INFECTIOUS LUNG DISEASE IN ALCOHOLICS

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ORGANIZATION OF PRESENTATION

1. Pathophysiology of pneumonia.

2. Clinical manifestations and epidemiology of individual organisms - literature review.

3. Parkland experience - One year review of all community acquired pulmonary infections.

4. Summary and conclusions.

INTRODUCTION

It is well recognized that alcoholics have a significant incidence of pulmonary infections. Certainly all of us who practice at Parkland are well aware of this association. The relative rate at which individual organisms cause pulmonary infections in alcholics in comparison to non alcoholics as well as their absolute rates are poorly described. This is due to several methodologic problems to include the fact that various authors frequently only look at one specific kind of pulmonary infection (i.e., pneumonia, lung abcesses, etc.) or organism (i.e., pneumococcus, etc.), and the frequent mixing of community acquired and nosocomial pulmonary infections in publications. The purpose of this presentation is to discuss and evaluate community acquired infectious lung disease in alcholics. This will eliminate all nosocomial pneumonias from discussion. However, it will not eliminate tuberculosis from consideration. The specific chronologic organization of this talk will be as follows:

1. Pathophysiology of pneumonia - this will be discussed in general and specifically as relates to alcoholics in order to set a framework upon which to interpret subsequent clinical data.

2. Review of published literature concerning the epidemiology and clinical characteristics of organisms believed to cause pneumonia in alcholics and nonalcoholics. Emphasis will be placed on gram negative rod pneumonias due to the commonly held belief that they cause a significant percentage of pneumonias in alcholics.

3. Review of community acquired pulmonary infections on the medical service in alcholics and non alcoholics at Parkland Memorial Hospital from July 1985 to June 1986 to include all bacterial pneumonias, mycobacterial infections, lung abcesses, and empyemas.
4. Summary and conclusion.

PATHOGENESIS

The presumed pathogenesis of pneumonia is demonstrated in Figure 26-1 (1).

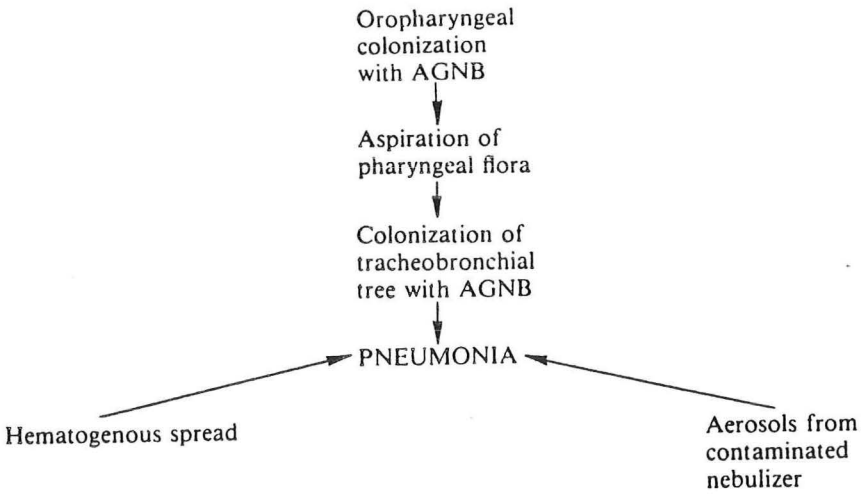


Figure 26-1 Routes of infection leading to AGNB pneumonia.

One can easily substitute any organism for the indicated gram negative bacilli (AGNB). As indicated these are basically three means of acquiring pneumonia; aspiration, hematogenous spread and aerosols from contaminated respiratory devices. Only aspiration type pneumonia will be addressed. In this scheme aspiration is one event that is accepted as clinically relevant by most authors and has been well shown to occur in aspiration prone patients and "normals" by Dr. Pierce and colleagues from this institution in 1978 (2). These authors demonstrated using isotope tagging techniques that 70% of presumably aspiration prone patients aspirated material from their nasopharynx into their lung during a several hour daytime observation period. During this time no "gross aspiration" such as swallowing of vomitus occurred. In addition, these authors observed that 45% of normal patients similarly studied aspirated during the night while asleep indicating a significant prevalence of sub-clinical aspiration in the normal "non aspiration prone" host. The relevance of aspiration in the pathogenesis of pneumonia in the alcholic is clear when one considers how frequently alcoholics "grossly aspirate" when intoxicated as well in the manner noted in this study.

If aspiration is accepted as a critical step in the pathogenesis of community acquired pneumonias it is clear from the initial figure that patients would aspirate whatever organisms were in their oropharynx at that time (i.e., whatever organisms colonized their oropharynx). There is published much data on colonization. Most focuses on the incidence of colonization of the oropharynx with aerobic gram negative rods in certain clinical setting. Doctors Johanson, Pierce, and Sanford from this institution in the late 1960's and early 1970's published several papers which show increased colonization with gram negative rods in patients with increasing degrees of illness (3). This is demonstrated in accompanying Table 2 (Results of Multiple-Culture Surveys).

TABLE 2. *Results of Multiple-Culture Surveys.*

Study Group	No. of Subjects	No. of Cultures	No. of Cultures/ Subject	Cultures Containing Gram-Negative Bacilli	Subjects with 1 or More Cultures with Gram-Negative Bacilli
				%	%
Normal subjects	33	139	4.2	3	6
Patients:					
Psychiatry service	18	88	4.9	2	6
Moderately ill	75	303	4.0	22	35
Moribund	11	27	2.5	63	73

Even among ICU patients the relative degree of illness seemed to further predict the incidence of oropharyngeal colonization with gram negative rods as as published in Table 3 (4).

Table 3. Variables Associated with Colonization of the Respiratory Tract with Gram-Negative Bacilli (GNB) in 213 patients*

Variable	GNB Colonization		
	Yes	No	
	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	$P < 0.001$
Hb $\leq$ 8 g/100 ml			
Yes	2	1	
No	93	117	NS

* Patients admitted to a medical intensive care unit. NS = not significant.
† Defined as loss of consciousness with no response to commands, may respond to painful stimuli.
‡ Systolic blood pressure less than 80 mm Hg or requiring vasopressors, for more than 4 hours.
§ Blood urea nitrogen.

These authors also demonstrated a correlation between colonization and respiratory infections in the ICU with gram negative rods. Valenti et al., at the University of Rochester subsequently published similar data in institutionalized elderly patients as shown in Table 1 (Prevalence of Etc.) (5).

Table 1. Prevalence of Gram-Negative Bacilli in the Oropharynx of Elderly Subjects According to Level of Care and Method of Culture.

Location	No. of Cultures	Bacilli on Direct Plating	Bacilli with Selective Broth
Acute hospital ward	25	10 (40±9.8)*	15 (60±9.8)
Skilled-nursing facility	223	50 (22±2.7)	83 (37±3.2)
Health-related facility	60	8 (12±4.4)	25 (42±6.3)
Private proprietary nursing home	53	5 (9±4.0)	12 (23±5.8)
Independent apartments	48	3 (6±3.4)	9 (19±5.6)
Employees	100	3 (3±1.7)	8 (8±2.7)

*Figures in parentheses denote % ± SD.

Irwin et al., subsequently demonstrated the colonization was transient in this type of institutionalized elderly patient (6). Colonization in aspiration prone patients has also been exclusively studied. Mackowiak et al., at the VA here in Dallas evaluated several groups of such patients and demonstrated in Table 1 (Prevalence of penicillin-resistant, etc.) that alcoholics and insulin dependent diabetics had an increased prevalence of gram negative rod colonization versus controls (7).

Table 1.—Prevalence of Penicillin-Resistant Microorganisms in Gargle Specimens From Aspiration-Prone Persons and Control Subjects*

P-R Microorganisms	Controls, No. (%)	Alcoholics, No. (%)	Diabetics, No. (%)	Epileptics, No. (%)	Addicts, No. (%)
Gram-negative bacilli	15 (18)	43 (35)†	15 (36)†	5 (17)	8 (20)
Two or more Gram-negative bacilli	0 (0)	2 (2)	2 (5)	0 (0)	1 (2)
P-R *Staphylococcus aureus*	0 (0)	2 (2)	1 (2)	1 (3)	3 (8)
No. subjects examined	84	124	42	30	40

*P-R indicates penicillin resistant.
†Percentage is significantly different from control subjects ($P < .05$ by Yates' modification of χ^2 analysis).

They also demonstrated that there was no relationship to smoking and oral hygeine. Other workers from the University of Puerto Rico have confirmed their data concerning alcoholics (8). These same investigators have demonstrated similar data after a respiratory viral illnesses in houseofficers (9). A positive relationship between and staphylococcal and gram negative rod colonization and viral illness was demonstrated indicated in the next Table 1.

Table 1.—Colonization of Oropharynx: Comparative Monthly Colonization by Gram-Negative Bacilli and *Staphylococcus aureus*

Month	No. of Participants	No. of Participants With URI	% Colonization			
			Gram-Negative Bacilli		*Staphylococcus aureus*	
			Illness-Free	URI	Illness-Free	URI
July	89	4	16	50	7	25
August	60	4	13	50	8	50
September	50	...	13	...	5	...
October	32	4	14	38	7	38
November	33	6	15	50	6	33
December	35	5	14	60	14	40
January	22	9	12	48	6	41
February	35	14	16	46	8	43
March	30	20	16	43	8	38
April	39	13	18	46	6	38
May	30	3	17	33	7	33
Total	455	82	14.9	46.0	7.0	38
			$P < .01$		$P < .01$	

*Study in subjects with upper respiratory tract infections (URI) and during an illness-free period.

The post operative setting has also been investigated. Johanson et al., in San Antonio prospectively followed surgical patients who had negative throat cultures for gram negative rods preoperatively (10). Post operatively there was an increased rate of colonization with gram negative rods which was specifically related to the "seriousness" of the surgery as indicated in Table 2 which demonstrates that major and prolonged surgery led to a higher incidence of post operative colonization.

TABLE 2

ASSOCIATION OF CLINICAL VARIABLES WITH POSTOPERATIVE RESPIRATORY TRACT COLONIZATION AND INCREASED ATTACHMENT OF *PSEUDOMONAS* TO BUCCAL CELLS *IN VITRO*

Variable	No. of Subjects	Colonized Postoperatively		Increased *Pseudomonas* Attachment Postoperatively*	
		(*no.*)	(%)	(*no.*)	(%)
Operation					
Major	13	8	62	10	77
Minor	19	3	16†	6	32†
Anesthesia					
General	23	7	30	9	39
Spinal	9	4	44	7	78
Duration of Surgery					
> 2 h	11	7	64	9	82
< 2 h	21	4	19†	7	33†
Blood Loss					
> 500 ml	6	4	67	4	60
< 500 ml	26	7	27	12	46
Underlying pulmonary disease					
Chronic bronchitis	10	8	80	8	80
None	22	3	14‡	8	36
Preoperative antimicrobial drugs					
Yes	19	9	47	11	58
No	13	2	15	5	38

* See text for definition.
† < 0.05 by Fisher's exact probability.
‡ < 0.001 by Fisher's exact probability.

Although it seems clear that certain clinical "insults" can increase the rate of colonization with gram negative rods the mechanism

of this occurrence and ultimately the clinical significance is not entirely clear. One proposed mechanism is that a delicate ratio of "normal" flora to "other" flora exists and that the "normal" flora "protect" the oropharynx from colonization by some "interference" mechanism. Sprunt and Redmon first proposed such a mechanism when they demonstrated that antibiotics which presumably altered this "balance" and decreased the "interference" by normal flora could be associated with a change in the flora of the oropharynx as shown in Figure 1 (11).

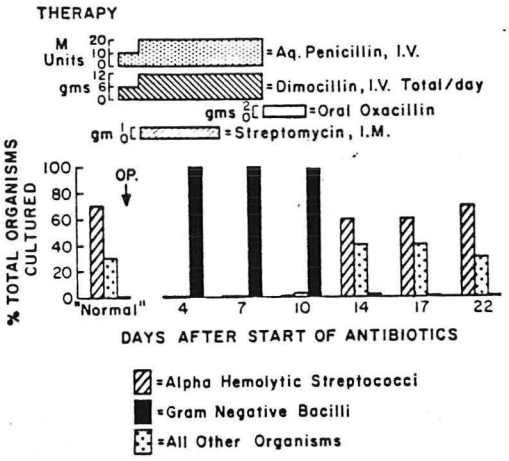


FIGURE 1. Organisms cultured from posterior pharynx of Patient L. D. before, during, and after therapy with antibiotics noted.

Soon thereafter other authors reached conflicting conclusions on the relevance of antibiotic therapy leading to "superinfection" of the lung with gram negative rod or other resistant organisms. Sanders et al., demonstrated a decreased amount of "growth inhibiting" organisms after antibiotics use in the oropharynx by an agar overlay technique (12). However, Johanson, Pierce, and Sanford in their original article had demonstrated no correlation of colonization with antbiotic use (Table 4) (3). In addition, Mackowiak and co-workers showed that bacterial interference was not an important variable in the increased isolation rate of gram negative rods from the throats of alcoholics and insuln dependent diabetes as shown next Figure 3 (13).

TABLE 4. *Prevalence of Gram-Negative Bacilli in Relation to Antibiotic Therapy.**

STUDY GROUP	PATIENTS RECEIVING ANTIBIOTICS			PATIENTS NOT RECEIVING ANTIBIOTICS		
	NO.	NO. WITH GRAM-NEGATIVE BACILLI	% WITH GRAM-NEGATIVE BACILLI	NO.	NO. WITH GRAM-NEGATIVE BACILLI	% WITH GRAM-NEGATIVE BACILLI
Moderately ill patients	14	5	36	67	21	31
Moribund patients	10	8	80	13	8	62

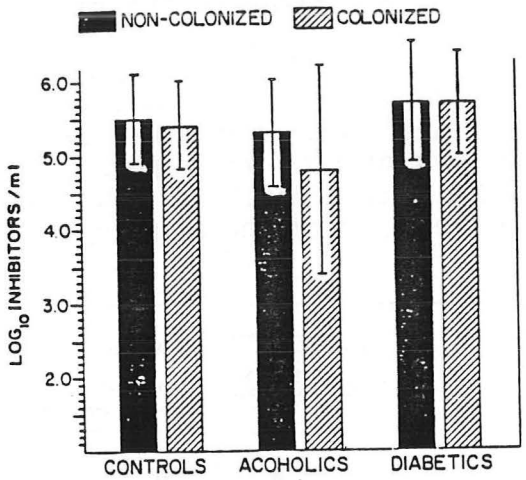


Fig. 3. Mean ± SD concentrations of total inhibitors in saline gargles from noncolonized and colonized subjects in each study population.

Thus, the importance of the use of antibiotics and bacterial interference in leading to a change in the oropharynx flora is controversial at best and has led investigators to look at host factors that might be involved in oropharyngeal colonization.

These investigators have focused on the adherence of binding of organisms to specific mucosal sites. Presumably an increased adherence would lead to increased colonization. Several clinical settings with a known increased incidence of colonization with gram negative rods and an increased incidence of pneumonia with gram negative rods have been evaluated in an effort to determine the relevance of adherence. Johanson, et al. initially documented the positive relationship of adherence and colonization in the intensive care unit setting and subsequently documented a similar relationship in the post operative setting as shown in the next Figure 1 (10).

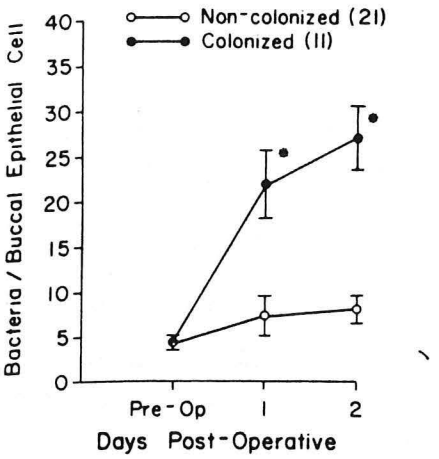


Fig. 1. Comparison of adherence of *Pseudomonas aeruginosa in vitro* to buccal cells of 11 patients who did and 21 patients who did not become colonized with gram-negative bacilli postoperatively. No patients were colonized preoperatively (Pre-Op). Significant differences by grouped t test ($p < 0.001$) are indicated by an asterisk (*).

In the same study they showed that the binding of concanavalin A to oropharyngeal cells was greater in patients who become colonized (Figure 5).

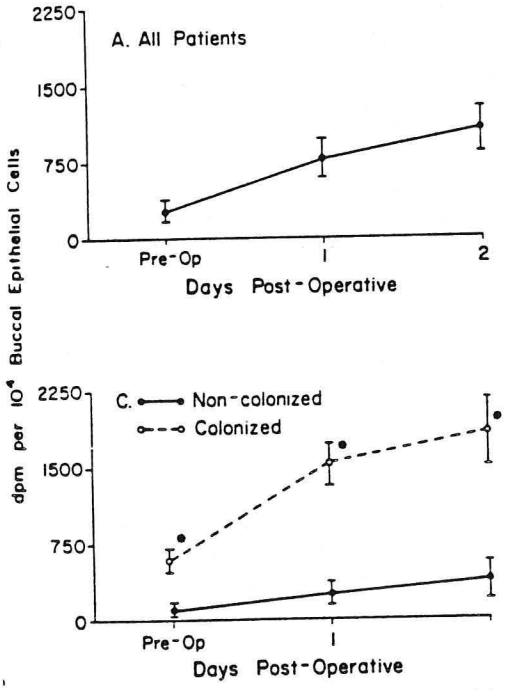


Fig. 5. Binding of ^{3}H-concanavalin A to buccal epithelial cells *in vivo*, expressed as dpm/10^4 cells. Data are shown for all patients (*A*) and separately for patients who did or did not become colonized postoperatively (*C*). Significant differences by grouped t test ($p < 0.003$) are indicated by an asterisk (*).

Since concanavalin A is a substance that binds to cells via a carbohydrate receptor they suggested that sugar containing adherence

sites on the cells surface were critical in bacterial binding to oropharyngeal cells. Feinstein et al., at Baylor College of Medicine, Houston looked at adherence in relation to influenza (15). They demonstrated as shown in Table 1 that after influenza infection there is increased adherence of Staph aures and gram negative rods but not of Strept pneumo.

Table 1. Bacterial adherence to pharyngeal cells from asymptomatic individuals and those with naturally acquired acute respiratory illness.

Organism	Asymptomatic	Infected
Control	3.5 ± 0.9	3.9 ± 0.9
Streptococcus viridans	3.6 ± 1.1	2.4 ± 1.0
Streptococcus pyogenes	3.2 ± 1.2	3.0 ± 1.1
Staphylococcus aureus	1.2 ± 1.2	10.1 ± 1.3*
Streptococcus pneumoniae type I	1.4 ± 1.0	1.2 ± 1.1
S. pneumoniae type III	1.2 ± 1.0	2.2 ± 1.2
Klebsiella pneumoniae	8.6 ± 1.7	5.0 ± 1.3†
Pseudomonas aeruginosa	7.9 ± 1.4	4.4 ± 1.0†
Serratia marcescens	8.5 ± 2.2	4.9 ± 0.9†

NOTE. Data are reported as the mean number of bacteria (± SE) adherent to 50 pharyngeal cells after subtraction of bacteria adherent to control pharyngeal cells in the case of gram-positive cocci.

* Significant difference in comparison with value obtained in asymptomatic subjects ($P < 0.001$).

† Significant differences in comparison with value obtained in asymptomatic subjects ($P < 0.01$).

After influenza vaccination as shown in Table 2 there was initially an increased adherence of Staph aures and Strep pneumonia on Day 1 and 2 followed by increased adherence of H. Flu days 3 and 4 with no change in gram negative rod adherence until day 5 and 6.

Table 2. Bacterial adherence to pharyngeal cells during experimentally induced infection with influenza virus vaccine.

Organism	Preinoculation	Day 1 and 2	Day 3 and 4	Day 5 and 6
Control	2.7 ± 0.8	3.8 ± 0.4*	3.6 ± 0.8*	3.3 ± 0.8
Streptococcus viridans	1.9 ± 0.7	1.0 ± 0.6	1.2 ± 0.9	1.1 ± 0.8
Streptococcus pyogenes	2.0 ± 0.6	1.8 ± 0.7	1.0 ± 0.6	1.2 ± 0.8
Staphylococcus aureus	1.0 ± 0.8	4.7 ± 1.6†	4.3 ± 1.3†	0.9 ± 0.9
Streptococcus pneumoniae type I	0.8 ± 0.9	1.8 ± 1.0*	2.0 ± 1.4*	0.3 ± 1.2
S. pneumoniae type III	1.2 ± 0.8	2.0 ± 0.9	2.3 ± 1.4	0.7 ± 1.4
Haemophilus influenzae	3.7 ± 0.6	5.8 ± 0.4	5.7 ± 1.3*	4.1 ± 1.6
Klebsiella pneumoniae	3.3 ± 1.0	4.3 ± 1.4	6.0 ± 1.7†	6.6 ± 1.5†
Pseudomonas aeruginosa	3.2 ± 1.1	4.2 ± 0.9	4.5 ± 1.0*	4.3 ± 1.3*
Serratia marcescens	2.5 ± 1.0	3.7 ± 0.9	4.0 ± 0.9†	4.3 ± 1.0†

NOTE. Data are reported as the mean number of bacteria (± SE) adherent to 50 pharyngeal cells after subtraction of bacteria adherent to control pharyngeal cells in the case of gram-positive cocci.

* Significant difference in comparison with base-line preinoculation values ($P < 0.01$).

† Significant difference in comparison with base-line preinoculation values ($P < 0.001$).

This data might be construed to fit with the known increased incidence of pneumococcal and staphylcoccal infections after influenza and the

problematic increased incidence of H. Flu and gram negative rods. Smokers have also been investigated. They have an increased incidence of pneumococcal adherence as shown in Figure 1 from Raman et al., from the University of Rochester (16).

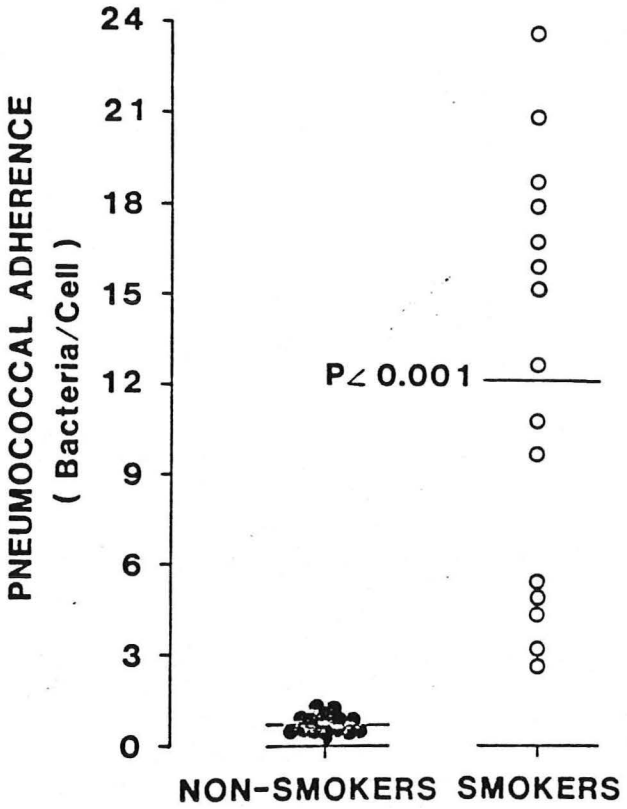


FIGURE 1. Pneumococcal adherence of 15 nonsmokers and 15 smokers.

In addition, these authors also showed that smoker's saliva increases the adherence of bacteria to non smoker's cells (Table 2) raising the issue of whether there is something in the saliva causing increased adherence.

Table 2—*Effect of Incubating Nonsmokers' Cells with Own, Other Nonsmokers', and Smokers' Saliva*

	Pneumococcal Adherence (Bacteria/Cell)		
	Own	Other Nonsmokers	Smokers
	0.4	0.9	13.3
	2.7	0.5	8.6
	1.0	0.8	5.5
	0.4	1.0	13.5
	0.6	0.9	4.4
	1.5	1.2	3.8
MEAN ± SD	1.1 ± 0.9	0.9 ± 0.2	8.2 ± 4.4

Feinstein and Musher from Baylor also showed that smokers have an increased adherence of staphylococcus and pneumococcus but not gram negative rods to their oropharyngeal cells and the that chronic bronchitics have an increased adherence of non type H. Flu (17).

The relevance of adherence of specific organisms has also been investigated. Pneumococcus has been demonstrated by several Swedish authors as shown in Table 4 to have increased adherence in patients with otitis media and not in these with sepsis, or menginitis (18).

TABLE 4. *Adherence to human pharyngeal epithelial cells of pneumococci in relation to clinical origin*

Diagnosis	Site of isolation	No. of strains	Mean adhesion (bacteria/cell)	% of strains with adhesion value >30	Level of significance (P)	Range (bacteria/cell)
Frequent acute otitis media	Nasopharynx	30	44	53	<0.01	0–152
Septicemia	Blood	30	18	17		0–167
Meningitis	Cerebrospinal fluid	30	22	20		0–88
Healthy carriers	Nasopharynx	22	39	36		0–342

This study might be extrapolated to indicated that increased adherence would (could) also be seen in other respiratory infections such as pneumonia. A pediatric study at Baylor College of Medicine demonstrated that non typeable H. Flu adhere much better than typeable strains potentially explaining the much higher incidence of pneumonia with non-typeable versus typeable (primarily Type B) (100).

The micromolecular basis of increased adherence has been further elucidated. Johanson and colleagues at San Antonio have looked at patients post CABG and also those with acute renal failure (29). They evaluated adherence and its association with fibronectin (a cell surface protein) concentration and salivary protease activity. Table 1 demonstrates increased adherence, decreased fibronectin concentrations and increased protease activity in the saliva in patients with acute renal failure compared to controls.

TABLE I

P. Aeruginosa Adherence, Buccal Cell Surface Fibronectin, and Protease Activity in Secretions in ARF Patients and Controls

	P. aeruginosa adherence*	Cell surface fibronectin‡	Protease activity§
ARF (10)	12.3±2.2¶	1.28±0.04¶	5.67±0.14¶
Control (10)	2.4±0.9	3.19±0.04	2.11±0.10

* Measured by radiolabel adherence assay. Data are given as mean±SEM number of bacteria attached per epithelial cell.

‡ Measured by radioimmunoassay; values represent mean ±SEM counts per minute ^{125}I-antifibronectin bound to 10^4 buccal cells times 10^{-3}.

§ Values represent mean±SEM counts per minute ^{125}I released from insoluble ^{125}I-fibrin matrix exposed to 1.0-ml secretions for 20 h at 37°C times 10^{-4}.

¶ Significantly different from the value for the controls ($P < 0.01$) by Student's t test.

These changes persisted throughout the entire episode of acute renal failure. In the patients post CABG they showed similar findings that

only lasted two days post operatively implying a transient insult caused by the surgery and consistent with the transient increase in gram negative rod colonization in this setting. They also showed in Table lll that saliva of these patients effected normal cells causing increased adherence and decreased fibronectin concentrations.

TABLE III
Effect of Salivary Fluid Treatment of Buccal Cells on P. Aeruginosa Adherence and Cell Surface Fibronectin Levels*

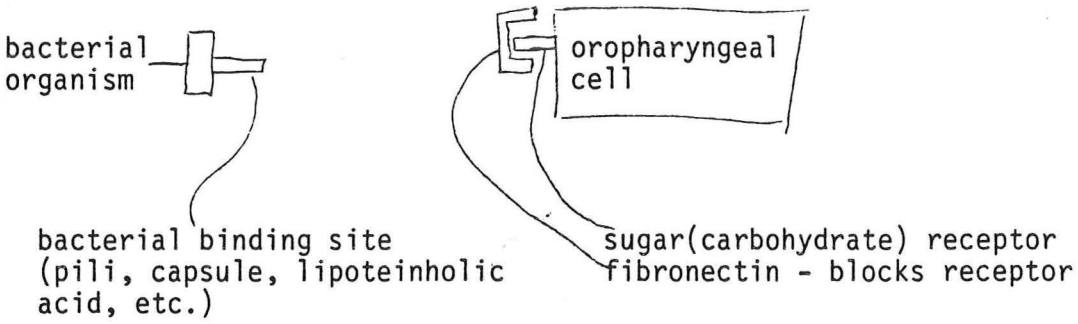
Source of salivary fluid‡	*P. aeruginosa* adherence§	Cell surface fibronectin‖
Normal control	2.4±0.7	3.7±0.4
Patient	16.7±3.0¶	1.15±0.03¶

* Epithelial cells scraped from buccal mucosa of a healthy adult.
‡ Sterilized saliva (protein concentration 10 μg/ml).
§ Measured by radiolabel adherence assay. Data are given as mean±SEM of five determinations of number of bacteria attached per epithelial cell.
‖ Measured by radioimmunoassay. Values represent mean ±SEM of five determinations of counts per minute ^{125}I-antifibronectin bound to 10^4 buccal cells times 10^{-3}.
¶ Significantly different from the value for the controls ($P < 0.01$) by Student's t test.

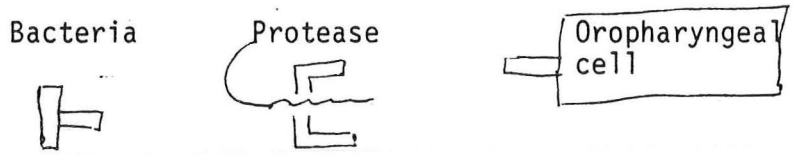
Hence, they proposed the following scheme in the Figure entitled "Pathogenesis of Increased Adherence" as illustrated: A respiratory tract cell has a sugar receptor to which an organism via its binding apparatus (pili, capsule, lipoteichoic acid, etc.) will bind (or adhere). Fibronectin, if present, blocks such attachment or binding of the organism to the cell and presumably prevents colonization and infection. In certain situations (to include patients with with acute renal failure, post CABG etc.) a protease or elastase of some nature (found in the saliva) presumably removes or destroys the fibronectin, "opens up" the sugar receptor on the cell and allows the bacteria to adhere to the cells causing increased colonization and presumed infection. Dr. Pierce and colleagues at this institution have further evaluated this thesis (20). They studied post CABG patients contrasting colonized and non colonized patients. As shown in Figure 1 patients who were colonized had increased salivary elastase activity for the first 48 hours post operatively and as shown in Figure 2 increased fibronectin digestive activity for the first 24 hours.

PATHOGENESIS OF INCREASED ADHERENCE

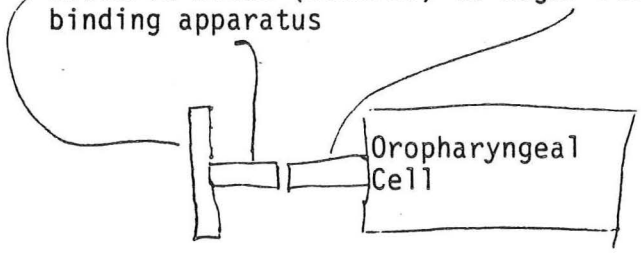
1. Normal



2. Illness
   A. Protease "destroy's fibronectin opening up sugar receptors on oropharyngeal cells



   B. Bacteria binds (adheres) to sugar receptor cell via its binding apparatus



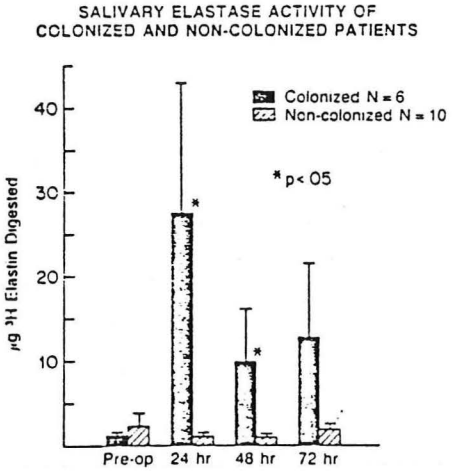


Fig. 1. Salivary elastase activity. Samples were obtained preoperatively and 24, 48, and 72 h postoperatively. Mean ± SEM values are shown for the patients who became colonized (*solid bars*) and the noncolonized patients (*hatched bars*). The colonized patients had increased elastase activity 24 h after surgery.

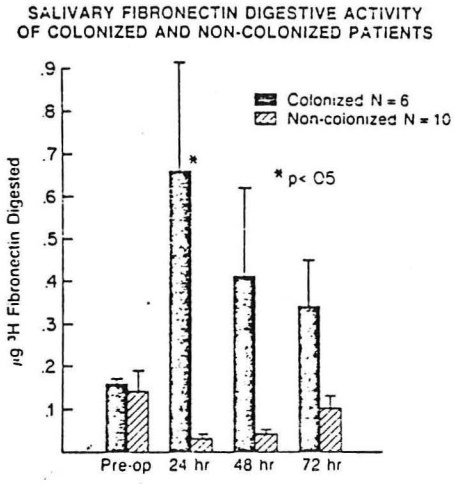


Fig. 2. Salivary fibronectin digestive activity. Samples were obtained preoperatively and 24, 48, and 72 h postoperatively. Mean ± SEM values are shown. The colonized patients had increased fibronectin digestive activity 24 h after surgery.

By the use of sophisticated inhibition studies they were then able to demonstrate as shown in Table 1 that it was polymophonuclear cells that were the source of the elastase and not macrophages or bacteria.

TABLE 1

THE EFFECT OF PROTEASE INHIBITORS ON SALIVARY FIBRONECTIN DIGESTIVE ACTIVITY*

Inhibitor Added	Inhibitor Specificity	μg H^3 Fibronectin Digested
None	—	0.83 ± 0.12
Z-glycine, 100 μM	Cathepsin G	0.75 ± 0.14
EDTA, 5 μM	Collagenase; macrophage and bacterial elastase	0.75 ± 0.09
DIFP, 20 μM	Serine proteases	0.25 ± 0.13†
Meo-succinyl, 25 μM	PMN elastase	0.43 ± 0.10†

Definitions of abbreviations: Z-glycine = Z-gly-leu-phe-CH_2Cl; EDTA = disodium ethylenediamine tetraacetate; DIFP = Di-isopropyl floro phosphate; Meo-succinyl = Meo-suc-ala-ala-pro-val CH_2Cl.

* Thirteen samples were tested. Values shown are mean ± SEM.

† $p < 0.01$ compared with no inhibitor.

Hence, colonization appears to be an important event an that "sets up" a patient for pulmonary infection with particular organisms when they aspirate. The cause of increased colonization is also difficult to evaluate. It would appear that antibiotics and bacterial interference play a minor role at best. The majority opinion at the present time

seems to be that increased bacterial adherence occurs due to decreased fibronectin blocking of cell associated receptors secondary to increased polymorphonuclear cell elastase activity. Increased adherence then leads to subsequent colonization by the adherent organisms. It should be noted that not all patients who have increased adherence become colonized but very rarely do patients without increased adherence become colonized. In addition, most of the work concerning those mechanisms has been performed in many clinical settings (post-op, acute renal failure, ICU, etc.) with gram negative rods as the study organism. Extrapolation of the results to other clinical settings and bacterial organisms (such as "normal" oral flora, etc.), is debateable at present. However, with these limitations in mind it would appear that the patholophysiology of the usual case of community acquired pneumonia would probably be as schematically drawn.

PATHOPHYSIOLOGY OF COMMUNITY ACQUIRED PNEUMONIA

It is important to comment on the immunologic states of the alcoholic before reviewing individual organisms that might infect these patients. The immunology of alcoholism is very complex, extensively studied, but poorly understood and will be mentioned only briefly (93-94). There are multiple aspects of host immunity that are altered in alcoholics. These include cell mediated immunity, complement, white blood cell quantitative counts and quantitative function and humoral immunity. Unfortunately the clinical relevance of these changes and their causes are problematic due to the complexity of the physiologic abnormalities in the alcoholic that potentially impact on host immunity. Among the principle physiologic variables in the alcoholic that effect immunity are:

A. Whether the patient is acutely intoxicated.

B. Whether the patient has liver disease.

C. Whether the patient has protein calorie malnutrition.

D. Whether the immune "memory" being tested is to recall old antigens or develop memory for new antigens.

Multiple systemic and local defects as relate to the pulmonary immunity have been documented but are of questionable relevance. However, it is accepted by all authors that alcoholics have an increased incidence of aspiration which would presumably lead to an increased incidence of pulmonary infection. The published literature would appear to confirm this assumption of an increased incidence of pneumonia in alcoholics.

Tapper et al., in their extensive review of the literature concluded that there was an increased in bacterial pneumonia and tuberculosis in alcoholics and that bacterial pneumonia was the number one cause of admissions in alcoholics (95). Nolan, et al., noted on a teaching service at Yale that alcoholics had an increased incidence of acute bacterial pneumonias and TB versus nonalcoholics (96). Schmidt and de Lint in Oslo also showed that pneumonia caused 3-5 times the expected number of deaths in alcoholics (97). Capps and Coleman at Cook County in 1911-17 and Painton, et al., in Buffalo City Hospital noted in the 1920's and 1930's an increased incidence of and mortality rate due to pneumonia in alcoholics (57). There clearly is an increased incidence of tuberculosis in alcoholics. At the Fulton County Hospital District tuberculosis clinic in Altenta it was shown that 50% of the patients were alcoholics (98). At Grady Memorial Hospital in Altanta, 60% of patients with tuberculosis were alcoholics. The reason for the increased incidence of TB in alcoholics is not clear and authorities debate whether or not it is due to decreased immunity to the organism or an increased exposure to the organism due to the lifestyle of alcoholics. The literature is also clear that if alcoholic patients take their anti-Tb drugs (which they unfortunately frequently do not) there is no difference in their morbidity and mortality compared to non-alcoholics (99).

The potential organisms causing this increased incidence of community aquired pneumonia in alcoholics are vast. The organisms to be discussed in detail will be those which the literature consistently demonstrates to occur at an increased incidence in the alcoholic. These organisms are pneumococcus, hemophilus, tuberculosis, anerobes and klebsiella. Tuberculosis has been covered in the previous paragraph.

Since Klebsiella is the most "famous" organism infecting alcoholics the data on it will be reviewed first. Klebsiella pneumonia is the most common aerobic gram negative rod believed to cause community acquired pneumonia. Its incidence is probably overestimated by the clinician due to the presumed unique clinical course that is emphasized in medical school and detailed in the attached table. A review of the published literature in chronologic order with the more recent literature in table form is quite revealing.

KLEBSIELLA PNEUMONIA
CLASSIC FEATURES

1. Clinical
   - A. Alcoholic Male
   - B. Sudden Onset
   - C. "Currant Jelly" Sputum
   - D. Toxic Appearance
   - E. Rapidly Fatal

2. Radiographic (46)
   - A. Single lobe - frequently upper
   - B. Bulging fissue
   - C. Sharp margin to infiltrate
   - D. Frequent cavity formation

KLEBSIELLA PNEUMONIA - OLD HISTORY

1882 - Friedlander - First case described.

1886 - Fraenkel - States pneumococcus most common cause of pneumonia and Klebsiella rare.

1902 - Philli - First positive sputum and blood culture isolate.

1908 - Apelt - Eight cases. Two cases with positive blood culture and 1 survival.

1915 - Sisson - First large series of 37 cases.

1919 - Zander - Outbreak in German prison camp - data doubted.

1930 - Alcott - Three blood culture positive cases (Total reported to date - six).

A. History

1. 1882 - Friedlander described a case of Klebsiella pneumonia pneumonia and believed that this was the most common cause of bacterial pneumonia.

2. 1886 - Frankel established that pneumococcus frequently caused bacterial pneumonia and stated that klebsiella was a rare cause.

3. 1886 - Weiselbaum confirmed that five to eight percent of bacterial pneumonias were due to klebsiella.

4. 1902 - Phillipi documented the first case with positive a sputum culture and a positive blood culture.

5. 1908 - Apelt reported eight cases, two with positive blood cultures and one patient recovered.

6. 1915 - Sisson reported 37 cases.

7. 1919 - Zander reported outbreak in German prison camp - data doubted.

8. 1930's - Alcott reported three blood culture positive cases bringing to six the total reported to date.

B. Recent literature - Data also attached in Tables.

KLEBSIELLA PNEUMONIA PNEUMONIA

Location/Yr	# Cases(Per Year)	Sepsis(Per Year)	% Alcoholic	Prognistic Factors	Associated Tuberculosis	% Death
1937 - Bellevue,NYC (33)	32 (3)	9 (2)	--	Not Bacteremia	--	97%
1927-36 - Harlem Hospital, NYC (34)	41 (4)	27 (3)	--	--	--	83%
1936-9 - Harlem Hospital NYC (36)	37 (10)	9 (3)	--	--	--	--
1940 - Bellevue and NY Hosp, NYC (36)	51	25	37%	--	3/51	50% (83% Complications)
1941 Wash Univ St. Louis (37)	1.5% of all pneumonia				--	82%
1944-9 Bellevue (38)	(3/yr)		Positive association	--	3	--
1951 - Harborview, Seattle WA (39)	(11)	(5)	--	--	--	--
1952-3 - Philadelphia General (40)	(2-4/yr)		--	--	--	--

KLEBSIELLA PNEUMONIA PNEUMONIA

Location/Yr	# Cases(Per Year)	Sepsis(Per Year)	% Alcoholic	Prognostic Factors	Associtaed Tuberculosis	% Death
1955 - D.C. General Washington, D.C. (41)	22 (9)	8 (3)	70%	Bacteremia ETOH	1	50%
1955-65 - Hennepin County, Minneapolis (42)	11 (1)	3 (1 q 3 y)	80%	--	2	50%
1948-58 - Hines VA-Chicago (43)	(4.5/yr)			--	10%	--
1937-56 - Cinncinati General (44)	(2/yr)	(1)	60%	Bacteremia	--	--
1961-D.C. General (45)		(2)	---		1	--

Narrative in order of data, authors, hospitals. 1. 1937 - Solomon - Reviewed all pneumonia at Bellevue Hospital, New York City (33). He definitively described the "classic" presentation of acute Klebsiella pneumonia pneumonia. Thirty-two cases were seen in eleven years or three per year out of 5,000 total pneumonias at Bellevue during that time (0.6% of all pneumonias). Positive blood cultures were found in 73% of patients. Six out of thirty-two patients developed abcesses/cavities, six out of thirty-two developed pleural effusions (two of the six were empyemas), and three out of thirty-two developed CNS spread.

2. 1937 - Bullowa - Harlem Hospital 1927-1936. The authors described forty-one cases (four to five per year) which constituted 1.1% of all pneumonias at that hospital over that time frame (34). Seventy-six percent of the patients had positive blood cultures and six out of forty-one had CNS spread.

3. 1939 - Pearlman and Bullowa - Harlem Hospital 1936-1939. They reported thirty-seven cases (ten per year) which constituted 1.5 percent of all pneumonias with three per year with positive blood cultures (35).

4. 1940 Hyde = and Hyde - Bellevue/New York Hospital. These authors reported fifty-one patients forty-five percent of whom positive blood cultures (36). Fifty percent of the patients died and only one out of six lived without complications. Complications noted were fifteen out of fifty-one who developed abcesses, two out of fifty-one with CNS spread, two out of fifty-one pericarditis and five out of fifty-one developed pleural effusion with three of these being empyemas. Three of fifty-one developed reactivation tuberculosis. Nineteen out of fifty-one were alcoholic.

5. 1941, Julianelle, et al. - Washington University, St. Louis. The authors noted Klebsiella to cause 1.5 percent of all pneumonia (37). The patients had positive blood cultures 50 percent of the time and a mortality of 82 percent with a five to ten percent incidence of development of a lung abscess.

6. 1944-1949 Wiley, et al, Bellevue Hospital. The authors reported three cases per year versus 0.3 percent per year a nearby private hospital (38). There was a positive association with alcohol. One out of three patients developed empyema, antibiotics decreased mortality and three patients reactivated their tuberculosis.

7. 1951 Kirby et al.- Harborview Hospital Seattle. The authors reported eleven cases in one year, five with positive blood cultures (39). Only two blood culture positive Strep pneumonas pneumonias occurred during the same time.

8. 1952-53 Weiss, et al. - Philadelphia General. The authors evaluated all patients with pneumonia with positive sputum cultures (40). Blood cultures were not systematically evaluated. They noted an incidence of two to four cases per year.

9. 1955 Limson et al. - D.C. General Hospital, Washington, D.C. The authors noted twenty-two cases in two years with fifteen out of the twenty-two being alcohol associated (41). Thirteen of the patients had acute disease and eight of these thirteen had positive blood cultures. All patients who died were alcoholics.

10. 1955-65 Hoffman, et al., Hennepin County Minneapolis. The authors noted one case per year, three out of eleven with positive blood cultures and a 50 percent mortality rate (42). Seven of eleven patients also had Strep pneumonia in their sputum. Nine out of eleven patients were alcholics and two out eleven with positive blood cultures also had reactivation tuberculosis.

11. 1948-58 Lampe, Hines VA Medical Center - Chicago. The authors noted a incidence of 4.5 cases per year by sputum culture criteria which were 0.65 percent of all pneumonias (43). Ten percent of the patients also had active tuberculosis.

12. 1937-56 - Hamburger et al. - Cinncinati General Hospital. These authors noted two cases per year by sputum culture criteria and one by blood culture criteria (44). Sixty percent of these patients had positive blood cultures and had a greater mortality rate then those with negative blood cultures. Seven percent developed lung abcesses.

13. 1961 - Ollsson and Romansky, D.C. General. The authors noted two cases per year by positive blood culture criteria and noted a single case of tuberculosis reactivation (45).

The classic paper on the x-ray findings was published by Felson et al., from the University of Cinncinati (46). The authors noted single lobe disease with a bulging fissure in 60 percent of the cases, sharp margins of the infiltrates in 64% versus and that pulmonary abcesses developed in thirty-three percent of the patients with Klebsiella pneumonia pneumonia by sputum and blood culture criteria. These rates were all markedly greater than in patients with Strep pneumonia pneumonia by blood culture criteria.

Thus, Klebsiella pneumonia overall would appear to be a rare infection. In public hospitals there are 1-2 bacteremia cases per year and possibly twice that number total. They constitute about 1% of all pneumonia and are associated with alcoholism which is also possibly a negative prognostic finding. The development of lung abcesses/cavities and pleural effusion is substantial and there is a distinct association with tuberculosis.

The clinical spectrum could be characterized as follows and tabulated in the accompanying chart.

KLEBSIELLA PNEUMONIA
SPECTRUM OF ILLNESS

1. Acute pneumonia
2. Cavity Disease - follows acute pneumonia
   A. Pulmonary gangrene
   B. Solitary cavity
3. Bacteremia
4. Other complications

1. Acute pneumonia.

2. Cavity disease - follows acute pneumonia.

   a. Pulmonary gangrene as reported by O'Reilley and Danner et al.(47-48). Characterized by rapid development over days of multiple small abcesses that rapidly destroy lung. Etiology reported as primarily Klebsiella pneumonia and occasionally anerobes and rarely Strep pneumo. Treatment recognized as antibiotics with question of whether radical surgery (i.e., pneumonectomy) is necessary due to high incidence of vascular thrombosis still controversial.

   b. Single Cavity - primary differential diagnosis is tuberculosis (note association of TBC with Klebsiella pneumonia) and anerobes. Klebsiella usually reported as "thin walled" and tuberculosis as thick walled.

3. Bacteremia at least 33%.

4. Other complications - CNS spread, empyemas, etc.

OTHER GRAM NEGATIVE RODS

Other gram negative rods are rarely reported to course community acquired pneumonia. Tillotson and Lerner reviewed their experience in 1963-64 at Detroit Receiving Hospital (49). These authors reported an incidence of 3.6% of all pneumonias with two thirds of the patients being alcoholic. Forty-five percent of blood cultures were positive. Twenty-one out of thirty-eight patients developed pleural effusions and eleven were empyemas. The mortality rate was forty-five percent and alcohol had no influence on this rate. One-half of their patients died of non pneumonic causes. No other authors either before or subsequently found such a high rate of community acquired gram negative rod pneumonia. Coker at a VA Hospital at the University of Alabama noted three cases per year, and one-half were alcohol associated. while Phair at VAMC Lakeside, Chicago in 1979-80 noted a similar incidence (55-56). Kass in 1961-1966 at Boston City Hospital evaluated 100 consecutive cases of gram negative sepsis and only three were due to pneumonia (54). Berk from East Tennessee State University reported seventeen cases of E. Coli pneumonia with thirty-three percent having positive blood cultures (50). Four out of the five cases with positive blood cultures were nosocomial and it is unclear what fraction of the others were also nosocomial pneumonias. Jonas and Cunha from New York City reported nine cases of bacteremic E. Coli pneumonia in two years (51). Two thirds were nosocomial pneumonia and an ill defined percentage of the rest were receiving antibiotics, steroids, or cytotoxic agents. Tillotson and Lerner, reported eight cases of E. Coli pneumonia with sepsis (49). "Few" were nosocomial. There was a high association with positive E. Coli isolates other areas of the body (i.e., urinary peritoneal fluid, etc.) raising the issue of whether these pneumonias were due hematogenous spread of the organism to the lung. Pseudomonas aeruginosa pneumonia is almost exclusively found as a nosocomial infection or as an infections in neutropenic hosts. Hoogwerf and Kahn did report one community acquired case in their extensive review of the topic (52). In addition Moretz, and Grieco reported one community acquired pneumonia due to Serratia marscens (53). Other isolated case reports due to these and other gram negative rods are scattered in the literature but their significance is difficult to judge.

The pneumococcus is the most common organism causing community acquired pneumonia in both the alcoholic and non alcoholic and will be reviewed next. The epidemiology of the organism has been well studied. Lipsky et al., at the Seattle VAMC evaluated all patients in the general medicine clinic who had positive cultures for Strep pneumo over a fourteen month period (64). Fifty percent of these patients had infections and with the organism and were designated the patient group. They were matched with other patients from the general medicine clinic with no positive cultures who were the controls. The incidence of pulmonary infection over five years was 6.3 per 1000 year in the patient group. Potential risk factors associated with infection were COPD, CHF, seizures, CVA and dementia by multivarite analysis. They speculated that the reasons for these positive association was gross aspiration in

these patients with CHF, seizures, CVA and dementia and increased adherence and decreased pulmonary clearance in those with COPD. The lack of a positive association with alcoholism was notable. There have also been several well described "epidemics" of pneumococcal disease. One occurred in a VA Hospital in Massachusetts in 1936 and a subsequent one in Western Massachusetts in 1938 (65-66). The latter outbreak was more throughly studied. It was found that the carriage rate for families of patients with disease was 12 percent and those with no disease 1.4 percent and that the attack rate in families of patients was 15 - 30 percent 0-2% in control families. The attack rate was thirty-three to fifty-six percent in children less than age 4 indicating that this is a mildly contagious organism particularly in young children. In 1980 there was an epidemic (40 cases in five months) in patients in Boston in a men's shelter with a high incidence of alcoholism (67). The authors cultured all the men in the shelter and noted 60 percent carriage rate. Although there was no control group in the study the authors site a 1-2 percent carriage rate from the literature in normal adults in the community. An excellent epidemiologic survey was done in Syracuse where the authors demonstrated over a six year period that forty percent of family members surveyed had at least one positive culture with 85% of positive cultures being in persons age less than 20 (68). The incidence was higher in families with children but they were unable to identify any relationship between carriage and disease. Thus, the organism does appear to be contagious in families and other closed settings (to which alcoholics would be expected to be exposed).

It is well accepted that pneumococcal pneumonia is the most common course of adult pneumonia especially in alcoholics. Thus, the observed incidence of clinical disease appears to correlate with the epidemiology of the organism. The attached table sumarizes the literature on pneumoccal pneumonia occurring in public hospitals such as Parkland.

PNEUMONOCOCCAL PNEUMONIA

Location/Years	# Cases	# Sepsis	Sepsis/Yr	% Alcoholic	Px Fx	% Death Sepsic Patients
Harlem Hospital, 1928-33(71)	1725	431	70	--	Sepsis	77%
Boston City, 1929-35(72)	1586	582	50	--	Sepsis,age,%lung involved	--
Cincinnati General,1936-50(73)	3215	733	48	--	Sepsis,age,purulent complications	
Johns Hopkins, 1946-52(74)	358	69	11	33%	age,% lung induced sepsis,leukopenia	
Kings County, 1952-62(76) Brooklyn	1130	339	40	--	% lung involved, sepsis	25%
Cook County, IL, 1967-70(75)	--	262	115		age, DM, uremia, cirrhosis	28%
Charlston City, SC, 1974-70(77) 4 Hospitals		44	22	42%	--	18%
Bellevue, NYC, 1922-81(78)		145	16	--	age, ETOH (patients less than age 64)	
Grady and VAMC, Atlanta,1980-81(79)		85	85	56%	leukopenia,thrombocytopenia	22.6%
Kings County, 1979-81(80)		6 (ARDS)			ARDS	
Sweden, 1964-80(81)		305	19	32%	age, ETOH	15%
Harborview, 1974-80(82)		120	20	70%	age, leukopenia	36%

Pneumococcal pneumonia is usually defined by positive sputum culture of some nature with an infiltrate and/or positive blood cultures. It should be noted the techniques for blood cultures differ markedly and have improved over time. It should also be noted that the demographics of these public hospitals changed over time and the number of total beds are ill defined in most cases. The incidence of pneumococcal sepsis per year varied between 115 at Cook County in 1967-70 to only 11 at Johns Hopkins from 1946-1952 and 16 at Bellevue from 1932-1981. The assocation with alcoholism is not mentioned in most older series but is positive in the more recent series varying from 32 to 76 percent. Prognostic factors for pneumococcal pneumonia are reasonably consisent, Sepsis clearly decreases survival rate. Other frequently mentioned negative prognostic factors are older age, amount of lung involved, purulent complications, (empyema, meningitis, etc.), decreased white count, and alcoholism, and cirrhrois sporadically. It should be noted that the association of bad prognosis with alcoholism frequently occurs in patients with a "syndrome" which is characterized by overwhelming sepsis/pneumonia, neutropenia, and ARDS. The death rate with sepsis understandably was very high in the preantibiotic era. In the antibiotic era it has decreased and very consistently ranged from fifteen to thirty percent with a median of approximately twenty-five percent. Interestingly, it has not declined since the 1950's. The reason for this lack of decline is poorly defined.

As previously noted aspiration is the "final pathway" for the development of pneumonia. Thus all patients with pneumonia technically have aspiration pneumonia. However, some patients have a disease process that is associated with not infrequent gross or massive aspiration (i.e., alcoholic, seizure states, etc.) that increases the chance for development of clinical pneumonia. A review of the "aspiration literature" is potentially informative. Lorber and Swenson at Temple University Hospital published their observations on both community acquired and nosocomial aspiration pneumonias in 1974 (83). These authors defined their cases as those patients who had a history of aspiration of oropharyngeal contents and clinical and x-ray evidence of pneumonia in a dependent pulmonary segment. Etiologic agents were determined by isolates from blood, pleural fluid and by transtracheal aspiration (greather than 10^6 organisms/cc). Two-thirds of these patients were alcoholics. Twenty-four patients had community acquired pneumonia and 23 nosocomial. The adjacent Table 1 sumarizes their data. Twenty-one out of twenty-four patients with community acquired pneumonia had anerobes isolated, thirteen exclusively, and they had three patients with positive blood cultures.

Table 1. Prevalence of Aerobes and Anaerobes in Aspiration Pneumonia

Aspiration Pneumonia	Total	Aerobes*	Aerobes† plus Anaerobes	Anaerobes
	←	— no. —		→
Community-acquired cases	24	3	8	13
Hospital-acquired cases	23	15	6	2

* Includes strict aerobes and facultative anaerobes.
† Includes only strict anaerobes.

Only one patient had aerobes exclusively isolated and had two positive blood cultures, one of which was Klebsiella and one of which was Strep pneumonia. Bartlett and Feingold in another carefully done study with similar bacterologic techniques also further characterized aspiration pneumonia and published similar data in which they analyzed 30 cases (84). Nine had mixed infections and two had only aerobes isolated by transtracheal aspirate, and 19 anerobes only (see Table 11).

TABLE II Microbiologic Results

	No. of Patients		
	Hospital-Acquired Infections	Community-Acquired Infections	Total
Anaerobes only	6	19	25
Anaerobes and aerobes	16	9	25
Aerobes only	2	2	4
Total	24	30	54

The group from Johns Hopkins have also published a review article which summarizes several other series in the literature as noted in the attached Table 1 (85).

TABLE I

Bacteriology of Aspiration Pneumonia and Primary Lung Abscess

Type of infection	Reference	Specimen source*	No. studied	No. with anaerobes
Aspiration pneumonia	9, 10	TTA, PF	70	61 (87%)
	11	TTA	17	17 (100%)
	12	TTA	47	29 (62%)
	13	TTA†	74	69 (93%)
Lung abscess	2, 14	TTA, PF	57	53 (93%)
	15	Transthoracic aspirate	26	22 (85%)
	13, 16	TTA†	10	19 (90%)

* TTA = transtracheal aspiration, PF = pleural fluid.
† Children aged 2 months to 18 years.

The predominance of anerobes in aspiration pneumonias is apparent.

Thus anaerobes clearly cause a significant amount of pulmonary disease, particularly in patients who are prove to "massive aspiration" aspiration. This makes sense because anerobes are the dominant organism in "normal flora". As previously noted the relevance of isolation of aerobic gram negative rods from the alcoholic's oropharynx and the lack of pneumonia due to these bugs is difficult to reconcile. However, sometimes the presence of "massive" aspiration is not clinically obvious and anerobes are not considered as likely a cause of individual infection as they should be. In addition, it should be noted that "massive aspirations" is not particularly common even among aspiration prone patients.

From an anatomical viewpoint anerobes can cause several different types of pulmonary disease such as pneumonitis (to include necrotizing pneumonia), abcesses, and empyemas. As a preliminary overview, the adjacent Table 2 from a review in 1987 by Bartlett gives an excellent perspective of the relative inportance of anaerobic pulmonary infections (86).

Table 2—*Incidence of Anaerobic Bacterial Infection of the Lung and Pleural Space**

Clinical Setting	No. Studied	No. with Anaerobes	Anaerobes Exclusively
Community-acquired pneumonia			
Ries et al[32]	89	29 (33)	17 (19)
Pollack et al[19]	74	16 (22)	. . .
Hospital-acquired pneumonia			
Bartlett et al[27]	159	56 (35)	11 (7)
Pulmonary abscess			
Bartlett et al[12]	57	53 (93)	32 (56)
Beerens and Tahon-Castel[25]	26	22 (85)	20 (77)
Brook and Finegold[29]	10	9 (90)	1 (10)
Aspiration pneumonia			
Bartlett et al[12]	70	61 (87)	32 (46)
Gonzalez-C and Calie[31]	17	17 (100)	6 (35)
Lorber and Swenson[18]	47	29 (62)	15 (32)
Brook and Finegold[30]	74	69 (93)	2 (3)
Empyema			
Bartlett et al[34]	83	63 (76)	29 (35)
Beerens and Tahon-Castel[25]	45	23 (51)	16 (36)

*Table data are numbers of cases; numbers within parentheses are percents.

Anaerobic Bacterial Infections of the Lung *(John G. Bartlett)*

The best article on anaerobic pneumonitis was published by Bartlett and Feingold in 1979 (87). They evaluated and compared patients who had pneumonia with only anerobes isolated from transtracheal aspirates to those who had pneumonia with only pneumococcus recovered from a transtracheal aspirate. The attached Table 1 shows the significant characteristics of and differences between the two types of pneumonia.

TABLE 1

CLINICAL FEATURES OF ANAEROBIC BACTERIAL PNEUMONITIS AND PNEUMOCOCCAL PNEUMONIA

	Anaerobic Bacterial Pneumonitis (46 patients)	Pneumococcal Pneumonia (46 patients)	Significance of Difference*
Age,† years	53 ± 2.3	61 ± 2.5	NS
History of chills	0	21 (46%)	< 0.001
Duration of symptoms before presentation† days	4.5 ± 0.7	2.6 ± 0.4	< 0.02
Associated condition			
Predisposition to aspiration	27 (59%)	11 (23%)	< 0.001
Bronchogenic neoplasm	8 (17%)	3 (6%)	< 0.05
Peak fever,† °F	102.3 ± 0.2	102.2 ± 0.2	NS
Peripheral leukocyte count, no. X 1,000/mm^3	15 ± 1	16 ± 0.9	NS
No. lobes involved by chest film†	1.4 ± 0.1	1.3 ± 0.1	NS
Putrid sputum	8 (18%)	0	< 0.05
Bacteremia	0	7 (15%)	< 0.05
Subsequent development of abscess on chest film	9 (20%)	0	< 0.001
Outcome			
Cured	40 (83%)	39 (85%)	NS
Died	6 (17%)	7 (15%)	NS

*Significance of the difference between the 2 groups is expressed as a P value for chi square analysis or t test of independent means; NS = not significant, i.e., P > 0.05.

†Values are given as mean ± SE.

Significant differences between the two groups included the incidence of chills, duration of symptoms before presentation (4.5 days in the anerobic and 2.6 days in the pneumococcal groups), presence or absence of diseases associated with aspiration (25% of patients with anerobic and 13% with pneumococcal pneumonia were alcoholics), presence of bronchogenic carcinoma, incidence of putrid sputum (which is low even in the anerobic group) incidence of bacteremia (fifteen percent in pneumococcal pneumonia patients versus 0 percent in the anerobic group) and the subsequent development of abcesses on chest films (twenty percent in the anerobic group versus zero percent in the pneumococcal). Significant similarities include white count, height of fever, number of lobes involved, and their outcome (fifteen percent mortality in both groups). It should be noted that in the anerobic group the fever persisted for 4.8 days versus 2.6 for these with pneumococcal disease after therapy was begun. It is clear that even though differences between the two types of pneumonia can be demonstrated it would be quite difficult to distinguish which type an individual patient had when they presented to the hospital. Another article which evaluated the relative incidence of anerobic disease were published in 1974 by Ries et al., from the Medical College of Pennsylvania (88). The primary problem with this study from the viewpoint of this presentation was that it is unclear what the percentage of the patients had nosocomial versus community acquired pneumonia (although it is implied most had the latter) and the authors did not rigorously define their criteria for pneumonia and/or a positive transtracheal aspirate. Overall they looked at 250 patients admitted with "pneumonia" 134 of whom had transtracheal aspiratates performed. Of these 134 patients 45 were determined not to have pneumonia. Six had COPD, one had tuberculosis, and four had nonbacterial pneumonia and 28 no bronchopulmonary infection. Thus a total of 89 patients were ultimately evaluated. The organisms isolated by transtracheal aspirate in predominant numbers were as follows: Strep

pneumo-36, gram negative rods 9, anerobes 29, Staph aureus, 4, and H. Flu 3.

There is also a significant amount of published data evaluating the efficacy and the clinical relevance of obtaining cultures from protected bronchoscopes which is applicable to anaerobic lung disease. The most imformative article was from the University of South Alabama where the authors evaluated patients with lower respiratory tract infections (presumed community acquired) with the protective bronchoscope performing quantitative cultures and correlating these data with positive blood cultures (89). They defined a positive broncoscopic culutre as greater than 10^3 organisms/cc. The adjacent Table 2 summarizes their data.

TABLE 2. Bacterial species isolated at $\geq 10^3$ CFU/ml from cases of pneumonia

Isolate	No. of isolates	Isolated as:	
		Single agent	Mixed flora
S. pneumoniae	38	24	14[a]
H. influenzae	17	6	11[a]
Other isolate	3	3	0
Aerobic-anaerobic mixed flora without a traditional pathogen	16	0	16

[a] Ten of these had anaerobes.

Overall there were 24 patients with pure Strep pneumonia isolated and 14 with Strep pneumo in mixed culture, There were 6 pure and 11 mixed H. Flu isolates but no pure and 16 mixed anaerobe isolates. Twelve of thirteen patients with positive blood culture had the same organism isolated from the bronchoscopic evaluation in significant numbers. Thus, this technique, though cumbersome, appears accurate and valid and confirms that anaerobes cause a significant amount of community acquired pneumonitis.

Necrotizing pneumonas are presumed to begin as routine pneumonitis and, for multiple reasons, the organisms overwhelm the host defensive mechanisms and progress and rapidly destroy large amounts of lung. Bartlett and Feingold again have presented the best data on this subject as relates to anerobic infections (90). They defined nectotizing pneumonias as multiple areas of small areas of cavitation within one or more pulmonary segments or lobes. The relative incidence of nectrotizing pneumonia as related to other anerobic lung diseases is shown in the attached table. The clinical characteristics of the infection as summarized in the attached Table 2 included a duration of symptoms prior to the onset of disease greater than seven days in 69% of patients with a mean of 23±29 days, a time for cavitation to appear after the onset of pneumonitis of 16±6 days and a mortality rate of eighteen percent of patients.

TABLE 2

ANALYSIS OF 28 CASES OF NECROTIZING PNEUMONIA

Findings	No. of Cases	% of Cases
Clinical features		
Mean age ± 1 SD (years), 54 ± 12		
Concurrent empyema	10	36
Underlying conditions		
Periodontitis (18 patients evaluated)	8	44
Suspected aspiration	18	64
Bronchogenic carcinoma	3	11
Miscellaneous	4	14
Fever (> 99.6° F)	28	100
Mean peak temperature ± 1 SD (° F), 102.4 ± 1.2		
Weight loss due to infection	12	43
Mean weight loss ± 1 SD (pounds) (12 patients) 23 ± 7		
Putrid discharge (sputum or empyema fluid)	17	61
Duration of symptoms prior to presentation		
> 7 days	19	69
Mean ± 1 SD (days), 23 ± 29		
Median, days, 10		
Hospital-acquired infection	8	29
Clinical laboratory findings		
Peak peripheral leukocyte count		
> 9,000/mm^3	27	96
Mean ± 1 SD (X 1,000/mm^3), 24.2 ± 13.4		
Hematocrit (< 38%)	18	64
Mean ± 1 SD (%), 35.6 ± 4.7		
Roentgenographic findings		
Abscesses on initial roentgenogram	18	64
Pneumonitis on initial roentgenogram, followed by cavitation	10	36
Time for cavitation to appear following documented aspiration		
Mean ± 1 SD (days) (8 patients) 16 ± 6		
Location of principal lesion		
Right upper lobe, anterior segment	2	
posterior segment	5	
Right middle lobe	3	
Right lower lobe, superior segment	5	
basilar segments	8	
Left upper lobe, apical posterior segment	4	
Left lower lobe, superior segment	9	
basilar segments	4	
Response to therapy		
Duration of fever*		
Mean ± 1 SD (days), 12 ± 16		
Median, days, 5		
Time for cure*†		
Mean ± 1 SD (days), 55 ± 24		
Median, days, 46		
Outcome		
Cure†	18	64
Improved, died of other cause	3	11
Improved, lost to follow-up	2	7
Died of infection	5	18
Bacteriologic results		
Only anaerobes recovered	20	71
Anaerobes and aerobes recovered concurrently	8	29
Average number of anaerobic species per case, 2.3		
Average number of aerobic species per case, 0.4		

Thus, it would appear that this disease process due to anaerobes is not fulminant, is difficult to distinguish from simple pneumonitis early in its course and different from the pulmonary gangrene syndrome due to aerobes noted previously as relates to the pace of the disease. However, it could also be difficult to distinguish from pulmonary gangrene in the invididual patient. Pulmonary gangrene has been stated by other authors to be primarily due to Klebsiella pneumonia. However, the adequacy of anerobic cultures in these cases was difficult to evaluate. Thus, it is possible that pulmonary gangrene and anaerobic nectrotizing pneumonia both represent different ends of the spectrum of a complication of anerobic pneumonitis and that Klebsiella occasionally leads to an infection on one end of this spectrum.

Lung abcess, as noted, are also a common type of anaerobic pulmonary disease. Predisposing factors have been best delineated by Bartlett and Feingold with 67% having periodonitis 64% "aspiration", and 9% bronchogenic carcinoma (Table 1) (90).

TABLE 1

ANALYSIS OF 45 CASES OF LUNG ABSCESS

Findings	No. of Cases	% of Cases
Clinical features		
Mean age ± 1 SD (years), 51 ± 12		
Concurrent empyema	9	20
Underlying conditions		
Periodontitis (33 patients evaluated)	22	67
Suspected aspiration	29	64
Bronchogenic carcinoma	4	9
Miscellaneous	6	13
Fever (> 99.6° F)	43	96
Mean peak temperature ± 1 SD (° F), 101.8 ± 1.4		
Weight loss due to infection	28	62
Mean weight loss ± 1 SD (pounds) (28 patients evaluated), 19 ± 11		
Putrid discharge (sputum or empyema fluid)	21	47
Duration of symptoms prior to presentation		
> 7 days	36	80
Mean ± 1 SD (days), 36 ± 52		
Median, days, 12		
Hospital-acquired infection	9	20
Clinical laboratory findings		
Peak peripheral leukocyte count		
> 9,000/mm^3	40	89
Mean ± 1 SD (X 1,000/mm^3), 14.4 ± 5.1		
Hematocrit (< 38%)	37	82
Mean ± 1 SD (%), 36 ± 6		
Roentgenographic findings		
Cavity size – mean ± 1 SD (diameter in cm), 4.5 ± 1.7		
Abscess on initial roentgenogram	29	64
Pneumonitis on initial roentgenogram, followed by cavitation	16	36
Time for cavitation to appear after documented aspiration		
Mean ± 1 SD (days) (11 patients), 12 ± 4		
Location of abscess		
Right upper lobe, anterior segment	2	
posterior segment	12	
apical segment	1	
Right middle lobe	3	
Right lower lobe, superior segment	3	
basilar segments	7	
Left upper lobe, apical posterior segment	7	
Lingula	3	
Left lower lobe, superior segment	4	
basilar segments	4	
Response to therapy		
Duration of fever*		
Mean ± 1 SD (days), 6.8 ± 5.7		
Median, days, 4		
Time for cavity closure		
Mean ± 1 SD (days), 31 ± 18		
Time for cure*†		
Mean ± 1 SD (days), 66 ± 33		
Median, days, 56		
Outcome		
Cure†	36	80
Improved, died of other cause	3	7
Improved, lost to follow-up	6	13
Relapse**	5	11

Clinically 80% of patients have symptoms greater than seven days before they present to the hospital, the time to cavitation after aspiration is 12±4 days, there is a median time of four days to become febrile after therapy starts, cavity closure average 31±8 days with therapy and normalization of the x-ray averages 66±33 days. The relapse rate with medical therapy is 11%. It interesting to note that Weiss, et al., in several series have demonstrated that alcoholics respond equally as well as nonalcoholics to therapy (Table 1).

TABLE 1

Probability of delayed cavity closure by certain host or disease characteristics

Characteristic	Total No.	No. With Delayed Cavity Closure	p
Pulmonary Segment:			
posterior segment, RUL	12	8	< 0.01
other segments	28	4	
Hemoglobin:			
less than 10 g	8	6	< 0.02
10+	32	6	
Age:			
Less than 50	30	6	< 0.10
50+	10	6	
Cavity Size, initial:			
less than 5 cm	24	5	< 0.10
5.0+ cm	13	7	
Highest Temperature:			
102°F+	29	11	0.20
less than 102°F	11	1	
Associated Conditions:			
Alcoholism	28	10	< 0.20
Nonalcoholism	12	2	
Symptoms Before Therapy:			
2–14 days	21	4	> 0.20
15+ days	16	7	

It should be noted that although uncommon, pneumococcal pneumonia can cavitate. One estimate from the literture review by Yangco et al., was that five percent cavitated (69). Another excellent article was from Hennepin County Hospital in Minnesota by Leatherman, et al. (70). They looked at patients with pneumonia and positive blood cultures for Strep pneumo and found that four out of twenty-four had cavitating pneumonias. Three were alcoholic. The cavities all occurred early in the course of the infection and clinically two patients had pulmonary gangrene. Positive associations with cavitation were alcoholism, putrid sputum and bilateral infiltrates raising the issue of whether there were two separate diseases in these patients (i.e., bacteremic pneumococcal pneumonia and anerobic lung abcess). Neither of these articles nor the rest of the literature allows a determination of the incidence of these two infections being present simultaneously. Although, this incidence is probably higher than appreciated it is possible that pneumococcal pneumonia can rarely cause pulmonary gangrene and/or lung abcesses without a concomitant anaerobic infection.

Empyemas are the final commonly recognized type of anerobic lung disease. The organisms isolated in Barlett and Feingold's series at two VA Hospitals and Cook County Hospital are indicated in the attached Table 1 (92).

TABLE 1—BACTERIOLOGICAL FINDINGS IN 83 CASES OF EMPYEMA

	Total cases	Anaerobes only	Anaerobes plus aerobic or facultative bacteria	Aerobic or facultative bacteria only
...spective cases.... C.H. and S.V.H.)	35	13 (37%)	12 (34%)	10 (29%)
...spective cases... W.H.C.)	48	16 (33%)	22 (46%)	10 (21%)
Total	83	29 (35%)	34 (41%)	20 (24%)

TABLE II—BACTERIOLOGICAL ISOLATES IN 83 CASES OF EMPYEMA

Organism	No.
Anaerobes:	
Gram-negative bacilli	
Fusobacterium nucleatum	16 (3)*
B. melaninogenicus	13
B. fragilis	13 (1)
B. oralis	8
B. pneumosintes	2
Unidentified	3
Cocci	
Peptostreptococcus	12
Peptococcus	14 (1)
Microaerophilic streptococcus	15 (5)
Veillonella	6
Gram-positive bacilli	
Eubacterium sp.	5 (1)
Propionibacterium sp.	4
Lactobacillus sp.	5
Unidentified catalase-negative non-sporulating	9
Clostridium spp. †	13 (1)
Actinomyces israelii	1
A. naeslundii	1
Aerobic and facultative bacteria:	
Cocci	
Staph. aureus	17 (6)
Staph. epidermidis	5
Strep. pneumoniae	5 (2)
Strep. faecalis	5
Strep. pyogenes	4
Streptococcus (other)	8
Gram-negative bacilli	
E. coli	11
Klebsiella sp.	6 (1)
Proteus mirabilis	2
Ps. aeruginosa	10 (2)
Haemophilus influenzae	1

* Number of cases isolated in pure culture

† Includes: *Cl. perfringens* (3), *ramosum* (1), *innocuum* (1), *subterminale* (1), *limosum* (1), *sporogenes* (1), and spp. (5).

Again it should be noted that the relative incidence of community acquired and nosocomial infections are not indicated. Anerobes are isolated more frequently than aerobes but mixed aerobic/anerobic infections are also very common. The individual organisms isolated are indicated in the attached Table 11 with Staph aurus being the predominant aerobe isolated and pneumococcus and gram negative rods being relatively infrequent. It should be noted that a high percentage of the patients with anaerobic empyemas (up to 70%) ultimately required open thoracotomy in this series and that it takes a mean 21±19 days for the patients to become febrile and 11 percent of the patients died.

Hemophilus influneza is an underappreciated cause of acute bacterial pneumonia. This is primarily due to its subtle staining characteristics on gram stain and the difficulty in determing the significance of a positive sputum isolate because it is frequently found as part of normal oral flora. In addition, as will be discussed, it has only recently been appreciated that non encapsulated organisms can be pathogenic.

The first positive blood culture in a patient with pneumonia was described in 1942 by Keefer and Rammellkamp (10). The subsequent pertinent literature is summarized in the attached tables. The "old" literature (before non-encapsulated were bugs believed pathogenic and before sputum and blood culture techniques were modernized) begins with

an article by Crowell and Loube from D.C. General Hospital, Washington, D.C. (21). They reported three patients with pneumonia with positive blood cultures were seen in four years. Two isolates were Type B and one was none B. Goldstein, et al. reviewed positive H. Flu blood isolates in adults from 1964-1966 at Boston City Hospital (22). Ten patients had pneumonias as the source of their blood isolate in eighteen months or a rate of 6/year. Six of the ten patients with pneumonia were evaluated more thoroughly. One of out of the six was alcoholic and five out of six organisms were typeable (two type B.) McGowan et al, also looked at positive blood and CSF isolates of H. Flu at Boston City Hospital during twelve selected years from 1935-1972 (23). In adults they found sixteen isolates in patients with pneumonia with a marked increase in the incidence in the later years. The reason for the increased incidence was not clear. Johnson, Kay and Wood reported one patient every seven years with septacemic pneumonia at New York Hospital from 1932-1967 due to H. Flu (24). There were no alcoholics in this patient population. The markedly decreased rate compared to the previous reviewed reports could potentially be ascribed to a more affluent, less alcoholic population. Their literature review to that date revealed fifteen cases of H. Flu pneumonia with sepsis in adults with six out of fifteen patients being alcoholics. Quanitiliani and Hyman reviewed all patients admitted to two Hartford, Conneticut hospitals (1 public and 1 private) from 1965-1969 with a diagnosis of pneumonia (25). They reported seven cases of H. Flu pneumonia with sepsis over these five years. All the isolates were Type B and their literature review revealed this to be very consistent with what had been previously reported. In 1977, Levin, et al. reported their review of patients with positive blood or pleural fluid cultures at three Denver hospitals (public, VA, private) from 1970-1974 (26). They found twenty-four patients over four years or six per year or two per year per hospital with H. Flu pneumonia/sepsis. They also noted a marked increased incidence at the VA Hospital in latter years of the study. Fifty percent of the patients were alcoholic and thirty-three percent of the patients died even with treatment. Their iterature review of H. Flu pneumonia with sepsis in adults revealed 84 cases reported to date with a male predominance, and an association with chronic lung disease and alcoholism.

HAEMOPHILUS INFLUENZA PNEUMONIA
OLD LITERATURE

Location/Years	# Patients	# Sepsis	Sepsis/Yr	% Type B	% Alcoholics	% Death
D.C. General (late 1940's)(21)	4	3	1	75%	25%	0%
Boston City (1964-6)(22)	10	10	6	33%	17%	33%
Boston City (1935-1972)(23)	16	16	--	--	--	33%
NY Hospital (1932-67)(24)	5	5	1 q 7 yr	60%	0%	0%
Hartford (1 public,1 private)(25)	7	7	1	100%	0%	0%
Denver, (VA,DGH,U of Colorado) (1970-74)(26)	24	24	6(2/Hosp)	--	50%	33%

In 1973-1976 Everett et al. at Brooke Army Medical Center in San Antonio began the "new" literature (27).

HAEMOPHILUS INFLUENZA PNEUMONIA
NEW LITERATURE

Location/Years	# Patients	# Sepsis	Sepsis/Yr	% Type B	% Alcoholics	% Death
Brooke Army Medical Center, San Antonio, (1973-1976)(27)	18	1	1/3	20%	--	17
Massachusetts General (1980)(29)	33	--	--	10%	14%	0
Baylor College of Medicine (2 public/1 VA) (1967-1977)(30)	41	23	6	--	--	--
				80% Bacteremic 40% non-Bacteremic	27%	57% Sepsis 11% Non-Sepsis
Baylor/Emory (4 Houston and 1 Atlanta Hospital) (1974-1980)(31)	58	58	9	37% Type B 50% Nontypeable (Bacteremia)	--	--

Unlike previous authors, their definition of pneumonia was an acute infiltrate on chest roentgenogram and a pure culture of H. Flu from a transtracheal aspiration. Thus, this was the first article that systematically evaluated non-septicemic H. Flu penumonia. They found eighteen cases in three years with one out of fifteen patients having positive blood cultures. Only one of five organisms typed were type B and the others were non typeable. Seventeen percent of the patients died. A later review by Hirshmann and Everett reported a positive association with alcohol and H. Flu pneumonia (28). In 1980 Simon, et al., at the Masschusetts General Hospital reviewed 100 consecutive sputum isolates of H. Flu with greater than thirty colonies per plate (29). It took eighteen months to accumulate this number of positive cultures. Two out of three patients were colonized and not infected by convential criteria. Only one of the eleven typed isolates from patients with infection was typeable. Wallace, Musher, and Martin at Baylor College of Medicine (2 public and 1 VA hospitals) evaluated H. Flu cultures of blood, pleural fluid and transtracheal aspirates from 1967 to 1977 (30). They noted a change in blood culture technique (either changed to liquid media that became cloudy when positive or subcultured all liquid culture to solid media before declaring the culture negative) during the study. These changes led to a marked increase in the incidence of isolation as noted in Table 1. Also as indicated in Table 1 the rates of isolation from the public hospitals were approximately two times that from the VA.

TABLE I Adult Patients with H. Influenzae Bacteremia (All Causes) Identified from 1967–1976

	Veterans Hospital			Ben Taub/Jefferson Davis Hospitals		
Year	Cases (no.)	Blood Cultures per Year (no.)	Adult Admissions (no.)	Cases (no.)	Blood Cultures per Year (no.)	Adult Admissions (no.)
1967	0	2,328	11,322	0	6,025	10,703
1968	0	2,839	12,034	1	5,175	12,031
1969	0	2,860	11,590	0	6,195	14,695
1970	1	3,998	11,850	0*	6,187	16,107
1971	0	3,920	12,807	0	5,958	13,226
1972	0	5,451	14,604	4	6,913	18,168
1973	1†	5,910	15,906	5	7,054	19,930
1974	3	5,850	15,746	2	9,250	20,067
1975	2	5,690	17,782	1†	10,579	20,394
1976	3	6,635	19,445	6	11,969	18,699

* Introduction of medium that showed partial turbidity with growth of H. influenzae.
† Introduction of routine subcultures to chocolate agar.

Slightly over 50% of patients were bacteremic. Comparisons of bacteremic and non bacteremic pneumonias was detailed in Table II.

TABLE II Clinical and Laboratory Findings in H. Influenzae Pneumonia in Adults

Parameters	Bacteremic	Nonbacteremic
Cases (no.)	23	18
Clinical		
Male:female ratio	1.3:1	5:1
Mean age (yr)	54	50
Alcoholism (no.)	6 (26)	5 (28)
COPD/asthma (no.)	13 (57)	5 (28)
No underlying disease (no.)	4 (17)	2 (11)
Mortality (no.)	13 (57)	2 (11)
Laboratory		
Infiltrates		
One lobe	5	4
Two lobes	10	13
Three or more lobes	8	1
Pleural effusion/pleurisy	12 (52)	8 (44)
Positive gram stain	5/22 (23)	12/17 (71)
Positive sputum culture	10/19 (53)	17/18 (94)
Typable strain	15/17 (88)	3/5 (60)

NOTE: Figures in parentheses are per cents. COPD = chronic obstructive pulmonary disease.

A total of twenty-three bacteremic pneumonias were found with 17 or 6 per year occurring in the last 3 years. Fourteen of seventeen (80%) typed organisms were Type B. Non bacteremic pneumonias occurred at the same rate and three out of five organisms typed were Type B. Alcoholism was prominent occurring in 27% of the patients. The death rate was 57% in bacteremic versus 11% for the non bacteremic pneumonia. In 1981, Wallace et al., published a landmark article in which they made both extensive in vitro and clinical observations (31). They specifically noted that typing of H. Flu with many antiserum lead to nonspecific agglutination (i.e., many organism that were not Type B would non specifically agglutinate with Type B antisera) and thus the incidence of Type B organisms had been grossly overestimated in the literature and many H. Flu pneumonias were due to non-typeable organism. They also

reviewed blood and CSF isolates from four Houston hospitals and one Atlanta hospital (public). There were 58 isolates from patients with pneumonia in nine years or six per year (or about 1 per year per hospital). Twelve out of twenty-four isolates were non typeable and only nine were Type B. Thus, these authors and Everett et al., completely changed many concepts conceiving of H. Flu pneumonia. They established that nontypeable organisms caused a significant amount of disease (both bacteremic and non-bacteremic). They noted a continued significant incidence of pneumonia and of sepsis per year (especially with new blood culture techniques) with the organism and they noted a continued positive association with alcohol.

There have been a series of articles published over the years concerning "pneumonias in municipal hospitals". The applicability of these articles to Parkland is obvious and hence a chronologic review is important. The data is also displaced in the accompanying table.

MUNICIPAL HOSPITAL PNEUMONIA

Location/Years	# Patients	# Sepsis Per Yr	Etiology	% ETOH	Prognostic Factors	% Death
Buffalo City (1927-1935)(57)	1300	--	--	5% with DT	ETOH	38.5
Philadelphia General (1936-1946)(58)	1283 (400/y) 3 separate one year periods	--	--	5%	--	
Philadelphia General (1952-1953)(59)	164	--	45 Tbc (include idiopathic pleural effusion)	20%	--	6%
			24 Klebsiella 95 Strept pneumo		--	--
Milwaukee County General (1969-1970) (6 months)(60)	148	see text		35%	Nosocomial	17%
Grady Memorial Hospital (61)	292	69	S. Pneumo 53 GNR 11(Blood culture) Staph 5	25%	+ Blood Culture + Age + GNR and Staph	24%
Johns Hopkins (1971-1972) 6 months(62)	154	10(20)	Blood Culture S. Pneumo 5 Klebsiella 4 H. Flu 1	38%	Not ETOH	6%

1. 1927-1935 Paintor. Buffalo City Hospital. The authors evaluated "lobar" pneumonias but only forty percent of the patients had a chest x-ray (57). Presumably the others were diagnosed based on physical examination. Alcoholics with DT's constituted only five to six percent of the patients. What percentage of the other patients were alcoholics without DT's is not mentioned. Alcohol did increase mortality two fold. The organisms causing the pneumonias were poorly document. Nine percent developed empyemas and 1.2 percent abcesses. Since this article was in the pre antibiotic era these complication notes could potentially be viewed as "the natural history of untreated bacterial pneumonia".

2. 1936-1946 - Israel Philadelphia General. The authors evaluted three separate one year periods during these years (58). Patients with tuberculosis were excluded but otherwise there were poor

definitions of the etiologies of the pneumonias. It was implied that most were pneumococcus. Alcoholics constituted five percent of the patients and they did not have an increased mortality.

3. 1952-1953 - Weiss - Philadelphia General - The authors evaluated 283 patients admitted with "pneumonia" (59). Twenty percent were determined to have tuberculosis, ten percent congestive heart failure, and five percent cancer. This is the only study in the literature that determined the relative incidence of bacterial pneumonia and tuberculosis in this patient population. Ten percent of the patients were said to have Klebsiella pneumonia pneumonia based on culture of the organism for from sputum. Twenty percent of the patients were alcoholic.

4. 1969-1970 (six month period) Dorff et al. - Milwaukee County General Hospital. Alcholics constituted thirty-five percent of 148 total cases (60). No data was presented on the organisms specifically infecting alcoholics or their alcoholics' mortaltiy rate. There were seventeen Strep pneumonic, two Staph aures, three Klebsiella and one E. Coli isolated from blood cultures in patients with pneumonia over six months. Unfortunately one third of all and greater than 50% of gram negative pneumonia they reported were nosocomial.

5. 1967-1968 - Sullivan - Grady Memorial Hospital, Atlanta Georgia. Alcoholics constituted twenty-eight percent of the patients and had a positive association with gram negative pneumonia and a questionable association with increased mortality (61). This is the first positive assocation of alcoholics and gram negative pneumonia. However, even the authors definitions of pneumonia (bacteremic and non bacteremic) were solid, it should be noted that this association is with all gram negative pneumonia and not the more definitive bacteremia gram negative pneumonia. Although not stated specifically the pneumonias did appear to be all community aquired pneumonias. The etiology of pneumonia in patients with positive blood cultures were fifty-three Strep pneumo, eleven gram negative rods (five Klebsiella) and five Staph aures in a one year period. Patients with positive blood culture for Strep pneumo had an increased mortality compared to those who were non bacteremic but those with positive gram negative rod blood cultures had a similar mortality to those with only a positive sputum cultures. Increasing age, gram negative rods and Staph aures pneumonia all were negative prognostic factors. The authors also reported an overview of 571 cases admitted with pulmonary symptoms. Two hundred ninety two had pneumonia, 131 nonpneumonia to include CHF, cancer, etc, and 142 miscellaneous diagnoses to include tuberculosis, COPD, etc. Unfortunately no definite statement of the incidence of tuberculosis in this latter group was made.

6. 1971-1972, Moore, et al. - Johns Hopkins Hospital - The authors specifically excluded patients with tuberculosis (62). Thirty-eight percent of patients were alcoholics. Unfortunately, the data it provides is problematic.

7. 1954-1963 - Chomet - VA Medical Center Westside Chicago, Illinois. Even though the VA is not a municipal hospital the data from this article seems to fit best at this point (63). The authors looked only at autopsies and found thirty-seven alcoholics who died over nine years with pneumonia. Twenty-one of thirty-seven patients were alcoholic. This is the only published series to date I could find which potentially looked specifically at the relative incidence of different causes of pneumonia as relates to alcoholism. There were five positive blood cultures, four Strep pneumona and one H. Flu. However, it was not stated if these patients with positive blood cultures were alcoholic. Obviously this is a somewhat shewed population as it is in VA Hospial and an autopsy series.

Thus, bacterial pneumonia in patients from a municipal or public hospital series appears to have a significant association with alcohol, to have a relative incidence of 5:1 or greater with tuberculosis based on one article from Philadelphia, to include an ill-defined number of gram negative pneumonia and to have a not in consequential mortality in some series.

Before looking at our data at Parkland it is important to summarize the literature from the perspective of what it would predict we would see at Parkland. It can is summarized in the accompanying table. This table is derived from articles previously mentioned in which individual organisms were reviewed from the same public hospital and from the articles previously mentioned when municipal hospital pneumonias were reviewed.

RELATIVE RATES ETIOLOGIC
AGENTS CAUSING PNEUMONIA

Location	Strept Pneumo	Gram Neg Rods	H. Flu	Anerobes	Tbc
[1]Bellevue (33,70)	20	2	-	-	-
[1]Harlen Hospital (34,71)	70	3	-	-	-
[1]Boston City Hospital (22,82)	50	-	6	-	-
D.C. General (21,41)	-	3	1	-	-
Cincinnati General (73)	52	1	-	-	-
Milwaukee County (6)	34	8	-	-	-
Johns Hopkins (62)	5([2]59)	4([2]7)	-	-	-
[1]Grady (61)	53	11	-	-	-
[2]Philadelphia General(59)	95	24	-	-	45
[3]Medical College Penn(88)	24	6	2	20	1
[4]Univ of South Alabama(89)	8	-	2	5	-

*[1]Blood culture positive cases per year unless stated
[2]Different Years Compared
[3]Sputum Culture Data
[4]Transtracheal Aspirates
[5]Cuffed Bronchoscope
-Not evaluated

1. Strep pneumo

   A. Expect 20 to 70 (about 40) bacteremic penumonia cases per year with up to 150-160 total pneumonias due to this orgamism per year.

   B. Fifteen percent of patients with bacteremia will die which will be a higher rate than non bacteremia patients.

   C. Alcholics will have an increased rate of disease.

   D. The ratio of Strep pneumo pneumonia to Klebsiella pneumonia will be 4-50/1 (average 10/1) and to Hemophilus influenza (septicemic type) about 10/1. The ratio compared to anerobic pneumonias would be at least 3:2.

2. Hemophilus influenza

   A. Expect one to two bacteremic pneumonia cases per year. Expect 50% to be type B.

   B. If aggressive transtracheal aspirates or compulsive sputum gram stains and cultures are performed expect at least six cases of non bacteremic pneumonia per year.

   C. Alcoholics will have an increased rate of disease compared to nonalcoholics.

D. There will be an increased death rate in bacteremic patients with an overall death rate of approximately ten to twenty percent.

3. Anerobic pulmonary disesae

A. Diagnosis will be difficult to prove unless transtracheal aspirates or cuffed bronchoscopes (protected cultures) are used frequently.

B. Overall rate approximately two thirds that of Strep pneumo and 6 times that of Klebsiella pneumonia.

C. Expect 75 to 100 cases.

D. Expect positive association with alcohol.

E. Lung abcesses - difficult to estimte expected rate but expect a positive association with alcoholics.

4. Empyemas - difficult to calculate expected rate but expect one third to be anerobic, one third aerobic, and one third mixed.

5. Klebsiella pneumonia.

A. One percent of all pneumonias.

B. Expect one to two bacteremic pneumonia cases per year. Expect total number of pneumonias to be 2 to 4. In these patients expect high incidence (ten percent) of pleural fluid or abscess development.

C. Anticipate five to ten percent assocation with tuberculosis.

D. Expect rate of 1/10 or less compared to pneumococcus, 1/6 the rate of anerobic disease and approximately same rate as bacteremic pneumonia due to H. Flu.

E. Mortality rate 50% in bacteremic patients.

6. Tuberculosis - Difficult to estimate relative rate of disease and even absoluate number of cases. However, expect to see significant number of patients, expect association with alcohol and Klebsiella and negligible mortality rate in hospital due to preveiling patient care patterns.

PARKLAND STUDY - JULY 1, 1985 - JUNE, 1986

MATERIALS AND METHODS

1. Patient selection. Patients for study were found by the following methods:

A. Charts of all patients admitted to Parkland Memorial Hospital from July 1, 1985 to June 30, 1986 who had a discharge diagnosis of any type of bacterial pneumonia, empyema, lung abcess, tuberculosis, or fungal disease of the lung were obtained for review.

B. Microbiology laboratory records were reviewed for the same time period. The charts of all patients with positive blood cultures for recognized respiratory pathogens and any species of Klebsiella were obtained for review.

C. Mycology and mycobacteriology laboratory records were reviewed for the same time period. The charts of all patients with an isolate of a mycobacteria, histoplasmosis, coccidiomycoses or blastomycosis from sputum or a sterile fluid were obtained for review.

2. Patients were excluded from the study if they met following criteria:

A. Preceeding antibiotics or hospitalization in the four weeks prior to admission.

B. Received cancer chemotherapy or radiation therapy in the last four weeks before admission.

C. Received cytotoxic therapy to include steroids for any reason in the last four weeks.

D. Development of pneumonia 48 hours or later after hospitalization - designated nosocomial pneumonia.

E. Preceeding surgery in the four weeks prior to admission.
F. AIDS (or known HIV positive status).

3. Definitions utilized in the study were as follows:

A. Clinical presentation: Infectious lung disease - infiltrate or CXR plus clinical illness to include sputum production, fever etc. compatible with infectious lung disease.

B. Underlying Diseases

1. Alcoholic - as stated in housestaff work up and/or patient has evidence of end organ disease not due to other obvious problems consistent with excessive alcoholic intake (i.e., chronic pancreatitis, etc.).

2. COPD - as stated in housestaff work up and/or with evidence of lung disease compatible with COPD (i.e., obstructive PFT, wheezes, AM sputum production).

3. Diabetes mellitus - diet or insulin controlled.

4. Congestive heart failure - any history suggesting congestive heart failure of any cause as long as cardiac function still abnormal even if on therapy.

5. Chronic renal failure - creatinine greater than 2.

6. Liver disease - due to any documented cause. Cirrhosis diagnosed only by biopsy. Liver failure diagnosed by convential criteria (i.e., flap change, mental status, etc.).

7. Central nervous system dysfunction - to include any change in mental status for any reason.

8. Cancer - tissue diagnosis required -

9. IVDU - patient actively using drugs.

4. Lab - Positive Cultures - 1) blood - all isolates felt by primary care physician to be clinically relevant based on notes, use antibiotics, etc. 2) Sputum - any single isolate in heavy (3rd streak) amount on initial sputum. 3) Sterile fluid - all isolates felt clinically relevant by housestaff etc. 4) Mycobacteria - all MTbc isolates significant. Other mycobacterial or fungal isolates significant if multiple with clinically compatible illness and no other compatible diagnosis.

5. Antibiotic therapy - Patients were grouped based on initial antibiotic therapy which was either broad spectrum or narrow spectrum. Broad spectrum therapy was considered to be parenteral use of a second or third generation cephalosporin an aminoglycoside or "anti" pseudomonal penicillin" or a combination of these drugs. Narrow spectrum therapy would include penicillin, erythromycin, cleocin, or ampicillin used as single drugs. Patients in the broad spectrum category were then subdivided as to whether or not they had an early (less than four days after admission) or late (greater than four days after admission) or no change in their therapy to more narrow spectrum therapy. The patients who initially received narrow spectrum therapy were subdivided into those having no change in their therapy, (i.e., stayed on the same drug or changed to a narrow spectrum oral drug) and those changed to broad spectrum therapy at any time during their course (102).

RESULTS - Administrative

Total charts requested -	716	
Total charts found -	645	(90.3% Retrieval Rate)
Exclusions -	309	
Study Group -	339	

RESULTS PATIENTS - BACTERIAL DISEASE

	Alcoholic	Non-Alcoholic
1. Positive Blood culture (see attached table for individual organisms)	17(24.3%)	31(18.2%)
Died	2(2 not pneumonia)	8(2 not pneumonia)
Pneumonia Death Rate	0%	20%
Lived	15	23
2. Negative Blood cultures	53	139
Died	6(3 not pneumonia)	18(10 not pneumonia)
Pneumonia Death Rate	6%	6%
Lived	47	121
3. Total	70	170
Died	8(6 not pneumonia)	26(12 not pneumonia)
Pneumonia Death Rate	4%	8%
Lived	62	144
4. Anatomy		
Pneumonia	59	153
Pleural effusion	12	24
Present on admission	7	21
Developed during Admission	5	3
Empyema	11	5
Abscess	11	7
5. Complications	23	47
ICU Outcome	6/7 died	7/10 died
6. Sputum Microbiology		
Gram stain	5 Mentioned 4 Strept Pneumo None grew	24 Mentioned 16 Strep Pneumo 3 grew Strept Pneumo 6 PMN only 2 Mixed flora
Culture		
Submitted to lab	19	50
Pathogen Isolated	2	3
Mixed Flora	17	47
None submitted	51 (70%)	120 (70%)
7. Estimate of Anaerobic Pneumonitis:		
Anaerobic (greater than 10 days symptoms or positive blood culture)	19 (27%)	39(23%)
Other Bacteria (positive blood culture, less than 10 days symptoms, or other means)	51 70	133 170
Anerobic Pneumonitis (Another Interpretation):		
Positive Strept Pneumo Blood Cultures	14	25
Presumed non-bacteremic Strept Pneumo Pneumonia	56	100
Calculated Total Strept Pneumo disease	70(99%)	125(74%)
Estimated anaerobic	Minimal	20-25%

	Alcoholic	Non-Alcoholic
8. Use of antibiotics		
Broad spectrum		
(never changed)	12	30
Died (pneumonia)	7(3)	18(12)
Change early	20	36
Died (pneumonia)	0	1(0)
Changed late	8	12
Died (pneumonia)	0	1(0)
Narrow spectrum		
Never change	18	82
Died (pneumonia)	0	6(2)
Charge to Broad	4	5
Died (pneumonia)	1(0)	0

Tuberculosis/Granulomatous Disease

	Alcoholic	Non Alcholic
Organsism		
M Tuberculosis	47	40
Pleural Disease (Isolated from pleural fluid/pleural time or granuloma or pleural biopsy)	5(10%)	7(17.5%)
Other Extra Pulmonary	1 CSF	3 Miliary
Other	6	3
MAI	2	2
M. Terrae	0	1
M. Kansasii	1	0
M. Cheloneii	1	0
Coccidiodomycoses	1	0
Aspergillosis	1	0
Outcome (M.TBC)		
Lived	42	37
Died	5(2 related to TBC)	3(1 related to TBC)
Death Rate from TBC	4%	2%

TBC Cases Initial Therapy - (Accuracy of Initial Diagnosis)	
Total M TBC Cases	87
Patient placed on anti-Tbc drugs only on admission	69(66%)
Patient placed on antibiotics	19(22%)
Patient placed on both on admission	9(11%)

POSITIVE BLOOD CULTURES

	Alcoholic	Non-Alcoholic
Strept Pneumo	14	25
H. Flu	1	1
Clostridia	1	2
Moraxella	1	0
Oral Strept	0	1

The attached chart looks at our results specifically relating them to what the literature would predict we should have found.

INFECTIOUS LUNG DISEASE AT PARKLAND

	Expected	Observed
	Cases per Year	
Strept Pneumo		
Sepsis	40	39
Death Rate	15%	14%
Total Cases	150	Less
Rate in Alcoholics	Increased	Probably Increased
H. Influenza		
Sepsis	1-2	2
Death Rate	10-20%	50%
Pneumonia	6(if do TTA)	--
Rate in Alcoholics	Increased	--
Klebsiella		
Sepsis	1-2	0
Death Rate	50%	0
Pneumonia	1% all pneumonia	0
Anaerobes		
Sepsis	Rare	3
Pneumonia	75-100	55(Conservative estimate)
Abcess	--	18
Empyema	--	5
Rate in Alcoholics	Increased	Not Increased
Tuberculosis		
Parenchymal Disease	¼ Rate S.Pneumo at most	87(Markedly greater than expected)
Pleural Disease	--	12
Death Rate	less than 5%	3%

SUMMARY OF RESULTS

The results of our study can be summarized as follows:

1. Alcoholics constitute a significant percentage of patients admitted with infectious respiratory disease at Parkland Memorial Hospital.

2. Almost 40% of respiratory infections in alcoholics were due to M. TBC. The incidence of pleural effusions with tuberculosis is substantial.

3. Pneumonia is probably caused by anerobes in 20-25% of patients. There was no difference between alcoholics and non alcoholics. An alternate estimate (based on positive Strept Pneumo blood cultures) of the incidence of anaerobic pneumonitis indicate minimal anerobic pneumonitis.

4. Lung abscess (presumed due to anerobes) were more common in alcoholics then nonalcoholics and comprised about 15% of infectious lung disease in alcholics. When combined with presumed anaerobic pneumonia rate means up to 40% infections due to anerobice disease in alcoholics.

5. Empyemas were rare, more common in non alcoholics and due to a vareity of organisms with anaerobes predominanting.

6. The rate of bacteremic pneumonias in alcoholics is similar to nonalcoholics and the death rate is no higher in alcoholics than nonalcoholics. Potentially 3/4 of infectious lung disesae in alcoholics at Parkland is due to tuberculosis and/or anerobes.

7. Gram stains and cultures are utilized minimally at Parkland.

8. Patients with pneumonias who need to be admitted to the ICU rarely survive.

9. The use of broad spectrum antibiotics to "cover" all possible causes of pneumonia on admission would appear to be a questionable practice except in the extremely ill patient.

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