

PULMONARY HOST DEFENSES AND ALCOHOL

Ping Zhang^{1,3}, Gregory J. Bagby^{1,2,3}, Kyle I. Happel^{1,3}, Warren R. Summer^{1,3}, and Steve Nelson^{1,3}

¹ Department of Medicine, Section of Pulmonary and Critical Care Medicine, ² Department of Physiology, and ³ Alcohol Research Center, Louisiana State University Health Sciences Center, New Orleans, LA 70112

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Alcohol, host defense, and pulmonary infection
 - 3.1. Historical overview and clinical manifestations
 - 3.2. Normal host defense in the respiratory tract
 - 3.3. Effects of alcohol on pulmonary host defense
 - 3.4. Immunomodulation of pulmonary infections in alcoholic hosts
4. Perspective
5. Acknowledgments
6. References

1. ABSTRACT

Alcohol abuse is a major risk factor for the development of many infectious diseases, particularly pulmonary infections. Bacterial pneumonia and other lung infections in alcohol-abusing patients are usually severe and associated with a high morbidity and mortality. Normal host defense mechanisms in the respiratory tract consist of both innate and acquired immunity which operate effectively in preventing the invasion of infectious pathogens. Numerous *in vivo* and *in vitro* studies have shown that alcohol is an immunosuppressive agent that compromises the function of various components of the immune defense system. In recent years, human immunodeficiency virus infection has become epidemic, especially in individuals who abuse alcohol and other substances. Treatment of pulmonary infections in these immunocompromised hosts has continued to be a major challenge in our health care system. Immunotherapy to improve or enhance pulmonary host defense function in conjunction with aggressive antimicrobial regimens may provide a new approach in the management of infections in these patients.

2. INTRODUCTION

It has long been recognized that alcohol abusers are susceptible to a wide range of infectious diseases, particularly pulmonary infections. The respiratory tract represents the largest epithelial surface area of the body and is continuously exposed to a vast array of airborne particles and invading organisms during normal respiration. Multiple

factors contribute to the development of pneumonia in alcohol-abusing patients. These include the loss of protective barriers, aspiration of oropharyngeal contents, nutritional deficiencies, liver disease, and inhibition of several components of the immune defense system. The immune system of the alcohol-consuming patient may become further compromised by human immunodeficiency virus (HIV) infection. Individuals, especially young people, who abuse alcohol and other substances are at significant risk for HIV infection (1, 2). Studies have shown that as many as 82% of HIV infected individuals consume alcohol, with 41% classified as alcoholics (3). This article will review recent advances in our understanding of the complex host-pathogen interactions that occur in the respiratory tract with an emphasis on how alcohol consumption adversely affects normal host defense mechanisms and predisposes the host to infections. New immunomodulatory strategies for improving host defense function in alcohol-abusing patients will also be discussed.

3. ALCOHOL, HOST DEFENSE, AND PULMONARY INFECTION

3.1. Historical overview and clinical manifestations

As early as in 1785, Benjamin Rush, the first Surgeon General of the United States, published "*An Inquiry Into the Effects of Ardent Spirits Upon the Human Body and Mind*" in which he noted that alcoholics were vulnerable to yellow fever, tuberculosis, pneumonia, and abscesses (4). Shortly after the turn of the last century, Sir

William Osler remarked that alcohol abuse was “perhaps the most potent predisposing factor to lobar pneumonia” (5). In 1923, Capps and Coleman reported their study on the influence of alcohol on the prognosis of pneumonia in Cook County Hospital (Illinois). They showed that the mortality rate of pneumonia was more than twice as high in alcoholics compared to nonalcoholics (6). Since then, the effects of alcohol abuse on the incidence and severity of pulmonary infections have drawn significant attention and numerous studies have been carried out in a wide range of medical settings and patient populations. A clinical study of 1722 alcoholic patients in Oslo during the years of 1925 to 1940 documented that the age-specific death rates caused by pneumonia were more than three times greater in alcoholics compared to those in the general population (7). Similarly, another study of 1298 patients treated for lobar pneumonia in Buffalo City Hospital (NY) from 1927 to 1935 showed that the mortality rate in alcoholics was approximately twice that of nonalcoholic patients (8). In 1965, Nolan reported a prospective study of 900 consecutively hospitalized patients at Grace-New Haven Community Hospital. One hundred twenty four (13.8 percent) patients were classified as alcoholics. Pneumonia as the reason for admission was identified in 17% of the alcoholic patients, while only 6.5% of nonalcoholic patients were admitted because of pneumonia (9). In 1969, Winterbauer and colleagues reported a study on the predisposing illness and clinical patterns of recurrent pneumonia (10). Among 158 patients treated for recurrent pneumonia at the Johns Hopkins Hospital, 40% of them were found to be associated with either acute or chronic alcohol intoxication. In 1972, Schmidt and De Lint reported an investigation of 6478 alcoholic patients treated at the Toronto Clinic of the Addiction Research Foundation during a 14 year period. The mortality rates of pneumonia in alcoholic men and women in this series were 3-fold and 7-fold greater, respectively, in comparison to those in the general population of Ontario (11). More recently, Fernandez-Sola and colleagues performed a two-phase study in middle-aged patients at the Hospital Clinic of University of Barcelona (12). Risk factors for community-acquired pneumonia were evaluated in a case-control study of 50 patients and 50 controls. Prognostic factors and clinical features were analyzed in a cohort study of the 50 patients with community-acquired pneumonia. Among the risk factors studied, high alcohol intake was the only independent risk factor for community-acquired pneumonia. Compared with nonalcoholic patients, alcoholic patients with pneumonia showed more severe clinical symptoms, required longer intravenous treatment and longer hospital stays, had more multilobar involvement and pleural effusions as well as slower resolution of pulmonary infiltrates. In addition, high alcohol intake was the only prognostic factor for mortality in this group of patients. Saitz et al studied a cohort of 23,198 pneumonia patients hospitalized in 1992 in Massachusetts and 6 bordering states (13). Multivariate analyses adjusting for comorbidity, pneumonia etiology, and demographics showed that for pneumonia cases with an alcohol-related diagnosis, risk-adjusted hospital charges were higher, length of hospital stay was longer, and intensive care unit use was more frequent. Marik reported a study on the

clinical and prognostic features of 148 patients with severe community-acquired pneumonia presenting in septic shock (14). The 28 day survival rate in this group of patients was 53%. Infection with *Pseudomonas aeruginosa* or *Acinetobacter* species carried a very high mortality (82%). The only clinical variables recorded in the database that could identify patients with *Pseudomonas* or *Acinetobacter* infection was a history of alcohol abuse. Musher et al reported a prospective study analyzing predisposing factors for pneumococcal pneumonia with and without bacteremia (15). The results showed that although the mean number of predisposing factors was greater among bacteremic patients than nonbacteremic patients, only alcohol consumption was significantly more common in patients with bacteremia.

In addition to community-acquired pneumonia, alcohol abuse has also been shown to be a significant risk factor for hospital-acquired pneumonia. In 2000, Everts and colleagues reported a one-year prospective study of consecutive patients hospitalized for general medical and surgical diseases (16). Nosocomial pneumonia developed in 126 patients representing 6.1 per 1000 admissions. Fourteen patients (11%) died as a consequence of pneumonia. Alcohol excess was identified as one of the most powerful predictors of a fatal outcome by univariate analysis.

Etiological studies have shown that bacterial pneumonias of all types including Gram-positive and Gram-negative, aerobic and anaerobic, as well as mycobacterial infections are more common in alcoholics as compared to nonalcoholics (17 - 19). In addition, alcohol abusers are also susceptible to pulmonary infections caused by “atypical pathogens”, fungi, and viruses (20). Clinical features of pulmonary infections in alcoholic patients are similar to those in the general population, except for a younger age of occurrence, more severe symptoms, a higher incidence of complications, more frequent recurrence, greater likelihood of developing infection with resistant pathogens, and poorer outcomes. Alcoholic patients with cirrhosis or bone marrow suppression have the poorest prognosis (17, 19). Among all bacterial pneumonias, *Streptococcus pneumoniae* has been reported to be the most frequent pathogen in the general population as well as in alcohol abusers (14, 17, 19, 21, 22). Alcoholic patients with pneumococcal pneumonia are at an increased risk to develop bacteremia and sepsis (15). Early studies have shown that alcoholic patients with pneumococcal pneumonia usually have prolonged fever, slow resolution of infiltrates, and more secondary complications (23). *Hemophilus influenzae* and *Klebsiella pneumoniae* are also frequently documented pathogens causing pneumonias in alcoholic patients (17, 19). In a report of 24 patients with *H. influenzae* pneumonia, fifty percent of them were alcoholics (24). Recently, a prospective study of 343 nonalcoholic and alcoholic patients with community-acquired pneumonia showed that among 167 microorganisms isolated from 144 cases, *H. influenzae* was found in 17 patients (21). *K. pneumoniae* has been identified as a frequently carried organism in the oropharyngeal cavities of chronic alcoholics (25). Pulmonary infection caused by *K. pneumoniae* is usually

Lung defenses and alcohol

life threatening and associated with a high frequency of complications and death. Bacteremia has been observed in as many as 50% of cases (17). Alcoholic patients with *Klebsiella pneumonia* complicated by bacteremia frequently develop septic shock and fulminant respiratory failure. The mortality in these patients approaches 100% (26). Alcoholic patients have been reported to have a high incidence of pulmonary infections with *Pseudomonas aeruginosa* and *Acinetobacter species* which frequently result in death (14). Anaerobic lung infections with *Fusobacterium nucleatum*, *Bacteriodes melaninogenicus*, and *Bacteriodes fragilis* are frequently observed in alcoholic patients (27). In fact, studies have shown that about 30% of all anaerobic pulmonary infections occur in excessive alcohol consumers (27, 28). Poor dentition is common among alcohol abusers who harbor large numbers of anaerobic bacteria in their oropharynx. Loss of consciousness by alcohol intoxication results in aspiration of bacteria-laden oropharyngeal secretions into the lower respiratory tract. Clinical presentations of anaerobic lung infection include simple pneumonitis, necrotizing pneumonia, lung abscess, and empyema (27).

Mycobacterial infections of the lung are more commonly observed among alcohol consumers. Numerous studies from various nations have shown that the incidence of pulmonary tuberculosis is significantly higher in alcohol abusers than in the general population (17 - 19, 29, 30). In 1954, Jones and colleagues reported a study of tuberculosis among homeless men in Minneapolis with an alcoholism rate of 70% (31). Their data showed that active new cases of pulmonary tuberculosis was 22 per 1000 homeless men, in contrast to 0.4 cases per 1000 people in the general population during the same period. The incidence of new active cases is as much as 55 times higher among homeless men. In 1991, Carpenter and Iluang reported that the case rate of pulmonary tuberculosis was still 55 times greater among alcoholics than that in the general population (32). Multiple investigators have analyzed additional alcohol-related social factors including occupation, living conditions, marital status, race, and smoking habits in relation to the development of tuberculosis in alcoholic patients. Results from these studies have shown that excessive alcohol consumption remains an independent risk factor linked with tuberculosis regardless of the presence or absence of other additional factors (33, 34). Literature concerning the effects of alcohol abuse on the severity of pulmonary tuberculosis in patients are inconsistent. Early clinical observations reported that alcoholics with pulmonary tuberculosis did not have more extensive disease compared to nonalcoholics (35). In contrast, other studies have shown that alcoholic patients have more extensive pulmonary disease, require longer treatment, have more complications from chemotherapy, and are more likely to be non-compliant (36). In 1988, Barnes reported a study on the short-term prognosis in patients with pulmonary tuberculosis (37), in which they showed that alcoholics had a greater extent of disease at the time of initial diagnosis. Consistent with the severity of the disease, alcoholics also had a higher risk of death during the initial hospitalization. Recently, Borgdorff et al reported that among tuberculosis patients in the Netherlands, addiction to

alcohol was listed as an independent risk factor for mortality (38). Thomsen performed forensic autopsies on 441 alcoholics and 255 controls (39). Tuberculosis was more frequently identified in alcoholics. Another study which examined factors contributing to the death of patients with active tuberculosis showed that the frequency of alcohol abuse was significantly higher ($p < 0.001$) among patients with tuberculosis as a primary or underlying cause of death (40). In 2000, Taylor and colleagues reported a prospective cohort study of 1493 tuberculosis patients who were followed from diagnosis to completion of therapy at 10 public health programs and area hospitals in the US (41). The results showed that patients who used alcohol excessively were at increased risk of hospitalization during treatment. A significant problem for the effective treatment of tuberculosis in alcoholic patients is the lack of patient compliance since a large percentage of alcoholic patients do not complete their recommended therapy (19, 42), which leads to a high rate of relapse and the development of multiple drug-resistant strains (17, 19, 30). The HIV epidemic, especially among substance abusers and alcoholics, has played an important role in the resurgence of tuberculosis in the US as well as in other countries around the world during the last two decades (29, 38, 41, 43).

Pulmonary infections caused by *Pneumocystis carinii* and other opportunistic pathogens in alcoholics have come to attention recently because of a high rate of HIV infection in this patient population (44). *P. carinii* pneumonia is usually observed in patients with compromised cell-mediated immunity and is one of the most common pulmonary complications in HIV-infected individuals (45, 46). Alcohol is immunosuppressive and exerts adverse effects on cell-mediated immunity. Experimental studies have shown that mice on a chronic alcohol-containing diet have a significantly increased rate (greater than 60% in the alcohol-fed group vs. none in control group) of *P. carinii* infection in the lung following an intrapulmonary challenge with this pathogen (47). In the clinic, *P. carinii* pneumonia has also been observed in alcohol abusers even in the absence of HIV infection (21).

3.2. Normal host defense in the respiratory tract

Normal individuals are quite resistant to the development of pulmonary infections. The respiratory tract possesses a sophisticated defense system which is very effective in protecting the host from invading pathogens. The normal host defense system in the airways includes both innate (nonspecific) and acquired (specific) immune defenses. Innate defense primarily consists of the structural defenses, the antimicrobial molecules generated in the airways, and the phagocytic defenses provided by the resident alveolar macrophages and the polymorphonuclear leukocytes (PMNs) that are recruited into the lung in response to pulmonary infection (48). Mechanical host defenses represent the initial barriers to the invasion of the lung by airborne particles and infectious agents (49). The mucociliary blanket lining the surface of the airways contains complex mucins, which trap microorganisms. These particles are then cleared by ciliary movement that propels the mucus up to the oropharynx. Coughing is an

important component of mechanical defense, which accounts for clearing large amounts of secretions from the airways. Particles less than 5 micrometer in diameter can bypass these defenses of the upper respiratory tract and gain access to the alveolar space. This is particularly relevant in the pathogenesis of pulmonary infection as most bacteria and mycobacteria are within this size range. Cells of the airways produce a variety of antimicrobial molecules which either possess direct antimicrobial activity or facilitate the elimination of infectious pathogens by phagocytes. These include lysozyme, complement, immunoglobulin A and G, fibronectin, lactoferrin, transferrin, LPS-binding protein, defensins, cathelicidins, and collectins (50 - 58).

Alveolar macrophages represent the first line of phagocytic defense against infectious agents that reach the gas-exchanging units of the lung (59). These cells have potent phagocytic, microbicidal, and secretory functions and play a pivotal role in initiating inflammatory and immune responses in the lung (60, 61). Alveolar macrophages are avidly phagocytic and responsible for the clearance of small loads of pathogenic organisms, thereby maintaining the sterility of the lung. Certain microorganisms, such as *Mycobacterium spp* and *Legionella spp*, are resistant to the microbicidal activities of alveolar macrophages and are capable of replicating intracellularly. The eradication of these pathogens requires the involvement of other immune defense mechanisms such as cell-mediated immunity. In the event that the invading pathogens either are too virulent or represent too large an inoculum to be contained by the macrophage alone, alveolar macrophages are capable of generating numerous mediators to orchestrate the recruitment of PMNs from the systemic circulation into the alveolar space. These recruited PMNs provide auxiliary phagocytic defenses which are critical for the effective eradication of offending pathogens (59, 62, 63). Alveolar macrophage-derived substances capable of eliciting PMN migration into the airways include chemotactic peptides such as interleukin-8 (IL-8), macrophage inflammatory protein-2 (MIP-2), and other CXC chemokines (59, 64, 65), complement fragments including C3a and C5a, and arachidonic acid metabolites such as leukotriene B₄.

Cytokines represent a large family of signal peptides responsible for communication between alveolar macrophages and other cellular components of the immune system. They play a key role in the regulation of the pulmonary host defense response including the initiation, localization, reinforcement, and ultimate resolution of the response (65, 66). Tumor necrosis factor-alpha (TNF-alpha), initially named for its ability to trigger the necrosis and involution of certain tumors, is now widely recognized as an important early mediator of the host response to infection. TNF is rapidly produced by alveolar macrophages following either antigen-specific or nonspecific stimulation and thus, has been designated as an early-response or "alarm" cytokine. Several clinical studies have shown that patients with pulmonary infections have high TNF levels in their bronchoalveolar lavage (BAL) fluid (67). Experimental studies have shown that

intrapulmonary challenges with either lipopolysaccharide (LPS) or bacteria cause a rapid increase in TNF-alpha in BAL fluid which is then followed by PMN influx into the alveolar space (68 - 72). Neutralizing this TNF response by using either an anti-TNF-alpha antibody or a replication-deficient adenovirus encoding a soluble TNF-alpha receptor suppresses PMN influx into the airways (73, 74). However TNF-alpha is not directly chemotactic for PMNs; rather, it is known to stimulate the production of chemokines in the lung.

Interleukin-8 (IL-8), a representative of the CXC chemokine family, is a potent chemoattractant and activator of PMNs in humans (75). Alveolar macrophages and other types of pulmonary cells are able to produce a large amount of IL-8 in response to infection and other pro-inflammatory stimuli (76, 77). Patients with pneumonia and other types of airway infections have increased IL-8 levels in their BAL fluid (78). The concentration gradient of chemoattractants across the alveolar-capillary membrane is a key factor that signals PMN migration from the blood into the alveolar space. Elimination of these CXC chemokines in the airways diminishes pulmonary PMN recruitment during lung infection and inflammation (79). In addition to mediating PMN recruitment, CXC chemokines also upregulate PMN functional activities including expression of surface receptors, phagocytosis, generation of reactive oxygen species, and delaying apoptosis (80, 81).

Interleukin-12 (IL-12) is another proinflammatory cytokine that plays an important role in pulmonary host defenses. IL-12 promotes Th1-type immune responses and enhances cell-mediated immunity against airway infections caused by viruses, mycobacteria, fungi, and parasites (82 - 86). In addition to enhancing acquired immunity, IL-12 also promotes innate immunity in the lung against bacterial infections in experimental animals (87, 88). Patients with IL-12 deficiency develop recurrent pneumococcal pneumonia with sepsis and other infections (89).

Granulocyte colony-stimulating factor (G-CSF) is a lineage-specific hematopoietic growth factor that selectively stimulates the proliferation and maturation of myeloid progenitor cells to PMNs (90, 91). Mononuclear phagocytes, including alveolar macrophages, are known to produce G-CSF when stimulated by cytokines or infectious pathogens (92). Alveolar macrophages obtained from patients with pneumonia spontaneously produce G-CSF *ex vivo* (92). G-CSF production in the lung increases during pulmonary infection (72). In addition, plasma levels of G-CSF are elevated in the presence of either a local (i.e. pulmonary) or systemic infection (72, 93 - 95). It is known that this cytokine plays a critical role in maintaining the normal blood level of PMNs and is responsible for increasing the number of circulating PMNs during infection. G-CSF also enhances the functional activities of PMNs including adhesion molecule expression, chemotaxis, oxygen metabolism, phagocytosis, and intracellular bacterial killing (69, 70, 96 - 101).

Interferon-gamma (IFN-gamma) produced by T lymphocytes was initially identified as a soluble factor with

antiviral and antitumor activities. It is now recognized that this peptide exerts profound effects on various aspects of host defense against pathogens including bacteria, fungi, and intracellular and extracellular parasites (102). IFN-gamma is a potent enhancer of cytokine production by alveolar macrophages. IFN-gamma itself does not induce TNF synthesis by alveolar macrophages, but augments LPS-induced TNF production by alveolar macrophages (103). Intratracheal administration of recombinant IFN-gamma to rats 24 hours prior to an aerosol challenge with *P. aeruginosa* enhances pulmonary production of TNF, PMN recruitment, and the bactericidal activity in the lung (66). Similar protective effects of IFN-gamma have been observed in animal models of *Legionella pneumophila* and *P. carinii* pneumonia (104, 105). IFN-gamma has been shown to play an important role in modulating CXC chemokine responses by macrophages and other types of leukocytes (106, 107). IFN-gamma also stimulates the respiratory burst of PMNs, release of lysosomal enzymes (108, 109), and actively modulates antigen presentation, cell differentiation, and cytotoxicity of immune effector cells.

Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine. IL-10 downregulates the production of a variety of proinflammatory cytokines and chemokines including TNF-alpha, interleukin-1-beta (IL-1beta), IFN-gamma, IL-12, MIP-2, and macrophage inflammatory protein-1alpha (MIP-1alpha) (65, 86, 110-112). In addition, IL-10 suppresses the functional activities of PMNs (113). This cytokine is thought to play an important role in mediating the resolution of the inflammatory response to infection.

An important feature of pulmonary host defense is the selective compartmentalization of certain cytokines and chemokines generated within the airways (48, 60, 68). Experimental studies in animals have shown that intratracheal challenges with LPS or bacteria induce a rapid increase of TNF-alpha and MIP-2 in the airways without an increase of these factors in the systemic circulation (68, 71, 72, 114). Similarly, intravenous administration of LPS elicits a serum TNF-alpha and MIP-2 response, but TNF-alpha and MIP-2 are not detectable in BAL fluid. Similar observations have been reported in humans. Human volunteers challenged with intravenous LPS develop a marked increase in circulating cytokines including TNF-alpha, IL-1, IL-6, and IL-8. No increase in these cytokines is observed in the BAL fluid of these volunteers (115). Patients with unilateral pneumonia have a compartmentalized inflammatory response within the infected lung with localized production of TNF-alpha, IL-1, IL-6, and IL-8 (67, 78). We speculate that this selective increase in proinflammatory cytokines is essential for localizing the inflammatory reaction within the infected compartment. Interestingly, not all cytokines are compartmentalized. Intrapulmonary challenge with LPS or bacteria causes increases in G-CSF and cytokine-induced neutrophil chemoattractant (CINC) in both the BAL fluid and systemic circulation in animal models (71, 72, 114, 116, 117). Whether a cytokine is compartmentalized or not most likely depends on its physiologic function. The

increase in serum G-CSF is pivotal for the effective recruitment of PMNs from the bone marrow to reinforce the host defense response to infection. CINC has been shown to activate PMNs and enhance PMN response to other chemokines (118). The decompartmentalization of these cytokines during infection is likely to be an important mechanism by which they are able to reach the target organ or tissue and exert their functions.

PMNs represent the largest population of intravascular phagocytes and are essential to host defense against many bacterial and other microbial infections (59, 119). Under normal conditions, the alveolar space contains only a few PMNs (120). A large number of PMNs is maintained in the lung vasculature, especially the capillary bed. The marginated pool of PMNs in the pulmonary vasculature constitutes approximately 40 % of the body's total PMNs (66). In response to the appropriate signals, these marginated PMNs are recruited into alveolar spaces to reinforce the phagocytic defenses of the airways. Animal studies have shown that an intrapulmonary challenge with either bacteria or LPS elicits a rapid recruitment of PMNs into the lung. By 3 to 4 hours after the challenge, they constitute 60% to 80% of the total cells recovered by BAL (68 - 70, 121, 122). In the process of recruitment PMNs become activated by exposure to a variety of proinflammatory cytokines and mediators contained within the infected compartment, including G-CSF, TNF-alpha, IL-8, MIP-2, and CINC. In addition to the ingestion and killing of invading pathogens, recruited PMNs also participate in the regulation of the local host defense response by producing a number of cytokines including TNF-alpha, IL-1beta, IL-6, and MIP-2 (123). Recent studies have shown that PMNs also trap and scavenge chemokines in the surrounding environment which may play an important role in signaling the resolution of the inflammatory response in the lung (124, 125).

Acquired (or specific) immune defense in the lung consists of both humoral and cellular immune components. Specific immunity is the mainstay of host defense against pathogens that are able to evade the innate immune defense system. Mounting a specific immune response in the lung involves a complex interplay between antigen presenting cells or accessory cells (such as alveolar macrophages and dendritic cells) and lymphocytes (T and B lymphocytes) (61, 126). Antigen presenting cells are responsible for capturing and processing antigen, and then presenting the processed antigen together with class II major histocompatibility complex (MHC) molecules on their surface membrane to CD4+ T lymphocytes. The activated CD4+ T lymphocytes subsequently develop to specific helper T (T_H) cells to produce various types of cytokines. These cytokines play a pivotal role in mediating the proliferation and activation of immune effector cells including B lymphocytes and cytotoxic T lymphocytes (CTL). The pattern of cytokines produced by the T_H cells determines whether the humoral or cell-mediated branches of the immune system are activated. In the lung, dendritic cells residing in the interstitium are potent antigen presenting cells. Alveolar macrophages are relatively weaker at presenting antigens compared to dendritic cells.

Table 1. Components of normal host defense in the respiratory tract

Innate immune defense		
Mechanical defenses		<ul style="list-style-type: none"> • Filtration by structures in upper airways • Sneezing and coughing • Mucociliary clearance
Antimicrobial factors		<ul style="list-style-type: none"> • Lysozyme • Complement • Fibronectin • Lactoferrin • Transferrin • LPS-binding protein • Defensins (alpha and beta) Cathelicidin • Collectins (surfactant-associated protein-A and D)
Phagocytic defenses		<ul style="list-style-type: none"> • Alveolar macrophages • Neutrophils
Cytokines and Chemokines		<ul style="list-style-type: none"> • Tumor necrosis factor-alpha • Interferon-gamma • Interleukin-8 • Interleukin-10 • Interleukin-12 • Macrophage inflammatory protein-2 • Granulocyte colony-stimulating factor
Acquired immune defenses		
Antigen presenting cells or accessory cells		<ul style="list-style-type: none"> • Dendritic cells • Alveolar macrophages
Cellular immunity		<ul style="list-style-type: none"> • CD4⁺ T lymphocytes (helper T lymphocytes) • CD8⁺ T lymphocytes (cytotoxic T lymphocytes) • Natural killer lymphocytes
Humoral immunity		<ul style="list-style-type: none"> • B lymphocytes • Plasma cells • Immunoglobulins

It has been proposed that alveolar macrophages may play a role in “antigen transfer” in which alveolar macrophages initially take up antigen and then transfer the processed peptides to dendritic cells for efficient presentation (61). In certain circumstances, such as HIV infection, alveolar macrophages have also been shown to have an enhanced activity in stimulating T-cell proliferation (127). In general, antigens in the alveolar space may either directly diffuse into regional lymphoid tissues or be captured by antigen presenting cells which then migrate to regional lymph nodes. Within these regional lymphoid tissues, the primary immune response is initiated and a large number of immune effector cells including CTLs and antibody producing B cells are produced. The generated effector B and T cells traffic back to the lung through the systemic circulation and eventually reside in the interstitium and alveolar space by means of their homing mechanisms. Mounting an initial specific immune response to a new antigen takes place over a period of days to weeks. Memory B and T cells are also created during this process. These memory cells can rapidly (hours to days) organize a response when the host is exposed again to the same antigen (61). In normal hosts, the predominant lymphocytes residing in the lung are memory cells (128). Normal pulmonary host defense mechanisms are summarized in table 1.

3.3 Effects of alcohol on pulmonary host defense

Alcohol exerts a wide range of effects on the immune defense system of the lung. Impairment of

neutrophil function is one of the most well-characterized immune defects caused by alcohol. An early study conducted by Pickrell in 1938 demonstrated that rabbits intoxicated with alcohol failed to mount an acute leukocyte response to pneumococcal infection in the lung (129). Since then studies on experimental animals and human subjects have repeatedly shown that alcohol intoxication blocks PMN delivery to tissue sites of infection and inflammation (130-132). In 1964, Green et al reported that pulmonary clearance of bacteria was suppressed by alcohol intoxication (133). Two decades later, Astry and colleagues reported their studies on the relationship between the alcohol-induced defects of PMN recruitment and pulmonary clearance of bacteria (134). Animals with or without acute alcohol intoxication were challenged by aerosol inhalation of either Gram-positive (*Staphylococcus aureus*) or Gram-negative (*Proteus mirabilis*) bacteria. Alcohol intoxication caused a dose-dependent inhibition of PMN recruitment into the lung following the bacterial challenge. In association with this impaired PMN influx in the alveolar space, pulmonary clearance of both the Gram- positive and -negative bacteria was suppressed by alcohol in a dose-dependent manner. At a high dose (1.0% body weight) of alcohol administration, pulmonary antibacterial defense against the Gram-negative bacteria was completely ablated, allowing for the proliferation of *P. mirabilis* in the lung. Similar observations have been reported in various experimental models with intrapulmonary challenges of different pathogens (70, 71, 121, 122).

The recruitment of PMNs from the peripheral circulation into tissue sites of infection and inflammation is a complex phenomenon requiring PMN margination, adhesion, and transendothelial migration. This multistep process involves an intricate interplay of various adhesion molecules on the surface of both PMNs and the endothelium of the microvasculature. As mentioned previously, the presence of chemoattractant concentration gradient is pivotal in guiding PMN migration to the infected focus (75). Alcohol has been shown to inhibit several important steps in this process. Normally, the expression of β_2 -integrin adhesion molecules CD11b/CD18 on PMNs is rapidly up-regulated upon activation. This adhesion molecule complex mediates the firm attachment of PMNs to endothelial cells and their subsequent transendothelial migration. *In vitro* alcohol inhibits formylmethionylleucyl-phenylalanine (fMLP)- and PHA-stimulated up-regulation of CD18 expression on PMNs (135) and suppresses fMLP-stimulated PMN “hyperadherence” to endothelial monolayers (136). *In vivo* alcohol intoxication suppresses systemic LPS-induced up-regulation of CD11b/c and CD18 expression on circulating PMNs (97). Alcohol administration has been shown to cause a dose-dependent fall in granulocyte adherence which correlates with the observed inhibition of PMN tissue delivery (131, 137).

In addition to impairing PMN adherence and margination, alcohol also inhibits the PMN response to chemoattractants. Experimental studies have shown that administration of alcohol to rats results in a significant decrease in PMN chemotaxis to LPS-activated normal rat serum (138). Clinical studies have reported that PMNs from chronic alcohol abusers exhibit a decreased chemotactic response (139, 140). In patients with alcoholic cirrhosis, LPS absorbed from the portal system may gain access to the systemic circulation due to either the development of a shunt between the two systems or impaired Kupffer cell function. This “spill-over” of LPS into the systemic circulation may induce a chronic inflammatory reaction in the host. Chemoattractants such as CXC chemokines (IL-8) and complement fragments (C5a) are elevated in the peripheral circulation of patients with alcoholic liver disease (18, 130, 141). It has been postulated that the blunted response of PMNs to chemoattractants is related to the chronic *in vivo* activation of PMNs in these hosts.

In contrast to the events that occur in chronic alcoholic patients, acute alcohol intoxication has been shown to produce a profound suppression of the CXC chemokine (MIP-2 and CINC) response in the lung during pulmonary infection and inflammation (70, 71). This inhibition of the CXC chemokine response by pulmonary cells occurs at the level of both gene expression and protein production. The failure to generate a sufficient chemokine response in the alveolar space following appropriate stimulation diminishes the chemotactic gradient across the alveolar-capillary membrane which is necessary for PMN recruitment into the lung during pulmonary infection and inflammation.

The release of PMNs from the bone marrow in response to bacterial infection is an important mechanism

to recruit additional phagocytic cells against invading pathogens. It has been reported that neither acute nor chronic drinking in a controlled environment affects PMN release from the bone marrow in response to appropriate stimulation (130). G-CSF is a lineage specific hematopoietic growth factor which stimulates both bone marrow myeloid progenitor cell proliferation to PMNs and the release of PMNs from bone marrow to the peripheral circulation (90, 91, 142). Certain CXC chemokines including IL-8 and MIP-2 have also been shown to promote bone marrow granulopoiesis and the release of granulocytes (143, 144). During pulmonary and systemic infections, the blood concentration of G-CSF and CXC chemokines increase markedly. Acute alcohol intoxication suppresses both the G-CSF and chemokine responses in experimental animals challenged with either pulmonary or systemic bacterial pathogens (71, 93, 145). At the present time, the effects of this alcohol-induced suppression of G-CSF and chemokine production on the bone marrow granulopoietic response and PMN release during bacterial infection remain to be further defined. However, a significant number of hospitalized alcohol-abusing patients with infections present with granulocytopenia at admission, which is a predictor of increased mortality (146, 147). Studies of bone marrow from alcohol-abusing patients show a significant reduction in the number of mature granulocytes with vacuolization of myeloid progenitor cells. Incubation of bone marrow cells with alcohol at concentrations commonly observed in intoxicated patients has been reported to suppress granulocyte colony formation (148, 149). In addition, *in vitro* studies have shown that alcohol at a concentration greater than 100 mg% inhibits granulocyte-macrophage colony-stimulating activity produced by T lymphocytes (149).

Alcohol is also known to exert various effects on the functional activity of PMNs. In addition to the inhibition of adhesion molecule expression and adherence of PMNs as mentioned previously, early observations reported that *in vitro* alcohol at concentrations of 6.4g/L and higher inhibited human PMN phagocytosis and intracellular killing of *S. aureus* (150). A recent study demonstrated that alcohol at clinically relevant levels inhibited fMLP-stimulated superoxide production by human PMNs in a dose-dependent manner. Degranulation (elastase release) and bactericidal activity (killing of *S. aureus*) of human PMNs were also inhibited by alcohol at concentrations between 0.2% to 0.3% (151). *In vivo* intoxication of animals with acute alcohol (blood alcohol concentration of 50-100 mM) results in a significant inhibition of PMN phagocytic activity (70, 121). In a series of clinical observations, it was determined that PMNs from alcohol intoxicated patients contained 31% less elastase activity than those from normal individuals and produced 25-27% less superoxide than controls in response to inflammatory stimuli (152).

Alveolar macrophages are the resident phagocytic cells that respond to infectious challenges in the terminal airways. The release of TNF from activated alveolar macrophages serves as a key step in triggering the inflammatory response in the lung (48, 66, 153). Acute

alcohol intoxication suppresses the pulmonary TNF response to bacterial challenges and is associated with an inhibition of PMN recruitment into the alveolar space and clearance of bacteria from the airways (68, 122, 153, 154). Recent studies show that alcohol-induced inhibition of TNF production by alveolar macrophages primarily occurs at a post-transcriptional level. In alveolar macrophages recovered from rhesus macaques incubated with alcohol (100 mM) 30 min before LPS stimulation, alcohol suppressed LPS-induced TNF protein production by 84% and 70% at 2 and 8 hrs, respectively, without affecting the up-regulation of TNF mRNA expression by these macrophages. (155). Exposure of monocytes/macrophages to alcohol results in a significant increase in cell-associated TNF in these cells following LPS stimulation (156, 157). These observations suggest that alcohol impairs mechanisms involved in the release of TNF from these cells.

IL-10 is an anti-inflammatory cytokine that down-regulates pro-inflammatory cytokine expression as well as other aspects of the immune response (158, 159). Alcohol enhances human monocyte production of IL-10 and this has been postulated to be one mechanism underlying the immunosuppressive effects of alcohol (160, 161). At the present time, it remains to be determined whether alcohol exerts the same effects on alveolar macrophage production of IL-10 and, thereby, modulates the pulmonary host defense response.

In vivo and *in vitro* studies have shown that alcohol suppresses the mobilization, adherence, phagocytosis, superoxide production, and microbicidal activity of alveolar macrophages (162-166). These alcohol-induced defects of alveolar macrophage function diminish the capacity of these cells to contain invading pathogens within the alveolar space. This may be of particular importance in tuberculosis where greater than 90% of inhaled mycobacteria are normally ingested and destroyed by alveolar macrophages (167). The initial interaction of alveolar macrophages with this pathogen is critical for eliminating the infection. Tubercle bacilli not killed by alveolar macrophages survive and proliferate intracellularly. *In vitro* studies have shown that intracellular growth of mycobacteria in human macrophages is enhanced by exposure to alcohol in the culture system (168, 169).

In addition to compromising the cellular components of the innate immunity in the lung, alcohol also impairs the mechanical defenses in the airways. Studies have shown that alcohol causes depression of ciliary function and reduction of surfactant production in the alveoli (170, 171).

A number of studies have shown that alcohol consumption suppresses acquired immune defenses including both cell-mediated immunity and the humoral immune response. In the process of mounting a cell-mediated immune defense response, a complex interaction occurs among accessory cells, helper T cells, and cytotoxic lymphocytes. Alcohol-abusing patients have a poor ability in developing delayed hypersensitivity skin test reactions to

a variety of antigens (172, 173). *In vitro* treatment of human monocytes with alcohol suppresses the capacity of these accessory cells to present antigen to antigen-specific T cells. Impairment of antigen presentation has also been observed in animals fed an alcohol-containing diet (174). Chronic alcohol abusers, especially those with liver disease, frequently develop lymphopenia (18, 175). Incubation of normal lymphocytes with alcohol results in inhibition of blast transformation in response to mitogen stimulation (148, 176, 177). Lymphocyte proliferative responses to specific antibodies against T-cell receptors are blunted in hosts intoxicated with alcohol (178). Chronic alcohol feeding has also been shown to result in atrophy of the thymus and spleen in experimental animals. (175). Analysis of lymphocyte subsets in lymphoid tissues have shown that the absolute numbers of CD4+ T lymphocytes decrease significantly in animals on a chronic alcohol diet (44). In addition, T lymphocytes isolated from alcoholic hosts have a diminished capacity to produce IFN-gamma, an important cytokine that stimulates cell-mediated immunity (179). Pulmonary recruitment of both CD4+ and CD8+ T lymphocytes in response to *P. carinii* infection in the lung has been shown to be suppressed by alcohol consumption (44, 180).

Alcohol-induced disturbances of humoral immunity include an increased production of immunoglobulins in the circulation of alcohol-abusing patients, especially those with alcoholic liver disease (175). This increased immunoglobulin level appears not to be protective. In contrast, chronic alcohol consumption has been reported to impair development of specific antibodies in response to challenges with new antigens in experimental animals (181). Since the development of specific antibodies is important in protecting the host against infections caused by certain bacterial pathogens such as *S. pneumoniae* (182), alcohol-induced defects of specific antibody responses may adversely affect the eradication of invading pathogens from the airways in patients with pneumonia. Alcohol-induced defects of pulmonary host defense are summarized in table 2.

3.4. Immunomodulation of pulmonary infections in alcoholic hosts

Antibiotic therapy is currently the mainstay for the treatment of pulmonary infections in both alcoholic and nonalcoholic patients. However, antibiotic therapy is becoming more problematic due to the emergence of drug-resistant microbes. Because of this, immunomodulation has been considered as adjuvant therapy in managing pulmonary infections in alcoholics (183).

As previously reviewed, alcohol-induced inhibition of the pulmonary innate immune response, especially the failure to effectively recruit PMNs into the terminal airways is a major risk factor for bacterial pneumonia. Strategies have been developed to augment pulmonary phagocytic defenses either by increasing the number and function of circulating PMNs or enhancing chemotactic signals for PMN migration and activation in the lung. In experimental animals, administration of exogenous G-CSF has been shown to stimulate PMN

Table 2. Alcohol-induced defects of pulmonary host defense

Defects of innate immune defense	
Impairment of mechanical defenses	<ul style="list-style-type: none"> • Poor dental hygiene with increased bacterial colonization • Depressed consciousness/increased aspiration • Diminished respiratory excursion • Suppressed ciliary function
Reduced antimicrobial factors	<ul style="list-style-type: none"> • Reduced production of surfactant-associated proteins • Impaired complement synthesis
Impairment of phagocytic defenses	<ul style="list-style-type: none"> • Suppressed alveolar macrophage function (phagocytosis, bactericidal activity, respiratory burst, migration, production of proinflammatory cytokines and chemokines) • Suppressed neutrophil function (neutropenia, neutrophil mobilization from the bone marrow, adhesion molecule expression, trans-endothelial migration, phagocytosis, oxygen metabolism, bacterial killing activity)
Defects of acquired immune defenses	
Impairment of accessory cell function	<ul style="list-style-type: none"> • Suppressed antigen trapping and processing
Impairment of cell-mediated immunity	<ul style="list-style-type: none"> • Diminished T lymphocyte mitogenesis • Impaired primary sensitization • Suppressed lymphocyte recruitment
Impairment of humoral immunity	<ul style="list-style-type: none"> • Disordered immunoglobulin production

release from the bone marrow and augment PMN recruitment into the lung in response to infectious stimuli (48, 60). In rats, subcutaneous injections of G-CSF (50 microgram/kg) twice daily for two days results in a 7-fold increase in circulating PMNs and 5-fold increase in PMNs influx into the alveolar space following an intratracheal LPS challenge (70). This G-CSF-enhanced recruitment of PMNs into the lung is not solely the result of an increased number of circulating PMNs. Studies suggest that the sensitivity of these PMNs to chemotactic signals can also be up-regulated by G-CSF treatment (124). The effects of G-CSF on the antibacterial defenses of the lung have been studied in ethanol-intoxicated rats infected with *K. pneumoniae* (154). In these studies, G-CSF augmented the pulmonary recruitment of PMNs in infected control rats and significantly attenuated the adverse effects of ethanol on PMN delivery into the infected lung. G-CSF also enhanced the pulmonary clearance of bacteria in both control and ethanol-treated rats and improved the survival of these animals. Both *in vivo* and *in vitro* G-CSF attenuates the adverse effects of alcohol on many PMN functions, including the expression of adhesion molecules and phagocytosis (69, 70, 184).

A recently completed phase III, multi-center clinical trial of 756 patients with community-acquired pneumonia has shown that subcutaneous administration of G-CSF (300 microgram/day) to patients for up to 10 days results in a 3-fold increase in blood PMN counts in the peripheral circulation (185). This G-CSF treatment is well-tolerated by patients. Patients treated with G-CSF exhibited a faster resolution of their X-ray abnormalities and developed fewer complications including the adult respiratory distress syndrome and disseminated intravascular coagulation. These data suggest that G-CSF may be an effective therapeutic agent in combination with

antibiotics for the treatment of pulmonary infections in a variety of clinical entities including patients immunocompromised by alcohol.

IFN-gamma enhances host defense against a wide range of infectious pathogens including virus, bacteria, fungi, and parasites (102). *In vitro* studies demonstrate that over 3 dozen different pathogens become susceptible to macrophages once stimulated by IFN-gamma (186). Treatment of experimental infections with IFN-gamma in conjunction with antibiotics has been shown to be synergistic or additive against certain pathogens (*S. aureus*, *P. carinii*, and *C. neoformans*) that cause pulmonary infections in immunocompromised hosts. Intrapulmonary administration of IFN-gamma via either instillation or aerosol inhalation results in activation of alveolar macrophages and augmentation of pulmonary microbicidal activities (66, 104, 105, 187). Administration of a recombinant adenoviral vector encoding the murine IFN-gamma complementary DNA to rat lung results in prolonged expression of biologically active IFN-gamma in the lung and significantly enhanced pulmonary TNF production, PMN recruitment, and bacterial clearance in both normal and alcohol-intoxicated animals following bacterial challenge (188, 189). Our recent studies (unpublished data) have shown that pretreatment with intrapulmonary IFN-gamma markedly enhances CXC chemokine MIP-2 and CINC response in the lung in rats challenged with intratracheal LPS. This IFN-gamma treatment also attenuates acute alcohol-induced suppression of the MIP-2 and CINC responses in the lung following intrapulmonary LPS challenge.

At the present time, clinical trials of IFN-gamma therapy in alcohol-abusing patients with infections have not yet been undertaken. Previous studies have shown that IFN-gamma administered either locally or systemically for the treatment of pulmonary and other infections is well-

tolerated by patients (102, 183, 190). In patients with disseminated atypical mycobacterial infection (*Mycobacteria avium complex*), IFN-gamma treatment in combination with antimycobacterial chemotherapy results in clinical improvement. The treated patients have rapid responses in clearing of infected foci and blood cultures, abatement of fever, and improvement in subjective well-being (190). This effect of IFN-gamma treatment has also been observed in AIDS patients with *M. avium complex* infections (191, 192). Aerosol-administration of IFN-gamma to patients with persistent *M. avium complex* infection has been shown to improve negative conversion of acid-fast bacilli in sputum (193). A recent clinical study of patients with multidrug resistant tuberculosis has reported that aerosol-administration of 500 microgram IFN-gamma three times a week for 1 month results in negative conversion of mycobacteria in sputum in all patients (194). In addition, objective decreases in the size of cavitory lesions in the lung have been observed in all patients at the conclusion of therapy.

4. PERSPECTIVE

Alcohol abuse is a well-known risk factor for the development of many infectious diseases especially pulmonary infections. Bacterial pneumonia and other lung infections are more common and severe in alcoholics. The normal host defense system operates quite effectively to maintain the sterility of the lung. Alcohol compromises the function of various components of the immune defense system. Treatment of pulmonary infections in these immunocompromised hosts is often problematic. Immunotherapy to improve or enhance pulmonary host defense function in conjunction with aggressive antimicrobial regimens may provide a new approach in the management of infections in these patients.

5. ACKNOWLEDGMENTS

This work was supported by NIH grant AA-09803 and Louisiana State HEF Grant 2000-05-06.

6. REFERENCES

- Fortenberry J. D.: Alcohol, drugs, and STD/HIV risk among adolescents. *AIDS Patient Care STDS* 12, 783-786 (1998)
- Specter S.: Drug of abuse and infectious diseases. *J Fla Med Assoc* 81, 485-487 (1994)
- Lefevre F., B. O'Leary, M. Moran, M. Mossar, P. R. Yarnold, G.J. Martin & J. Glassroth: Alcohol consumption among HIV- infected patients. *J Gen Intern Med* 10, 458-460 (1995)
- Rush B.: An inquiry into the effects of ardent spirits upon the human body and mind. *Q J Stud Alcohol* 4, 321-341 (1943)
- Olser W: The Principles and Practice of Medicine. New York, Appleton (1905)
- Capps J. A., G. H. Coleman: Influence of alcohol on prognosis of pneumonia in Cook County Hospital. *JAMA* 80, 750-752 (1923)
- Sundby P.: Alcoholism and mortality. Oslo, Universitetsforlaget, National Institute for Alcohol Research, Publ. No. 6 (1976)
- Painton J. F., H. J. Ulrich: Lobar pneumonia; an analysis of 1298 cases. *Ann Intern Med* 10, 1345-1364 (1937)
- Nolan J. P.: Alcohol as a factor in the illness of university service patients. *Am J Med Sci* 249, 135-142 (1965)
- Einterbauer R. H., G. A. Bedon & W. C. Ball Jr.: Recurrent pneumonia. Predisposing illness and clinical patterns in 158 patients. *Ann Intern Med* 70, 689-700 (1969)
- Schmidt W., J. De Lint: Causes of death of alcoholics. *Q J Stud Alcohol* 33, 171-185 (1972)
- Fernandez-Sola J., A. Junque, R. Estruch, R. Monforte, A. Torres & A. Urbano-Marquez: High alcohol intake as a risk and prognostic factor for community-acquired pneumonia. *Arch Intern Med* 155, 1649-1654 (1995)
- Saitz R., W. A. Ghali & M. A. Moskowitz: The impact of alcohol-related diagnoses on pneumonia outcomes. *Arch Intern Med* 157, 1446-1452 (1997)
- Marik P. E.: The clinical features of severe community-acquired pneumonia presenting as septic shock. Norasept II Study Investigators. *J Crit Care* 15, 85-90 (2000)
- Musher D. M., I. Alexandraki, E. A. Graviss, N. Yanbeiy, A. Eid, L. A. Inderias, H. M. Phan & E. Solomon: Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. *Medicine* 79, 210-221 (2000)
- Everts R. J., D. R. Murdoch, S. T. Chambers, G. I. Town, S. G. Withington, I. R. Martin, M. J. Epton, C. Frampton, A. Y. Cheresky & M. I. Schousboe: Nosocomial pneumonia in adult general medical and surgical patients at Christchurch Hospital. *N Z Med J* 113, 221-224 (2000)
- Macgregor R. R., D. B. Louria: Alcohol and infection. *Curr Clin Top Infect Dis* 17, 291-315 (1997)
- Cook R. T.: Alcohol abuse, alcoholism, and damage to the immune system - a review. *Alcohol Clin Exp Res* 22, 1927-1942 (1998)
- Adams H. G., C. Jordan: Infections in the alcoholic. *Med Clin North Am* 68, 179-200 (1984)
- Ikawa H., Y. Hayashi, C. Ohbayashi, H. Tankawa & H. Itoh: Autopsy case of alcoholic hepatitis and cirrhosis treated with corticosteroids and affected by *Pneumocystis carinii* and cytomegalovirus pneumonia. *Pathol Int* 51, 629-632 (2001)

Lung defenses and alcohol

21. Luna C. M., A. Famiglietti, R. Absi, A. J. Videla, F. J. Nogueira, A. D. Fuenzalida & R. J. Gene: Community-acquired pneumonia: etiology, epidemiology and outcome at a teaching hospital in Argentina. *Chest* 118, 1344-1354 (2000)
22. Ruiz M., S. Ewig, A. Torres, F. Arancibia, F. Marco, J. Mensa, M. Sanchez & J. A. Martinez: Severe community-acquired pneumonia. Risk factors and follow-up epidemiology. *Am J Respir Crit Care Med* 160, 923-929 (1999)
23. Van Metre T. E.: Pneumococcal pneumonia treated with antibiotics. *N Engl J Med* 251, 1048-1054 (1954)
24. Levin D. C., M. I. Schwarz, R. A. Matthay & F. M. LaForce: Bacteremic *Hemophilus influenzae* pneumonia in adults. A report of 24 cases and a review of the literature. *Am J Med* 62, 219-224 (1977)
25. Fuxench-Lope Z., C. H. Ramierz-Ronda: Pharyngeal flora in ambulatory alcoholic patients: prevalence of gram negative bacilli. *Arch Intern Med* 138, 1815-1816 (1978)
26. Jong G. M., T. R. Hsiue, C. R. Chen, H. Y. Chang & C. W. Chen: Rapidly fatal outcome of bacteremic *Klebsiella pneumoniae* pneumonia in alcoholics. *Chest* 107, 214-217 (1995)
27. Bartlett J. G., S. M. Finegold: Anaerobic infections of the lung and pleural space. *Am Rev Respir Dis* 110, 56-77 (1974)
28. Kharkar R. A., V. B. Ayyar: Aetiological aspects of lung abscess. *J Postgrad Med* 27, 163-166 (1981)
29. Brudney K., J. Dobkin: Resurgent tuberculosis in New York city. Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *Am Rev Respir Dis* 144, 745-749 (1991)
30. Nelson S., C. Mason, G. Bagby & W. Summer: Alcohol, tumor necrosis factor, and tuberculosis. *Alcohol Clin Exp Res* 19, 17-24 (1995)
31. Jones H., J. Roberts & J. Brantner: Incidence of tuberculosis among homeless men. *JAMA* 155, 1222-1223 (1954)
32. Carpenter J. L., D. Y. Iluang: Community-acquired pulmonary infections in a public municipal hospital in the 1980s. *South Med J* 84, 299-306 (1991)
33. Brown K. E., A. H. Campbell: Tobacco, alcohol and tuberculosis. *Br J Dis Chest* 55, 150-158 (1961)
34. Lewis J. G., D. A. Chamberlain: Alcohol consumption and smoking habits in male patients with pulmonary tuberculosis. *Br J Prev Soc Med* 17, 149-152 (1963)
35. Segarra F., D. S. Sherman: Relapses in pulmonary tuberculosis. *Dis Chest* 51, 59-63 (1967)
36. Milne R. C.: Alcoholism and tuberculosis in Victoria. *Med J Aust* 2, 955-960 (1970)
37. Overturf G. D., R.L. Modlin: Predictors of short-term prognosis in patients with pulmonary tuberculosis. *J Infect Dis* 158, 366-371 (1988)
38. Borgdorff M. W., J. Veen, N. A. Kalisvaart & N. Nagelkerke: Mortality among tuberculosis patients in The Netherlands in the period 1993-1995. *Eur Respir J* 11, 816-820 (1998)
39. Thomsen J. L.: Diseases of the airways and lungs in forensic autopsy material of alcoholics. *Med Sci Law* 37, 23-26 (1997)
40. Zafran N., E. Heldal, S. Pavlovic, D. Vuckovic & J. Boe: Why do our patients die of active tuberculosis in the era of effective therapy? *Tuber Lung Dis* 75, 329-333 (1994)
41. Taylor Z., S. M. Marks, N. M. Rios Burrows, S. E. Weis, R. L. Stricof & B. Miller: Causes and costs of hospitalization of tuberculosis patients in the United States. *Int J Tuberc Lung Dis* 4, 931-939, (2000)
42. Kok-Jensen A.: The prognosis of pulmonary tuberculosis in patients with abuse of alcohol. *Scand J Resp Dis* 51, 42-48 (1970)
43. Centis R., A. Ianni & G.B. Migliori: Evaluation of tuberculosis treatment results in Italy, report 1998. Tuberculosis section of the National AIPO Study Group in Infectious Disease and the SMIRA Group. *Monaldi Arch Chest Dis* 55, 293-298 (2000)
44. Shellito J. E.: Alcohol and host defense against pulmonary infection with *Pneumocystis carinii*. *Alcohol Clin Exp Res* 22, 208S-211S (1998)
45. Wallace J. M., N. I. Hansen, L. Lavange, J. Glassroth, B. L. Browdy, M. J. Rosen, P. A. Kvale, B. T. Mangura, L. B. Reichman & P. C. Hopewell: Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med* 155, 72-80 (1997)
46. Survival and progression of HIV disease in women attending GUM/HIV clinics in Britain and Ireland. Study Group for the MRC Collaborative Study of HIV Infection in Women. *Sex Transm Infect* 75, 247-52 (1999)
47. D'Souza N. B., J. F. Mandujano, S. Nelson, W. R. Summer & J. E. Shellito: Alcohol ingestion impairs host defenses predisposing otherwise healthy mice to *Pneumocystis carinii* infection. *Alcohol Clin Exp Res* 19, 1219-1225 (1995)
48. Zhang P., W. R. Summer, G. J. Bagby & S. Nelson: Innate immunity and pulmonary host defense. *Immunol Rev* 173, 39-51 (2000)
49. Mercer R.R., J. D. Crapo: Normal anatomy and defense mechanisms of the lung. In Textbook of Pulmonary

Diseases, sixth edition. Eds: Baum G. L., Crapo J. D., Celli B. R. & Karlinsky J. B. Lippincott-Raven Publishers, Philadelphia, 23-45 (1998)

50. Coonrod J.: The role of extracellular bactericidal factors in pulmonary host defense. *Semin Respir Infect* 1,118-129 (1986)

51. Kaltreider H. B.: Immune mechanisms in the normal lung. *Semin Respir Med* 12,143-155 (1991)

52. Martin T. R., J. C. Mathison, P. Tobias, D. J. Leturcq, A. M. Moriarty, R. J. Maunders & R. J. Ulevitch: Lipopolysaccharide binding protein enhances the responsiveness of alveolar macrophages to bacterial lipopolysaccharide. Implications for cytokine production in normal and injured lung. *J Clin Invest* 90, 2209-2219 (1992)

53. Hiratsuka T., M. Nakazato, Y. Date, J. Ashitani, T. Minematsu, N. Chino & S. Matsukura: Identification of human beta-defensin-2 in respiratory tract and plasma and its increase in bacterial pneumonia. *Biochem Biophys Res Commun* 249, 943-947 (1998)

54. Schnapp D., A. Harris: Antibacterial peptides in bronchoalveolar lavage fluid. *Am J Respir Cell Mol Biol* 19, 352-356 (1998)

55. Ashitani J., H. Mukae, M. Nakazato, T. Ihi, H. Mashimoto, J. Kadota, S. Kohno & S. Matsukura: Elevated concentrations of defensins in bronchoalveolar lavage fluid in diffuse panbronchiolitis. *Eur Respir J* 11,104-111 (1998)

56. McCray P. B. Jr., L. Bentley: Human airway epithelia express a defensin. *Am J Respir Cell Mol Biol* 16, 343-349 (1997)

57. Bals R., X. R. Wang, M. Zasloff & J. M. Wilson: The peptide antibiotic LL-37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. *Proc Natl Acad Sci USA* 95, 9541-9546 (1998)

58. Crouch E. C.: Collectins and pulmonary host defense. *Am J Respir Cell Mol Biol* 19, 177-201 (1998)

59. Sibille Y., H. Y. Reynolds: Macrophages and polymorphonuclear neutrophils in lung defense and injury. *Am Rev Respir Dis* 141, 471-501 (1990)

60. Nelson S., W. R. Summer: Innate immunity, cytokines, and pulmonary host defense. *Infect Dis Clin N Am* 12, 555-567 (1998)

61. Twigg P. H. III: Pulmonary host defenses. *J Thorac Imag* 13, 221-233 (1998)

62. Ozaki T., M. Maeda, H. Hayashi, Y. Nakamura, H. Moriguchi, T. Kamei, S. Yasuoka & T. Ogura: Role of alveolar macrophages in the neutrophil-dependent defense system against *Pseudomonas aeruginosa* infection in the

lower respiratory tract. *Am Rev Respir Dis* 140,1595-1601 (1989)

63. Toews G. B.: Determinants of bacterial clearance from the lower respiratory tract. *Semin Respir Infect* 1, 68-78 (1986)

64. Reynolds H. Y.: Lung inflammation: role of endogenous chemotactic factors in attracting polymorphonuclear granulocytes. *Am Rev Respir Dis* 127, S16-S25 (1983)

65. Standiford T. J., S. L. Kunkel, M. J. Greenberger, L. L. Laichalk & R. M. Strieter: Expression and regulation of chemokines in bacterial pneumonia. *J Leukoc Biol* 59, 24-28 (1996)

66. Nelson S., C. M. Mason, J. Kolls & W. R. Summer: Pathophysiology of pneumonia. *Clin Chest Med* 16, 1-12 (1995)

67. Dehoux M. S., A. Boutten, J. Ostinelli, N. Seta, M. C. Dombret, B. Crestani, M. Deschenes, J. L. Trouillet & M. Aubier: Compartmentalized cytokine production within the human lung in unilateral pneumonia. *Am J Respir Crit Care Med* 150, 710-716 (1994)

68. Nelson S., G. J. Bagby, B. G. Bainton, L. A. Wilson, J. J. Tompson & W. R. Summer: Compartmentalization of intraalveolar and systemic lipopolysaccharide-induced tumor necrosis factor and the pulmonary inflammatory response. *J Infect Dis* 159, 189-194 (1989)

69. Zhang P., G. J. Bagby, D. A. Stoltz, J. A. Spitzer, W. R. Summer & S. Nelson: Modulation of the lung host response by granulocyte colony-stimulating factor in rats challenged with intrapulmonary endotoxin. *Shock* 7, 193-199 (1997)

70. Zhang P., G. J. Bagby, D. A. Stoltz, W. R. Summer & S. Nelson: Granulocyte colony-stimulating factor modulates the pulmonary host response to endotoxin in the absence and presence of acute ethanol intoxication. *J Infect Dis* 179, 1441-1448 (1999)

71. Boé D. M., S. Nelson, P. Zhang & G. J. Bagby: Acute ethanol intoxication suppresses lung chemokine production following infection with *Streptococcus pneumoniae*. *J Infect Dis* 184, 1134-1142 (2001)

72. Quinton L. J., S. Nelson, D. M. Boé, P. Zhang, Q. Zhong, J. K. Kolls & G. J. Bagby: The granulocyte colony-stimulating factor response following intrapulmonary and systemic bacterial challenges. *J Infect Dis* (In press)

73. Nelson S., G. J. Bagby & W. R. Summer: Anti-tumor necrosis factor- α antibody suppresses pulmonary antibacterial defenses. *Am Rev Respir Dis* 143, S393 (1991)

74. Kolls J., D. Lei, S. Nelson, W. R. Summer, S. Greenberg & B. Beutler: Adenovirus-mediated blockade of tumor necrosis factor in mice protects against endotoxin

- shock yet impairs pulmonary host defense. *J Infect Dis* 171, 570-575 (1995)
75. Miller M. D., M. S. Krangel: Biology and biochemistry of the chemokines: a family of chemotactic and inflammatory cytokines. *Crit Rev Immunol* 12, 17-46, (1992)
 76. Maus U., S. Rosseau, U. Knies, W. Seeger & J. Lohmeyer: Expression of pro-inflammatory cytokines by flow-sorted alveolar macrophages in severe pneumonia. *Eur Respir J* 11, 534-541 (1998)
 77. Beck G. C., B. A. Yard, A. J. Breedijk, K. Van Ackern & F. J. Van Der Woude: Release of CXC-chemokines by human lung microvascular endothelial cells (LMVEC) compared with macrovascular umbilical vein endothelial cells. *Clin Exp Immunol* 118, 298-303 (1999)
 78. Boutten A., M. S. Dehoux, N. Seta, J. Ostinelli, P. Venembre, B. Crestani, M. C. Dombret, G. Durand & M. Aubier: Compartmentalized IL-8 and elastase release within the human lung in unilateral pneumonia. *Am J Respir Crit Care Med* 153, 336-342 (1996)
 79. Ulich T. R., S. C. Howard, D. G. Remick, A. Wittwer, E. S. Yin, K. Guo, J. K. Welply & J. H. Williams: Intratracheal administration of endotoxin and cytokines VI. Antiserum to CINC inhibits acute inflammation. *Am J Physiol* 268, L245-L250 (1995)
 80. Dunican A. L., S. J. Leuenroth, A. Ayala & H. H. Simms: CXC chemokine suppression of polymorphonuclear leukocytes apoptosis and preservation of function is oxidative stress independent. *Shock* 13, 244-250 (2000)
 81. Seo S. M., L. V. McIntire & C. W. Smith: Effects of IL-8, Gro-alpha, and LTB(4) on the adhesive kinetics of LFA-1 and Mac-1 on human neutrophils. *Am J Physiol* 281, C1568-1578 (2001)
 82. Hogan S. P., P. S. Foster, X. Tan & A. J. Ramsay: Mucosal IL-12 gene delivery inhibits allergic airways disease and restores local antiviral immunity. *Eur J Immunol* 28, 413-423 (1998)
 83. Qureshi M. H., T. Zhang, Y. Koguchi, K. Nakashima, H. Okamura, M. Kurimoto & K. Kawakami: Combined effects of IL-12 and IL-18 on the clinical course and local cytokine production in murine pulmonary infection with *Cryptococcus neoformans*. *Eur J Immunol* 29, 643-649 (1999)
 84. Wakeham J., J. Wang, J. Magram, K. Croitoru, R. Harkness, P. Dunn, A. Zganiacz & Z. Xing: Lack of both types 1 and 2 cytokines, tissue inflammatory responses and immune protection during pulmonary infection by mycobacterium bovis bacille Calmette-Guerin in IL-12-deficient mice. *J Immunol* 160, 6101-6111 (1998)
 85. Hoag K. A., M. F. Lipscomb, A. A. Izzo & N. E. Street: IL-12 and IFN-gamma are required for initiating the protective Th1 response to pulmonary cryptococcosis in resistant C.B-17 mice. *Am J Res Cell Mol Biol* 17, 733-739 (1997)
 86. Gazzinelli R. T., M. Wysocka, S. Hieny, T. Scharon-Kersten, A. Cheever, R. Kuhn, W. Muller, G. Trinchieri & A. Sher: In the absence of endogenous IL-10, mice acutely infected with *Toxoplasma gondii* succumb to a lethal immune response dependent on CD4+ T cells and accompanied by overproduction of IL-12, IFN-gamma and TNF-alpha. *J Immunol* 157, 798-805 (1996)
 89. Haraguchi S., N. K. Day, R. P. Nelson Jr., P. Emmanuel, J. E. Duplantier, C. S. Christodoulou & R. A. Good: Interleukin 12 deficiency associated with recurrent infections. *Proc Natl Acad sci U S A* 95, 13125-13129 (1998)
 90. Clark S. C., R. Kamen: The human hematopoietic colony-stimulating factors. *Science* 236,1229-1237 (1987)
 91. Groopman J. E., J. M. Molina & D. T. Scadden: Hematopoietic growth factors. Biology and clinical applications. *N Engl J Med* 321, 1449-1459 (1989)
 92. Tazi A., S. Nioche, J. Chastre, J. M. Smiejan & A. J. Hance: Spontaneous release of granulocyte colony-stimulating factor (G-CSF) by alveolar macrophages in the course of bacterial pneumonia and sarcoidosis: endotoxin-dependent and endotoxin-independent G-CSF release by cells recovered by bronchoalveolar lavage. *Am J Respir Cell Mol Biol* 4, 140-147 (1991)
 93. Bagby G. J. , P. Zhang, D. A. Stoltz & S. Nelson: Suppression of the granulocyte colony-stimulating factor response to *Escherichia coli* challenge by alcohol intoxication. *Alcohol Clin Exp Res* 22, 1740-1745 (1998)
 94. Kawakami M., H. Tsutsumi, T. Kumakawa, H. Abe, M. Hirai, S. Kurosawa, M. Mori & M. Fukushima: Levels of serum granulocyte colony-stimulating factor in patients with infections. *Blood* 76,1962-9164 (1990)
 95. Pauksen K., L. Elfman, A. K. Ulfgren & P. Venge: Serum levels of granulocyte-colony stimulating factor (G-CSF) in bacterial and viral infections, and in atypical pneumonia. *Brit J Haematol* 88, 256-260 (1994)
 96. Zhang P., G. J. Bagby, D. A. Stoltz, W. R. Summer & S. Nelson: Enhancement of peritoneal leukocyte function by granulocyte colony-stimulating factor in rats with abdominal sepsis. *Crit Care Med* 26, 315-321 (1998)
 97. Zhang P., G. J. Bagby, M. Xie, D. A. Stoltz, W. R. Summer & S. Nelson: Acute ethanol intoxication inhibits neutrophil beta₂-integrin expression in rats during endotoxemia. *Alcohol Clin Exp Res* 22, 135-141 (1998)
 98. Roilides E., T. J. Walsh & P. A. Pizzo: Granulocyte colony-stimulating factor enhances the phagocytic and

bactericidal activity of normal and defective human neutrophils. *J Infect Dis* 163, 579-583 (1991)

99. Sullivan G. W., H. T. Carper & G. L. Mandell: The effect of three human recombinant hematopoietic growth factors (granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and interleukin-3) on phagocyte oxidative activity. *Blood* 81, 1863-1870 (1993)

100. Yong K. L., D. C. Linch: Differential effects of granulocyte- and granulocyte-macrophage colony-stimulating factors (G- and GM-CSF) on neutrophil adhesion *in vitro* and *in vivo*. *Eur J Haematol* 49, 251-259 (1992)

101. Nelson S., G. J. Bagby: Granulocyte colony-stimulating factor and modulation of inflammatory cells in sepsis. *Clin Chest Med* 17, 319-332 (1996)

102. Murray H. W.: Current and future clinical applications of interferon-gamma in host antimicrobial defense. *Intensive Care Med* 22, S456-S461, (1996)

103. Luedke C. E., A. Cerami: Interferon-gamma overcomes glucocorticoid suppression of cachectin/tumor necrosis factor biosynthesis by murine macrophages. *J Clin Invest* 86, 1234-1240 (1990)

104. Beck J. M., H. D. Liggitt, E. N. Brunette, H. J. Fuchs, J. E. Shellito & R. J. Debs: Reduction in intensity of *Pneumocystis carinii* pneumonia in mice by aerosol administration of gamma interferon. *Infect Immun* 11, 3859-62 (1991)

105. Skerrett S. J., T. R. Martin: Intratracheal interferon gamma augments pulmonary clearance of *Legionella pneumophila* in immunosuppressed rats. *Am Rev Respir Dis* 145, A12 (1992)

106. Kopydlowski K. M., C. A. Salkowski, M. J. Cody, N. van Rooijen, J. Major, T.A. Hamilton & S. N. Vogel: Regulation of macrophage chemokine expression by lipopolysaccharide *in vitro* and *in vivo*. *J Immunol* 163, 1537-1544 (1999)

107. Cole A. M., T. Ganz, A. M. Liese, M. D. Burdick, L. Liu & R. M. Strieter: Cutting edge: IFN-inducible ELR-CXC chemokines display defensin-like antimicrobial activity. *J Immunol* 167, 623-627 (2001)

108. Figari I., N. Mori & M. J. Palladino Jr.: Regulation of neutrophil migration and superoxide production by recombinant tumor necrosis factors-alpha and -beta: Comparison to recombinant interferon-gamma and interleukin-1alpha. *Blood* 70, 979-984 (1987)

109. Kowanko I., A. Ferrante: Stimulation of neutrophil respiratory burst and lysosomal enzyme release by human interferon- gamma. *Immunology* 62, 149-151 (1987)

110. Greenberger M. J., R. M. Strieter, S. L. Kunkel, J. M. Danforth, R. E. Goodman & T. J. Standiford: Neutralization of IL-10 increases survival in a murine model of *Klebsiella pneumoniae*. *J Immunol* 155, 722-729 (1995)

111. Standiford T. J., R. M. Strieter, M. J. Greenberger & S. L. Kunkel: Expression and regulation of chemokines in acute bacterial pneumonia. *Biol Sign* 5, 203-208 (1996)

112. Isler P., B. G. de Rochemonteix, F. Songeon, N. Boehringer & L. P. Nicod: Interleukin-12 production by human alveolar macrophages is controlled by the autocrine production of interleukin-10. *Am J Respir Cell Mol Biol* 20, 270-278 (1999)

113. Laichalk L. L., J. M. Danforth & T. J. Standiford: Interleukin-10 inhibits neutrophil phagocytic and bactericidal activity. *FEMS Immunol Med Microbiol* 15, 181-187 (1996)

114. Zhang P., S. Nelson, M. C. Holmes, W. R. Summer & G. J. Bagby: Compartmentalization of macrophage inflammatory protein-2, but not cytokine-induced neutrophil chemoattractant, in rats challenged with intratracheal endotoxin. *Shock* 17, 104-108 (2002)

115. Boujoukos A. J., G. D. Martich, E. Supinski & A. F. Suffredini: Compartmentalization of the acute cytokine response in humans after intravenous endotoxin administration. *J Appl Physiol* 74, 3027-3033 (1993)

116. Nelson S., P. Zhang, W. Summer & G. Bagby: Granulocyte colony-stimulating factor is not compartmentalized following an intrapulmonary bacterial challenge. *Am J Respir Crit Care Med* 161, A216 (2000)

117. Balckwell T. S., L. H. Lancaster, T. B. Blackwell, A. Venkatakrishnan & J. W. Christman: Chemotactic gradients predict neutrophilic alveolitis in endotoxin-treated rats. *Am J Respir Crit Care Med* 159, 1644-1652 (1999)

118. Shibata F., K. Konishi, H. Kato, N. Komorita, M. Al-Mokdad, M. Fujioka & H. Nakagawa: Recombinant production and biological properties of rat cytokine-induced neutrophil chemoattractants, gro/CINC-2alpha, CINC-2beta, and CINC-3. *Eur J Biochem* 321, 306-311 (1995)

119. Lehrer R. I., T. Ganz, M. E. Selsted, B. M. Babior & J. T. Curnutte: Neutrophils and host defense. *Ann Intern Med* 109, 127- 142 (1988)

120. Cohen A. B., M. Rossi: Neutrophils in normal lungs. *Am Rev Respir Dis* 127, S3-S9 (1983)

121. Zhang P., S. Nelson, W. R. Summer & J. A. Spitzer: Acute ethanol intoxication suppresses the pulmonary inflammatory response in rats challenged with intrapulmonary endotoxin. *Alcohol Clin Exp Res* 21, 773-778 (1997)

122. Nelson S., G. J. Bagby, B. G. Bainton & W. R. Summer: The effects of acute and chronic alcoholism on tumor necrosis factor and the inflammatory response. *J Infect Dis* 160, 422-429 (1989)
123. Zhou X., M. Jordana, H. Kirpalani, K. E. Driscoll, T. J. Schall & J. Gauldie: Cytokine expression by neutrophils and macrophages *in vivo*: Endotoxin induces tumor necrosis factor- α , macrophage inflammatory protein-2, interleukin-1 β , and interleukin-6 but not RANTES or transforming growth factor- β 1 mRNA expression in acute lung inflammation. *Am J Respir Cell Mol Biol* 10, 148-153 (1994)
124. Zhang P., G. J. Bagby, J. K. Kolls, D. A. Welsh, W. R. Summer, J. Andresen & S. Nelson: The effects of granulocyte colony-stimulating factor and neutrophil recruitment on the pulmonary chemokine response to intratracheal endotoxin. *J Immunol* 165, 458-468 (2001)
125. Holmes M. C., Zhang P., S. Nelson, W. R. Summer & G. J. Bagby: Neutrophil modulation of the pulmonary chemokine response to lipopolysaccharide. *Shock* (In press)
126. Reynokds H. Y.: Pulmonary host defenses. *Alcohol Clin Exp Res* 19, 6-10 (1995)
127. Twigg H.L., M. F. Lipscomb, B. Yoffe, D. Barbaro & J. C. Weissler: Enhanced accessory cell function by alveolar macrophages from patients infected with the human immunodeficiency virus: potential role for depletion of CD4+ T cells in the lung. *Am J Respir Cell Mol Biol* 1, 391-400 (1989)
128. Saltini C, M. Kirby, B. C. Trapnell, N. Tamura & R. G. Crystal: Biased accumulation of T lymphocytes with "memory" - type CD45 leukocyte common antigen gene expression on the epithelial surface of the human lung. *J Exp Med* 170, 1123-1140 (1990)
129. Pickrell K. L.: The effect of alcoholic intoxication and ether anesthesia on resistance to pneumococcal infection. *Bull Johns Hopkins Hosp* 63, 238-260 (1938)
130. Moses J. M., E. H. Geschickter & R. H. Ebert: The relationship of enhanced permeability to leukocyte mobilization in delayed inflammation. *Br J Exp Pathol* 49, 386-394, (1968)
131. MacGregor R. R., S. G. Gluckman: Effect of acute alcohol intoxication on granulocyte mobilization and kinetics. *Blood* 52, 551-559 ((1979)
132. Brayton R. G., P. E. Stokes, M. S. Schwartz, D. B. Louria: Effect of alcohol and various diseases on leukocyte mobilization, phagocytosis and intracellular bacterial killing. *N Engl J Med* 282, 123-128 (1970)
133. Green G. M., E. H. Kass: Factors influencing the clearance of bacteria by the lung. *J Clin Invest* 43, 769-776 (1964)
134. Astry C. L., G. A. Warr & G. J. Jakab: Impairment of polymorphonuclear leukocyte immigration as a mechanism of alcohol-induced suppression of pulmonary antibacterial defenses. *Am Rev Respir Dis* 128, 113-117 (1983)
135. Nilsson E., P. Lindström, M. Patarroyo, B. Ringertz, R. Lerner, J. Rincon & J. Palmblad: Ethanol impairs certain aspects of neutrophil adhesion *in vitro*: comparisons with inhibition of expression of the CD18 antigen. *J Infect Dis* 163, 591-597 (1991)
136. MacGregor R. R., M. Safford & M. Shalit: Effect of ethanol on functions required for the delivery of neutrophils to sites of inflammation. *J Infect Dis* 157, 682-689 (1988)
137. MacGregor R. R., P. J. Spagnuolo & A. L. Lentnek: Inhibition of granulocyte adherence by ethanol, prednisone, and aspirin measured with a new assay system. *N Engl J Med* 291, 642-646 (1974)
138. Lister P. D., M. J. Gentry & L. C. Preheim: Ethanol impairs neutrophil chemotaxis *in vitro* but not adherence or recruitment to lungs of rats with experimental pneumococcal pneumonia. *J Infect Dis* 167, 1131-1137 (1993)
139. Gluckman S. J., V. C. Dvorak & R. R. MacGregor: Host defenses during prolonged alcohol consumption in a controlled environment. *Arch Intern Med* 137, 1539-1543 (1977)
140. MacGregor R. R., S. J. Gluckman & J. R. Senior: Granulocyte function and levels of immunoglobulins and complement in patients admitted for withdrawal from alcohol. *J Infect Dis* 138, 747-753 (1978)
141. Sheron N., G. Bird, J. Koskinas, B. Portmann, M. Ceska, I. Lindley & R. Williams: Circulating and tissue levels of the neutrophil chemotaxin interleukin-8 are elevated in severe acute alcoholic hepatitis, and tissue levels correlate with neutrophil infiltration. *Hepatology* 18, 41-46 (1993)
142. Dale D. C., W. C. Liles, W. R. Summer & S. Nelson: Granulocyte colony-stimulating factor - role and relationships in infectious diseases. *J Infect Dis* 172, 1061-1075 (1995)
143. Laterveet L., I. J. D. Lindley, D. P. M. Heemskerk, J. A. J. Camps, E. K. J. Pauwels, R. Willemze & W. E. Fibbe: Rapid mobilization of hematopoietic progenitor cells in rhesus monkeys by a single intravenous injection of interleukin-8. *Blood* 87, 781-788 (1996)
144. Wang J., N. Mukaida, Y. Zhang, T. Ito, S. Nakao & K. Matsushima: Enhanced mobilization of hematopoietic progenitor cells by mouse MIP-2 and granulocyte colony-stimulating factor in mice. *J Leukoc Biol* 62, 503-509 (1997)
145. Zhang P., G. J. Bagby, D. M. Boé, Q. Zhong, P. Schwarzenberger, J. K. Kolls, W. R. Summer & S. Nelson:

Lung defenses and alcohol

Acute alcohol intoxication suppresses the CXC chemokine response during endotoxemia. *Alcohol Clin Exp Res* 26, 65-73 (2002)

146. Liu Y. K.: Effects of alcohol on granulocytes and lymphocytes. *Semin Hematol* 17, 130-136 (1980)

147. McFarland W., E. P. Libre: Abnormal leukocyte response in alcoholism. *Ann Intern Med* 59, 865-877 (1963)

148. Tisman G., V. Herbert: *In vitro* myelosuppression and immunosuppression by ethanol. *J Clin Invest* 51, 1410-1414 (1973)

149. Imperia P. S., G. Chikkappa & P. G. Phillips: Mechanism of inhibition of granulopoiesis by ethanol. *Proc Soc Exp Biol Med* 175, 219-225, (1984)

150. Hallengren B., A. Forsgren: Effect of alcohol on chemotaxis, adherence and phagocytosis of human polymorphonuclear leucocytes. *Acta Med Scand* 204, 43-48 (1978)

151. Tamura D. Y., E. E. Moore, D. A. Partrick, J. L. Johnson, P. J. Offner, T. J. Harbedk & C. C. Silliman: Clinically relevant concentrations of ethanol attenuate primed neutrophil bactericidal activity. *J Trauma* 44, 320-324 (1998)

152. Sachs C. W., R. H. Christensen, P. S. Pratt & W. S. Lynn: Neutrophil elastase activity and superoxide production are diminished in neutrophils of alcoholics. *Am Rev Respir Dis* 141, 1249-1255 (1990)

153. Nelson S., G. Bagby, J. Andresen, C. Nakamura, J. Shellito & W. Summer: The effects of ethanol, tumor necrosis factor, and granulocyte colony-stimulating factor on lung antibacterial defenses. *Adv Exp Med Biol* 288, 245-253 (1991)

154. Nelson S., W. Summer, G. Bagby, C. Nakamura, L. Stewart, G. Lipscomb & J. Andresen: Granulocyte colony-stimulating factor enhances pulmonary host defenses in normal and ethanol-treated rats. *J Infect Dis* 164, 901-906 (1991)

155. Stoltz D. A., S. Nelson, J. K. Kolls, P. Zhang, R. P. Bohm Jr., M. Murphey-Corb & G. J. Bagby: *In vitro* ethanol suppresses alveolar macrophage TNF-alpha during simian immunodeficiency virus infection. *Am J Res Crit Care Med* 161, 135-140 (2000)

156. Zhang Z., J. Cork, P. Ye, D. Lei, P. O. Schwarzenberger, W. R. Summer, J. E. Shellito, S. Nelson & J. K. Kolls: Inhibition of TNF-alpha processing and TACE-mediated ectodomain shedding by ethanol. *J Leukoc Biol* 67, 856-862 (2000).

157. Kolls J. K., J. Xie, D. Lei, S. Greenberg, W.R. Summer & S. Nelson: Differential effects of *in vivo* ethanol

on LPS-induced TNF and nitric oxide production in the lung. *Am J Physiol* 268, L991-L998 (1995)

158. Spits H., R. de Waal Malefyt: Functional characterization of human IL-10. *Int Arch Allergy Immunol* 99, 8-15 (1992)

159. Mosmann T. R., K. W. Moore: The role of IL-10 in crossregulation of TH1 and TH2 responses. *Immunol Today* 12, A49-A53 (1991)

160. Szabo G., P. Mandrekar, L. Girouard & D. Catalano: Regulation of human monocyte functions by acute ethanol treatment : Decreased tumor necrosis factor-alpha, interleukin-1 beta and elevated interleukin-10, and transforming growth factor-beta production. *Alcohol Clin Exp Res* 20, 900-907 (1996)

161. P. Mandrekar, D. Catalano, L. Girouard & G. Szabo: Human monocyte IL-10 production is increased by acute ethanol treatment. *Cytokine* 8, 567-577 (1996)

162. Dorio R. J., H. J. Forman: Ethanol inhibition of signal transduction in superoxide production by rat alveolar macrophages. A proposed mechanism for ethanol related pneumonia. *Ann Clin Lab Sci* 18, 190-194 (1988)

163. Castro A., D. L. Lefkowitz & S. S. Lefkowitz: Effects of alcohol on murine macrophage function. *Life Sci* 52, 1585-1593 (1993)

164. Rimland K.: Mechanisms of ethanol-induced defects of alveolar macrophage function. *Alcohol Clin Exp Res* 8, 73-76 (1983)

165. Rimland D., W. L. Hand: The effect of ethanol on adherence and phagocytosis by rabbit alveolar macrophages. *J Lab Clin Med* 95, 918-926 (1980)

166. Guarneri J. J., G. A. Laurenzi: Effect of alcohol on the mobilization of alveolar macrophages. *J Lab Clin Med* 72, 40-51 (1968)

167. Dannenberg A. M.: Immune mechanisms in the pathogenesis of pulmonary tuberculosis. *Rev Infect Dis* 11, S369-S378 (1989)

168. Bermudez L., L. S. Young: Ethanol augments intracellular survival of *Mycobacterium avium* complex and impairs macrophage responses to cytokines. *J Infect Dis* 163, 1286-1292 (1991)

169. Bermudez L. E.: Effect of ethanol on the interaction between the macrophage and *Mycobacterium avium*. *Alcohol* 11, 69-73 (1994)

170. Okeson G. C., M. V. Divertie: Cilia and bronchial clearance: The effects of pharmacologic agents and disease. *Mayo Clin Proc* 45, 361-373 (1970)

171. Bomalaski J. S., J. P. Phair: Alcohol, immunosuppression, and the lung. *Arch Intern Med* 142, 2073-2074 (1982)

172. Berenyi M. R., B. Straus, & D. Cruz: *In vitro* and *in vivo* studies of cellular immunity in alcoholic cirrhosis. *Am J Dig Dis* 119, 199-205 (1974)
173. Bjorkholm M.: Immunological and hematological abnormalities in chronic alcoholism. *Acta Med Scand* 207, 197-200 (1980)
174. Miksza J. A., C. Waltenbaugh & B. S. Kim: Impaired antigen presentation by splenocytes of ethanol-consuming C57BL/6 mice. *Alcohol* 12, 265-271 (1995)
175. MacGregor R. R.: Alcohol and immune defense. *JAMA* 256, 1474-1479 (1986)
176. Roselle G.A., C. L. Mendenhall: Alteration of *in vitro* human lymphocyte function by ethanol, acetaldehyde, and acetate. *J Clin Lab Immunol* 9, 33-37 (1982)
177. Glassman A. B., C. E. Bennett & C. L. Randall: Effects of ethyl alcohol on human peripheral lymphocytes. *Arch Pathol Lab Med* 109, 540-542 (1985)
178. Domiati-Saad R., T. R. Jerrells: The influence of age on blood alcohol levels and ethanol-associated immunosuppression in a murine model of ethanol consumption. *Alcohol Clin Exp Res* 17, 382-8 (1993)
179. Chadha K.C., I. Stadler, B. Albini, S. M. Nakeeb & H. R. Thacore: Effect of alcohol on spleen cells and their functions in C57BL/6 mice. *Alcohol* 8, 481-485 (1991)
180. Shellito J. E., R. Olariu: Alcohol decreases T-lymphocyte migration into lung tissue in response to *Pneumocystis carinii* and depletes T-lymphocyte numbers in the spleens of mice. *Alcohol Clin Exp Res* 22, 658-663 (1998)
181. Loose L.D., N. R. Di Luzio: The influence of acute and chronic ethanol or bourbon administration on phagocytic and immune responses in rats. *Exp Mol Pathol* 23, 459-72 (1975)
182. Mulholland K: Strategies for the control of pneumococcal diseases. *Vaccine* 17, S79-S84 (1999)
183. Kolls J. K., S Nelson: Immune modulation in the treatment of respiratory infection. *Respir Res* 1, 9-11 (2000)
184. Stoltz D. A., P. Zhang, S. Nelson, R. P. Bohm Jr., M. Murphey-Corb & G. J. Bagby: Ethanol suppression of the functional state of polymorphonuclear leukocytes obtained from uninfected and simian immunodeficiency virus infected rhesus macaques. *Alcohol Clin Exp Res* 23, 878-884 (1999)
185. Nelson S., S. M. Belknap, R. W. Carlson, D. Dale, B. DeBoisblanc, S. Farkas, N. Fotheringham, H. Ho, T. Marrie, H. Movahhed, R. Root & J. Wilson: A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. CAP Study Group. *J Infect Dis* 178, 1075-1080 (1998)
186. Murray H. W.: Interferon-gamma and host antimicrobial defense. *Am J Med* 97, 459-467 (1994)
187. Jaffe H. A., R. Buhl, A. Mastrangeli, K. J. Holroyd, C. Saltini, D. Czerski, H. S. Jaffe, S. Kramer, S. Sherwin S & R. G. Crystal: Organ specific cytokine therapy. Local activation of mononuclear phagocytes by delivery of an aerosol of recombinant interferon-gamma to the human lung. *J Clin Invest* 88, 279-302 (1991)
188. Kolls J.K., D. Lei, D. Stoltz, P. Zhang, P. O. Schwarzenberger, P. Ye, G. Bagby, W. R. Summer, J. E. Shellito & S. Nelson: Adenoviral-mediated interferon-gamma gene therapy augments pulmonary host defense ethanol-treated rats. *Alcohol Clin Exp Res* 22, 157-162 (1998)
189. Lei D., J. R. Lancaster Jr., M. S. Joshi, S. Nelson, D. Stoltz, G. J. Bagby, G. Odom, J. E. Shellito & J. K. Kolls: Activation of alveolar macrophages and lung host defenses using transfer of the interferon-gamma gene. *Am J Physiol* 272, L852-L859 (1997)
190. Gallin J. I., J. M. Farber, S. M. Holland & T. B. Nutman: Interferon-gamma in the management of infectious diseases. *Ann Intern Med* 123, 216-224 (1995)
191. Squires K. E., W. F. Murphy, L. C. Madoff & H. W. Murray: Interferon-gamma and *Mycobacterium avium-intracellulare* infection. *J Infect Dis* 159, 599-600 (1989)
192. Squires K. E., S. T. Brown, D. Armstrong, W. F. Murphy & H. W. Murray: Interferon-gamma treatment for *Mycobacterium avium-intracellulare* complex bacillema in patients with AIDS (Letter). *J Infect Dis* 166, 686-687 (1992)
193. Williams L. M., D. C. Snyder, P. Deblieux, J. Ali, D. Kuebel, B. P. DeBoisblanc & W. R. Summer: Safety and feasibility of combined aerosolized and subcutaneous interferon-gamma as adjuvant treatment of *Mycobacterium avium* complex pulmonary infection in non-HIV infected hosts. *Am J Respir Crit Care Med* 149, A110 (1994)
194. Condos R., W.N. Rom & N. W. Schluger: Treatment of multidrug-resistant pulmonary tuberculosis with interferon-gamma via aerosol. *Lancet* 349, 1513-1515 (1997)

Key Words: Lung, Infection, Immune Defense, Alcohol, Immunotherapy, Review

Send correspondence to: Dr Steve Nelson, Section of Pulmonary and Critical Care Medicine, Department of Medicine, Louisiana State University Health Sciences Center, 1901 Perdido Street, Suite 3205, New Orleans, LA 70112, Tel.:504-568-4634, Fax:504-568-4295, E-mail: snelsol@lsuhsc.edu