudomonas bacteremia, and low or normal temperature.

Table 3.—Correlation of Temperature During Bacteremia With Shock and Mortality

Temperature (F)	No. of Patients	Average Age	Shock No.	Shock (%)	Mortality, %
95-100.9	24	60	12	(50)	71*
101-102.9	70	55	16	(23)	31*
>103	124	56	32	(26)	27*

* Significance of higher mortality in patients with bacteremia and temperature less than 101 F by X^2 ($P<0.001$).

The absence of fever, or relative absence of fever, is a poor prognostic sign (13).

Table 4.—Mortality Associated With Bacterial Species Causing Bacteremia

Bacteria	Rapidly Fatal No	Rapidly Fatal (% Mortality)	Ultimately Fatal No	Ultimately Fatal (% Mortality)	Nonfatal No	Nonfatal (% Mortality)	Total No	Total (% Mortality)
E coli	4	(75)	23	(30)	56	(13)	83	(21)
Klebsiella-Enterobacter	6	(100)	15	(33)	36	(22)	57	(33)
Pseudomonas	9	(88)	22	(77)	14	(50)	45	(71)*
Proteus	2	(50)	4	(50)	13	(0)	19	(16)
Bacteroides	—	—	1	(100)	6	(17)	7	(29)
Miscellaneous Gram-negative bacilli	—	—	2	(50)	5	(0)	7	(8)

* Significance of higher mortality ($P<0.001$) by X^2.

The particular significance of Pseudomonas bacteremia is also noted (13).

Cardiac surgery is again a relatively new area which may be added as a risk factor in sepsis (83,89).

Immunosuppressive therapy, uremia and the combination of the two are special risk factors. The frequency of bacteremia in one renal transplant unit is noted below.

Before transplantation (70 patients)

Gram positive organisms 2 (3%)
Gram negative organisms 5 (7%)

After transplantation (45 patients)

Gram positive organisms 5 (11%)
Gram negative organisms 13 (29%)

Incidence of bacteremia before and after renal transplantation (57)

The post-transplant patients are of course subject to a wide variety of infections in addition to gram-negative rod bacteremia, including such things as Pneumocystis carinii infections and a variety of relatively non-pathogenic yeast and fungi. For example in 20 patients with cardiac transplants at Stanford, Remington has reported the following infections identified in 12 (85).

E. coli	4
Hepatitis	1
Klebsiella	5
Aspergillus	5
Staphylococcus	3
Enterococcus	1
Pneumocystis	2
Rhizopus	1
Toxoplasma	2
Mixed anaerobic	2
Trichomonas	1
Cytomegalovirus	9
Proteus	1
Bacteroides	2
Streptococcus	1

A number of other procedures have led to additional risk factors. Problems with inhalation therapy apparatus have been elucidated by Doctors Pierce and Sanford and their associates in a number of studies here at Parkland (82). The techniques they have developed for the care and monitoring of respiratory therapy instruments have led to substantial improvement in this risk factor.

An additional factor of particular importance has to do with the use of polyethylene catheters for the maintenance of venous lines for fluid therapy. The significance of this was pointed out as long ago as 1956 by Collins in analyzing the causes for staphylococcal bacteremia at the Memorial Hospital (18). Collins considered then that the "cut-down" was the single most important mechanism involved in the production of staphylococcal bacteremia in that hospital. A recent resurgence in the interest of this has apparently resulted from an increasingly wide-spread use of small plastic catheters inserted through a needle for maintenance of fluid therapy, as well as the more common use of measurement of central venous pressure and the utilization of so-called total parenteral nutrition (TPN). Several reports now have documented the hazards of prolonged venous catheterization (5,20,29,81,96)

TABLE 3. *Results of Culture of Polyethylene Catheters in Relation to Duration of Use.*

Result of Culture	Days of Catheterization								Total	
	1		2		3		≥4			
	no.	*%*	*no.*	*%*	*no.*	*%*	*no.*	*%*	*no.*	*%*
Negative	42	77.8	43	62.3	27	58.7	28	63.6	140	65.7
"Contaminant"	8	14.8	15	21.7	9	19.6	4	9.1	36	16.9
"Pathogen"	4	7.4	11	15.9	10	21.7	12	27.3	37	17.4
Totals	54		69		46		44		213	

Reference 20

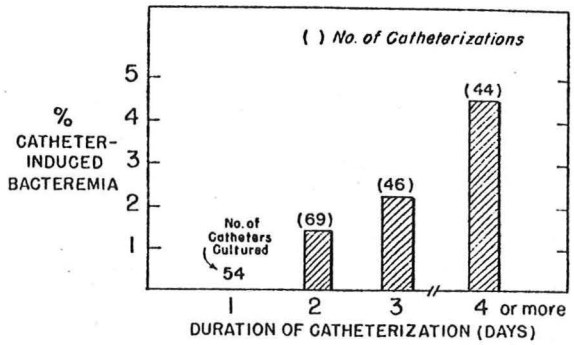


FIGURE 1. *Relation of Duration of Catheterization to Bacteremia.*

These authors (20) studied 213 catheterizations in 176 patients. One-third of all the catheters were positive by culture at removal and the risk of local infection with pathogenic organisms increased with use. The risk of catheter induced bacteremia in these patients was 2% and was a major contributing cause of death in 1%.

A prospective study done in a pediatric hospital is of special interest also (81).

Table I. Incidence of positive cultures from tips of needles and catheters

Cultures	*Scalp vein needle*	*Catheter*	*Significance**
Total No. cultures	142	25	—
No. positive cultures	12 (8.5%)	6 (24%)	$p < 0.06$
Contaminants	9 (6.4%)	1 (4%)	Not significant
Pathogens	3 (2.1%)	5 (20%)	$p < 0.001$†

*Chi square analysis.

†With Yates correction.

Reference 81

Table II. Organisms recovered from culture of needles and catheters

Organisms and pathogens	*Scalp vein*	*Catheter*
Contaminants		
Staphylococcus epidermis (coagulase-negative)	8	1
Bacillus subtilis	2	1
Subtotal	10	2
Pathogens		
Staphylococcus aureus (coagulase-positive)	0	1
Escherichia coli	1	2
Streptococcus faecalis	0	1
Escherichia—Paracolon	2	0
Pseudomonas	0	1
Herellea	0	1
Subtotal	3	6
Total organisms	13	8
No. of patients with positive cultures	12	6

Reference 81

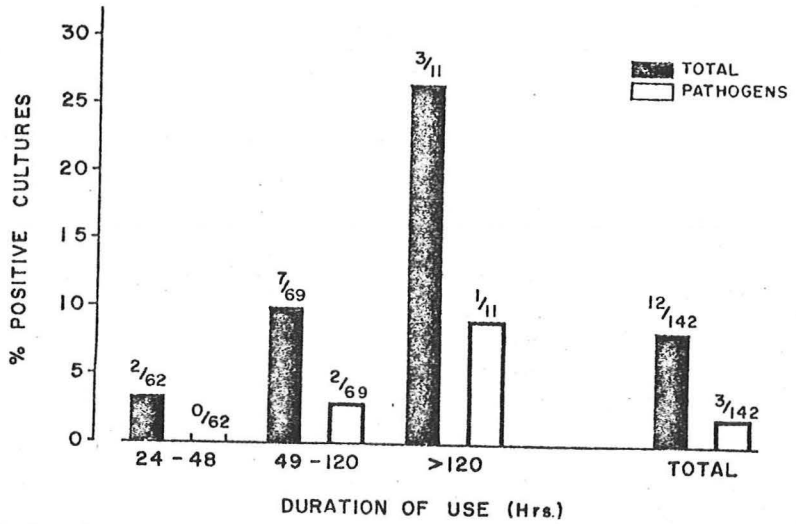


Fig. 1. Scalp vein needle cultures. Relationship of duration in situ to incidence of positive cultures.

This reference is of special interest in that despite the fact that some local infection occurred from scalp vein needles (8.5%), it was significantly less than that with catheters (24%). Bacteremia occurred only in association with catheters. The authors attribute the difference in bacteremia to the fact that local infection in scalp vein needles is less frequent and they do not stay in place as long.

The special problem which appears to exist in patients receiving parenteral hyperalimentation has been mentioned (4,27). Curry and Quie (27) observed 33 patients with fungal septicemia during an 18 month period. Twenty-two of these thirty-three had received parenteral hyperalimentation. They felt that this fungal septicemia was not related to steroid therapy or immunologic deficiency but was related to prolonged intravenous catheterization. Subsequently a prospective study of all patients receiving parenteral hyperalimentation yielded 13 of 49 patients developing fungal septicemia. Similar results have been reported by Ashcraft and Leape (4), although very recent report by Dillon and his associates suggests (32) that TPN is not as hazardous a procedure as the other literature would have us believe. At the same time, they point out that in their study "meticulous care of the catheter site was emphasized". Care of the catheter has been shown to be of great importance (23). In any case, candidemia is a serious problem and one which is difficult to evaluate and to manage. The article by Ellis and Spivack is recommended as a good summary of this problem (36).

A recent study by a group from Minnesota has described a possible mechanism to explain the increased hazard of hyperalimentation. Craddock and his associates (25) have noted both in experimental animals and in man that infections during hyperalimentation occurred chiefly in those patients with severe degrees of hypophosphatemia. Hypophosphatemia is a regular accompaniment of TPN, and the infections occurred when the serum phosphorus reached levels of 0.5 mgm/100 ml or less. This in turn was associated with a decrease in cellular ATP, and a concomitant marked decrease in phagocyte motility, a function which is dependent on ATP-requiring contractile proteins. The reported incidence of septicemia is given in the table published by Goldman and Maki (45) who collected at the CDC, data from all over the country.

Reported Incidence of Septicemia Complicating Total Parenteral Nutrition

Reference	Year	No. of Patients	Rate of Septicemia, All Pathogens, %	Rate of Candidemia, %
Dudrick et al[15,16]	1969	47	6	4
Groff[18]	1969	18	17	?
Filler and Eraklis[4]	1970	109	15	7
Ashcraft and Leape[19]	1970	22	23	23
McGovern[5]	1970	25	12	4
Curry and Quie[14]	1971	49	27	16
Winters et al[20]	1972	30	6	6
Ryan et al[21]	1972	355*	7	3
Helmuth et al[10]	1972	4	25	25
Peden and Karpel[11]	1972	13	23	0
Driscoll et al[12]	1972	9	11	11
Center for Disease Control	1972	2,078	7	4

*Number of catheters.

This table lists a good many reports from the literature and shows that the rate of septicemia is generally high and the rate of candidemia is also high. As a result of these experiences the CDC has issued an excellent set of guidelines for insertion and maintenance of plastic venous catheters (14) and more recently detailed guidelines for infection control in total parenteral nutrition (45). The recommendations contained in this reference are very stringent and should be reviewed in detail by those undertaking this procedure. The essentials of the recommendations are as follows:

1) Careful consideration of the risks prior to initiation of therapy.
2) A team should be responsible for all TPN.
3) A strict protocol should be drawn up including detailed infection control measures.
4) Careful aseptic techniques should be followed in mixing the components of TPN solutions. The fluid should be used immediately and never stored at room temperature.
5) Insertion of the catheter is a surgical procedure ideally performed in an operating room or a treatment room with handwashing, gowns, masks and gloves as for any other surgical procedure.
6) Careful preparation of the skin at the site of catheter placement.
7) Secure anchoring of the catheter to avoid movement. Topical antibacterial, antifungal iodophor ointment is applied.
8) With aseptic technique the catheter site should be inspected and disinfected periodically.

9) Discontinuance of a catheter site at the first signs of inflammation.
10) Some routine for re-establishment of the line in the absence of infection (no recommendation of time here).
11) The line is not used for other purposes.
12) Possible use of Micropore filters.
13) Changing administration sets every 12 hours.
14) Always consider the TPN system as the source of fever unless proven otherwise.

One should now add to this the administration of supplemental phosphate to all patients with hypophosphatemia. Brennan and his associates (9) have recently published a technique for repeated flushing of the IV line with amphotericin as a potential means of prevention of candidemia. The effectiveness of this needs to be further evaluated.

Treatment

It is obvious in this discussion that to consider thoroughly the management of sepsis, a variety of surgical problems and virtually all of the antibiotics would need to be considered, and thus we can deal only in broadest of generalities (2,6, 12,26,36,53,56,98,106). It is worth asking in the beginning however, whether or not appropriate antibiotic therapy really is important. It is surprising how very little information directly bears on this topic in the management of sepsis. Hodgin and Sanford (50) dealt with this.

Correlation of Mortality and Antibiotic Therapy

	Entire Group		Patients in Shock	
		Mortality		Mortality
Antibiotics	No.	(%)	No.	(%)
"Appropriate"	65	42	26	62
"Inappropriate"	35	63	12	67
	$p < 0.02$		N.S.S.*	

*Not statistically significant.

As indicated in this table, in the Parkland series the mortality in the shock patients was not significantly different whether the antibiotics were appropriate or inappropriate. In this connection, it is only fair to say that this article was written in 1965 when not so many antibiotics were available as now. Nevertheless, it is not certain that this figure would be changed at the present time. As also indicated in the table, in the entire group of patients, the mortality was significantly different if appropriate antibiotics happened to be chosen at the outset. Bryant et al (13) dealt with the same question

Table 7-Effect of Antibiotic Therapy on Mortality of Gram Negative Rod Bacteremia

	Underlying Disease Category								
	Rapidly Fatal			Ultimately Fatal			Nonfatal		
	No.	(% Mortality)	*P* value*	No.	(% Mortality)	*P* value*	No.	(% Mortality)	*P* value*
Appropriate antibiotic therapy	14	(86)	>0.10	49	(39)	<0.02	95	(12)	<0.02
Inappropriate antibiotic therapy	7	(71)	>0.10	18	(72)	<0.05	35	(29)	<0.05
Appropriate antibiotic therapy, penicillin, colistimethate and kanamycin	5	(80)		24	(42)		40	(8)	

* Using X^2 test.

As indicated previously, their patients are divided up as to the underlying disease category whether rapidly fatal, ultimately fatal or non-fatal. In the patients with rapidly fatal underlying disease, appropriate antibiotic therapy was not more effective than inappropriate therapy. In the other two categories however the therapy was helpful.

The task of actually conducting a controlled study in this most complex situation is a difficult one and even attempts at this have rarely been made. Martin and his co-workers (62) made an effort at this soon after gentamicin became available. The general plan of the study was that certain arbitrary drug regimens were selected and then patients suspected of having sepsis were randomized into the different groups. They received the initial drugs for usually less than six days, the drugs being stopped if bacteremia was not demonstrable or if the sensitivity tests of the isolated organism suggested a better antibiotic. This latter limitation obviously is of considerable importance in evaluating results but nevertheless the results in this study are of considerable interest.

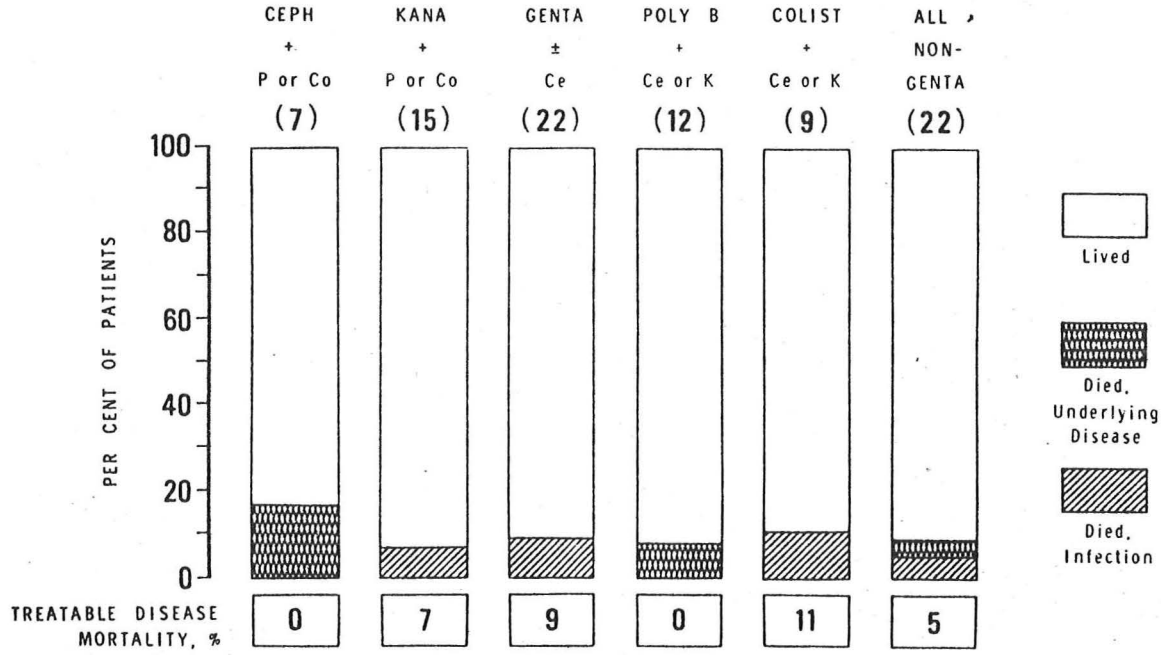


Figure 5. Results of various initial therapies in 44 adults with acute gram-negative rod infections with neither bacteremia nor shock (pooled groups). (Numbers of patients in parentheses.)

This graph shows the results of therapy in the patients in this study who had neither bacteremia nor shock. The number of patients treated are indicated in parentheses. The lower blocks, "treatable disease mortality", is essentially the mortality from the infection excluding patients who died during this acute phase as a result of their underlying disease. In none of these treatment groups was the mortality high (62).

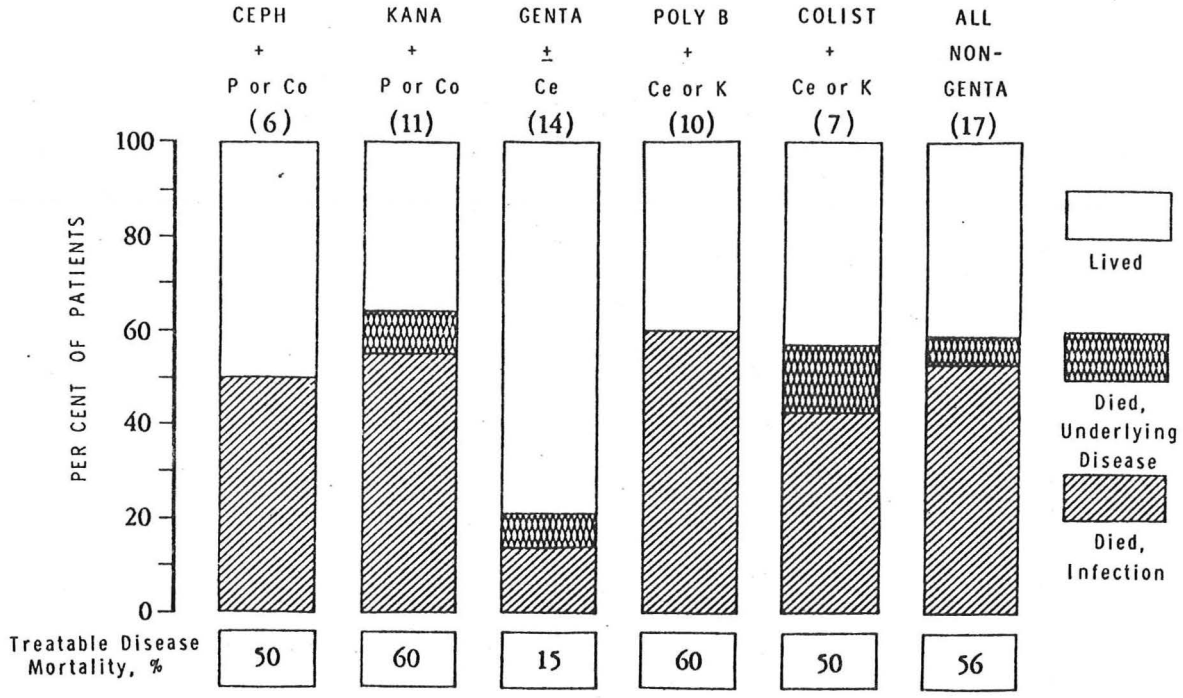


Figure 6. Results of various initial therapies in 31 adults with gram-negative rod bacteremia (pooled groups). (Numbers of patients in parentheses.)

The situation obviously changed in those patients in whom bacteremia was demonstrable (62). Noteworthy is the fact that the gentamicin group looks quite favorable.

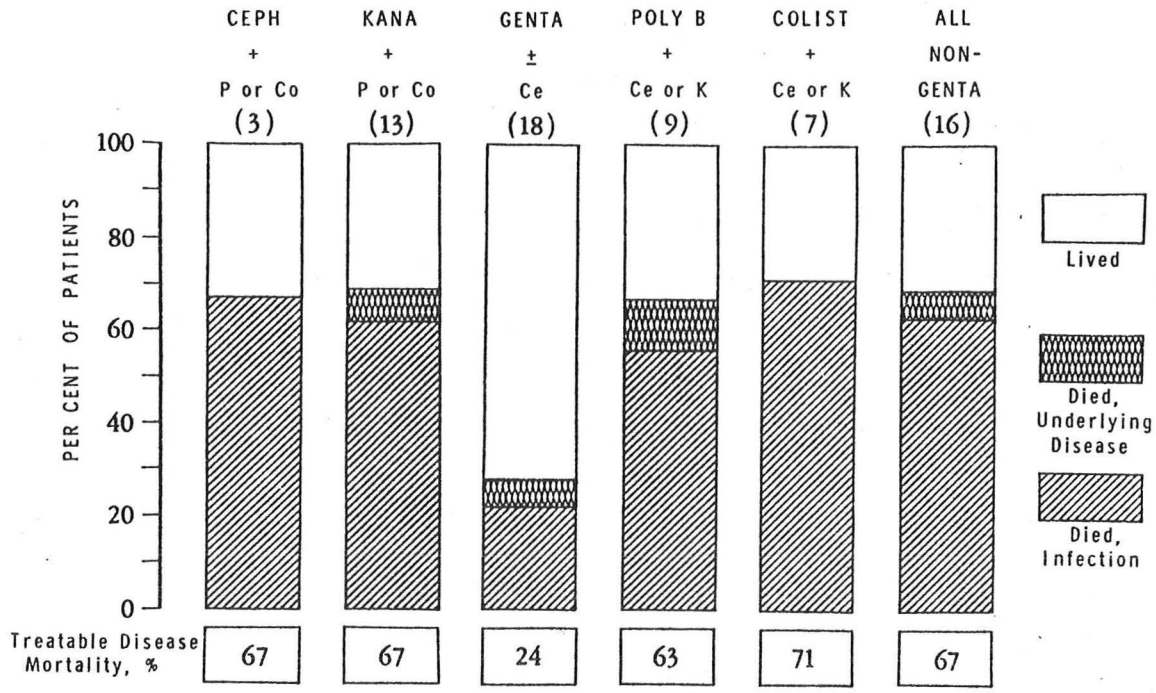


Figure 8. Results of various initial therapies in 34 patients with acute gram-negative rod infections in shock prior to therapy (pooled groups). (Numbers of patients in parentheses.)

The situation then looks even worse in those patients who had gram negative rod infections with shock, but again the gentamicin group looked better than others. It should be mentioned also, that in addition to the antimicrobial therapy in this group, the general method of MacLean and his co-workers, to which we have already referred, was followed in the treatment of shock. Adrenal corticosteroids were used in only a few of these patients.

The preponderance of the literature on antimicrobial therapy at the present time has to do with the uses of carbenicillin and gentamicin. These drugs are potent individually and have also been reported to be synergistic in their action (11,97). It is evident in considering these two drugs that it is very difficult to discover exactly how effective they are because of the complex clinical situations in which they have been used and because in the most severely ill patients, they are generally used together. Before proceeding to this however, it might be worth reviewing an example of a less pessimistic view of the situation prior to the introduction of these drugs. Thoburn and Fekety (100) have published an interesting paper on combined therapy with cephalothin,kanamycin and colistin in patients with presumed bacteremia. They simply chose an arbitrary three drug regimen and treated all patients suspected of having gram negative rod bacteremia.

Outcome in Patients with Gram negative bacteremia treated with the combination (100)

Clinical condition during the infection	Number of patients	Number of deaths	Mortality rate %
No hypotension	3	0	0.0
Hypotension (total)	13	4	30.7
Hypotension without oliguria	5	1	20.0
Severe hypotension with oliguria (shock)	8	3	37.5
Total episodes	16	4	25.0
Total patients	14	4	28.6

It will be noted here that in comparison with the figures quoted previously, this drug combination looks very favorable. Whether this reflects simply good drug therapy or whether it represents the variability of the patient population is uncertain. A few references to therapy with gentamicin alone are included (1,6,24,70). These articles, in addition to some others, record effective use of gentamicin in patients with gram negative rod sepsis. Assessment of carbenicillin therapy alone is more difficult (7,8,26,71), but it too has generally been considered effective. The article by Bodey (87) and his co-workers which showed a conversion of the mortality rate in Pseudomonas bacteremia with these two drugs from 90% to 30% is an impressive paper. The study by Schimpff (90) and his associates utilized carbenicillin and gentamicin as empiric therapy for patients with cancer and granulocytopenia. In 48 patients with documented infections, 21 of which were Pseudomonas infections, the results with the two drugs together were generally good. Results in the treatment of Pseudomonas infection were superior to that of the other gram negative rod infections. In the year before they started using carbenicillin and gentamicin at the Baltimore Cancer Research Center, 20 of 22 patients died of Pseudomonas bacteremia. Since this therapy was initiated, 4 deaths in 13 patients have occurred. It is of special interest that in a setting of Pseudomonas bacteremia with granulocytopenia, gentamicin alone failed in 7 of 8 patients (87,111). Other articles of interest on the combination of carbenicillin and gentamicin are listed in the references (6,53,80, 87,90).

Two considerations are of special importance in the use of gentamicin and carbenicillin. First is that the various penicillin compounds, especially carbenicillin, will inactivate gentamicin in intravenous infusion fluids (78,80). Thus gentamicin should never be mixed with these drugs in IV fluids. The second has to do with the problems of administration of gentamicin and the difficulty in adjusting dosage. The intravenous use of gentamicin presumably does not give erratic levels. It is, however, fraught with some hazards, both because of the concern about peak concentrations and ototoxicity, and also because of the more immediate concern of neuromuscular blockade (15,76,99,103). A variety of suggestions have been offered for the guidance of gentamicin therapy. As presented recently here by Dr. Sanford, the levels on intramuscular injection are very unpredictable even in patients with normal renal function. Techniques are available for the measurements of blood levels (52,88,94). The microbiologic method is good but many other antibiotics interfere with it. The chemical method will probably prove to be superior. It has a theoretical disadvantage in that the test organism (E.coli) is a gentamicin resistant organism

possessing an R-factor which is capable of transmitting gentamicin resistance to other gram negative rods. The possibility certainly exists that general distribution of this organism might be hazardous as far as the future usefulness of gentamicin is concerned (95).

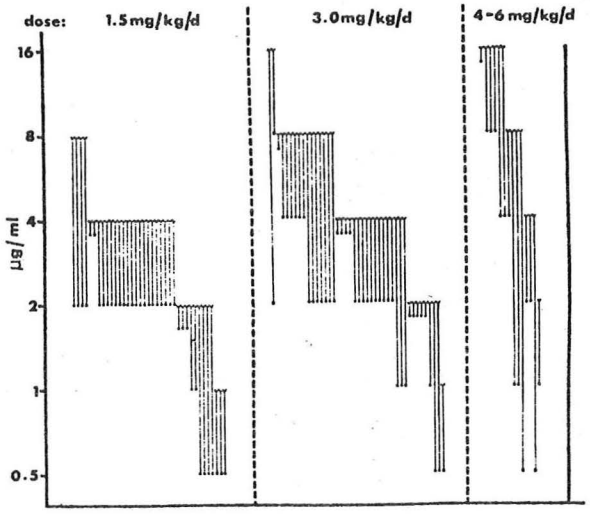
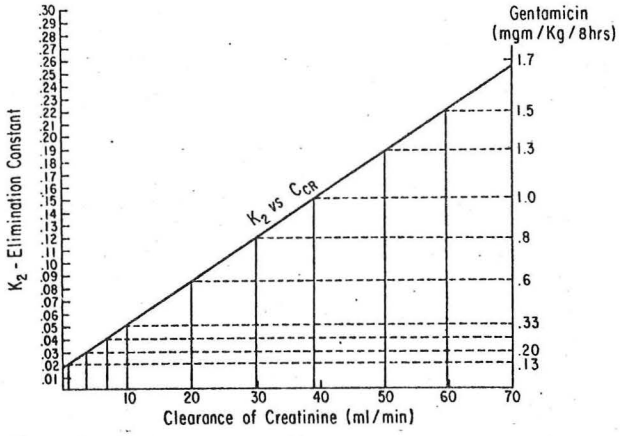


Figure 2. Peak and trough levels of gentamicin in serum in patients with normal renal function.

This figure shows the peak and trough blood levels of gentamicin in patients with normal renal function after three different dosages. The overlap is so great as to make it clear that unpredictability is a major factor in the drug administration. Moreover, there is good documentation with this particular drug that inadequate levels are related to failure of treatment (51).

Various nomograms have been constructed such as the one by Chan, Benner and Hoeprich (16).



This nomogram relates the proposed dosage to creatinine clearance. Drug level

measurements however appear to be the most useful and the most reliable way to avoid this problem.

Much remains to be learned about the treatment of septic shock. It is not our purpose to deal with this in detail here except to relate the current opinion as to its treatment (59,60,101,105).

1) Circulating blood volume is usually inadequate and fluid replacement is indicated. In patients with hypotension or patients with serious degrees of illness, and especially with the risk factors indicated above, in particular older patients, central venous pressure should be monitored immediately.

If the CVP is not high, fluid therapy is indicated with the response being judged by the blood pressure, urine output and CVP. An attempt is made to keep the CVP between 5 and 15 cm. Considerable discussion exists about the relative use of saline, albumin, dextran and whole blood. Certainly patients should receive blood if they are anemic. Most people do not favor the use of dextrans.

2) Isoproterenol is useful in patients who initially or subsequent to fluid therapy have a CVP above 15.

3) Appropriate ventilation is mandatory. Careful assessment of the possibility of congestive heart failure must be made at all times and digitalis used if indicated.

4) Corticosteroids are the subject of much discussion. The general belief is that proof of their value has not been forthcoming. Many investigators feel that the absence of any harmful effects over a few days warrant their use. When used it is usually recommended that they be used in large doses (e.g. the equivalent of 5 grams of hydrocortisone initially followed by 1-2 grams q4-6h).

5) Despite some enthusiasm for the use of heparin in patients with disseminated intravascular coagulation, it would appear at present that this drug is seldom if ever useful (21). Additional measures such as granulocyte transfusions (46) are of great interest but have not been fully evaluated.

Finally, it should be emphasized that although this discussion has touched only briefly on surgical considerations in sepsis, in many instances surgery is by far the most important aspect of the patient's care. Whenever a surgically correctible lesion in a patient with sepsis can be dealt with, this frequently adds the most significant part of the therapy.

Summary

We have attempted to present a clinically useful description of the syndrome of "sepsis", to describe it as it is now being seen in the hospital setting, and to indicate the current spectrum of the microbiologic as well as certain pathophysiologic abnormalities. Finally we have dealt to a limited extent with some of the major aspects of therapy.

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