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Nosocomial Respiratory Tract Infections Associated with the Use of Ventilatory Support Systems: Epidemiological and Bacteriological Study of the Effect of Changing Breathing Circuits at 24 or 48 Hours

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Nosocomial Respiratory Tract Infections Associated with the Use of Ventilatory Support Systems: Epidemiological and Bacteriological Study of the Effect of Changing Breathing Circuits at 24 or 48 Hours

A dissertation submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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INTRODUCTION

Nosocomial (hospital-acquired) pneumonia (HAP) continues to be an important cause of morbidity and mortality in the hospital. HAP is the third most common nosocomial infection after urinary tract and surgical wound infections (13). In addition, HAP is the nosocomial infection with the highest mortality rate (93). These infections are often difficult to treat, because most are caused by Gram-negative bacilli (GNB) that may be highly resistant to antimicrobial agents (12). HAPs frequently occur in intensive care patients with underlying lung and/or systemic diseases (45,39). Many patients are intubated and are on assisted ventilation. Several sources of infection associated with ventilators or respirators have been described in the past. Most of these sources have been eliminated by improvement in techniques used in the disinfection and cleaning of ventilator equipment (25). Today, the focus of concern is microbial contamination of the breathing circuit of the ventilator (90). The Centers for Disease Control (CDC) recommend that the ventilator breathing circuits be changed every 24 hours. The very limited epidemiological and microbiological data from one medical center (17,20) demonstrate that it may not be

necessary to change these circuits as often as every 24 hours. However, before changing this conservative recommendation, more data are needed to establish the safety of changing circuits at longer intervals. The approximate cost of the ventilator circuit is $15. It is estimated that changing ventilator breathing circuits at 48 hours rather than 24 hours would amount to $50,000 per year in savings at the Medical College of Virginia. On a national scale the savings would amount to millions of dollars.

Most patients who are placed on ventilatory assistance are supported by continuous volume respirators (Fig. 1). Air is humidified when it is passed through a cascade or wick humidifier. After passage through the humidifier, the gases are delivered to the patient by the inspiratory tubing in the breathing circuit. The inspiratory tubing is connected to the endotracheal tube of the patient by a Y-connector and swivel adaptor. Expired gases from the patient are conducted away by the expiratory tubing which connects to the other limb of the Y-connector. Condensate frequently collects in the respiratory breathing circuit. The warm moist environment of the respiratory circuit is conducive to growth of any microorganisms that may enter the circuit. When the respiratory circuit is contaminated with microorganisms, there is the potential for delivery of bacteria or fungi to the patient's lower respiratory tract. Whether or not infection takes place is determined by one or a combination of several factors including the virulence of

the organisms, the size of the inoculum, the presence of foreign bodies in the respiratory tract and the status of host defenses.

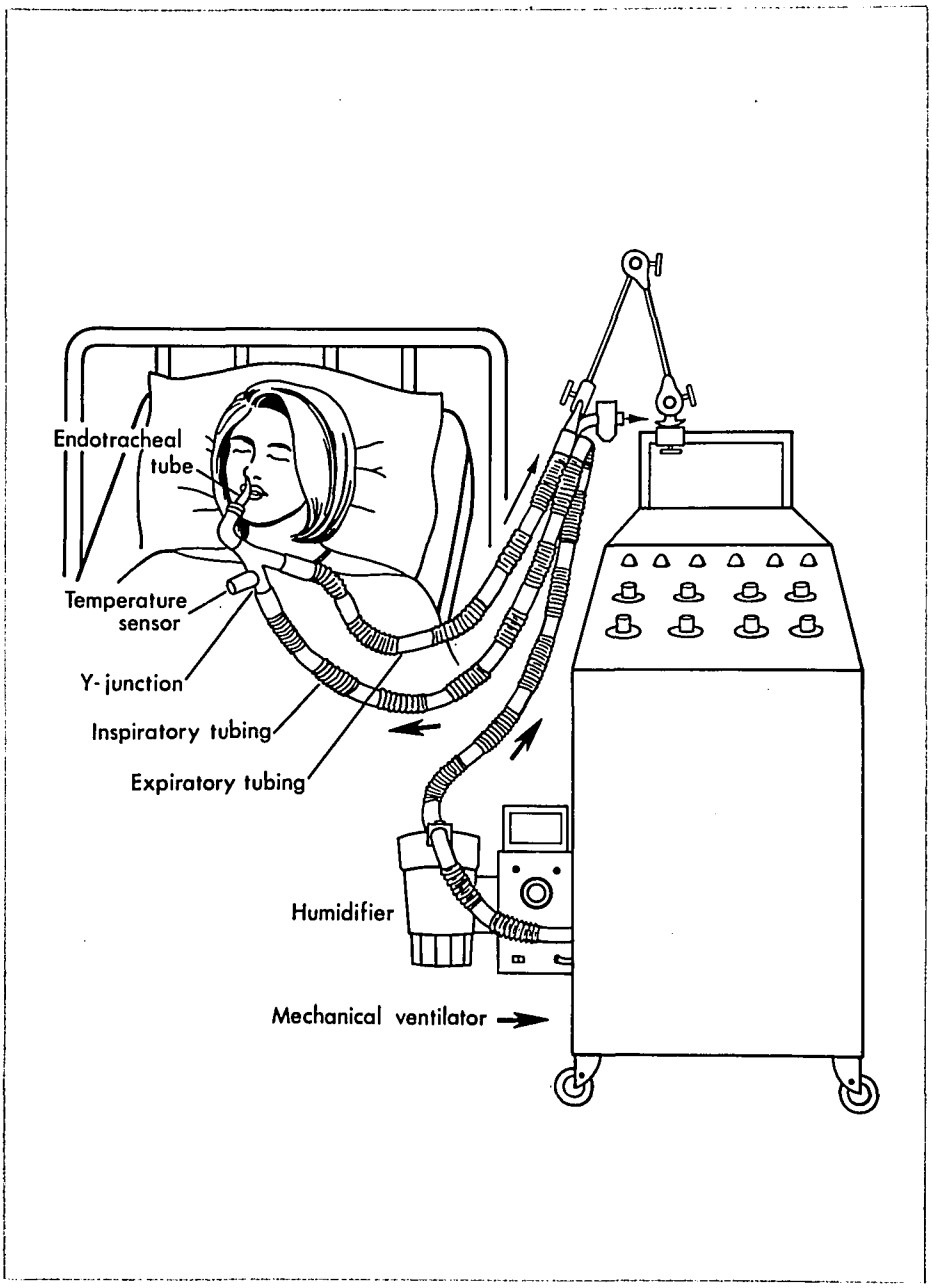

Figure 1. Patient on mechanical ventilation.

LITERATURE REVIEW

Normal Lung Anatomy

The tracheobronchial tree of humans consists of the trachea, bronchi,and bronchioles. The main bronchus is subdivided into two branches known as the nonrespiratory bronchioles. From these bronchioles branch the terminal bronchioles and respiratory bronchioles. Distal to the terminal bronchioles are the alveoli, where oxygen and CO_2 exchange takes place.

Normal Host Defenses

Humans are provided with a variety of non-specific defenses against invasion of the lungs by foreign particles. First, the size of the particle determines where it will be deposited (87,64). The aerodynamic defenses of the respiratory tract remove particulate matter from the airstream by impaction or sedimentation. In the nose this process begins with filtration by the nasal hairs of very large particles (10-20u in size). These particles will impact on the surfaces of the nasal septum and turbinates. As the airstream then changes direction at the nasopharynx, particles of approximately 10u in size will impact on the posterior wall of the pharynx. The airway above the vocal cords is narrow and irregular, creating turbulence and

forcing both large and smaller particles onto the mucociliary blanket which lines the tracheobronchial tree. This blanket which extends from the nasopharynx to the terminal bronchioles rests on the cilia of the respiratory epithelial cells. Each epithelial cell is laden with approximately 200 cilia. The upward movement of the respiratory cilia (more than 14 times per second) sweeps the overlying mucus blanket towards the oropharynx where the mucus and its entrapped material are swallowed or expectorated.

Below the vocal cords, sedimentation, which removes most particles of 5.0 u to 0.2 u, becomes more important than impaction. The airstream velocity slows as it enters the progressive bifurcations of the tracheobronchial tree. Larger particles are removed in the more proximal bronchial tree, and smaller ones may reach the peripheral airways before being deposited onto the mucociliary blanket. A few of these small particles can settle in the lower respiratory tract. Particles smaller than 0.1 u are distributed randomly throughout the airways by their brownian motion, and most of them are exhaled (3,66).

In the air exchange units other components of the host defenses become important. The substances lining the alveoli include surfactant, iron-containing proteins (transferrin), IgG, opsonins and properdin (78). Surfactant is a substance secreted by alveolar cells into the alveoli which reduces the surface tension. The remaining substances are present in the blood. Transferrin is important in the transport of

iron, IgG is an immunoglobulin fraction which contains antibodies, opsonins prepare bacteria for phagocytosis and properdin is a nonspecific antibody-like substance that kills bacteria and viruses and lyses certain red blood cells.

The airway reflexes are an important adjunct to the other defenses of the respiratory tract. The cough removes excessive secretions and foreign materials from the tracheobronchial tree. Bronchoconstriction prevents or reduces penetration of inhaled materials into the distal areas of the respiratory tract.

Several local factors inhibit adherence of GNB. Oral secretions contain IgA antibody which has been shown to coat various bacteria and prevent their adherence (102). The adherence of GNB to epithelial cells of the oropharynx is due to an alteration of the cells' receptors (66,104). Woods and associates have shown that the host alterations associated with increased susceptibility to Pseudomonas aeruginosa colonization are due to the loss of fibronectin from the cell surface. They examined buccal epithelial cells from 12 seriously ill patients who were colonized with P. aeruginosa and from uncolonized controls. They found that the presence of fibronectin prevented adherence of GNB. The function of fibronectin in the lung is uncertain (78). Fibronectin is an adhesive substance secreted by alveolar macrophages which also coats microorganisms and facilitates attachment to phagocytic cells.

In addition, the oropharynx contains a large and complex resident bacterial flora. These normal microflora are acquired shortly after birth and remain constant over time in a given individual, but often differ among individuals. Although the upper respiratory tract is bathed with secretions which are in constant motion in the oropharynx, the resident bacterial flora is not disturbed (104). It has been found that the microbial composition of a region is determined by the relative abilities of the individual species to attach to the epithelial cells of that region (32). Organisms which are unable to attach to the cell surfaces are removed by secretions and thus fail to colonize mucosal surfaces. Gram-negative bacteria are unusual pharyngeal isolates in normal humans. The normal oral defenses against GNB are highly effective and seem to involve both physical clearance and local bactericidal activity. LaForce (51) studied the elimination of GNB from the mouth of individuals after gargle challenge. Suspensions of GNB (10^8 organisms per ml) were gargled by normal volunteers, and then pharyngeal cultures were taken over a period of time. Suspensions of Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis were used. Bacterial counts rapidly decreased and less than 1% of the original inoculum was recovered after three hours. Using piliated and nonpiliated strains of E.coli, LaForce demonstrated that GNB do not adhere well to normal buccal epithelial cells unless the GNB are piliated. Stevens et al (95) also demonstrated in vitro that meningococci with pili

consistently attach to human nasopharyngeal cells in greater numbers than meningococci without pili.

Pathophysiology of Hospital Acquired Pneumonia

Microorganisms that cause Hospital Acquired Pneumonia

Data from the National Nosocomial Infection Study (NNIS) of the CDC indicated that the majority of hospital acquired pneumonias were caused by GNB. NNIS is an ongoing study of nosocomial infections among 51 national hospitals. P. aeruginosa was the most common causative microorganism followed by Staphylococcus aureus and Klebsiella (14). The pathogen most frequently associated with HAPs on all services was P. aeruginosa. S. aureus was the second most common pathogen on all but the Gynecology and Newborn services (14). A recent prospective study by Bartlett and colleagues (6) examined HAP in 159 patients during a 42-month study period. Bacteriological studies were limited to transtracheal aspirates, pleural fluid and blood cultures. Gram-negative bacilli were the causative agent in 46%. The predominant microorganisms in this survey were Klebsiella sp.(23%).

LaForce stated "that the frequency with which GNB cause HAP is due to 1) the ease with which these microorganisms are recovered from culture; 2) the fact that these microorganisms are ubiquitous in intensive care units (and also are capable of becoming resistant to commonly used antibiotics); and 3) the ease with which these bacteria

colonize the oropharynx in ill persons" (52).

Routes of Infection

According to Levison, pathogens "reach the lung by one of five mechanisms: 1)inhalation of small airborne particles; 2) aspiration of resident naso-oropharyngeal flora or large airborne infectious particles after deposition in the naso-oropharynx; 3) hematogenous spread of particles to the lung from another site of infection; 4) direct extension of bacteria from a contiguous site of infection; or 5) exogenous penetration and contamination of lung parenchyma by bacteria" (55). The aerogenic routes of inhalation and aspiration are the most common mechanisms.

Several studies have shown normally that the airways below the vocal cords are sterile. In a study of 100 patients, Potter and associates (73) collected expectorated sputa, pharyngeal cultures and cultures from the trachea and mainstem bronchi during bronchoscopy. Only one patient yielded a potential respiratory pathogen from bronchial cultures. Lees examined 42 patients and found all bronchial secretions from "normal people" to be sterile (54). Pierce and Sanford (72) stated that only 2% of normal persons are at risk for developing pneumonia due to GNB, because the oropharynx does not provide a suitable environment for the growth of GNB. In Johanson's study (45) of colonization in hospitalized groups of patients, 25% of the colonized patients developed pneumonitis as compared to only 3% of those patients who were not colonized. The latter study indicated that the pharyngeal clearance of GNB is impaired

in ill patients.

Oropharyngeal Colonization

Colonization of the upper respiratory tract with GNB normally occurs in only 2% to 18% of healthy subjects. In 1969, Johanson and coworkers (45) demonstrated that the prevalence of colonization increased as the severity of illness increased in a study of 230 patients from five groups of adults: nonhospital-associated normal subjects; hospital-associated normal subjects; physically normal hospitalized patients; moderately ill hospitalized patients; and moribund patients. Oropharyngeal cultures were obtained from all subjects. Prevalence rates of colonization with GNB were markedly increased in the moderately ill and moribund patients. Johanson suggested that the increased prevalence of GNB might have been the result either of increased exposure to GNB or a diminished capacity to clear such organisms from the pharynx. In 1972, Johanson and associates (46) performed a prospective study of 213 patients in a medical intensive care unit, and 45% of them became colonized (mostly with GNB) during the first four days of hospitalization (22% on the first hospital day). Nosocomial respiratory infections developed in 12.2% of the patients. Pneumonia occurred in 23% of the colonized patients compared to 3.3% of the noncolonized patients . The presence of coma, hypotension, expectoration of sputum, the use of endotracheal intubation, treatment with antibiotics, acidosis, azotemia, and either leukocytosis or leukopenia

was significantly associated with colonization. There was no consistent influence of diet on colonization. Of the 95 patients who became colonized with GNB, 59% were taking solid food, 7% only liquids and 34% were receiving nothing by mouth. There appeared to be no difference in the invasiveness of the bacterial species. K. pneumoniae, P. aeruginosa, E. coli and species of Enterobacter were the most commonly isolated organisms. In a prospective study of 149 patients by Tillotson and Finland, 25% of 88 colonized patients developed nosocomial infection (98). Most were due to colonizing GNB. In another study of 34 intensive care unit patients, Johanson and colleagues (47) observed that 53% of the patients were colonized with GNB. He suggested that epithelial cells of the upper respiratory tract contain binding sites (receptors) for GNB and that factors associated with serious illness appear to increase the availability of these binding sites. Such colonization by GNB appeared to precede the development of pneumonia.

Johanson et al's observation that colonization occurred during the first few hospital days (46) suggested to Pierce and Sanford that there is a "susceptible pool" of patients in the hospital who are particularly predisposed to colonization (72). The concept of a susceptible pool was further supported by another study by Johanson and coworkers when they found colonization rates due to GNB of 35% in moderately ill hospitalized patients and of 73% in moribund hospitalized patients (45). Valenti and coworkers (99) performed throat culture surveys on persons over 65 years of

age who were living independently in apartments and elderly hospitalized persons. Nine percent of the oropharyngeal cultures from the first group were culture positive for GNB, and 60% of cultures from patients in the hospital were positive for GNB. Multivariate analysis suggested that the presence of respiratory disease and a bedridden existence were the two most important variables in predicting colonization. Factors not significantly associated with oropharyngeal colonization included age, mental status, bowel incontinence, poor dental hygiene, the presence of dentures, cigarette smoking or functional limitations due to diabetes, neurologic disease or collagen vascular disease.

There also are some specific clinical conditions which may predispose a person to colonization by GNB. Mackowiak et al (56) demonstrated that alcoholics and diabetics have colonization rates with aerobic GNB of 35% and 36%, respectively. Niederman and colleagues (69) suggested a relationship between nutritional status and colonization. They observed a relationship between nutritional status and both tracheal cell adherence and colonization of the lower airways. Greater degrees of nutritional impairment based on the prognostic nutritional index were associated with higher levels of tracheal cell adherence than was observed in patients who had less nutritional depletion. They noted less binding of Pseudomonas to tracheal epithelial cells when they improved the caloric intake of patients with chronic tracheostomies.

The patients in intensive care units (ICUs) are at markedly increased risk for HAP. Johanson reported (47) a colonization rate of 22% on the first day of hospitalization in medical ICU patients. The colonization rate rose sharply over the first four days in the unit, then leveled off to a rate of 45%. Rose and Babcock (82) cultured multiple body sites of 64 patients admitted to a medical ICU and 85 patients admitted to a surgical ICU to determine the frequency of colonization with GNB. Sites cultured included oropharynx, rectum, urethral catheters, endotracheal or tracheostomy tubes, nasogastric tubes, nasal oxygen cannulae, and several other types of less commonly used tubes. The pharyngeal carrier rate among the surgical patients increased by a total of 34 strains of GNB compared to 14 strains among medical patients. The authors interpreted this to mean that surgical patients carried more GNB because they had more tubes, and thus had a larger reservoir of GNB available for pharyngeal colonization. The most frequently recovered organisms were E. coli, Klebsiella, Enterobacter, Serratia, Pseudomonas and Proteus.

Also the administration of antibiotics may be related to the colonization of the respiratory tract. Johanson and his associates (46) provided evidence for this relationship in their study of 213 medical ICU patients. Antimicrobial drugs were administered to 50 of the 213 patients (23.4%). The authors studied a subset of 38 patients and obtained cultures before, during and after antimicrobial therapy. They noted colonization by GNB in 21/38 patients (55%)

before therapy and in 30/38 patients (79%) during or after therapy. They suggested that antimicrobial agents may have increased the rate of colonization, but pointed out that there was a high level of colonization before therapy.

Major surgery also may influence colonization of the oropharynx. Johanson et al (48) demonstrated that following major surgery, there was an increased adherence of GNB to squamous buccal cells. They studied the adherence of ^{14}C-labeled *P. aeruginosa*, *K. pneumonia*, *E. coli* and *P. mirabilis* to buccal squamous cells of 32 noncolonized patients undergoing elective surgery. Buccal mucosal cells were taken from patients both pre- and post-surgically. The *in vitro* test results were correlated with the *in vivo* occurrence of bacillary colonization. Preoperatively, the mean adherence was 4.3 bacilli/cell and postoperatively it was greater than 8.3 bacilli/cell. Sixty-nine percent of the 16 patients in the postoperative group with adherence of greater than 8.3 bacilli/cell became colonized with GNB, whereas none of the 16 patients with adherence of less than 8.3 bacilli/cell postoperatively became colonized.

Raman et al. (75) suggested that there may be a constituent present in smoker's saliva that is responsible for increased adherence of organisms. Using an *in vitro* assay, they examined the buccal epithelial cells of smokers, nonsmokers and exsmokers for adherence of *Streptococcus pneumoniae*. The background counts using cells washed with phosphate buffered saline in the three groups were similar.

Smokers had a markedly increased pneumococcal adherence ($p<0.001$). The authors also noted significantly increased ($p<0.001$) adherence of the bacteria to cells of nonsmokers when they were incubated with the saliva of smokers.

Gastric Colonization and Amplification

duMoulin and coworkers (28) studied the gastric and upper-airway flora of 60 patients from a respiratory-surgical ICU who were treated with antacids or cimetidine. In 87% of the patients, one or more organisms were cultured simultaneously from the upper airway and stomach. A sequence of transmission was demonstrated in 17 of these patients. In 11 patients, the upper-airway colonization occurred after the organism first appeared in the stomach. Pneumonia due to GNB occurred in 31 of these patients(52%). No pneumonia developed in the eight patients whose gastric and upper-airway flora differed. The pH of the fluid correlated positively with the concentration of GNB in gastric fluid. The authors concluded that maintenance of high gastric pH led to increasing concentrations of GNB in the stomach. Atherton and White (5) studied 10 adults on ventilatory support who had paralytic ileus. There was microbial overgrowth of GNB in the stomach of 9 patients. In 6 patients, the bacteria multiplying in the stomach corresponded with those found in the trachea. In 3 patients, the organism first appeared in the gastric contents. These studies demonstrated that overgrowth of bacteria in the stomach may provide a reservoir for colonization of the esophagus, mouth, nasopharynx and

trachea.

Intubation of the Respiratory Tract

Patients who require ventilatory support are always intubated or have a tracheostomy. Endotracheal tubes can be introduced through the nares (i.e.,nasotracheal tube) or through the mouth (i.e.,orotracheal tube). A tracheostomy is a surgical opening into the trachea through which a tracheostomy tube is inserted. Nasotracheal and orotracheal tubes generally are used on patients who require short-term ventilation. Patients on prolonged ventilation or with secretion problems generally require tracheostomies. All tubes inserted into the trachea are surrounded by a cuff which may be inflated. Inflation of the cuff (balloon) occludes the trachea around the tubes to prevent aspiration. Although inflation of the endotracheal tube cuff prevents aspiration of large volumes of gastric content or oropharyngeal secretions, very small quantities of oropharyngeal secretions still may be aspirated (48). This was substantiated by Macrae and colleagues (58) who studied a patient after resection of the middle third of the esophagus. Barium was instilled into the upper esophagus to evaluate the anastomosis. Chest X-ray showed that barium had spilled over into the oropharynx and tracked around the folds of the inflated cuff into the trachea and the left main bronchus. Patients requiring artificial airways are predisposed to HAPs because these tubes bypass the upper airway defense mechanisms and preclude effective coughing.

In 1981, Cross and Roup (22) studied 13,086 patients prospectively over 11 months for the development of HAP. Of these, 814 patients had intubation or intubation plus ventilation for at least 24 hours. Fifty-nine of the 814 patients (7.2%) developed pneumonia. Twelve of these (1%) occurred in patients with endotracheal tubes who were ventilated and 10 (1%) occurred in patients with tracheostomies and ventilation. Thirteen HAPs (1.6%) occurred in persons who had only tracheostomies. One case (0.1%) occurred in a patient who had only an endotracheal tube, and twenty-three (2.8%) occurred in patients who had an endotracheal tube and either intermittent positive pressure ventilation or nasal oxygen therapy.

In 1985, Sanderson (85) examined 37 intubated patients (most of whom were surgical patients) to determine whether or not pharyngeal bacteria were carried into the trachea during intubation. Pre-intubation pharyngeal swabs were taken, and pre- and post-operative tracheal aspirates were obtained with a sterile catheter introduced through the endotracheal tube. Thirteen (38%) of the tracheal samples taken post-operatively revealed potential pathogens (Hemophilus influenzae, S. pneumoniae, coliforms and S. aureus). In each case the organisms had also been isolated from the pharyngeal swab taken prior to intubation. This illustrated the frequency with which organisms could be introduced to the respiratory passages by intubation," even when carried out without difficulty." Mehta (61) studied 90 patients undergoing surgery during endotracheal

anaesthesia. He placed 20 ml of contrast medium on the back of the tongue in patients lying supine on the operating table after obtaining an airtight seal in the trachea by inflating the cuff of the endotracheal tube. In 18 patients contrast medium passed through the larynx and accumulated in the trachea above the inflated cuff, and entered the lungs at the end of the operation when the cuff was deflated.

Dixon cites two ways in which persons with artificial airways may aspirate oropharyngeal flora (25). Persons with such devices are unable to clear their oral secretions effectively, and those secretions collect in the posterior pharynx. Even when oropharyngeal suctioning is performed effectively, the pooled secretions enter the tracheobronchial tree whenever the cuff is deflated. Evidence that pooled respiratory secretions may be the source of microorganisms that enter the tracheobronchial tree in intubated patients was provided by Schwartz and associates (89). They observed that many isolates of bacteria recovered from endotracheal tubes, particularly Enterobacteriaceae, had been recovered in prior cultures from the hypopharynx. Spray (92) also noted that these pooled respiratory secretions above the tube cuff are heavily colonized with bacteria. Every four hours, she placed Evan's blue dye on the tongues of one hundred medical and surgical patients with endotracheal tubes. If blue dye was obtained on suctioning, it was considered evidence for aspiration. Aspiration was detected in 40 of the 100

patients an average of 14 hours after placement of the dye on the tongue. Also according to Dixon, the presence of the airway itself reduces the effectiveness of local tracheobronchial defense mechanisms through local trauma and drying (25).

Aspiration

Aspiration of oropharyngeal secretions is probably the most important mechanism by which pneumonia develops. However, pneumonia also may occur as a consequence of inhalation of small airborne particles. Aspiration takes place when fluid in the oropharynx passes into the lower tracheobronchial tree during respiration. Aspiration may be followed by no adverse effects or it may result in damage to the lung parenchyma. When fluid is aspirated, it may carry microorganisms into the lower respiratory tract. The macrophage constitutes the principal cellular defense of the alveolus. There is about one cell per three to four alveoli. In most instances, bacteria are inactivated by these cells. When aspiration takes place with a large bacterial inoculum or with a particularly virulent microorganism, the respiratory macrophages may be overwhelmed (78). A second line of cellular defense is constituted by the polymorphonuclear leukocytes. They are located in capillaries in the interstitial space. They migrate to the alveoli in response to a chemotactic stimulus. Chemotactic factors are produced by alveolar macrophages and by activation of the alternate complement pathway by bacterial endotoxins. Green and Kass (34)

aerosolized labeled bacteria (p32-tagged staphylococci) into the lungs of mice and immediately sacrificed the animals and examined the lungs histologically. The authors demonstrated that bacteria do not remain on the alveolar surface, but within minutes are almost all ingested by macrophages without histologic evidence of an inflammatory response. They repeated the experiment with Gram-negative organisms and demonstrated that ingestion takes place more slowly with these organisms.

Several studies show that nonintubated normal and ill adults may aspirate during sleep. In 1929, Quinn and Meyer (74) demonstrated aspiration in 5 of 11 sleeping patients after instillation of iodized oil into their noses. A chest X-ray taken in the morning identified the oil in small quantities in both lower lobe bronchi. Based on these observations, the authors stated that aspiration of infective material also might be possible. In 1953, Amberson introduced iodized oil into the mouth of sleeping patients. Chest X-ray the following morning revealed the oil in the lungs of some of the adults (unpublished study by J.B.Amberson, cited in 103). In a study of 8 patients, Winfield and coworkers (103) attempted to reproduce the earlier experiments by injecting 2-3 ml of contrast material into the posterior nasopharynx during sleep. However, they were unable to confirm the earlier work as in no instance was the opaque medium visible in the lungs or trachea on chest X-ray the next morning. On the other hand, by

injecting indium chloride[111] into the posterior nasopharynx of twenty normal subjects and ten patients with depressed consciousness, Huxley and colleagues (43) were able to demonstrate the occurrence of aspiration. The thorax of all subjects was scanned within 4 hours of completing the posterior pharyngeal injections with radioactive tracer. Forty-five percent of the normal subjects aspirated during deep sleep and aspiration was observed in 70% of the patients with depressed consciousness.

The rare occurrence of pneumonia following aspiration is evidence of the lung's remarkably efficient and effective clearance mechanisms. If, however, the aspirated inoculum is large or contains virulent bacteria, the clearance mechanisms may be overcome. In 1972, Bryant et al (8) studied the bacterial colonization profile of the patient with tracheal intubation undergoing mechanical ventilation. The author examined serial tracheal cultures of 129 patients who required tracheal intubation for greater than 48 hours. Tracheal cultures became positive for pathogens in 115 patients (89%). Although the initial cultures often demonstrated normal flora of the upper respiratory tract, within a few days pathogens (*Pseudomonas, Klebsiella, Proteus, Candida, and S. aureus,* etc.) displaced the normal flora. The author noted that, frequently, one pathogen replaced another, and 43% of the patients became colonized with two or more GNB. Tracheobronchitis occurred in 31 patients, 47 had pneumonitis, and 28 developed colonization without evidence of respiratory infection.

Removal of Respiratory Secretions with Suction Catheters

An additional risk factor for HAP is the introduction of suction catheters into artificial airways to remove respiratory secretions. Demers stated that there were three adverse effects of suctioning. This repeated procedure predisposes the patients to pneumonia by: 1) direct injury to the endobronchial mucosa; 2)by inducing hypoxemia; and 3) by causing atelectasis (24). In addition if aseptic technique is not practiced, bacteria can be introduced into the lower respiratory tract.

Epidemiology

Definition of Hospital Acquired Pneumonia

Hospital acquired pneumonias are defined as those respiratory infections that develop in hospitalized patients in whom the infection was neither present nor incubating at the time of admission (11). These infections usually are not manifest in the first 48 hours of hospitalization. They occur as a result of the introduction of microorganisms into the lungs during hospitalization. Pneumonia often is difficult to diagnose. Johanson (45) classified infections as "definite" or "probable". A diagnosis of "definite" infection required the presence of all four determinants: 1) the appearance of a new or progressive infiltrate on chest X-ray; 2) fever; 3)leukocytosis; and 4)purulent tracheobronchial secretions. A diagnosis of "probable" infection was based on 3 criteria: 1) fever; 2)leukocytosis; and 3) either a new or progressive pulmonary infiltrate on

chest X-ray or the presence of purulent secretions. Results of cultures were not used . In their review, Crane and Lerner (16) relied on bacterial isolation from sputum for definite diagnosis of pneumonia. They required: 1)isolation of the same predominant bacteria from two or more consecutive sputum cultures; or 2) isolation in close temporal proximity of the same species from blood and sputum; or 3) isolation of appropriate bacteria from pleural fluid. The definition for the diagnosis of HAP used by NNIS of the CDC requires purulent sputum production more than 48 hours after admission in a patient with no evidence of prior pulmonary infection or increased production of purulent sputum with reappearance of fever in a patient admitted with pulmonary disease. In addition, there must be one of the following: 1) an infiltrate on chest X-ray; 2) characteristic clinical manifestations of pneumonia; or 3) the patient must have cough, fever or pleuritic chest pain.

The most precise published criteria for HAP are those of Craven and colleagues (20). These include 1) purulent sputum with a Gram stain having greater than 25 leukocytes and less than 10 squamous epithelial cells per high power field; 2) a significant respiratory or nosocomial pathogen isolated from sputum cultures and/or bacteria seen on Gram stained smears of the sputum; 3) a peripheral leukocyte count of greater than 10,000 per mm^3 ;4) fever of greater than 100.4 ^{o}F; and 5)a new and persistent infiltrate on chest X-ray. Garibaldi and coworkers (30) used fever, purulent

sputum, clinical findings and abnormalities on chest X-ray to define HAP (30). They used three categories for HAP. Patients with microbiologically proven pneumonia were categorized as Class 1. Patients were placed in Class 2 when they had clinical evidence of pneumonia without microbiologic confirmation. Pneumonia was categorized as Class 3 when patients had fever, purulent sputum, or suggestive chest X-rays. In Sanford's opinion, the CDC definition should be employed "unless there are specific justifications in a study for not doing so" (85).

Diagnosis of Hospital Acquired Pneumonia

Respiratory secretions obtained as a coughed sputum specimen are frequently contaminated by oropharyngeal flora which may obscure the identity of the causative agent. Numerous studies have demonstrated the discrepancy between cultures of sputum and pathogens present in the lower respiratory tract (6,23). In a bacteriologic study of respiratory secretions obtained by transtracheal aspiration from 488 patients, Bartlett (6) studied the diagnostic accuracy of cultures obtained by this technique when compared with clinical parameters and final diagnosis. Three hundred and sixty-nine patients yielded potential pathogens from sputum cultures. Three hundred and thirty-five cultures were true positives, and cultures from 34 patients were false positives for a false positivity rate of 9.2%. One hundred and nineteen patients yielded no pathogen. In 71 of these patients, criteria for pneumonia were not met. Forty-eight of these patients had a bacterial infection of the

pulmonary parenchyma, but 44 of the 48 had received antimicrobial drugs before the procedure. The author concluded that transtracheal aspiration is a reliable technique for determining the cause of bacterial infections of the pulmonary parenchyma if there has been no prior treatment with antimicrobial drugs.

Davidson (23) and colleagues studied 25 adult Navaho Indian patients with acute pneumonia and compared cultures of sputum, transtracheal aspirate and fluid obtained by direct-needle aspiration of the lung. Multiple potential pathogens were recovered from 83% of the sputum specimens, from 27% of the transtracheal aspirates, and from 16% of lung aspirates. Eighty percent of the positive lung aspirate cultures yielded a single bacterial isolate. The authors concluded that lung aspiration was more likely to yield single, definitive bacterial isolates than the other sampling techniques.

Adult Respiratory Distress Syndrome (ARDS) is a respiratory condition due to acute lung injury with multiple causes. This syndrome is characterized by hypoxemia, increased lung stiffness and diffuse infiltration of the lung parenchyma as seen on radiographic examination of the chest. All of these abnormalities are related to an increase in the permeability of pulmonary capillary endothelium (42). Conditions frequently associated with ARDS include shock, septicemia, pulmonary infection, trauma, aspiration, inhaled toxins and metabolic disorders (67). The

presence of ARDS makes the diagnosis of pneumonia difficult and further confusion may arise due to the frequent colonization of the sputum of these patients with Gram-negative bacilli (45). Andrew reviewed the postmortem histology of 24 patients with ARDS, and found that the accuracy of the clinical diagnosis of pneumonia in the ARDS patient was only 64% (4).

Descriptive Epidemiology

The reported incidence of pneumonia will vary from institution to institution, but data obtained from NNIS (14) in 1984 indicated that 6.0 cases of nosocomial pneumonia occurred per 1,000 patients discharged from U.S. hospitals. This represented 17.8% of all hospital associated infections. In addition, data from the 1986 NNIS study reported the incidence of HAPs by service. Among large teaching hospitals, the Surgical service accounted for 11.2 cases of HAP per 1000 discharges, and the Medical service for 10.2 cases per 1000 discharges, the Pediatrics service for 3.9 cases per 1000 discharges, the Newborn service for 2.9 cases per 1000 discharges, the Gynecology service for 2.6 cases per 1000 discharges and the Obstetrics service for 0.5 cases per 1000 discharges. In 1974, Pierce and Sanford (72) stated that nosocomial pneumonia has been estimated to occur in from 0.5 to 5% of all patients. Dixon stated that approximately 5 to 10 of every 1,000 hospitalized persons will develop an HAP, and he estimated that 238,000 persons acquire these infections in the United States each year (25).

Certain hospital areas have appeared to experience an increased incidence of HAPs. Hemming (39) reported that 7.2% of the patients in a newborn intensive care unit developed an HAP. Johanson and co-workers (46) observed an HAP rate of 12.2% in patients hospitalized in a general medical intensive care unit, and 17.5% of the postoperative patients in the study of Garibaldi et al developed an HAP (30).

In a retrospective study by Stevens (96), 153 patients with pneumonia were identified during the first 2 1/2 years of operation of a respiratory-surgical ICU. Patients who had pneumonia due to GNB other than P. aeruginosa had a mortality of 33%. On the other hand, isolation of Pseudomonas from respiratory cultures obtained from patients with pneumonia was associated with a mortality of 70%. Data from the Comprehensive Hospital Infections Project (CHIP) (93) showed that HAP had a case-fatality ratio of 56% for bacteremic patients and 19% for nonbacteremic patients. The CHIP study was performed by the CDC in 1977 and was based on nosocomial infections reported from eight national hospitals over a two year period. Gross and colleagues (36) studied 100 consecutive patients who died at Columbia-Presbyterian Medical Center and 100 consecutive patients who died at Hackensack Hospital to assess the importance of nosocomial infections as a contributory cause of death in patients who die in the hospital. By definition, these nosocomial infections were considered to be "contributing to death"

when the infection was an active infection of a major organ and "causally related to death" when the infection was not controlled at the time of death. Of 52 patients where hospital acquired infection (HAI) either contributed to or caused death, 31(60%) had HAP. In a study of 159 cases of HAP, Bartlett and associates (6) observed a mortality rate of 19% and in 13% of these patients, HAP contributed to death.

HAPs have a significant financial impact. In 1977, Wenzel estimated this cost to be $208 per infection (101). Haley took this 1977 figure and adjusted it for inflation to predict the 1985 hospital costs. The average hospital charges for HAPs in 1985 were $4,947 per infection and the maximum costs were $41,628 (38). Dixon estimated the average per diem hospital cost resulting from HAPs in 1984 to be $385 and the average prolongation of stay to be 4.0 days (26).

Risk Factors

Demographic factors. Stamm and associates observed in 1977 that advanced age was a risk factor for the development of HAP (93). As a part of the Study on the Efficacy of Nosocomial Infection Control (SENIC), Hooten et al (40) developed an index of intrinsic patient risk. The SENIC study was carried out by CDC over a period of 10 years and included 338,000 general medical and surgical patients in 338 hospitals (38). In the SENIC study, Haley et al (37) found that 13% of all nosocomial infections were HAPs. They observed that an increase in age from 18 to 85 years

was associated with a three-fold increase in the rate of HAP's, but did not indicate whether this was a statistically significant relationship. Unlike Stamm et al and Haley et al, Garibaldi and co-workers did not find a significant relationship between age and HAP.

Stamm and associates (93) and the SENIC study (37) concur with respect to male sex being a risk factor for HAP. Stamm and associates found that males were approximately 3 times more likely to develop HAP than females. The SENIC study found a greater male to female ratio (17.1:1) for the acquisition of HAP. On the other hand, Garibaldi and co-workers (30) were unable to demonstrate a significant relationship between the male sex and HAP.

Underlying disease. Hooten et al (41) found that diagnosis was an important determinant for infection when they constructed their risk index for HAP. Immunocompromised patients were at increased risk for HAP. Host defenses of these patients may be suppressed by underlying illness, or by treatment with corticosteroids, cytotoxic agents or other immunosuppressive drugs. Data from the SENIC study showed that persons on immunosuppressive therapy were 5.3 times more likely to develop HAP than persons not on such therapy. Sobel (91) stated that pneumonias account for as much as 25% to 50% of all infectious deaths among patients with hematologic malignancies. He also pointed out that the most important cause of death in acute leukemia is infection and that the

most common site is the lower respiratory tract. Similarly, Garibaldi and co-workers found a significant association between HAP and underlying non-malignant disease ($p<0.005$). A history of smoking ($p<0.001$) was also significantly associated with HAP, but no significant relationship was found between HAP and massive obesity (30).

Duration of hospitalization. In the two studies that have assessed duration of hospitalization as a risk factor for HAP, both found a significant association between duration and infection. Stamm and associates (93) observed that hospitalization for more than 7 days significantly increased the risk for HAP. Although Haley and associates (37) also found duration a risk factor, they observed that the increased risk occurred only after 40 days of hospitalization (37).

Presence of remote infection. Infection at various sites in the body may be a risk factor for hospital acquired infection. Two studies have shown that infection at a remote site is a risk factor for the development of postoperative wound infection (68,7). Only one study has assessed remote infection as a possible risk factor for HAP. Haley and associates (37) noted that previous infections at any site, regardless of whether these were community-acquired or hospital-acquired, were associated with a fourfold increase in the risk of HAP.

Surgery. Prior surgery was an important factor in the risk index developed by Hooten and associates (41). They observed that 74% of all pneumonia cases in adults occurred

in surgical patients (37). On the other hand, Garibaldi and co-workers found that 17.5% of 520 patients who underwent elective thoracic, upper abdominal and lower abdominal surgery developed HAP (31). Haley and associates found that patients who had combined thoraco-abdominal surgery had a risk 38 times that of other types of surgical procedures. When thoracic and abdominal operations were examined separately, there was a fourteen-fold greater risk for thoracic surgery and the risk was 3.4 times greater for abdominal operations than for other types of surgery (37). Garibaldi and co-workers (31) also observed that location of surgery was a risk factor for HAP. They found that pneumonia was highly associated with thoracic or upper-abdominal surgery ($p<0.001$). Another risk factor related to surgery is duration of operation. The SENIC study found a 49-fold increase in HAP in operative procedures of greater than 150 minutes (37).

Ventilators. Patients exposed to ventilatory support have an especially high risk of acquiring HAP, although it is difficult to separate the contribution of respiratory care from that of intrinsic host susceptibility (25). The SENIC study found a 21-fold increase in risk for persons on ventilatory support compared to those not on ventilatory support (41).

During the 1960s and early 1970s, respiratory care equipment was reported to be a major source of HAP (77,72,94,35,49). Due to changes in procedures for cleaning

and disinfection or sterilization of respiratory therapy equipment, there has been a major reduction in hospital acquired pneumonia. A review by Cross and Roup (22) in 1981 stated that respiratory equipment is now rarely a direct cause of HAPs.

Nevertheless, mechanical ventilation is still a risk factor for HAP. Cross and Roup prospectively studied 13,086 patients hospitalized at Walter Reed Army Medical Center over an 11-month period and found that HAP developed in 7.7% of patients who received respiratory support compared to 0.3% of patients who had no exposure to such therapy. No case of HAP occurred in patients on ventilators less than 24 hours, but the risk of HAP increased significantly after the fifth day of respiratory therapy. The highest incidence of HAP occurred in patients with tracheostomy combined with ventilatory support (66.7%). The rate of infection for patients with tracheostomy who were not on a ventilator was 25%. The rate of HAP was lower still for patients who had endotracheal intubation and ventilatory support, and was lowest for patients who were intubated but did not require ventilatory support (1.3%).

Because of the potential for bacterial contamination of the system (i.e., the breathing circuit which connects to the endotracheal tube), the CDC recommends that the circuit be changed every 24 hours. There are no data to support this recommendation, and workers from the CDC acknowledge that the risk is probably low (90). In general, the CDC recommendations to change solutions or equipment are based

on control measures practiced during equipment-associated outbreaks.

In 1984, Craven and colleagues (18) reported on ventilator circuit practices in the United States. Two hundred and forty-nine hospitals across the nation were surveyed. The majority (94.4%) changed their ventilator tubing every 24 hours, and 5.6% changed the circuits every 48 hours. The scientific data available to guide hospitals in the routine change of ventilatory circuits is very limited. Most hospitals indicated that "self-study" was used to determine the time interval of ventilator circuit changes (19). Although the microbial study by Craven and co-workers indicated that there was no difference in contamination of circuits changed at 24 or 48 hours, only epidemiologic studies that provide rates of HAP can lead to definitive recommendations. In 1986, Craven and coworkers (21) published the results of their prospective, randomized, epidemiologic study of the effect of 24 versus 48 hour circuit changes on the rate of HAP. They found a significantly higher rate of HAP in patients whose ventilator circuits were changed every 24 hours. These authors suggested that ventilator circuits now may be changed safely every 48 hours.

Outbreaks

Under normal conditions the upper airway humidifies inspired air and prevents drying of mucus membranes of the bronchial tree. This maintains normal function of the

mucociliary apparatus, hydration of the bronchial tree, and prevents bronchial secretions from becoming thick and inspissated.

Humidification by Nebulizers

A nebulizer is one means of providing humidification of the gases from a respirator. Most commonly, these are fine particle reservoir nebulizers which operate on the venturi principle. A gas under pressure is directed across the mouth of a capillary tube in which the lower end of the tube is submerged in a reservoir of water. The negative pressure produced at the mouth of the capillary tube by the rapidly flowing gas, draws water from the reservoir into the gas stream. The water is impacted against a baffle, dispersed into droplets, and carried out of the nebulizer in particulate form (50). From there, it passes through the breathing circuit to the patient. Nebulizers create an aerosol that contains particles (1-2 u) that can be deposited into the lower respiratory tract (90). Units utilizing nebulizers have been shown to be hazardous, because the water droplets constitute an excellent vector for transmitting bacteria (77).

Nebulizers may also generate an aerosol with ultrasound produced by rapidly vibrating crystals or by centrifugal force where liquid is dropped onto a rapidly spinning disk (100). Nebulizers produce droplets of different size. Small droplets are most useful for the treatment of respiratory therapy patients. Smaller droplets are distributed more uniformly in the lung tissue and

hydrate the patient more evenly and slowly. Therefore, larger droplets usually are removed from the treatment aerosol by a baffle (59).

Humidification by Humidifiers.

The alternative method for providing moisture for these gases is by a humidifier designed to deliver a water vapor to the patient as molecular water. The gas is heated, and the water vapor content is increased by either a bubble-type humidifier or a wick humidifier. In the bubble-type humidifier, the gas bubbles through 250-300 cc. of heated water (approximately 36 °C). In the wick-type humidifier, gas is humidified by passing over a wick which is moisturized by a reservoir of water. The gas cools as it is transported to the patient, and cooling causes the water vapor to condense in the delivery tube (77). Because water droplets are not produced, humidifiers are considered a low risk as potential sources of infection.

Microbiology of Nebulizers and Humidifiers

Nebulizers The first microbiologic study of respiratory therapy equipment was reported in 1958 by Macpherson (57). He examined water from the reservoir, oxygen from the wall connection, several valves, and outlet ducts of nebulizers in use at Ohio State. He recovered large numbers of microorganisms only from water and outlet ducts. The majority (greater than 43%) were members of the family Enterobacteriaceae. The remainder were made up of a variety of organisms (yeast, Gram-positive

organisms and Pseudomonas). Alarmingly, Clostridium welchii also was isolated. Therefore, the author initiated several techniques designed to prevent contamination. These were probably the first infection control guidelines for inhalation therapy equipment. These guidelines were:

1. Use only sterile water;
2. Limit use to one week;
3. Discard residual water prior to refilling;
4. Clean and disinfect the reservoir prior to the next use;
5. Replace defective washers prior to the next use;
6. Autoclave the metal top of the humidifier between patients or after one week;
7. Store all apparatus in the dry state;
8. Use disposable tubing whenever possible;
9. Take bacteriological samples at regular intervals.

In 1965, Reinarz and coworkers cultured respiratory therapy equipment from six hospitals (77). Using an Andersen air sampler, 226 ventilators with and without nebulizers were sampled. Between 75-91% of all the tested equipment yielded significant numbers of GNB in the effluent air of the ventilators. There was a difference, however, between ventilators with and without mainstream nebulizers. Nearly all of the devices with mainstream nebulizers were contaminated. Forty-five percent generated aerosols with particles that ranged between 1.4 and 3.5 u. Further, there were 2,500 viable bacteria per 7.5 L of air. The prevalence and degree of contamination were similar in each hospital. Only 16% generated aerosols with viable particle counts as

low as those in ambient air (not exceeding 5 particles per 7.5 L of air). Contaminated aerosols never were obtained from the 52 ventilators without mainstream reservoir nebulizers, suggesting that the contamination was related to the reservoir nebulizer. Correlation between fluid samples from the nebulizers and the aerosol samples was performed. In 81% of the samples there was correlation of all organisms or the predominant organisms. The major contaminants were Pseudomonas species, Flavobacteria species, Herellea (Acinetobacter) species, and Achromobacter species.

Morris (65) evaluated bacterial contamination of aerosol generating equipment. Bacteria were recovered from 46% of 382 water specimens that were collected from the nebulizers used on 15 patients. Twenty-four percent of the specimens were contaminated with GNB. P.aeruginosa accounted for 54% and Providencia stuartii for 21% of all GNB isolated. The remainder of the cultures yielded Staphylococcus species and Bacillus species.

While most infections related to use of nebulizers have been due to contaminated mainstream nebulizers, contamination of medication nebulizers also may produce infectious aerosols resulting in ventilator-associated pneumonia. Two outbreaks of infection due to contamination of aerosol solutions in medication nebulizers have been reported (62,84). Medication nebulizers are infrequently associated with production of contaminated aerosols, because the small volume of these nebulizers permits drying between

use (72). Craven and coworkers (20) observed that 79% of cultures from in-use medication nebulizers were positive culturally for Gram-negative bacilli, frequently in heavy growth. In addition, it was shown that 71% of the nebulizers which were culturally positive produced bacterial aerosols. These observations were corroborated by in vitro studies in which bacteria were added to these nebulizers. The authors demonstrated that, under these conditions, the nebulizers also produced aerosols. Further, these aerosols were made up of particles with a diameter small enough to allow deposition in the alveoli. Thus, it would appear that although medication nebulizers usually provide a low risk to patients, they should be cleaned after each use.

In their review of the literature, Simmons and Wong (90) pointed out that nebulizers can become contaminated by the introduction of nonsterile fluids, by manipulation of the nebulizer reservoir and perhaps by retrograde flow of condensate from the inspiratory limb of the breathing circuit. Bacteria in the reservoir can multiply to high concentrations within 24 hours, and place the patient at high risk for infection.

Humidifiers. Introduction of bubble-type humidifiers in 1967 reduced the risk of bacterial contamination of gases during humidification. Schulze, Edmondson, Pierce and Sanford (88) examined 100 humidifiers for bacterial contamination after use. In 90% of the samples taken from the gas stream of ventilators using bubble-type humidifiers, the concentration of bacteria in the gas was comparable to

the concentration of bacteria in room air. Bacterial concentrations greater than 2,500 CFU per 7.5 L of gas were found in the effluent of only 2% of the machines. The authors compared these results to those of Reinarz and coworkers (77) who had demonstrated bacterial contamination at a concentration greater than 2,500 CFU per 7.5 L of gas in a high percentage of machines using mainstream reservoir nebulizers. They concluded that the machines with bubble-type humidifiers are unlikely to produce respiratory infection.

There is widespread belief that bubble-type humidifiers do not produce aerosols. Using an unheated bubble-type humidifier with 10^5 to 10^6 microorganisms/ml of Pseudomonas, and water, Ahlgren recovered bacteria from the effluent air of the humidifier at a flow rate of 5 L/min (1). In 1986 Rhame and associates (79) demonstrated that bubble-type humidifiers may aerosolize water. They added P. aeruginosa (6.4×10^6 organisms per ml) to the water of various types of unheated humidifiers, and then sampled the air discharged from each humidifier. With a gas flow between 10 and 80 L per minute, bubble-type humidifiers produced between 460 and 999 water droplets. With wick-type humidifiers, no water particles were produced. Although the risk for infection to patients is unknown, the authors supported the recommendation that sterile water be used in bubble-type humidifiers. On the other hand, Goularte and coworkers (33) showed that even with a high inoculum, essentially no

bacteria were recovered from the effluent when the humidifier was heated and operated at a flow rate that is commonly used for patients on artificial ventilation.

Description of Outbreaks

Reinarz, Pierce et al (77,71) reviewed autopsy records at Parkland Memorial Hospital in Dallas to determine the incidence of necrotizing pneumonia in the years 1952, 1957 and 1963. These years were chosen since they were prior to the widespread use of respiratory therapy equipment. The authors found that the rate of pneumonia caused by GNB had increased from 0.8% in 1952, to 1.8% in 1957, and to 9% in 1963. They suggested that this increase was due to the use of reservoir nebulizers with contaminated water, since other predisposing factors, including broad spectrum antibiotics and steroids, had been introduced prior to the use of reservoir nebulizers. They then instituted guidelines for the care of nebulizers. In 1966-67 they supported this interpretation when they reported a decrease in the presence of pneumonia (from 9% to 2.2% and 2.1%, respectively) and the parallel decrease in the contamination of nebulizers from 84% to less than 10%.

During the 1960s and 1970s many epidemics of Gram-negative pneumonia were investigated, and various components of respiratory care equipment were found to be contaminated with the epidemic strains (70,62,80,65,77). In 1965, Phillips and Spencer (70) investigated eight patients who had been treated by tracheostomy and mechanical ventilation and had become infected. The authors cultured the

ventilators, the humidifier and breathing inspiratory tubing. All were heavily contaminated with the causative organism which was being delivered to the patients' tracheas. The routine cleaning method did not eliminate the organism. They then recommended disinfection by ethylene oxide. In addition, they proposed that a suitable bacterial filter be developed and placed in the respiratory circuit.

Mertz et al (62) reported on an outbreak of pneumonia caused by K. pneumoniae. The outbreak occurred over a period of 22 days and involved 5 patients who had received contaminated bronchodilator solution and developed pneumonia. All 5 patients died. K. pneumoniae Type II was isolated from bottles of bronchodilator stock solution and the throat of a therapist who occasionally prepared these solutions. It was not indicated whether the therapist was the original source of the strain. To control the epidemic, the author suggested that all medications and solutions be prepared daily and that prolonged storage of premixed solutions no longer be permitted.

Sanders and co-workers (84) reported on an outbreak due to Serratia marcescens which involved 374 patients during a ten-month period. The organism was isolated from sputum of 229 patients, the urine in 127 patients, surgical wounds in 47 patients, blood in 14 patients and other sites in 56 patients. Medications were stored for prolonged periods because they had been purchased in large volume (100 to 500 ml). Even under refrigeration, bacterial contaminants

multiplied to high concentrations. These authors found that 12 of 17 medication nebulizers were contaminated with S. marcescens, the same microorganism as that recovered from the contaminated medication bottles. The outbreak was controlled, but not eliminated, when medications were purchased in small volumes (30-60 ml) and were discarded at the end of each eight hour shift.

Ringrose and colleagues (81) described an outbreak in which nineteen patients became colonized or infected with S. marcescens over a two month period. In their investigation, they sampled the aerosol of two ultrasonic nebulizers. Cultures yielded a heavy growth of S. marcescens. When these machines were removed from use, the isolation of Serratia appeared to return to baseline rates.

Cartwright and Hargrave (10) reported on an outbreak of infection by P. aeruginosa. The authors demonstrated that the heating elements in the humidifier on the ventilator were the source of contamination. Tap water had been used to fill the humidifier over a 26-month period and the organism had formed a scale on the surfaces of the heating element.

During the ten-year period between 1971 and 1980, CDC investigated only one nosocomial epidemic in the United States attributed to contaminated respiratory therapy devices (69). During the outbreak, 16 persons on ventilatory support had sputum that was positive culturally for Acinetobacter calcoaceticus. Four patients were colonized with the organism, seven patients had

tracheobronchitis and five pneumonia. All organisms exhibited a common biotype and a characteristic antibiogram. The epidemic strain could not be cultured from the environment, but pooled hand cultures from Respiratory Care personnel were positive for the epidemic isolate. The investigators found that the hands of only one Respiratory Care therapist were colonized with A. calcoaceticus. The therapist calibrated and assembled ventilators prior to use. He had had a mild dermatitis of his hands for many months. This outbreak was not caused by contaminated nebulizers or medications, but by extrinsic contamination of respiratory therapy equipment from the hands of a Respiratory Care therapist.

Redding and McWalter (76) reported on an outbreak of Pseudomonas fluorescens in an ICU. Seven patients on ventilators for four days or more became colonized or infected. Bacteriologic examination of the ventilators revealed that humidifiers were the only source for P. fluorescens. The distilled water container (8 L in size) used to fill the humidifiers also yielded the organism and was thought to be the reservoir for the Pseudomonas.

In a prospective study, Im et al (44) attempted to identify the source of P. aeruginosa that caused infection in three patients on mechanical ventilation in an ICU. All patients developed pneumonia with the same strain as that recovered from the ventilator tubing. In each case, this organism was recovered from the ventilator tubing prior to

its recovery from the trachea. The authors implicated the ventilator as the source of the organism that caused pneumonia in these patients. They stated that ventilator tubing disinfection was ineffective due to trapping of air and inadequate drying, allowing the proliferation of microorganisms in the tubing.

Epidemiology of Ventilator Breathing Circuits

Little information is available on the effect of ventilator breathing circuit changes on contamination or HAP. In 1978 Lareau et al (53) found no differences in the risk of HAP in patients exposed to ventilator breathing circuits changed at 8, 16, or 24 hour intervals. There were two independent approaches used in her study. First, she performed a bacteriologic as well as epidemiologic study on 130 patients. In use aerosol sampling of 513 ventilator treatment periods showed bacterial contamination in 1.8% of 8 hour cycles, in 2.5% of 16 hour cycles, and 5.4% of 24 hour cycles. These differences in contamination were not significant. In a second retrospective study, she compared the incidence of pneumonia in patients on ventilators for two one-year periods when ventilator circuits were changed every 8 hours or 24 hours. In 1973 ventilator circuits were changed every 8 hours on 213 patients receiving a total of 1,096 days of ventilatory therapy. In 1976, when ventilator circuits were changed every 24 hours, 271 patients were treated for a total of 2,098 days. The incidence of HAP was the same for the one year periods (0.015 cases of pneumonia

per ventilator day). The author concluded that changing ventilator circuits every 24 hours provided adequate protection from HAP.

In 1982 Craven and co-workers (17) found no statistically significant difference in the rates of bacterial contamination of breathing circuits changed at 24 hour intervals (Group I) versus 48 hour intervals (Group II). In a prospective bacteriological study, ninety-five patients on continuous ventilation were studied. Two hundred and forty aerosol samples of the inspiratory tubing were obtained. Twenty percent of the aerosol cultures from Group I versus 14% of aerosol samples from Group II yielded high-level contamination. The high rates of air contamination were attributed to an artifact of sampling; during the extended sampling period, culture plates were contaminated by droplets of condensate. Quantitative analysis of colonization of the tubing also was performed. Ninety-three cultures taken from twenty-three patients in Group I and eighty cultures taken from thirty-one patients in Group II showed no significant difference in colonization rates between circuits changed at 24 and 48 hours. Concentration of microorganisms in the broth used in the broth washout culture technique ranged between 10^2 and 10^7 organisms per ml. Colonization at this level occurred in 15 patients from each group. The organisms isolated from the sputum were predominantly GNB (i.e., *Pseudomonas*, *Acinetobacter* and *Klebsiella*). The author suggested that the contamination of the tubing originated from the

patient's respiratory flora.

In 1984, Craven and co-workers (18) provided further support for the concept that respiratory breathing tubing is usually colonized by the bacteria present in the patients' secretions. They suggested that condensate may be contaminated and pose a risk for HAP. They cultured 58 ventilator circuits by taking samples of the proximal end of the inspiratory breathing tubing (end closest to patient) at 2, 4, 6, 8, 12, and 24 hours. After 24 hours, greater than 1000 CFU were present in the end of the tubing nearest the patient whereas there was no contamination in the distal tubing (end closest to machine). At 2 hours 33%, at 12 hours 67%, and at 24 hours 80% of proximal tubing sampled was colonized. Condensate from the breathing tubing was collected from 20 patients. The median level of colonization was 3.0×10^5 organisms/ml. Seventy-six percent of the organisms isolated were GNB. The survival of Gram-negative and Gram-positive bacteria (*K. pneumoniae*, *A. calcoaceticus*, *P. aeruginosa* and *S. aureus*) in sterile water was examined. No significant increase or decrease in bacterial concentrations was observed. The author concluded that retrograde contamination from patients is the primary mode of condensate colonization.

In 1985, Malecka-Griggs (60) reported a microbiological study of neonates' ventilator circuits that were changed at 24 and 48 hour intervals. The author evaluated the significance of changes in microbial concentrations during

the two intervals. Over a two year period, 379 fluid samples and 100 aerosol samples were obtained from the disposable circuits of 23 premature infants. Only three of 23 infants had respiratory tract colonization with pathogenic bacteria. One case of colonization occurred in phase I of the study when circuits were changed every 24 hours, and two cases occurred in phase II when circuits were changed every 48 hours. During the second phase, the author noted increased colonization by potential pathogens, and this led to a restoration of 24-hour circuit changes. Two infants were infected, one with K. pneumoniae and S. aureus and the other with P. aeruginosa. With 24 hour changes of circuits (phase I), a 2.5% contamination rate was observed. With 48 hour changes of circuits (phase II), the contamination rate increased to 19%. These data suggested to the author that frequent changing of the neonate circuits reduces colonization and cross-infection with P. aeruginosa.

In 1986, Craven and colleagues (20) reported from Boston City Hospital the risk factors for pneumonia and fatality in 233 intensive care unit patients receiving continuous mechanical ventilation over a 15 month period. Hospital acquired pneumonia was diagnosed in 49 (21%) of the 233 patients. The authors reported on eight risk factors significantly associated with the development of pneumonia: intracranial pressure monitoring, craniotomy, head trauma, treatment with cimetidine, 24-hour changes of the ventilator circuit, hospitalization during the Winter-Fall season, steroid treatment and coma. However, when the data were

analysed by stepwise logistic regression analysis, only the presence of an intracranial pressure monitor, treatment with cimetidine, hospitalization during the Winter-Fall seasons, and mechanical ventilator circuit changes every 24-hours remained significant. Age, sex, race, type of intensive care unit, shock, admission with pneumonia and positive end expiratory pressure were not significantly associated with pneumonia. Pneumonia was less frequent in patients who received ampicillin ($p<0.03$) or gentamicin ($p<0.03$) and more frequent for patients who received vancomycin ($p<0.04$).

Ninety-five (41%) of the patients died in the hospital. Seventy-eight (82%) were receiving mechanical ventilation or had received mechanical ventilation within 48-hours of death. Patients who died during hospitalization had a significantly higher mean age than the survivors ($59\pm$ 17 years versus $52\pm$ 18 years [$p=0.03$]). After multivariate analysis, the significant risk factors for fatality were: creatinine equal to or greater than 1.5 mg/dl, admission with pneumonia, not having received nebulized bronchodilators, a long duration of mechanical ventilation, having no abdominal surgery, being transferred from another hospital or hospital ward and having coma on admission.

Objectives of Study

1. To determine the bacterial contamination rate of the breathing circuit at 24 or 48 hours
2. To determine the incidence of pneumonia that develops in patients on ventilatory support where the breathing

circuit is changed either every 24 or 48 hours

3. To study the bacterial flora of the patient who is intubated (i.e.has a nasotracheal, orotracheal, or tracheostomy tube)

MATERIALS AND METHODS

The study was a prospective, randomized, double-blinded study and included all adult patients who were admitted to intensive care units and received mechanical ventilation during the period from January 1, 1984 until December 31,1984. Patients with pneumonia on admission, burn patients and persons younger than 17 years of age were excluded. Patients who were previously on a ventilator at another hospital could be enrolled in the study, but were excluded if they had pneumonia.

Respiratory Therapy Equipment

Each patient received mechanical ventilation via a nasotracheal, (National Catheter, Glen Falls, New York; Portex, Wilmington, Massachusetts) endotracheal (National and Portex) or tracheostomy tube (Shiley, Irvine, California; National Catheter, Portex) connected to one of the following volume ventilators: 1) Bennett MA-1 (Puritan Bennett, Linthicum Heights, Maryland); 2) Bear (Bournes Medical Systems, Riverside, California); 3) Emerson (J.H. Emerson, Cambridge, Massachusetts); and 4)Engstrom (Engstrom- division Gambro Inc., Barrington, Illinois). A Bennett MA-1 respirator was used by the majority of patients. These ventilators were used with one of the following humidifiers: 1) Cascade bubbling humidifiers

(Puritan Bennett); 2) Conchatherm wick humidifiers (Respiratory Care Inc, Arlington Heights, Illinois) and 3) Bird wick humidifiers (Bird Corp., Palm Springs, California). Only sterile distilled water was used in the humidifiers. All ventilators utilized a non-sterile disposable circuit (Dart Industries, Ocala, Florida). Prior to the study, all tubing and the connectors had been changed every 24 hours.

Randomization

The patients were randomized by the Respiratory Care personnel into two groups. Group I consisted of patients who had their entire ventilator circuit and humidifier changed every 24 hours. Group II consisted of patients who had their entire ventilator circuit and humidifier changed every 48 hours. Patients were enrolled in the study by Respiratory Care personnel when in their estimation a given patient met the criteria for enrollment. Before placing a patient on ventilation, the Respiratory Care personnel selected a sealed envelope containing an index card on which were either the numbers 24 or 48 (Group I or II). Envelopes had been prepared by a person not associated with the study using a computer generated table of random numbers. After randomization, the card containing the number was reinserted in the envelope and the patient's name, hospital number and the date, time and results of randomization were written on the outside of the envelope, and the envelope was stored for future reference. A form indicating that the patient was enrolled in the study was taped onto the ventilator.

Blinding

The author was blinded with respect to final diagnosis (infection versus no infection). Two pulmonary physicians evaluated all patients for lower respiratory tract infection. These physicians were blinded with respect to the timing of ventilator circuit changes. The technician in the Hospital Epidemiology Laboratory who processed cultures from the ventilators, and technicians from the Hospital Laboratory who processed sputum for culture also were blinded with respect to the timing of ventilator circuit changes.

Epidemiology

At the time of randomization, Respiratory Care personnel or Nursing personnel obtained a baseline specimen of respiratory secretions using a sterile suction catheter inserted into the endotracheal or tracheostomy tube. The specimen was collected as soon as possible after enrollment. These specimens were cultured in the Hospital Laboratory. The author maintained a log book of all persons randomized. Each morning, she reviewed the chart of each patient enrolled during the preceding 19 hours. Patients who did not meet criteria for enrollment were removed from the study at that time.

When patients were enrolled in the study, the following information on each patient was collected: name, hospital number and location, age, sex, race, date of admission, all patient diagnoses, type of intubation, smoking history,

underlying pulmonary diseases, and other underlying diseases, and the presence of a ventriculostomy. While the patient was on ventilatory support, additional data collected included inclusive dates of ventilation, treatment with antibiotics*, muscle relaxants and antacids, surgical operations+ (including type of operation, region of incision, and duration of surgery), and results of blood cultures and daily cultures of respiratory secretions.

If present at the time of collection of the daily sputum specimen, the author would macroscopically evaluate the sputum for absence or presence of "purulence". Otherwise, the description of the patient's sputum in the chart was used. Clinical and laboratory data for each patient (including temperature, blood pressure, the presence of chills, serum albumin and chest X-ray interpretations) were recorded daily by the investigator.

Collection of Microbiologic Samples

Patients on ventilatory support were followed by the author and cultures were obtained for the duration of ventilation, up to a period of 30 days. At the discontinuation of ventilation, the patients were followed clinically, bacteriologically, and radiographically for 72 hours. On completion of followup, the author would supply the pulmonary physicians with all of the data on the patient

* Only antibiotics given intravenously for $\geq$ 48 hours during the period from 48 hours before the start of ventilatory support to the end of ventilatory support were recorded.

+ Surgical procedures were recorded from 1 week prior to ventilation to discontinuation from the study.

except the microbiological results from the ventilator and timing of ventilator changes. Using the definitions given below, the physicians reviewed the clinical data and the chest X-rays to determine whether or not the patients had developed an HAP or bacteremia. This information was transferred to a computer form.

When the patient's ventilatory circuit and humidifier were changed, the patient was ventilated with a resuscitation bag. When the circuit was disconnected from the patient, bacteriological cultures of the inspiratory phase gas were taken using quantitative methods. The ventilator was adjusted to a standard tidal volume of 2 L per minute, a ventilatory rate of 25 breaths per minute, and to the maximum flow rate for each ventilator used (75-125 L/min). A 2-stage Andersen air sampler (Andersen Sampler, Inc, Atlanta, Georgia), was used to size the bacterial particles into those small enough to reach the lower respiratory tract and larger particles that would be filtered out in the upper respiratory tract. A sterile cup was attached to the end of the inspiratory tubing that had been proximal to the patient, and was placed over the sampling head of the sampler. The tubing was held flush to the sampler intake for one minute. An agar plate containing trypticase soy agar with 5% sheep blood was present in each stage of the sampler.

When the Respiratory Care personnel detached the circuit from the ventilator, the author cultured the distal and proximal segments of the inspiratory and expiratory

tubing. The ends of the tubing were cultured by inserting a swab to a depth of 3 cm using a spiral motion. As the swab was withdrawn, it was moved in the opposite direction. The swab was streaked over 1/2 of a blood agar plate at the bedside. The two limbs of the Y-connector were cultured using the same technique. The condensate from the inspiratory tubing was drained from the distal orifice into a sterile container. An equal volume of double strength Brain Heart Infusion (BHI) broth was then added. Fifty ml of BHI broth were aseptically poured into the inspiratory tubing at the proximal orifice. The tubing was rotated back and forth 10 times. The tubing was stretched as it was emptied so that all internal surfaces of the convoluted tubing came into contact with the broth. The broth then was collected in a sterile cup. Next, the author gently swirled the humidifier to mix the water and aspirated a 1-3 ml sample with a sterile syringe.

To determine the extent to which contamination from the act of sampling itself contributed to positive cultures, 49 unused circuits were cultured in the laboratory using the above described techniques. Only 25 of 400 samples from surfaces and fluids (6.3%) were positive. Only Micrococcus sp., coagulase-negative staphylocci and alpha hemolytic streptococci were recovered. Most cultures were positive at less than ten colonies. Thirteen of 22 (59%) of air samples were culture positive. However, eleven of thirteen (84.6%) had only one or two colonies recovered. The other two

positive air cultures had 3 and 7 colonies recovered, respectively. The only microorganism recovered in air cultures was coagulase-negative staphylococci. No pathogenic species were isolated from any of these cultures.

Definitions

Microorganisms were considered either pathogenic or non-pathogenic. Microorganisms defined as non-pathogens are shown in Table 1. All other microorganisms were considered pathogenic. Pneumonia was defined as the appearance of purulent sputum, and a new or progressive infiltrate on chest X-ray. When these signs were present without microbiologic data, the case was considered clinically confirmed. When these criteria were met and cultures of respiratory secretions yielded a potentially pathogenic organism, the case was considered microbiologically confirmed (31,97,11). Tracheobronchitis was defined when sputum was purulent but chest X-ray revealed a stable infiltrate or no infiltrate. Tracheobronchitis also was confirmed microbiologically or clinically. Ventilator-associated infection was defined as pneumonia or tracheobronchitis that developed at least 48-hours after start of ventilation or within 72 hours after ventilation was discontinued. Septicemia was defined as two or more positive blood cultures with a pathogenic organism in conjunction with two or more of the following clinical signs: fever equal to or greater than 100 ^{o} F, chills, and hypotension.

Table 1. Non-pathogenic Microorganisms

Microorganisms
Bacillus sp.
Candida albicans
Candida tropicalis
Diphtheroids
Enteric streptococci
Micrococcus sp.
Neisseria sp.
Coagulase-negative staphylococci
Alpha hemolytic streptococci
Non-hemolytic streptococci
Yeast (not further identified)

Microbiology

Cultures of respiratory secretions were processed in the Hospital Microbiology Laboratory and were planted on eosin methylene blue agar (EMB), blood agar (BA), and chocolate agar (CA). Cultures were semi-quantitated using the following definitions. When growth was present in all three streaks, growth was considered to be heavy. When growth appeared only in the primary and secondary streaks, it was considered moderate. Growth limited to the primary streak was considered light. All microorganisms were identified using standard techniques (2,29).

All cultures from ventilators were processed in the Hospital Epidemiology Laboratory. The BA plates and broth cultures were incubated at 37 ^{o}C. The agar plates were examined for growth at 24 and 48 hours, and colonies were counted and recorded. Broth cultures were incubated for 48 hours and subcultured to BA and EMB agar. Duplicate quantitative cultures of the water from the humidifiers were performed. Prior to culturing, the specimens were agitated for ten seconds. One tenth ml of the specimen was inoculated on the surface of a BA plate and spread with a glass rod. One ml aliquots of water were inoculated into 1.0 ml of double strength BHI broth. Broth was incubated for 48 hours and subcultured to BA and EMB agar. All microorganisms were identified by standard techniques (2,29).

Statistical Analysis

Data were analyzed using the university computer (IBM 3081 mainframe computer). The SAS Statistical package was used in summarizing and analyzing the data (83). Categorical data were analyzed using a two-tailed Fisher's exact test. A t-test for test of equality of means was used in the analysis of continuous variables. The statistical power for detection of true differences between rates was determined by a method described by Cohen (15). Multivariate analysis was performed using the procedure for stepwise logistic regression in the SAS statistical package (83). Variables included in the models for logistic regression analysis were those found to have a significant or borderline significant association with infection by univariate analysis.

RESULTS

Four hundred and sixty patients thought to be without respiratory tract infection were randomized to receive circuit changes at 24 hours (Group I) or 48 hours (Group II). Two hundred and forty-nine persons were eliminated from analysis. One hundred and seventy-one of these persons were eliminated because ventilatory support was discontinued before the first circuit change (61 persons in the 24-hour group and 110 persons in the 48-hour group). Fifty of the 249 persons were eliminated, because it was later determined that pneumonia was present at the time ventilatory support had been initiated (25 persons were in the 24-hour group and 25 persons were in the 48-hour group). Five patients were eliminated from analysis, because they were ventilated for more than thirty days. All of these were in the 24-hour group. Twenty-three persons in the 24-hour group were eliminated from analysis, because the period of ventilation was less than 48 hours. Thus, only patients having ventilatory support that lasted for at least 48 hours (Group I and Group II) were included in the analysis.

Two hundred and eleven persons were evaluable. Of these, 116 persons were in Group I and 95 persons were in Group II. There were 17 persons who had two separate

courses of ventilatory support and one person with three courses of ventilatory support. Thus, there were 230 courses of artificial ventilation.

Infections and Outcome of Infections

Pneumonia. Thirty-five patients developed pneumonia after being on ventilatory support. Thirty-five of 211 patients (16.6%) developed pneumonia and 35 of 230 ventilatory courses (15.2%) were complicated by pneumonia. Patients who developed pneumonia were on ventilatory support for an average of 9.4 days prior to infection (range 2-29 days). The mean age of patients with pneumonia was 50.2 years. Twenty-three patients were male and 12 were female. There were 19 whites and 16 blacks. Pathogens isolated from the sputum of patients with pneumonia are shown in Table 2. No pathogen was isolated from the sputum of ten patients (28.6%). Sputum yielded one pathogen in 14 patients (40%), two pathogens in nine patients (25.7%) and three pathogens in two patients (5.7%).

Tracheobronchitis. One hundred and eighteen patients developed tracheobronchitis while on ventilatory support. One hundred and eighteen of 211 patients (56.0%) developed tracheobronchitis, and one hundred and eighteen of 230 ventilatory courses (51.3%) were complicated by tracheobronchitis. Patients who developed tracheobronchitis were on ventilatory support for an average of 6.3 days prior to infection (range 1-29 days). The mean age of patients with tracheobronchitis was 52.2 years. Sixty-three were

Table 2. Pathogens Isolated from the Sputum of Patients with Pneumonia

Causative Organism	Frequency*	% of Pneumonias+
No Pathogen Isolated	10	28.6
Pseudomonas aeruginosa	6	17.1
Enterobacter cloacae	5	14.3
Escherichia coli	5	14.3
Hemophilus influenza	4	11.4
Proteus mirabilis	4	11.4
Klebsiella pneumoniae	4	11.4
Staphylococcus aureus	3	8.6
Enterobacter aerogenes	2	5.7
Klebsiella oxytoca	2	5.7
Acinetobacter calcoaceticus	2	5.7
Citrobacter diversus	1	2.9
Providencia stuartii	1	2.9

* The total number of isolates is greater than the total number of cases of pneumonia because some cases had more than one causative organism

+ Numbers in this column add up to greater than 100 because some patients had more than one isolate

Table 3. Pathogens Isolated from the Sputum of Patients with Tracheobronchitis

Causative Organism	Frequency*	% of Tracheobronchitis+
No Pathogen Isolated	41	34.7
Proteus mirabilis	23	19.5
Pseudomonas aeruginosa	18	15.3
Staphylococcus aureus	18	15.3
Escherichia coli	13	11.0
Hemophilus influenza	11	9.3
Enterobacter cloacae	11	9.3
Klebsiella pneumoniae	8	6.8
Serratia marcescens	7	5.9
Enterobacter aerogenes	6	5.1
Acinetobacter calcoaceticus	5	4.2
Klebsiella oxytoca	4	3.4
Citrobacter freundi	3	2.5
Streptococcus pneumoniae	3	2.5
Pseudomonas maltophilia	1	0.6
Serratia liquefaciens	1	0.6

* The total number of isolates is greater than the total number of cases of tracheobronchitis because some cases had more than one causative organism.

+ Numbers in this column add up to greater than 100 because some patients had more than one isolate

male and 55 were female. There were 58 whites and 60 blacks. Pathogens isolated from the sputum of patients with tracheobronchitis are shown in Table 3. No pathogen was isolated from the sputum of 41 patients (34.7%). Sputum yielded one pathogen in 52 patients (44.1%), two pathogens in 16 patients (13.6%) and three pathogens in 9 patients (7.6%).

Bacteremia. There were eleven cases of bacteremia in 211 patients (5.2%). Isolates from blood and sputum of these patients are shown in Table 4. In two patients with pneumonia and three patients with tracheobronchitis, the species recovered from blood also was recovered from sputum before or at the same time it was recovered from blood.

Outcome of Infections: Mortality. Ventilator associated pneumonia was associated significantly with a fatal outcome ($p= 0.0076$). On the other hand, tracheobronchitis was not associated significantly with mortality ($p = 0.71$).

Epidemiology

Twenty-four versus Forty-eight Hour Circuit Changes. The results of randomization are shown in Tables 5-8. Randomization of patients to either 24-hour or 48-hour circuit changes (Group I or Group II) resulted in only two significant differences between Group I and Group II. Patients in Group II were significantly more likely to have a diagnosis of chest injury ($p=0.04$), and were significantly more likely to have received antacids ($p=0.03$). Thus, randomization worked very well as the two groups differed significantly in only two of fifty-four characteristics

Table 4. Cases of Septicemia: Microorganisms from Blood and Sputum

Microorganisms from Blood	Respiratory Infection	Microorganisms from Sputum
Enteric streptococci	Pneumonia	*C. diversis*
P. aeruginosa	Pneumonia	*P. aeruginosa*
S. aureus	Pneumonia	*S. aureus*
S. pneumoniae	Pneumonia	*P. mirabilis*
K. pneumoniae	Tracheobronchitis	*E. coli* *S. aureus*
P. aeruginosa	Tracheobronchitis	*P. aeruginosa*
P. mirabilis	Tracheobronchitis	*S. aureus*
S. aureus	Tracheobronchitis	*S. aureus*
S. aureus	Tracheobronchitis	*P. mirabilis* *E. coli*
S. marcescens	Tracheobronchitis	*S. marcescens*
S. marcescens	Tracheobronchitis	*K. pneumoniae*

Table 5. Results of Randomization: Demographic Factors

Factor	Group I	Group II	P value
AGE (mean)	51.49	51.35	0.96*
SEX (male/female)	70/46	48/47	0.17+
RACE (white/black)	62/54	43/52	0.27+

* t-test

\+ Fisher's exact test (2-tail)

Table 6. Results of Randomization: Admitting Diagnoses

Characteristic	Group I Absent	Group I Present	Group II Absent	Group II Present	P value*
Infectious Diseases	112	4	91	4	1.00
Diabetes mellitus	99	17	74	21	0.21
Hematologic Diseases	112	4	94	1	0.38
Neurologic Diseases	108	8	86	9	0.61
Coma	114	2	94	1	1.00
Seizures	110	6	91	4	1.00
Head Injury	97	19	78	17	0.85
Cardiac Diseases	70	46	47	48	0.13
Cerebrovascular Disease	103	13	84	11	1.00
Peripheral Vascular Diseases	102	14	85	10	0.83
Respiratory Diseases	96	20	68	27	0.07
Chest Injury	111	5	83	12	0.04
Gastrointestinal Diseases	95	21	82	13	0.45
Skin and Subcutaneous Tissue Diseases	115	1	95	0	1.00
Skeletal Diseases	112	4	93	2	0.69
Renal Diseases	100	16	74	21	0.15
Renal Transplant	116	0	93	2	0.20
Neoplastic Diseases	87	29	82	13	0.06

* Fisher's exact test (2-tail)

Table 6. Results of Randomization:

Admitting diagnoses(cont'd.)

Characteristic	Group I Absent	Group I Present	Group II Absent	Group II Present	P value*
Neoplastic Diseases	87	29	82	13	0.06
Psychiatric Diseases	113	3	92	3	1.00
Ethanol Abuse	101	15	80	15	0.56
Drug Abuse	115	1	95	0	1.00

* Fisher's exact test (2-tail)

Table 7. Results of Randomization: Medications

Medication	Group I Absent	Group I Present	Group II Absent	Group II Present	P value
Any Antibiotics	33	83	33	62	0.37*
Aminoglycosides	83	33	71	24	0.64*
Cephalosporins	76	40	64	31	0.88*
Penicillins	74	42	63	32	0.77*
Number of Antibiotics(mean)	1.19		1.09		0.52+
Antacids	72	44	44	51	0.03*
Cimetidine	78	38	67	28	0.66*
Pancuronium	96	20	75	20	0.49*

* Fisher's exact test (2-tail)

\+ t-test

Table 8. Results of Randomization:

Epidemiologic Characteristics

Characteristic	Group I Absent	Group I Present	Group II Absent	Group II Present	P value
Ventilated in Fall-Winter	54	62	45	50	1.00*
Smoking History					
Current Smoker	36	60	33	41	0.43*
Ever Smoked	23	73	27	47	0.09*
Type of intubation					
Nasotracheal	62	54	55	40	0.58*
Orotracheal	64	52	49	46	0.68*
Tracheostomy	105	11	82	13	0.39
ICU location					
General Medical	93	20	78	17	1.00*
Respiratory	108	5	88	7	0.39*
Coronary	105	8	91	4	0.55*
Neuroscience	76	37	65	30	0.88*
General Surgery	70	43	58	37	1.00*
Surgical Operations	40	76	39	56	0.39
Types of Surgery					
Cranial	54	22	43	13	0.55*
Thoracic	54	22	43	13	0.55*
Abdominal	46	30	26	30	0.12*
Other	13	63	12	44	0.65*
Ventriculostomy	109	7	90	5	1.00*
Duration of Surgery	4:42		4:55		0.66+
Ventilation Duration	5.3 d.		7 d.		0.0532+

* Fisher's exact test (2-tail)
\+ t-test

examined.

There were fifteen cases of pneumonia in Group I (13%) and twenty cases of pneumonia in Group II (21.1%). The difference in infection rates between Group I and Group II was not significant (p=0.14). With these rates and the sample size of 211 patients on ventilatory support, the probability of detecting a significant difference is 47% (statistical power = 47%). Thus, it would be possible to detect a true difference in these rates only about half of the time. A sample size of 523 persons would have been required to reach 80% power.

There were 68 cases of tracheobronchitis in Group I (58.6%) and 50 cases of tracheobronchitis in Group II (52.6%). The difference between the tracheobronchitis rates was not significant (p = 1.00). With these rates and the sample size of 211 patients on ventilatory support, the probability of detecting a significant difference is 21.8% (statistical power = 21.8%). Thus, it would be possible to detect a true difference in these rates only about one fifth of the time. A sample size of 1,704 persons would have been required to reach 80% power.

Risk Factors for Infection. Three sets of analysis for identification of risk factors were performed. First, patients with pneumonia were compared to patients without pneumonia. In the second analysis, patients with pneumonia were compared to patients who had no infection (patients with tracheobronchitis were excluded from the group of patients without pneumonia). In the third analysis,

patients with tracheobronchitis were compared to patients who had no infections.

Results of the first analysis are shown in Tables 9-12. Risk factors for pneumonia included head injury, chest injury, other types of surgery (surgery that was not cranial, thoracic or abdominal), having been hospitalized in the neurosciences ICU and a longer duration of ventilation. Two factors were identified that appeared to protect patients from developing pneumonia. These included having received any antibiotics, and having a nasotracheal tube rather than an orotracheal tube or tracheostomy.

Results of the second analysis are shown in Table 13-16. For this analysis, patients with tracheobronchitis were removed from the group of patients without pneumonia. Thus, in this analysis, patients with pneumonia were compared with patients without any respiratory tract infection. When the analysis was performed in this manner, chest injury and other types of surgery were no longer risk factors for pneumonia. However, three additional risk factors were identified including use of pancuronium, ventilation by way of a tracheostomy and presence of a ventriculostomy. This analysis appeared to sharpen the differences between pneumonia and patients who did not develop pneumonia while on ventilatory support. As in the first analysis, duration of ventilation was significantly associated with development of pneumonia. Use of antibiotics and nasotracheal intubation were again found to be protective.

Table 9. Patients with Pneumonia versus Patients without Pneumonia: Demographic Factors[++]

Factor	Pneumonia	No Pneumonia	P value
AGE (mean)	50.20	51.67	0.68*
SEX (male/female)	23/12	95/81	0.26[+]
RACE (white/black)	19/16	86/90	0.58+

* t-test

\+ Fisher's exact test (2-tail)

++ Patients with tracheobronchitis are included in the group of patients without pneumonia

Table 10. Patients with Pneumonia versus Patients without Pneumonia + Admitting Diagnoses

Characteristic	Pneumonia Absent	Pneumonia Present	No Pneumonia Absent	No Pneumonia Present	P value *
Infectious Diseases	35	0	168	8	0.36
Diabetes mellitus	33	2	140	36	0.051
Hematologic Diseases	33	2	173	3	0.19
Neurologic Diseases	33	2	161	15	0.74
Coma	35	0	173	3	1.00
Seizures	33	2	168	8	0.67
Head Injury	22	13	153	23	0.002
Cardiac Diseases	23	12	94	82	0.20
Cerebrovascular Diseases	32	3	155	21	0.77
Peripheral Vascular Diseases	32	3	155	21	0.77
Respiratory Diseases	29	6	135	41	0.51
Chest Injury	28	7	166	10	0.01
Gastrointestinal Diseases	29	6	148	28	0.81
Skin and Subcutaneous Diseases	35	0	175	1	1.00
Skeletal Diseases	34	1	171	5	1.00

+ Patients with tracheobronchitis are included in the group of patients without pneumonia

* Fisher's exact test

Table 10. Patients with Pneumonia versus Patients without Pneumonia: Admitting Diagnosis (cont'd.)

Characteristic	Pneumonia Absent	Pneumonia Present	No Pneumonia Absent	No Pneumonia Present	P value*
Renal Diseases	33	2	141	35	0.051
Renal Transplant	35	0	174	2	1.00
Neoplastic Diseases	32	3	137	39	0.10
Psychiatric Diseases	34	1	171	5	1.00
Ethanol Abuse	30	5	151	25	1.00
Drug Abuse	35	0	175	1	1.00

* Fisher's exact test (2-tail)

Table 11. Patients with Pneumonia versus Patients without Pneumonia: *
Medications

Medication	Pneumonia Absent	Pneumonia Present	No Pneumonia Absent	No Pneumonia Present	P value
Any Antibiotics	17	18	49	127	0.03+
Aminoglycosides	29	6	125	51	0.21+
Cephalosporins	24	11	116	60	0.85+
Penicillins	26	9	111	65	0.25+
Number of antibiotics (mean)	0.83		1.21		0.5++
Antacid	9	16	97	79	1.00+
Cimetidine	23	12	122	54	0.69+
Pancuronium	25	10	146	30	0.15+

* Patients with tracheobronchitis are included in the group of patients without pneumonia

\+ Fisher's exact test (2-tail)

++ t-test

Table 12. Patients with Pneumonia versus Patients without Pneumonia*: Epidemiologic Characteristics

Characteristics	Pneumonia Absent	Pneumonia Present	No Pneumonia Absent	No Pneumonia Present	P value
Ventilated in Fall-Winter	82	94	17	18	0.85+
Smoking History					
Current Smoker	11	15	58	86	0.83+
Ever Smoked	8	18	42	102	1.00+
Type of intubation					
Nasotracheal	25	10	92	84	0.04+
Orotracheal	17	18	96	80	0.58+
Tracheostomy	28	7	159	17	0.09+
ICU location					
General Medical	32	2	139	35	0.051+
Respiratory	31	3	165	9	0.42+
Coronary	32	2	164	10	1.00+
Neuroscience	17	17	124	50	0.026+
General Surgery	24	10	104	70	0.25+
Surgical Operations	109	23	67	12	0.71
Type of Surgery					
Cranial	16	7	81	28	0.61+
Thoracic	18	5	79	30	0.80+
Abdominal	16	7	56	53	0.17+
Other	15	8	92	17	0.04+
Ventriculostomy	31	4	168	8	0.12
Duration of Surgery	4:35		4:50		0.77**
Ventilation Duration	9.4 d.		5.4 d.		0.0038**

* Patients with tracheobronchitis are included in the group of patients without pneumonia
\+ Fisher's exact test (2-tail)
** t-test

Table 13. Patients with Pneumonia versus Patients without Infection: Demographic Factors

Factor	Pneumonia	No Pneumonia	P value
AGE (mean)	50.20	49.89	0.94*
SEX (male/female)	23/12	32/26	0.39+
RACE (white/black)	19/16	28/30	0.67+

* t-test

\+ Fisher's exact test (2-tail)

Table 14. Patients with Pneumonia versus Patients without Infection: Admitting Diagnosis

Characteristic	Pneumonia Absent	Pneumonia Present	No Pneumonia Absent	No Pneumonia Present	P value*
Infectious Diseases	35	0	55	3	0.28
Diabetes mellitus	33	2	47	11	0.12
Hematologic Diseases	33	2	57	1	0.55
Neurologic Diseases	33	2	52	6	0.71
Coma	35	0	57	1	1.00
Seizures	33	2	55	3	1.00
Head Injury	22	13	50	8	0.012
Cardiac Diseases	23	12	36	22	0.83
Cerebrovascular Diseases	32	3	55	3	0.67
Peripheral Vascular Diseases	32	3	53	5	1.00
Respiratory Diseases	29	6	46	12	0.79
Chest Injury	28	7	53	5	0.13
Gastrointestinal Diseases	29	6	47	11	1.00
Skeletal Diseases	34	1	57	1	1.00
Renal Diseases	33	2	46	12	0.07
Neoplasms	32	3	43	15	0.06
Psychiatric Diseases	34	1	55	3	1.00
Ethanol Abuse	30	5	49	9	1.00

* Fisher's exact test (2-tail)

Table 15. Patients with Pneumonia versus Patients without Infection: Medications

Medication	Pneumonia Absent	Pneumonia Present	No Pneumonia Absent	No Pneumonia Present	P value
Any Antiobiotics	17	18	15	43	0.042 *
Aminoglycosides	29	6	45	13	0.61 *
Cephalosporins	24	11	34	24	0.38 *
Penicillins	26	9	39	19	0.64 *
Number of Antibiotics (mean)	0.83		1.14		0.15 +
Antacid	19	16	36	22	0.52 *
Cimetidine	23	12	44	14	0.34 *
Pancuronium	25	10	53	5	0.018 *

* Fisher's exact test (2-tail)

+ t-test

Table 16. Patients with Pneumonia versus Patients without Infection: Epidemiologic Characteristics

Characteristic	Pneumonia Absent	Pneumonia Present	No Pneumonia Absent	No Pneumonia Present	P value
Ventilated in Fall-Winter	17	18	28	30	1.00*
Smoking History					
Current Smoker	11	15	18	29	0.81*
Ever Smoked	8	18	13	34	0.79*
Type of intubation					
Nasotracheal	25	10	25	33	0.01*
Orotracheal	17	18	35	23	0.29*
Tracheostomy	28	7	55	3	0.038*
ICU location					
General Medical	32	2	46	12	0.07*
Respiratory	31	3	55	3	0.67*
Coronary	32	2	55	3	1.00*
Neurosciences	17	17	43	15	0.02*
General Surgery	24	10	33	25	0.27*
Surgical Operations	42	23	16	12	0.50
Type of Surgery					
Cranial	16	7	37	5	0.10*
Thoracic	18	5	27	15	0.28*
Abdominal	16	7	21	21	0.19*
Other	15	8	36	6	0.07*
Ventriculostomy	31	4	58	0	0.018*
Duration of Surgery	4:35		4:17		0.62+
Ventilation Duration	9.4 d.		3.5 d.		0.0001+

* Fisher's exact test (2-tail)
\+ t-test

Table 17.Patients with Tracheobronchitis versus Patients without Infection: Demographic Factors

Factor	Infected	Noninfected	P value
AGE (mean)	52.53	49.89	0.38*
SEX(male/female)	63/55	32/26	0.87+
RACE (white/black)	58/60	28/30	1.00+

* t-test

+ Fisher's exact test (2-tail)

Table 18. Patients with Tracheobronchitis versus Patients without Infection: Admitting Diagnosis

Characteristic	Infection Absent	Infection Present	No Infection Absent	No Infection Present	P value*
Infectious Diseases	113	5	55	3	0.72
Diabetes mellitus	93	25	47	11	0.84
Hematologic Diseases	116	2	57	1	1.00
Neurologic Diseases	109	9	52	6	0.57
Coma	116	2	57	1	1.00
Seizures	113	5	55	3	0.72
Head Injury	103	15	50	8	0.82
Cardiac Diseases	58	60	36	22	0.11
Cerebrovascular Disease	100	18	55	3	0.08
Peripheral Vascular Disease	102	16	53	5	0.46
Respiratory Disease	89	29	46	12	0.70
Chest Injury	113	5	53	5	0.30
Gastrointestinal Disease	101	17	47	11	0.51
Skin and Subcutaneous Disease	117	1	58	0	1.00
Skeletal Disease	114	4	57	1	1.00
Renal Diseases	95	23	46	12	0.84
Renal Transplant	116	2	58	0	1.00
Neoplastic Disease	94	24	43	15	0.44
Psychiatric Disease	116	2	55	3	0.33
Ethanol Abuse	102	16	49	9	0.82
Drug Abuse	117	1	58	0	1.00

* Fisher's exact test (2-tail)

Table 19. Patients with Tracheobronchitis versus Patient without Infection: Medications

Medication	Tracheobronchitis Absent	Tracheobronchitis Present	Non Infected Absent	Non Infected Present	P value
Any Antibiotics	34	84	15	43	0.72*
Aminoglycosides	80	38	45	13	0.22*
Cephalosporins	82	36	34	24	0.18*
Penicillins	72	46	39	19	0.51*
Number of antibiotics(mean)	1.25		1.14		0.53+
Antacids	46	72	30	28	0.20*
Cimetidine	78	40	44	14	0.22*
Pancuronium	93	25	53	5	0.053*

* Fisher's exact test (2-tail)

\+ t-test

Table 20. Patients with Tracheobronchitis versus Patients without Infection: Epidemiologic Characteristics

Characteristic	Tracheobronchitis Absent	Tracheobronchitis Present	Non Infected Absent	Non Infected Present	P value
Ventilated in Fall-Winter	54	64	45	48	1.00*
Smoking History					
Current Smoker	40	57	18	29	0.86*
Ever Smoked	29	68	13	34	0.85*
Type of intubation					
Nasotracheal	67	51	25	33	0.11*
Orotracheal	61	57	35	23	0.33*
Tracheostomy	104	14	55	3	0.19*
ICU location					
General Medical	93	23	46	12	1.00*
Respiratory	110	6	55	3	1.00*
Coronary	109	7	55	3	1.00*
Neurosciences	81	35	43	15	0.60*
General Surgery	33	25	71	45	0.62*
Surgical Operations	42	67	16	51	0.049*
Types of Surgery					
Cranial	44	23	37	5	0.01*
Thoracic	52	15	27	15	0.19*
Abdominal	35	32	21	21	0.85*
Other	36	6	56	11	1.00*
Ventriculostomy	110	8	58	0	0.054*
Duration of Surgery	5:11		4:17		0.10+
Ventilation Duration	6.3 d.		3.5 d.		0.0001+

* Fisher's exact test (2-tail)
\+ t-test

Results of the third analysis are shown in Tables 17-20. Only three risk factors were identified for tracheobronchitis. They were surgical operations in general, cranial operations and duration of ventilation. There were no factors that appeared to protect against development of tracheobronchitis.

Multivariate analysis. Because many of the risk factors identified by univariate analysis may have been interrelated, these risk factors were subjected to multivariate analysis using a stepwise logistic regression procedure. All variables with a significant association or a borderline significant association with the occurrence of infection were included in the models.

In the first analysis, where patients with pneumonia were compared with patients without pneumonia, variables included in the model for the logistic regression procedure included head injury, chest injury, other surgery, duration of ventilation, not having received antibiotics, not having a nasotracheal tube, location in the general medical ICU, and location in the neurosciences ICU. After logistic regression analysis, three variables remained associated significantly with pneumonia. These included duration of ventilation ($p \leq 0.00009$), not having received an antibiotic ($p = 0.0013$), and having sustained a chest injury ($p = 0.0019$).

In the second analysis, where patients with pneumonia were compared with patients without infection, variables included in the model for the logistic regression procedure

included head injury, treatment with pancuronium, having had a tracheostomy, duration of ventilation, location in the neurosciences ICU, not having received antibiotics, and not having a nasotracheal tube. After logistic regression analysis, three variables remained associated significantly with pneumonia. These included duration of ventilation ($p = 0.0001$), not having received an antibiotic ($p = 0.002$), and having received pancuronium ($p = 0.0463$).

For multivariate analysis of the factors associated with tracheobronchitis, variables included in the model for stepwise logistic regression were having had any surgical operation, having had cranial surgery, having received pancuronium and duration of ventilation. When these variables were analysed by this procedure, only duration of ventilation remained significantly associated with the occurrence of tracheobronchitis.

Microbiology

Ten thousand and ten cultures were obtained from 1,247 breathing circuits and 56.5% were positive. Ten and seven-tenths percent of all cultures taken yielded a pathogen. Ninety and four-tenths percent of all cultures taken from the internal surfaces of the ventilator circuits were positive, and 6.6% of internal surface cultures of the ventilator circuits were positive for a pathogenic species. For condensate and humidifier water, the culture positivity rate was lower (74.7% and 3.2%, respectively). Pathogens were recovered from 38.2% of condensate cultures and 1.6% of the cultures of humidifier water. Forty-eight and two-

tenths percent of stage 1 air cultures were positive. Only about one-half as many stage 2 air cultures were positive (26.3%). Pathogens were recovered from 9.5% of stage 1 air cultures and 4.7% of stage 2 air cultures. The rates of positive cultures for Group I and Group II circuits are shown in Table 21.

Microorganisms Isolated from Circuits. The microorganisms isolated from circuits changed at 24 hours or 48 hours are shown in Tables 22 and 23. Any microorganisms were isolated from 94.1% of Group I circuits and 93.7% of Group II circuits, and pathogens were isolated from 61.3% of Group I circuits and 66.2% of Group II circuits. The great preponderance of pathogens isolated from both 24 and 48 hour circuits were Gram-negative bacilli. S. aureus was the major Gram-positive pathogen isolated from Group I and Group II circuits and outnumbered all other Gram-positive pathogens from 7:1 to 10:1.

Cultures of Air. Microorganisms isolated from the air of the inspiratory limb of the circuit are shown in Tables 24 and 25. Microorganisms were recovered from air of 54% of Group I circuits and 51.6% of Group II circuits. Twenty-four percent of Group I positive air cultures yielded a pathogenic organism. Thirty-seven percent of the positive air cultures from Group II had one or more pathogens isolated. Fifteen to 20% of the agar plates in stage 1 were contaminated by condensate that dripped out of the proximal inspiratory limb during air sampling. Of all the pathogenic microorganisms present in respiratory circuits, only a

Table 21. Rates of Positive Cultures for Circuits Changed at 24 Hours versus 48 Hours

Type of Culture	Group I		Group II	
	Number	Rate(%)	Number	Rate(%)
Internal surfaces of circuits	496	88.6	304	92.1
Condensate	397	73.7	236	75.6
Water	16	3.0	10	3.3
Air	276	54.0	146	51.6
stage 1	256	50.4	129	45.9
stage 2	142	28.0	68	24.5

Table 22. Microorganisms Isolated from Circuits Changed every 24 Hours*

Microorganism	Frequency	% of Total Isolates
Gram-positive cocci:		
Staphylococcus aureus	90	3.1
Streptococcus pneumoniae	7	0.2
Streptococcus pyogenes	2	0.1
Gram-negative bacilli:		
Pseudomonas aeruginosa	478	16.3
Klebsiella pneumoniae	303	10.4
Escherichia coli	257	8.8
Proteus mirabilis	232	7.9
Serratia marcescens	213	7.3
Acinetobacter calcoaceticus	142	4.9
Enterobacter aerogenes	80	2.7
Enterobacter cloacae	75	2.6
Citrobacter freundii	41	1.4
Pseudomonas maltophilia	10	0.3
Pseudomonas species	7	0.2
Klebsiella oxytoca	6	0.2
Hemophilus influenzae	6	0.1
Serratia liquefaciens	2	0.1
Citrobacter diversus	1	0.03
Non-pathogens	973	33.3
Total	2925	100

* Includes cultures of all internal surfaces of the ventilator circuit, condensate, and water from the humidifier

Table 23. Microorganisms Isolated from Circuits *
Changed every 48 Hours

Microorganism	Frequency	% of Total Isolates
Gram-positive cocci:		
Staphylococcus aureus	81	4.3
Streptococcus pyogenes	4	0.2
Streptococcus pneumoniae	3	0.2
Gram-negative bacilli:		
Pseudomonas aeruginosa	477	25.4
Acinetobacter calcoaceticus	143	7.6
Klebsiella pneumoniae	130	6.9
Proteus mirabilis	122	6.5
Enterobacter aerogenes	90	4.8
Enterobacter cloacae	86	4.6
Serratia marcescens	86	4.6
Escherichia coli	72	3.8
Enterobacter agglomerans	10	0.5
Citrobacter freundii	5	0.3
Serratia liquefaciens	5	0.3
Klebsiella oxytoca	4	0.2
Pseudomonas maltophilia	4	0.2
Pseudomonas species	4	0.2
Hemophilus parainfluenza	2	0.1
Hemophilus influenza	1	0.1
Non-pathogens	547	29.2
Total	1876	100

* Includes cultures of all internal surfaces of the ventilator circuit, condensate, and water from the humidifier.

Table 24. Microorganisms Isolated from Air of Ventilator Circuits Changed every 24 Hours *

Microorganism	Frequency	% of Total Cultures
Pseudomonas aeruginosa	28	9.6
Staphylococcus aureus	8	2.7
Acinetobacter calcoaceticus	7	2.4
Serratia marcescens	6	2.1
Escherichia coli	5	1.7
Klebsiella pneumoniae	5	1.7
Proteus mirabilis	5	1.7
Enterobacter cloacae	2	0.7
Enterobacter aerogenes	2	0.7
Citrobacter freundii	2	0.7
Non-pathogens	222	76.0
Total	292	100

* Isolates from stage 1 and stage 2 of the Andersen air sampler combined

Table 25. Microorganisms Isolated from Air of Ventilator Circuits Changed every 48 Hours*

Microorganism	Frequency	% of Total Cultures
Pseudomonas aeruginosa	32	19.8
Serratia marcescens	5	3.1
Staphylococcus aureus	5	3.1
Enterobacter aerogenes	4	2.5
Klebsiella pneumoniae	4	2.5
Acinetobacter calcoaceticus	3	1.9
Enterobacter cloacae	3	1.9
Proteus mirabilis	2	1.2
Enterobacter agglomerans	1	0.5
Escherichia coli	1	0.5
Non-pathogens	102	63.0
Total	162	100

* Isolates from stage 1 and stage 2 of the Andersen air sampler combined

limited number could be recovered from the air. The only pathogens isolated from Group I and Group II air cultures were S.aureus and the nine GNB most commonly isolated from circuit cultures (Tables 22 and 23). With one exception, the pathogenic species isolated from the air of Group I circuits were the same as those isolated from Group II circuits. Only two-thirds (8 of 12) of the pathogenic species isolated from the sputum of patients with pneumonia (Table 2) also were isolated from the air of respiratory circuits. However, P. aeruginosa which was the pathogen most frequently isolated from the sputum of patients with pneumonia, was also the pathogen most frequently isolated from the air cultures.

Cultures from Subgroups of Patients Randomized to Receive Circuit Changes at 24 Hours. In a subset of 23 patients (Group IA), randomized to receive circuit changes at 24 hours, ventilatory support was discontinued after only one circuit change. In a subset of 116 patients (Group IB), randomized to received circuit changes at 24 hours, ventilatory support was continued for 48 or more hours. Since all circuits in Group IA were exposed only during the first 24 hours of ventilation, it was decided that Groups IA and IB should be analyzed separately. Results of the analyses where Group IA is compared with Group IB are shown in Tables 26 and 27. As can be seen in Table 26, circuits in Group IB are significantly more likely to be culture positive than cultures in Group IA when circuit cultures (all components) and internal surfaces of circuits are

Table 26. Culture Results from Circuits in Group IA and Group IB: Positive Cultures versus Negative Cultures *

Source of Culture	Group IA Microbial Growth Absent/Present		Group IB Microbial Growth Absent/Present		P value+
Circuit cultures (all components)	5	21	33	527	0.02
Circuit cultures (internal surfaces)	8	18	64	496	0.008
Condensate	8	13	142	397	0.31
Humidifier Water	20	1	511	16	0.49
Air cultures (Andersen air sampler)	9	9	235	276	0.81
1st stage only	12	6	252	256	0.23
2nd stage only	12	5	364	142	1.00

* Group IA was made up of patients who were on the ventilator for less than 48 hours and in most cases had only one circuit culture. Group IB was made up of patients who were on ventilatory support for at least 48 hours and who had two or more circuits cultured.

+ Fisher's exact test (2-tail)

Table 27. Culture Results from Circuits in Group IA and Group IB: Pathogens versus Absence of Pathogens*

Source of Culture	Group IA Pathogen Absent	Group IA Pathogen Present	Group IB Pathogen Absent	Group IB Pathogen Present	P value*
Circuit cultures (all components)	21	5	217	343	0.00009
Circuit cultures (internal surfaces)	22	4	231	329	0.00009
Condensate	18	3	299	240	0.006
Humidifier Water	21	0	520	7	1.00
Air cultures (Andersen air sampler)	17	1	457	54	0.71
1st stage only	17	1	464	44	1.00
2nd stage only	17	0	486	20	1.00

* Group IA was made up of patients who were on the ventilator for less than 48 hours and in most cases had only one circuit culture. Group IB was made up of patients who were on ventilatory support for at least 48 hours and who had two or more circuits cultured.

+ Fisher's exact test (2-tail)

compared. It can be seen in Table 27, where only pathogenic isolates are compared, that the differences between Group IA and Group IB are even greater. Also, when cultures of condensate that yielded pathogens are compared, it can be seen that cultures from Group IB are significantly more likely to be positive. Since Group IB circuits were significantly more likely to be culture positive than Group IA circuits, only data from Group IB circuits were used for comparison of circuits changed at 24 hours and circuits changed at 48 hours.

Microbial Contamination of Circuits Changed at 24 Hours versus Circuits Changed at 48 Hours. Results of this analysis are presented in Tables 28 and 29. As can be seen in Table 28, there were no significant differences in the results of any cultures taken from circuits in Group I and Group II. The only significant difference between Group I and Group II with respect to the presence of pathogens was in the air cultures. Although there was a significantly higher percentage of positive air cultures in circuits changed at 48 hours, the difference for stage 1 cultures was of borderline significance and the difference between Group I and Group II in the stage 2 air cultures was not significant. These results indicate that there is no important difference between the results of air cultures from Group I and Group II. Only viable particles from stage 2 can reach the lower respiratory tract. Since there was no significant difference in stage 2 cultures, it can be concluded that changing circuits at 48 hours places the

Table 28. Culture Results from Circuits in Group I* and Group II: Positive Cultures versus Negative Cultures

Source of Culture	Group I Microbial growth Absent	Group I Microbial growth Present	Group II Microbial growth Absent	Group II Microbial growth Present	P value+
Circuit cultures (all components)	33	527	21	313	0.88
Circuit cultures (internal surfaces)	64	496	30	304	0.26
Condensate	142	397	76	236	0.57
Humidifier water	511	16	295	10	0.84
Air cultures (Andersen air sampler)	235	276	137	146	0.55
1st stage only	252	256	152	129	0.23
2nd stage only	364	142	210	68	0.31

* Data for Group I in this table are the same as the data from Group IB described in the previous section and shown in Tables 26 and 27.

+ Fisher's exact test (2-tail)

Table 29. Culture Results from Circuits in Group I* and Group II: Pathogens versus Absence of Pathogens

Source of Culture	Group I Pathogen Absent	Group I Pathogen Present	Group II Pathogen Absent	Group II Pathogen Present	P value+
Circuit cultures (all components)	217	343	113	221	0.15
Circuit cultures (internal surfaces)	231	329	118	216	0.09
Condensate	299	240	163	149	0.39
Humidifier water	520	7	298	7	0.40
Air cultures (Andersen air sampler)	457	54	239	44	0.04
1st stage only	464	44	244	37	0.050
2nd stage only	486	20	259	19	0.09

* Data for Group I in this table are the same as the data from Group IB described in the previous section and shown in Tables 25 and 26.

+ Fisher's exact test (2-tail)

patient at no greater risk that changing circuits at 24 hours.

DISCUSSION

Thirty-five of 211 patients (16.6%) developed pneumonia during my study. There is very little published data with which to compare this rate. In the SENIC study, Hooten and co-workers (41) reported infection rates by level of risk. From the lowest level of risk, stratum 1, the infection rate was 0.02% and from the highest level of risk, stratum 9, the infection rate was 15.3%. In this report, ventilatory support was not examined as a risk factor. The only other published study that evaluated patients on ventilatory support was that of Craven and co-workers (20). Twenty-one percent of their artificially ventilated patients developed pneumonia. Thus, the rate of 16.6% in my study was similar to that of Craven and co-workers.

Although no definitive studies have evaluated ventilatory support as a risk factor for pneumonia, it would appear that this type of therapy places persons at high risk of pneumonia. To date, only one study has examined ventilatory support as a risk factor. This study, by Stevens and co-workers (96), was retrospective and there was difficulty in determining when pneumonia occurred with respect to when the patient was placed on controlled ventilation. Although never proven in a prospective, epidemiologic study, artificial ventilation would appear to

be an important risk factor for pneumonia since my rate and that of Craven and co-workers were both higher than the rate in the highest risk stratum from the CDC SENIC study (41).

More than one half (56%) of the patients developed tracheobronchitis while on ventilatory support. To my knowledge, this is the first study to define the rate of tracheobronchitis in patients on artificial ventilation. It is unclear as to why patients on respirators have a rate of tracheobronchitis that is nearly four times that of pneumonia. It is also unclear as to whether tracheobronchitis and pneumonia have a similar pathogenesis. It would be interesting to speculate that tracheobronchitis is a precursor of pneumonia in ventilated patients. This is suggested by the observations that tracheobronchitis occurs at a mean time three days earlier than pneumonia, while the pathogens isolated from patients with tracheobronchitis are the same as those isolated from patients with pneumonia.

Changing ventilator circuits at 24 or 48 hours was not related significantly to occurrence of pneumonia (13% versus 21.1%, respectively, $p = 0.14$). Whether circuits were changed at 24 or 48 hours also had no significant impact on the rate of tracheobronchitis (58.6% versus 52.6%, $p = 1.00$).

When patients were randomized to 24 or 48 hour circuit changes, there were significant differences in two of the 54 characteristics examined. One of these factors was chest injury. As will be seen below, I found that chest injury was a risk factor for pneumonia. Patients randomized to 48

hour circuit changes were significantly more likely to have chest injury. This risk factor would tend to increase the infection rate in Group II. In spite of this increased risk for Group II patients, there was no significant difference in infection rates between Group I and Group II. Patients in Group II also had a significantly higher number of patients receiving antacids. Although I did not find antacids to be a risk factor for infection in this population, duMoulin, Craven and Donowitz (28,20,27) found that administration of antacids was a risk factor for pneumonia. Once again, however, in spite of a potentially higher risk of infection in Group II patients, there was no significant difference in infection rates between patients having their circuits changed at 24 hours or 48 hours.

I analyzed the risk factors for pneumonia using two different approaches. In the first approach, patients with pneumonia were analyzed versus all other patients without pneumonia. Because the latter group contained patients with tracheobronchitis, and therefore would tend to make this group more like the infected group, I decided that a second analysis should be carried out in which patients with pneumonia were compared to patients with no respiratory infections.

In the first analysis, where patients with pneumonia were compared with patients without pneumonia, five risk factors for pneumonia were identified. These five factors included head injury, chest injury, surgical operation other

than cranial, thoracic or abdominal, being hospitalized in the neurosciences ICU, and duration of ventilation. Having received antibiotics and having been intubated by the nasotracheal route appeared to protect against development of pneumonia, and absence of each of these factors could be considered a risk factor.

The only published prospective study in patients on controlled ventilation is that by Craven and co-workers (21). The only risk factors for pneumonia in patients on controlled ventilation, identified both by me and Craven and co-workers, were head injury and not having received antibiotics during assisted ventilation. Four other variables that I identified as risk factors, including chest injury, absence of a nasotracheal tube, location in the neurosiences ICU, and other types of surgery, were not examined by Craven and co-workers nor, to my knowledge, in any other published studies.

As in the study of Craven and co-workers, I also examined intracranial pressure monitoring, craniotomy, treatment with cimetidine, timing of circuit changes, Winter-Fall season of ventilation (September 21-March 21), and coma. I did not find any of these factors to be risk factors for pneumonia. Failure to identify coma as a risk factor in my study may have been due to the very low numbers of patients with coma when head injury patients were excluded. Except for ventilation in the Winter-Fall season, I am unable to determine why Craven and co-workers showed these latter characteristics to be risk factors and I did

not. With respect to ventilation in the Winter-Fall season, this may have been a risk factor for patients at Boston City Hospital where there may have been a higher proportion of indigent patients and where the winters were more severe.

Stepwise logistic regression analysis of my data revealed that the most powerful predictors of ventilator-associated peumonia were duration of ventilation, never having reveived an antibiotic and having had a chest injury. These results of multivariate analysis are very different from those of Craven and co-workers. However, the only variable common to the models for logistic regression in my study and that of Craven and co-workers was head injury. Although the latter authors found that not having received an antibiotic was a risk factor for pneumonia by univariate analysis, they did not include this variable in their model for logistic regression analysis. Unlike Craven and co-workers, I found that duration of ventilation, not having reveived an antibiotic and presence of chest injury were more powerful predictors of pneumonia in patients on controlled ventilation than presence of head injury.

When patients with pneumonia were analysed versus patients with no infections, risk factors identified included head injury, treatment with pancuronium, presence of a tracheostomy, presence of a ventriculostomy, a prolonged duration of ventilation, and hospitalization in the neurosciences ICU. Again, treatment with antibiotics and presence of a nasotracheal tube were protective against

pneumonia. If the absence of the latter two factors are considered risk factors, then eight risk factors were identified in this analysis. In the first analysis, chest injury and other types of surgery were risk factors for infection, but these factors were not associated with a significantly increased risk of infection in the second analysis. It is unclear why other types of surgery dropped out as a risk factor. Chest injury could no longer be shown to be a risk factor for pneumonia, because when the tracheobronchitis patients were removed from the patients without pneumonia, insufficient numbers of patients remained in that group to accurately access chest injury as a risk factor. In this analysis, treatment with pancuronium, presence of a tracheostomy and presence of a ventriculostomy were identified as risk factors, because removal of tracheobronchitis patients from the group of patients without pneumonia heightened the differences between the groups with and without pneumonia. As in the study of Craven and co-workers (17), ventriculostomy was identified as a risk factor for pneumonia.

Analysis of patients with pneumonia versus patients with no infection appeared to be more informative than analysis of patients with pneumonia versus patients with no pneumonia. While one important risk factor, chest injury, was lost in the second analysis, three new risk factors were identified. However, multivariate analysis of this data once again showed duration of ventilation, and absence of treatment with antibiotics to be the most powerful

predictors of ventilator-associated pneumonia.

In the third analysis, patients with tracheobronchitis were compared with patients without infection. Only three risk factors could be identified for tracheobronchitis. These included having had any type of surgical operation, having had cranial surgery and having had a prolonged duration of ventilation. Thus, only prolonged duration of ventilation was a risk factor for both pneumonia and tracheobronchitis. I am unable to explain why cranial surgery and surgical operations are risk factors for tracheobronchitis. Cranial surgery may have been interrelated with the effects of ventriculostomy and administration of pancuronium, both of which had a borderline significant relationship with tracheobronchitis. Patients who had cranial operations frequently had ventriculostomies and were frequently treated with pancuronium. However, multivariate analysis showed that only duration of ventilation was a strong independent predictor for the occurrence of tracheobronchitis.

Sixty-three percent of cultures from breathing circuits were positive for pathogens. The culture positivity rate in my study was higher than that observed by Craven and co-workers (17) of 45.5%. Craven and co-workers cultured only effluent gases, water from the humidifier and internal surfaces of the tubing with a broth washout technique. In addition to these cultures, I cultured condensate drained from the tubing, and internal surfaces of the ends of the

tubing and Y-connector using swabs.

There are few data in the literature on microorganisms that contaminate ventilator circuits. The only report with which to compare my data is that of Malecka-Griggs and Reinhardt (59). The only microorganism isolated by these authors that was not isolated from circuits in my study was Flavobacterium meningosepticum. On the other hand, I isolated eleven species not recovered by these authors. This may have been due to the much greater number of circuits cultured in my study.

Fifty-four percent of Group I air cultures and 51.6% of Group II air cultures were positive. These rates are nearly twice the rates of 30% and 32% from Group I and Group II patients of Craven and co-workers. My study and that of Craven and co-workers are not strictly comparable, because the ventilators were set at different flow rates. Further, my data were all generated using the Andersen air sampler, and the study of Craven and co-workers used three different methods including the Andersen air sampler, the Aerotest air sampler, and the tube-broth method for culturing inspiratory-phase gas. Twenty-four percent of the Group I air cultures and 37% of the Group II air cultures in my study yielded pathogenic organisms. To my knowledge, my study is the first to differentiate pathogenic and non-pathogenic organisms from air cultures. It would appear that only a small number of the pathogenic microorganisms present in the circuits could be aerosolized, because the only pathogens aerosolized were the ones that were present

the greatest number of times in the circuits. I found that two-thirds of the pathogenic species present in air cultures were also present in the sputum of patients. P. aeruginosa was the most frequently isolated pathogen from air cultures and, interestingly, was the pathogen most commonly recovered from the sputum of patients with pneumonia. Craven and co-workers also observed that pathogenic species recovered from inspiratory-phase-gas were also frequently isolated from the sputum of patients. The studies of Lareau and Craven and co-workers (53,17) both suggested that these pathogens frequently appear in sputum before they appear in inspiratory-phase-gas cultures.

In this study, patients who were randomized to 24 hour circuit changes (Group I), but who were on the ventilator for less than two circuit changes, were not used for comparison of infection rates between Group I and Group II patients. These patients were excluded from analysis of Group I and Group II infection rates, because they would have all been exposed to the ventilator for less time than any person randomized to 48 hour circuit changes. The results of the analysis of patients randomized to 24 hour circuit changes where cultures from the group who were on the ventilator for less than two circuit changes (Group IA-Tables 26 and 27) were compared with the cultures from the group who were on ventilation for two or more changes (Group IB-Tables 26 and 27), showed several significant differences between these two groups. Thus, when positive versus

negative cultures were examined (Table 26), it was seen that circuits in general and internal surfaces of circuits were significantly more likely to be positive in Group IB than in Group IA. Similarly, when only recovery of pathogens was examined, it could be seen that cultures of circuits in general, internal surfaces of circuits, and condensate were significantly more likely to have been positive in Group IB than in Goup IA (Table 27). The observation that the circuits in Group I that were used at the beginning of ventilation, and in many instances early in hospitalization, were significantly less likely to be culture positive than those circuits changed at 24 hours later in the course of controlled ventilation supported the observations of others (53,20) that circuits were frequently contaminated by the patients themselves. Thus, it would appear that the longer patients were on the ventilator and in the hospital, the more likely they would have been colonized with nosocomial pathogens and the more likely they themselves would have contaminated the circuits used later in the course of ventilation. These data also supported the exclusion of patients from Group I who were randomized to 24 hour circuit changes but who were on ventilation for less than two circuit changes prior to the comparison of infection rates in Group I and Group II. Patients who were randomized to the 24 hour circuit changes and who were on the ventilator for less than two circuit changes would have been likely to skew the infection rate in Group I, because they represented a subgroup less likely to be colonized with pathogens and

less likely to develop HAP.

The results of the cultures of Group I and Group II circuits supported the observation from the epidemiologic portion of the study that there was no difference in infection rates between patients whose circuits were changed at 24 hours and patients whose circuits were changed at 48 hours. When one examines the data from Table 28 (Positive Cultures versus Negative Cultures) and the data from Table 29 (Pathogens versus Absence of Pathogens), it can be seen that there were only two significant differences in cultures from Group I and Group II. Pathogens were significantly more likely to be isolated from the air cultures of patients in Group II. This difference was likely due to the significantly higher percentage of stage 1 air cultures in patients in Group II that were positive. However, the stage 1 cultures are not indicative of a significantly greater risk of infection in Group II patients. First, stage 1 cultures were less precise than stage 2 cultures, because 15-20% were contaminated by condensate. Second, particles carrying microorganisms that are trapped in stage 1 are too large to reach the lower respiratory tract. When culture data from stage 2, the only stage that measures numbers of respirable particles, are considered, it can be seen that there is no significant difference between Group I and Group II. The microbiological data from this study confirm the observation of Craven and co-workers (20).

In summary, the epidemiological and microbiological

data from this study corroborates the studies of Craven and co-workers (17,20). However, I identified risk factors for ventilator-associated pneumonia that have not been reported previously in the literature. These included duration of ventilation, the most powerful predictor for occurrence of pneumonia and tracheobronchitis, presence of chest injury, and administration of pancuronium. Although previously reported by Craven and co-workers (20), not having received antibiotics was the second most powerful predictor of pneumonia after duration when the data were analyzed by logistic regression analysis.

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Appendix

Adm # [,] (1-9) [,] (10, 11)

DEMOGRAPHICS

Admission Date [, / , / ,] (12-17) Age [,] (24, 25)

Patient died y.__ Yes (26)

Sex: m.__ Male
f.__ Female (27)

Race: b.__ Black
w.__ White (28)
o.__ Other

Smoking: (29)
p.__ Past
c.__ Current
n.__ Never

Year started [,] (30, 31)
Year stopped [,] (32, 33)
Number of packs/day [.] (34, 35)

Diagnoses (ICD9-CM)

[, , . ,] (36-40) [x] _____
[, , . ,] (41-45) [x] _____
[, , . ,] (46-50) [x] _____
[, , . ,] (51-55) [x] _____

Underlying Diseases

Pulmonary:
a.__ COPD (56)
b.__ Bronchiectasis (57)
c.__ Chronic interstitial fibrosis (58)
d.__ Cystic fibrosis (59)
e.__ Previous pneumonia (60)

Other:
a.__ CHF (61)
b.__ DM (62)
c.__ Chronic renal failure (63)
d.__ Neoplastic disease (64)
e.__ Hypertension (65)
f.__ Etanol abuse (66)
g.__ Malnutrition (67)
h.__ Obesity (68)
i.__ Organic Heart disease (69)

[,] (1-9) [A,1] (10, 11)
Adm #

MEDICATIONS

Type		Date Started		Date Stopped		
, ,	(12-14)	, / , / ,	(15-20)	, / , / ,	(21-26) [x]	_____
, ,	(27-29)	, / , / ,	(30-35)	, / , / ,	(36-41) [x]	_____
, ,	(42-44)	, / , / ,	(45-50)	, / , / ,	(51-56) [x]	_____
, ,	(57-59)	, / , / ,	(60-65)	, / , / ,	(66-71) [x]	_____

Dup Columns 1-9 [A,2] (10, 11)

, ,	(12-14)	, / , / ,	(15-20)	, / , / ,	(21-26) [x]	_____
, ,	(27-29)	, / , / ,	(30-35)	, / , / ,	(36-41) [x]	_____
, ,	(42-44)	, / , / ,	(45-50)	, / , / ,	(51-56) [x]	_____
, ,	(57-59)	, / , / ,	(60-65)	, / , / ,	(66-71) [x]	_____

Dup Columns 1-9 [A,3] (10, 11)

, ,	(12-14)	, / , / ,	(15-20)	, / , / ,	(21-26) [x]	_____
, ,	(27-29)	, / , / ,	(30-35)	, / , / ,	(36-41) [x]	_____
, ,	(42-44)	, / , / ,	(45-50)	, / , / ,	(51-56) [x]	_____
, ,	(57-59)	, / , / ,	(60-65)	, / , / ,	(66-71) [x]	_____

Dup Columns 1-9 [A,4] (10, 11)

, ,	(12-14)	, / , / ,	(15-20)	, / , / ,	(21-26) [x]	_____
, ,	(27-29)	, / , / ,	(30-35)	, / , / ,	(36-41) [x]	_____
, ,	(42-44)	, / , / ,	(45-50)	, / , / ,	(51-56) [x]	_____
, ,	(57-59)	, / , / ,	(60-65)	, / , / ,	(66-71) [x]	_____

Dup Columns 1-9 [A,5]

, ,	(12-14)	, / , / ,	(15-20)	, / , / ,	(21-26) [x]	_____
, ,	(27-29)	, / , / ,	(30-35)	, / , / ,	(36-41) [x]	_____
, ,	(42-44)	, / , / ,	(45-50)	, / , / ,	(51-56) [x]	_____
, ,	(57-59)	, / , / ,	(60-65)	, / , / ,	(66-71) [x]	_____

[,] [,] (1-11) [0,1] (12, 13)
Adm # Circuit #

OPERATIONS

Operation [, , . ,] (14-18) (ICD9-CM) Date [, / , / ,] (19-24) [x] _____ Type of Operation

Region of incision: a.__ Abdominal
c.__ Cranial
(25) t.__ Thoracic
o.__ Other

Anesthesia: g.__ General
(26) l.__ Local
s.__ Spinal

Duration of operation [,] : [,] (27-30)
Hrs Mins

Operation [, , . ,] (31-35) (ICD9-CM) Date [, / , / ,] (36-41) [x] _____ Type of Operation

Region of incision: a.__ Abdominal
c.__ Cranial
(42) t.__ Thoracic
o.__ Other

Anesthesia: g.__ General
(43) l.__ Local
s.__ Spinal

Duration of operation [,] : [,] (44-47)
Hrs Mins

Operation [, , . ,] (48-52) (ICD9-CM) Date [, / , / ,] (53-58) [x] _____ Type of Operation

Region of incision a.__ Abdominal
c.__ Cranial
(59) t.__ Thoracic
o.__ Other

Anesthesia: g.__ General
(60) l.__ Local
s.__ Spinal

Duration of operation [,] : [,] (61-64)
Hrs Mins

, ,	, ,	(1-11)	V , 1	(12, 13)
Adm #	Circuit #			

VENTILATION

Patient's Name [x] _____

	Date	Time	
Breathing circuit started	, / , / ,	, : ,	(14-23)
stopped	, / , / ,	, : ,	(24-33)

Technical change of ventilator:

c._circ. change
d._temp.disc.
n._none

Location (where breathing circuit was started and where it was maintained):

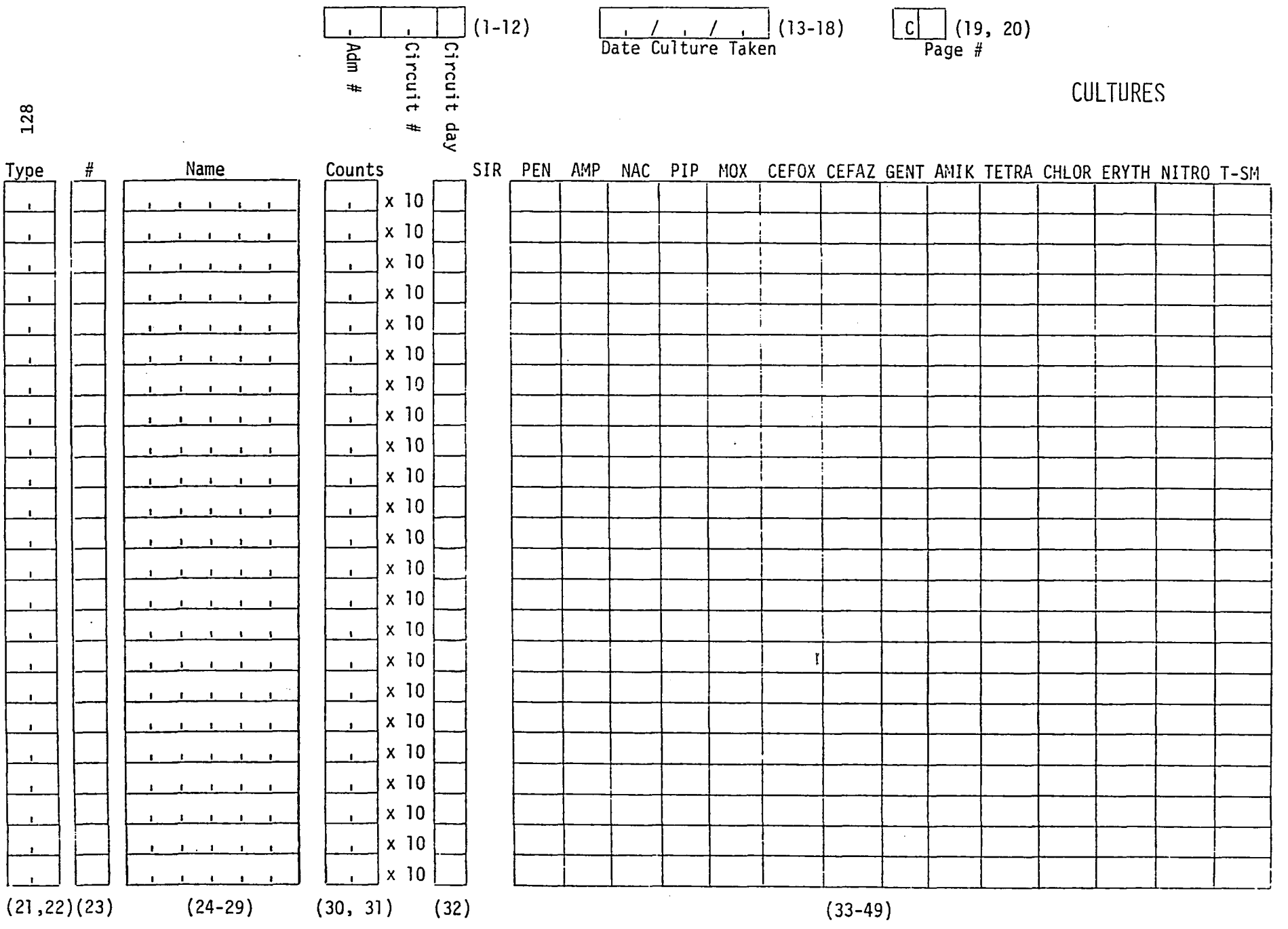
m.__ GMICU (35)
s.__ GSICU (36)
n.__ NSICU (37)
c.__ CICU (38)
r.__ RICU (39)

Dup columns 1-11 | V,2 | (12, 13)

Intubation	Date Started		Date Stopped	
(14) o.__ Oral-tracheal	, / , / ,	(15-20)	, / , / ,	(21-26)
(27) n.__ Naso-tracheal	, / , / ,	(28-33)	, / , / ,	(34-39)
(40) b.__ Bronchoscopy	, / , / ,	(41-46)	, / , / ,	(47-52)
(53) t.__ Tracheostomy	, / , / ,	(54-59)	, / , / ,	(60-65)
(66) l.__ Lung biopsy	, / , / ,	(67-72)		

a.__ Percutaneous aspiration
b.__ Transbronchial biopsy (73)
c.__ Open lung biopsy

Purulent sputum noted: ____ y. (74)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SEPTICEMIA

SEPTICEMIA is defined by:

a. two or more positive blood cultures with a pathogenic organism (excluding diphtheroids, Bacillus and coagulase-negative Staphylococcus)

b. any two of the following clinical signs: 1) fever
2) chills
3) hypotension

Date of Diagnosis Organism

|____/____/____|(12-17) [x] _____|____|(18,23)

Septicemia was secondary to pneumonia? y.__ (24)

[,] (1-9) [R,1] (10, 11)
Adm #

RESPIRATORY INF

PNEUMONIA is defined by:

a. appearance of purulent sputum

b. appearance of new or progressive infiltrate on CXR

c. respiratory secretions positive or negative for organisms

Date of Diagnosis [, / , / ,] (12-17)

Organisms

[x] _____ [, , , , ,] (18, 23)
[x] _____ [, , , , ,] (24, 29)
[x] _____ [, , , , ,] (30, 35)

Please call Archer Lamb, Beeper 718, when a positive diagnosis occurs.

TRACHEOBRONCHITIS is defined by:

a. appearance of purulent sputum

b. stable or absent pulmonary infiltrate on CXR

c. respiratory secretions positive or negative for organisms

Date of Diagnosis [, / , / ,] (36,41)

Organisms

[x] _____ [, , , , ,] (42, 47)
[x] _____ [, , , , ,] (48, 53)
[x] _____ [, , , , ,] (54, 59)

No respiratory tract infection: y.__ (60)

Date patient exits study (72 hours after ventilator discontinued) [, / , / ,] (61,66)